

Cor et Vasa

Post mortem genetické testování

MicroRNA-221/222
and Cardiovascular Diseases

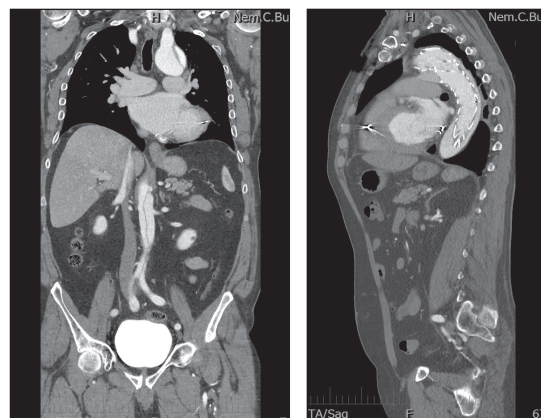
Inclisiran: new era of lipid-lowering therapy?

Fixní kombinace bisoprolol/perindopril
u hypertoniků s ICHS

Myokarditidy u dětí

Prosthetic valve thrombosis

Atherogenic Index of Plasma and
Cardiovascular Disease



CTAG – disekce aorty typu B (obr. vlevo), CTAG po debranchingu a implantaci stentgraftů (obr. vpravo). (Švejda J, Pešl L, Haniš J, Mokráček A. Katetrizační uzávěr perzistující Botallovy dučeje u pacienta po endovaskulární léčbě aortální disekce typu B. Kazuistika, str. 107–112).



Cor et Vasa

S PŘÍLOHOU Kardio

Časopis České kardiologické společnosti a České společnosti kardiovaskulární chirurgie *Cor et Vasa* vychází šestkrát ročně a pokrývá všechny aspekty kardiologie, angiologie, kardiovaskulární chirurgie, kardiovaskulárního zobrazování, pediatrické kardiologie, hypertenze, kardiovaskulární prevence a některé z aspektů intervenční radiologie.

Obsahuje úvodníky, původní sdělení, přehledové články i krátká sdělení z klinické a experimentální kardiologie. Počínaje rokem 2012 jsou v *Cor et Vasa* publikovány také souhrny (5 000 slov) z doporučených postupů Evropské kardiologické společnosti, připravené předními českými odborníky.

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Adresa pro korespondenci s vedoucím redaktorem časopisu *Cor et Vasa*
Prof. MUDr. Michael Aschermann, DrSc., FESC, FACC (vedoucí redaktor)
II. interní klinika kardiologie a angiologie,
1. lékařská fakulta Univerzity Karlovy a Všeobecná fakultní nemocnice,
U Nemocnice 2, 128 08 Praha 2, Česká republika
E-mail: Aschermann@seznam.cz

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Vydavatel

Česká kardiologická společnost, z. s.
Netroufalky 6b, 625 00 Brno

Předseda

Prof. MUDr. Aleš Linhart, DrSc., FESC, FCMA

Odpovědná redaktorka

Mgr. Klára Procházková
Tel.: +420 607 932 545
E-mail: ProchazkovaKlara@email.cz

Inzerce

Bc. Denisa Ebelová
Tel.: +420 725 777 880
E-mail: ebelova@kardio-cz.cz

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It features editorial, original articles, review articles, as well as short communications from clinical and experimental cardiology. Beginning 2012, *Cor et Vasa* has also been publishing summaries (5 000 words) of the European Society of Cardiology guidelines, developed by leading Czech experts in the field.

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Address for correspondence with the Editor-in-Chief of *Cor et Vasa*
Prof. MUDr. Michael Aschermann, DrSc., FESC, FACC (Editor-in-Chief)
2nd Department of Internal Medicine – Cardiology and Angiology
School of Medicine I, Charles University and General University Hospital
U Nemocnice 2, 128 08 Prague 2, Czech Republic
E-mail: Aschermann@seznam.cz

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President

Prof. MUDr. Aleš Linhart, DrSc., FESC, FCMA

Managing Editor

Mgr. Klára Procházková
Tel.: +420 607 932 545
E-mail: ProchazkovaKlara@email.cz

Advertising information

Bc. Denisa Ebelová
Tel.: +420 725 777 880
E-mail: ebelova@kardio-cz.cz

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Michael Aschermann, 2nd Department of Internal Medicine – Cardiology and Angiology, School of Medicine I, Charles University and General University Hospital, Prague, Czech Republic, e-mail: mascher@vfn.cz

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Vyhlášení soutěže o nejlepší publikaci v roce 2023

Vážené kolegyně, vážení kolegové,

výbor České kardiologické společnosti a redakční rada časopisu *Cor et Vasa* vyhlašují pro rok 2023 soutěž o nejlepší publikaci mladých autorů v *Cor et Vasa*. Do soutěže budou zařazeny všechny typy článků – review, originální články, kazuistická sdělení – publikované v roce 2023, první autor pak musí být členem ČKS a pracovní skupiny Kardio 35 ve věku do 35 let.

Publikované práce bude hodnotit sedmičlenná porota tvořená členy výboru ČKS. Nejlepší práce bude ohodno-

cena odměnou 40 000 Kč, druhé místo odměnou 20 000 Kč a třetí místo odměnou 10 000 Kč. Vyhodnocení všech publikovaných článků bude provedeno v lednu 2024.

*Za výbor ČKS a redakční radu Cor et Vasa
prof. MUDr. Michael Aschermann, DrSc., FACC, FESC,
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Poděkování recenzentům

Chtěli bychom poděkovat recenzentům, kteří pro časopis *Cor et Vasa* vypracovali recenze v roce 2022. Jsou jimi Věra Adámková, Dinara Akhmetzhanova, Hussein Akroos, Ali Al Imam, Panagiotis Artemiou, Michael Aschermann, Ondřej Aschermann, Alena Broulíková, Miroslav Brtko, Alan Bulava, Jan Bultas, Matteo Casale, Cenk Conbayir, Sergio Crosca, Richard Češka, Giuseppe Dattilo, Ibrahim Erdinc, Jan Filipovský, Pavel Gregor, Jan Harrer, Robert Hatala, Štěpán Havránek, Jaroslav Hlubocký, Tomáš Hnátek, Jaromír Hradec, Martin Hutýra, Miroslav Chochola, Tomáš Janota, Petr Kala, Gabriel Kamensky, Jiří Kettner, Jiří Král, Jan Krejčí, Peter Kubuš, Nazira Kudaibergenova, Petr Kuchynka, Jaroslav Lindner, Zuzana Mořovská, Omarov Nazarbek, Unal Orcun, Didem Melis Oztas, Tomáš Paleček, Fateme Parooie, Jan Pirk, Jiří Plášek, Rudolf Poruban, Miroslav Pšenička, Michal Rezek, Vilém Rohn, Vladimír A. Shvartz, Zdeněk Slavík, Eliška Sovová, Miloš Táborský, Murat Ugurlucan, Ivo Varvařovský, Jiří Vítovec, Giampiero Vizzari, Jan Vojáček, Jiří Widimský, Michael Želízko.

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Post mortem vyšetření obětí náhlé srdeční smrti a navazující kaskádový rodinný screening v ČR

(Postmortem genetic testing in sudden cardiac death victims and genetic screening of relatives at risk in the Czech Republic)

Alice Krebsová^a, Štěpánka Pohlová Kučerová^b, Pavel Votýpka^c, Petra Peldová^c, Markéta Kulvajtová^d, Petra Dohnalová^e, Matěj Bílek^{e,f}, Veronika Stufka^f, Kristina Rücklová^g, Iva Grossová^h, Hanka Wünschová^a, Terezia Tavačová^{ch}, Jana Hašková^a, Markéta Segetová^a, Andrea Gřegořováⁱ, Veronika Zoubková^c, Jana Petřková^{j,k,l}, Martin Dobiáš^m, Michal Makušaⁿ, Alžběta Blanková^o, David Veitr^o, Hynek Řehulka^p, Ivan Šubrt^q, Alexander Pilin^f, Petr Tomášek^e, Jan Janoušek^{ch}, Josef Kautzner^a, Milan Macek Jr.^c

^a Klinika kardiologie, Institut klinické a experimentální medicíny, Praha

^b Ústav soudního lékařství, Lékařská fakulta Univerzity Karlovy a Fakultní nemocnice Hradec Králové, Hradec Králové

^c Ústav biologie a lékařské genetiky, 2. Lékařská fakulta Univerzity Karlovy a Fakultní nemocnice Motol, Praha

^d Ústav soudního lékařství, 3. Lékařská fakulta Univerzity Karlovy a Fakultní nemocnice Královské Vinohrady, Praha

^e Ústav soudního lékařství, Fakultní nemocnice Bulovka, Praha

^f Ústav soudního lékařství, 1. Lékařská fakulta Univerzity Karlovy a Všeobecná fakultní nemocnice v Praze, Praha

^g Klinika dětí a dorostu, 3. Lékařská fakulta Univerzity Karlovy a Fakultní nemocnice Královské Vinohrady, Praha

^h Vojenský ústav soudního lékařství, Ústřední vojenská nemocnice – Vojenská fakultní nemocnice, Praha

^{ch} Dětské kardiocentrum, 2. Lékařská fakulta Univerzity Karlovy a Fakultní nemocnice Motol, Praha

ⁱ Ústav biologie a lékařské genetiky, Fakultní nemocnice Ostrava, Ostrava

^j I. interní klinika – kardiologická, Lékařská fakulta Univerzity Palackého v Olomouci a Fakultní nemocnice Olomouc, Olomouc

^k Ústav lékařské genetiky, Fakultní nemocnice Olomouc, Olomouc

^l Ústav patologické fyziologie, Lékařská fakulta Univerzity Palackého v Olomouci, Olomouc

^m Ústav soudního lékařství, Fakultní nemocnice Olomouc, Olomouc

ⁿ Soudně-lékařské oddělení, Nemocnice České Budějovice, České Budějovice

^o Ústav soudního lékařství a toxikologie, Krajská nemocnice Liberec, Liberec

^p Ústav soudního lékařství, Fakultní nemocnice Plzeň, Plzeň

^q Ústav lékařské genetiky, Fakultní nemocnice Plzeň, Plzeň

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Prevence

SOUHRN

Náhlá srdeční smrt (SCD) je u jedinců mladších 40 let velmi často způsobena dědičným kardiovaskulárním onemocněním. Identifikace těchto případů, provedení *post mortem* genetického vyšetření a kardiologického screeningového vyšetření přírodních příbuzných jsou předpokladem k primární prevenci srdeční zástavy u pozůstalých. Cílem práce je analýza výsledků takového programu, který byl zaveden v České republice.

Soubor a metodika: V období od 2016 do 2021 jsme v rámci grantového projektu řešili celkově 133 případů náhlého úmrtí, z nichž bylo podrobné kardiogenetické diagnostice podrobeno 115 úmrtí jedinců ve věku 0–59 let, celkem ze 110 rodin. Mrtví byli na základě pitevní diagnózy rozřazeni do kategorií dle typu kardiomyopatie (hypertrofická, dilatační nebo arytmogenní), kategorie bez nálezu strukturálního onemocnění srdce (SADS) nebo bez jasného pitevního nálezu (SUD/SUDI), případně náhlé úmrtí novorozence (SIDS) a akutní disekce velké cévy. Celkem 328 příbuzných bylo geneticky konzultováno a kardiologicky vyšetřeno. Po informovaném souhlasu následovala molekulární analýza metodou sekvenování nové generace (Sophia Genetics) celkem u 106 případů, kde byl k dispozici vhodný materiál pro analýzu.

Výsledky: Anamnéza náhlého úmrtí či blízký příbuzný se srdečním selháním a/nebo komorovou arytmií byla zaznamenána v 33/115 případů (28,6 %) rodin. Velmi pravděpodobná nebo jistá molekulární příčina onemocnění (klasifikace 4 a 5) byla nalezena u 21/106 (19,8 %) v genech *RYR2*, *KCNH2*, *KCNQ1*, *SCN5A*, *FLNC*,

Adresa pro korespondenci: MUDr. Alice Krebsová, Ph.D., Centrum dědičných kardiovaskulárních onemocnění, Klinika kardiologie, Institut klinické a experimentální medicíny, Vídeňská 1958/9, 140 21 Praha 4, e-mail: alice.krebsova@ikem.cz

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GLA, TTN, TNNT2, RBM 20, MYBPC3, MYPN, FHL1, TGFB1 a COL3A1. Záchyt příčinných variant kyseliny desoxyribonukleové (DNA) byl ve skupině náhlých úmrtí s předchozí rodinnou anamnézou 16/49 (32,6 %). Klinickým a genetickým vyšetřením bylo identifikováno 86/328 (26,2 %) příbuzných v riziku.

Závěr: Multidisciplinární spolupráce spolu s centralizovanou molekulárně-genetickou diagnostikou umožnila odhalit jistou molekulární příčinu SCD v 19,8 % případů. Významná část rodin měla pozitivní rodinnou anamnézu (28,6 %). Je možné tedy usoudit, že náhlé smrti by bylo možné zabránit provedením kaskádového rodinného screeningu až u jedné třetiny zemřelých.

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ABSTRACT

Sudden cardiac death (SCD) in individuals younger than 40 years has a heritable cause in a significant subset of cases. Identification of SCD, postmortem genetic analysis along with the cardiological screening in first degree relatives represents an important tool for the primary prevention of cardiac arrest in victim's relatives and requires multicentric and multidisciplinary collaboration. Between 2016 and 2021 we dealt with totally 133 cases of sudden death, the complex cardiogenetic analysis was performed in 115 cases at the age of 0–59 years with post mortem diagnosis of cardiomyopathy, acute aortic dissection and cases without morphological finding explaining the cause of death (sudden arrhythmic death or sudden unexplained death). DNA was isolated from post mortem collected tissue samples or relative's blood and subjected to massively parallel sequencing (SophiaGenetics, Switzerland). Genetic counselling and cardiological examinations were carried out in 328 family members. Highly likely or certain molecular aetiology (i.e. based on presence of ACMG.net classification 4 to 5 variants) was disclosed in 19.8% of analysed cases in *RYR2*, *KCNH2*, *KCNQ1*, *SCN5A*, *FLNC*, *GLA*, *TTN*, *TNNT2*, *RBM 20*, *MYBPC3*, *MYPN*, *FHL1*, *TGFB1*, and *COL3A1* genes. With cardiogenetic screening we identified 83/328 (26.2%) relatives at risk of life threatening arrhythmias, who were offered individualised care.

Conclusion: Our study with postmortem analysis could reveal a pathogenic DNA variant in 19.8% of cases and in 32.6% in cases with positive family history. A relevant number of studied victims had a positive family history, which indicates the importance of family cascade screening in patients with heart failure or malignant arrhythmias of unclear aetiology for primary prevention of sudden cardiac death.

Keywords:

Family cascade screening
Genetic analysis
Inherited cardiovascular diseases
Prevention
Sudden cardiac death

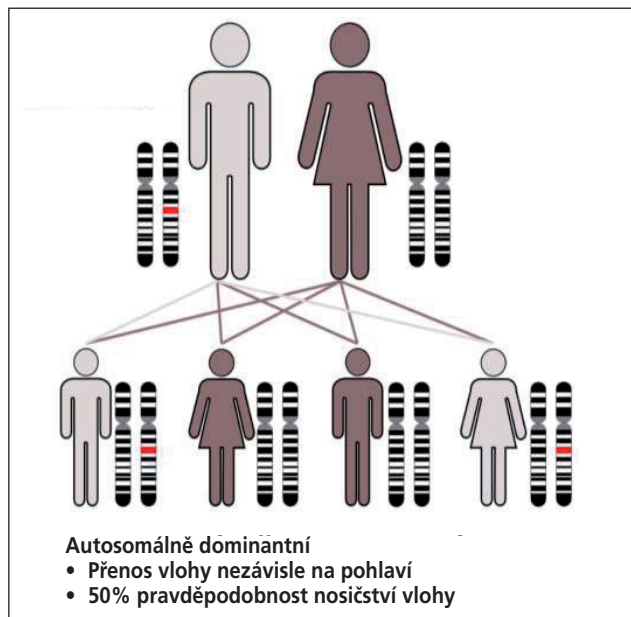
Úvod

Náhlá smrt (sudden death, SD) je definována jako neočekávané úmrtí z přirozených příčin, které nastává do jedné hodiny od začátku příznaků u doposud zdravého jedince, případně u jedince, jehož onemocnění nebylo natolik závažné, aby se očekávalo jeho úmrtí, nebo byl naposledy viděn zdrav před méně než 24 hodinami, pokud se jedná o úmrtí bez svědků.¹

SD je ve většině případů způsobena onemocněním srdce a je označována jako náhlá srdeční smrt (sudden cardiac death, SCD).² Na rozdíl od vyšších věkových skupin, kde jako příčina dominují aterosklerotické změny věnčitých tepen, jsou za většinu případů SCD u jedinců mladších 40 let zodpovědná dědičná kardiovaskulární onemocnění typu kardiomyopatií, arytmiických syndromů a dědičných aortopatií.^{3–5}

Vzhledem k tomu, že se vlohá pro většinu dědičných kardiovaskulárních onemocnění dědí s pravděpodobností 50 % bez závislosti na pohlaví, existuje u prvostupňových příbuzných významné riziko rozvoje identického onemocnění a srdeční zástavy (obr. 1).

Existující nejednotnost a variabilita v definici SD a SCD, společně s nejednotným systémem pitevní praxe ve světě mají za následek chybní přesných epidemiologických dat o incidenci obou jednotek.⁶ S jistotou víme, že incidence SCD stoupá s věkem, v korelaci se stoupající incidencí ischemické choroby srdeční. U osob ve věku 60 let se pohybuje mezi 2–200/1 000 za rok. Naproti tomu ve věkové skupině < 40 let je udávána okolo 1/100 000/rok.^{7,8} Vzhle-



Obr. 1 – Dědičná kardiovaskulární onemocnění: kardiomyopatie, arytmiické syndromy (kanálopatie) a aortopatie a jejich dědičnost

dem k předpokládané příčině je proto doporučováno provedení genetického vyšetření *post mortem*. To má být následováno kardiologickým screeningovým vyšetřením prvostupňových příbuzných.⁵ Rozsah vyšetření pozůstalých v riziku je definován v dokumentu světové organizace pro poruchy srdečního rytmu (APHRS/HRS).⁶

Tabulka 1 – Definice pojmů a nálezů v případech náhlého úmrtí – upraveno podle ^{5,10}

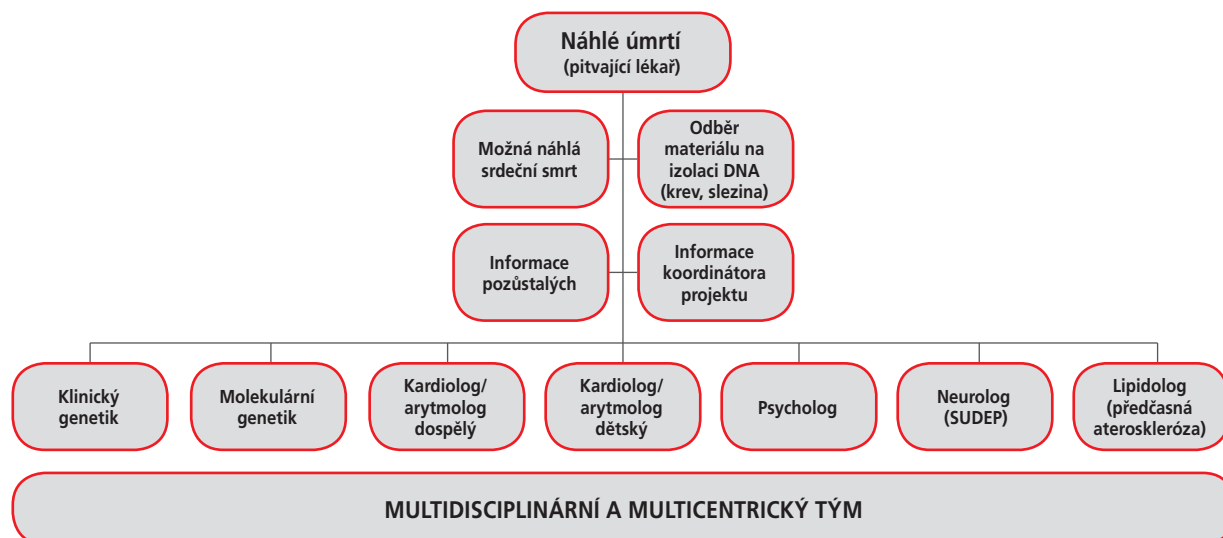
Kategorie pitevních nálezů	Definice
SD – sudden death	Smrt nastala během hodiny od počátku obtíží v případě přítomnosti svědků a smrt beze svědků během 24 hodin od posledního kontaktu a svědectví o životě osoby
SCD – sudden cardiac death	SD z kardiálních příčin
SADS – sudden arrhythmic death syndrome (náhlá arytmiická smrt), synonymní s výrazem: „autopsy negative sudden unexplained death“	Nevyjasněná příčina úmrtí u jedince staršího 1 roku s negativním patologickým a toxikologickým nálezem
SUD(S) – sudden unexplained death (syndrome)	Nevyjasněná příčina úmrtí u jedince staršího 1 roku, kdy jsou přítomny nespecifické strukturální změny srdce nesplňující kritéria pro jistou kardiomyopatii nebo náhlou arytmiickou smrt nebo pitva nebyla provedena
SUDI – sudden unexplained death in infancy (náhlé úmrtí dítěte mladšího 1 roku), synonymní s pojmem SUID (sudden unexplained infant death)	Nevyjasněná příčina úmrtí u jedince mladšího 1 roku, kdy jsou přítomny nespecifické strukturální změny srdce nesplňující kritéria pro jistou kardiomyopatii nebo náhlou arytmiickou smrt, nebo pitva nebyla provedena
SUDEP – sudden unexpected death in epilepsy	Náhlé úmrtí u osoby se známou epilepsií v předchorobí, bez známek traumatu, s negativním patologickým a toxikologickým nálezem <i>post mortem</i>
SIDS – sudden infant death syndrome	Náhlé úmrtí jedince mladšího 1 rok, nevyjasněná příčina úmrtí s negativním patologickým a toxikologickým nálezem

Tabulka 2 – Post mortem diagnózy vhodné indikovat k post mortem genetickému vyšetření – upraveno dle ³

DOPORUČENÉ DIAGNOSTICKÉ KATEGORIE PRO INDIKACI POST MORTEM GENETICKÉHO VYŠETŘENÍ	OMEZENÍ/UPŘESNĚNÍ
SADS – sudden arrhythmic death syndrome (žádné strukturální změny srdce, včetně histologie)	Jedinci mladší 50 let (možnou příčinou je porucha převodního systému srdce, tedy dědičný arytmiický syndrom)
SUDS – sudden unexplained death syndrome (přítomny nespecifické strukturální změny srdce nesplňující kritéria pro jistou kardiomyopatii)	Jedinci mladší 50 let (možná počínající kardiomyopatie nebo i arytmiický syndrom)
Kardiomyopatie (HCM, DCM, ACM, LVNC)	Bez věkového omezení
Předčasná ateroskleróza věnčitých tepen/akutní infarkt myokardu	Muži mladší 40 let, ženy mladší 50 let (pravděpodobná přítomnost familiární hypercholesterolemie)
Disekce aorty (vyjma případů disekce u pokročilé aterosklerózy ve vyšším věku)	Bez věkového omezení – typicky zmirají kolem 50. roku života (pravděpodobný dědičný aortální syndrom, např. Marfanův syndrom)
SUDEP – sudden unexpected death in epilepsy	Bez věkového omezení
SIDS – sudden infant death syndrome	Děti mladší 1 roku
SUDI – sudden unexpected death in infancy (náhlé úmrtí dítěte mladšího 1 roku)	Děti mladší 1 roku

Prvním krokem je standardizované pitevní vyšetření oběti SCD, včetně spektra doplňujících laboratorních vyšetření. Toto popisují doporučené pitevní postupy vytvořené v rámci Association for European Cardiovascular Pathology (AECVP).^{3,9} Dle výsledků pitvy a na podkladě zjištěných makroskopických a mikroskopických nálezů jsou mezinárodně definovány kategorie typů SCD: 1) kardiomyopatie, 2) náhlá arytmiická smrt (sudden arrhythmic death syndrome, SADS) a náhlá nevyjasněná smrt u jedinců mladších nebo starších jednoho roku (sudden unexplained death syndrome, SUDS nebo sudden unexplained deaths in infant, SUDI). Odděleně je zmiňováno náhlé úmrtí epileptika (sudden unexplained death in epilepsy, SUDEP), kdy může být epilepsie nesprávně stanovenou diagnózou pro bezvědomí provázející setrvalé komorové arytmie, případně některé epilepsie mohou představovat vzácné formy současných mozkových i srdečních kanálopatí (tabulka 1).^{5,6,10}

Doporučené postupy AECVP dále vymezují případy, u kterých by mělo být provedeno *post mortem* genetické vyšetření, někdy nazývané jako molekulární pitva. Jeho cílem má být přesné určení příčiny SCD a následné primární prevence srdeční zástavy u příbuzných^{3,5} (tabulka 2). *Post mortem* genetické vyšetření u zemřelého jedince by mělo být následováno nebo za ideálních podmínek současně doprovázeno klinickogenetickou konzultací a kardiologickým screeningovým vyšetřením prvostupňových příbuzných.^{3,11,12} Takové vyšetření by mělo být provedeno u všech případů SUDS/SADS u jedinců mladších 40 let nebo v případě zjištěné kardiomyopatie a akutní disekce velké cévy bez věkového omezení. V případech SUDEP bez věkového omezení a v případech náhlého úmrtí pro akutní infarkt myokardu u mužů mladších 40 let a žen mladších 50 let pro pravděpodobnou familiární hypercholesterolemii (tabulka 2).



Obr. 2 – Multidisciplinární řešení případů náhlé srdeční smrti

Zjištění příčin SCD u mladších jedinců je multidisciplinárním procesem, do kterého jsou zapojeni pitvající lékaři, kliničtí genetici, molekulární genetici, kardiologové, případně psycholog, neurolog, lipidolog, praktický lékař a další odbornosti dle jednotlivých konkrétních případů^{5,12,13} (obr. 2). S ohledem na komplexní problematiku se tento typ diagnostiky soustřeďuje do center terciární péče (tedy především na fakultní a univerzitní pracoviště).

Cílem této práce je popsat výsledky multicentrického a multidisciplinárního řešení případů SCD v ČR v letech 2016–2021, které bylo finančně zastřešeno grantem Ministerstva zdravotnictví ČR s reg. č. NV18-02-00237. Tento projekt byl zaměřen na zavedení výše popsaného vyšetřovacího postupu do reálné praxe. V první fázi byl identifikován reprezentativní soubor případů SCD. Následně na základě zájmu příbuzných a po získání informovaného souhlasu osob blízkých zemřelému byly vyšetřeny molekulární příčiny SCD. Nakonec byly zhodnoceny výstupy a dopady tohoto vyšetření na péči o prvostupňové příbuzné s cílem zajistit primární prevenci život ohrožujících poruch srdečního rytmu.

Metodika

Do projektu se postupně zapojila většina pracovišť soudního lékařství v Česku a na Moravě, klinicko-genetickou konzultaci prováděli genetici v IKEM, FN Motol Praha a FN Olomouc. Kardiologické screeningové vyšetření a dle potřeby individualizovanou péči o příbuzné v riziku provádí pracoviště: Klinika kardiologie IKEM a Dětské kardiocentrum FN Motol v Praze, I. interní kardiologická klinika FN Olomouc a Klinika pediatrie FN Královské Vinohrady v Praze. Molekulárně-genetická diagnostika se prováděla centrálně v laboratoři Ústavu biologie a lékařské genetiky FN Motol v Praze (tabulka 3).

Pitvající lékař odebral v případě podezření na SCD dle instrukcí tkáň vhodnou pro izolaci DNA (tabulka 4). Byl preferován vzorek tkáně bohatý na lymfocyty (slezina, játra, uzliny o velikosti 2 cm³) či vzorek periferní krve odebrané do K₃EDTA. Odebraná tkáň byla uložena do hluboko mrazících boxů na –80 °C (v případě, že pracoviště nemělo možnost hlubokého zamrazení vzorku, bylo doporučeno zmrazit tkáň v běžném laboratorním mrazáku

Tabulka 3 – Seznam spolupracujících pracovišť pro řešení možných dědičných příčin náhlé srdeční smrti

Ústavy soudního lékařství	Kardiologie	Genetika	Pediatrická péče
1., 2., 3. LF UK a ÚVN Praha	IKEM Dětské kardiocentrum FN Motol	IKEM (klinický genetik/kardiogenetik) ÚBLG FN Motol – molekulárně- genetická laboratoř a klinicko-genetické poradenství	Klinika pediatrie FN KV Praha Ambulance pro rizikové děti a SIDS, Thomayerova nemocnice Praha
FN Olomouc	FN Olomouc	FN Olomouc (klinický genetik/kardiogenetik)	
FN Hradec Králové	FN Hradec Králové	FN Hradec Králové (klinický genetik)	
FN Ostrava		FN Ostrava (klinický genetik)	
FN Plzeň		FN Plzeň (klinický genetik)	
Liberec České Budějovice			

Tabulka 4 – Zásady odběru materiálu pro genetickou analýzu na soudnělékařských pracovištích

Kdy odebírat	Dle indikačních dg. kategorií (viz tabulku 2)
Co odebírat	Tkáň bohatá na lymfocyty (slezina, játra, uzliny) o velikosti 2 cm ³ nebo periferní krev v EDTA
Jak uchovávat	Nativní tkáň zamrazit na –80 °C / –20 °C / v roztoku RNALater v +8 °C
Kam dopravit	Dle dohody s koordinátory
Kdy dopravit	Co nejdříve, jak je to možné
Koho informovat	Hlavní koordinátor: scd@ikem.cz, kardiogenetik MUDr. A. Krebsová, Ph.D., krea@ikem.cz, scd@ikem.cz, ev. koordinátora lokálního multidisciplinárního týmu
Doprovodný materiál pro klinického kardiogenetika	Podepsaný informovaný souhlas pozůstalých a/nebo telefonní/elektronický kontakt na příbuzné, pitevni protokol, soudnělékařská diagnóza, histologický náález na myokardu
Kdy likvidovat materiál v případě nevyužití	Nejdříve za 3 měsíce (ideálně uchovávat delší dobu dle kapacitních možností pracoviště)

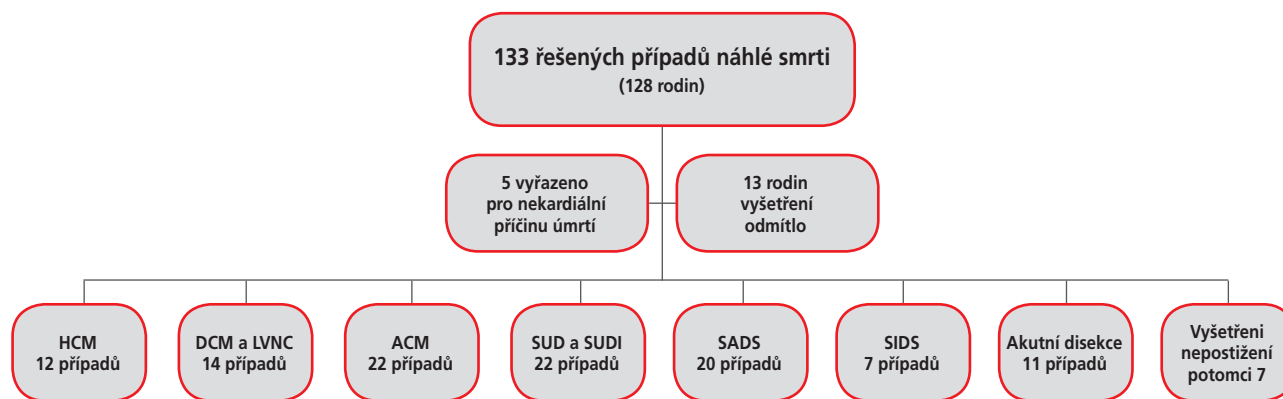
a zajistit jeho co nejčasnější transport ke genetické analýze). Alternativou bylo skladování vzorku tkáně v roztoku RNALater, a následné uchování až po dobu čtyř týdnů v chladicím boxu. V dalším kroku kontaktoval pitvající lékař příbuzné, kterým vysvětlil jeho podezření a předal jim informační dopis, kde je podstata vyšetření zemřelého spolu s nabídkou kardiologického vyšetření příbuzných srozumitelně popsána. V informačním dopise jsou uvedeny důležité telefonické i elektronické kontakty, které mohou pozůstalí využít. Pokud pozůstalí předběžně s vyšetřením zemřelého souhlasili a projevíli zájem o vlastní kardiologické vyšetření, zanechali u pitvajícího lékaře podepsaný informovaný souhlas a kontakt na sebe. Současně byli informováni koordinátoři studie, kteří zajistili přepravu materiálu na molekulárně-genetické pracoviště a v rozumném intervalu (přibližně tři měsíce) po náhlém úmrtí kontaktovali pozůstalé a pozvali je na konzultaci, pokud tak již sami neučinili.

Kromě případů SCD rozeznávaných a odeslaných lékaři provádějícími pitvu byly v rámci projektu řešeny další případy, na které byli kardiogenetici upozorněni příbuznými, kteří si možnost *post mortem* vyšetření a jejich vlastní screeningové vyšetření sami vyhledali nebo jim toto vyšetření bylo doporučeno ošetřujícím lékařem, nejčastěji

kardiologem. Některé rodiny s případem náhlého úmrtí kojence byly doporučeny na vyšetření přes specializovanou ambulanci v Thomayerově nemocnici (www.ftn.cz/ambulance-pro-rizikove-deti-a-sids/).

Na podkladě studia pitevních protokolů, soudnělékařských diagnóz a výsledků histologického vyšetření srdce byly případy SCD rozděleny do kategorií SADS, SIDS, SUDS/SUDI, aneurysma/disekce hrudní aorty a kardiomyopatie hypertrofická (HCM), arytmogenní (ACM), dilatovaná (DCM) a nekompaktní (left ventricle non-compact cardiomyopathy, LVNC) (tabulka 1, obr. 3).

K izolaci DNA z dodaného biologického vzorku byl použit automatický izolátor MagCore HF16 plus (RBC Bioscience, Tchaj-wan) pracující na principu extrakce na magnetických kuličkách. Kvalita extrahované DNA byla kontrolována na fluorimetru Qubit 2.0 (Invitrogen, USA). Sekvenační knihovna byla připravena s použitím cílených prób pro 100 vybraných genů pro kardiovaskulární onemocnění a prostřednictvím exomových panelů od firmy Sophia Genetics: Sophia Clinical Exome Solution a Sophia Whole Exome Solution, od firmy Twist Bioscience panel Twist Comprehensive Exome. Samotná sekvence byla prováděna na analyzátoru Next Generation Sequencing (NGS) (Illumina, USA). Získaná sekvenační data byla hod-

**Obr. 3 – Rozložení řešených případů náhlé srdeční smrti řešených v rámci projektu**

Tabulka 5 – Charakteristika řešených případů náhlé kardiální smrti včetně anamnestických dat

Post mortem dg.	Počet	Pohlaví (Nr.)		Věk	Věkový průměr	RA (Nr.)	Nedávná infekce	Prvostupňový příbuzný s preexist. onemocněním	Denní doba úmrtí			Kde nastalo úmrtí			
		Muž	Žena						Den	Noc	NZ	Doma	Práce	Nemocnice	
SUD/SUDI	21/1	14/1	7/0	1–54/2M	30,4/2M	2	4	0	12/1	5/0	4/0	14/0	1/0	1/1	
SADS	20	12	8	4–55	31	4	3	3	10	8	2	14	1	0	
SIDS	7	5	2	3Tý–5M	2,7M	0	2	1	3	4	0	6	0	0	
ARVC	22	12	10	17–56	36	4	4	5	11	6	5	17	2	0	
HCM	12	11	1	14–59	37,8	3	3	6	6	4	2	4	1	0	
DCM	13	10	3	8–48	33,4	5	2	9	9	1	3	8	1	2	
LVNC	1	1	0	35	35	0	0	1	0	1	0	1	0	0	
Disekce	11	10	1	16–49	33,3	2	0	4	4	5	2	6	0	2	
Nepostižení příbuzní	7	5	2	35–62	47,7	1	1	2	3	1	3	4	0	0	
Celkem	115	81	34	3Tý–62	31,8	22	19	35	59	35	21	74	6	6	

nocena v programu Sophia DDM (Sophia Genetics, Švýcarsko) s použitím pomocných programů a databází (Alamut, ClinVar, Franklin Genoox aj.). Detekované varianty byly klasifikovány na základě standardů ACMG/AMP (American College of Medical Genetics and Genomics/Association for Molecular Pathology) do pěti tříd DNA (klasifikace 1–5): benigní = klasifikace 1, pravděpodobně benigní = klasifikace 2, varianta nejasného významu = klasifikace 3, pravděpodobně patogenní = klasifikace 4, patogenní = klasifikace 5.¹⁴ U variant třídy 3–4, 4 a 5 byla provedena segreganční analýza u příbuzných pomocí sekvenování cíleného úseku Sangerovým sekvenováním.

Pokud se výše uvedenými metodami nepodařilo získat dostatečně kvalitní materiál od zemřelého, bylo diagnostické genetické vyšetření pomocí NGS zacíleno na jasné postižené prvostupňového příbuzného nebo na oba žijící rodiče (při předpokladu, že vloha pro onemocnění musela být od jednoho z nich zděděna). Genetické screeningové vyšetření u zdravých potomků náhle zemřelého při absenci materiálu bylo v iniciální fázi projektu také prováděno, ale později s ohledem na minimální výpovědní hodnotu bylo od tohoto vyšetřování upuštěno.

Příbuzní byli objednáni nejdříve ke klinicko-genetické konzultaci, kde s nimi byla událost podrobně probírána, zjištěny okolnosti úmrtí včetně odebrání co nejpodrobnější osobní a rodinné anamnézy zemřelého. Příbuzným byla vysvětlena povaha pravděpodobné dědičné příčiny, vysvětlen způsob dědičnosti a z toho vyplývající rizika pro další rodinné příslušníky. Během konzultace byl sestaven rodokmen alespoň ve třech generacích. Dále byl získán souhlas s vyžádáním lékařské dokumentace náhle zemřelého i s molekulárně-genetickým vyšetřením zemřelého a jich samotných. Toto iniciovalo návazné laboratorní vyšetření. Příbuzní byli následně pozváni na odpovídající

kardiologická screeningová vyšetření⁵ a konzultaci jejich výsledků spolu s výsledkem molekulárně-genetického vyšetření v intervalu přibližně šesti měsíců.

Materiál a pacienti

V rámci časového intervalu studie (2016–2021) bylo řešeno celkem 133 případů náhle zemřelých osob (36 žen a 97 mužů, průměrný věk 30,7 roku). Tyto případy pocházely z celkem 128 rodin, v 5 rodinách se jednalo o vícenásobné úmrtí (obr. 3). V 75/133 případů (56,4 %) se jednalo o přímou indikaci pitvajících lékařů. U zbylých 58 případů byli řešitelé přímo kontaktováni pozůstalými na základě doporučení lékaře nebo jejich osobní iniciativy.

S genetickým vyšetřením zemřelého a kardiologickým screeningovým vyšetřením nevyslovili příbuzní či blízcí zemřelého primárně souhlas ve 4/133 (3,0 %) případů. Svůj prvotní souhlas s vyšetřením později odvolalo či nepotvrdilo dalších 9/133 příbuzných (6,8 %). V 5/133 případů (3,8 %) jsme po podrobné analýze pitvěního nálezu a okolností úmrtí nakonec vyloučili nebo neprokázali jistou kardiální příčinu a molekulárně-genetické vyšetření nebylo indikováno (obr. 3). Celkem se tedy naše klinická a anamnestická analýza náhlých srdečních úmrtí s indikací genetického vyšetření týkala 115 případů (34 žen a 81 mužů) ze 110 rodin.

Ze skupiny rodin, které si možnost vyšetření vyžádaly samostatně, se v 7/58 případů (12,1 %) nepodařilo získat materiál ze zemřelého ani jeho obou rodičů, nejčastěji z důvodu příliš dlouhého intervalu od události. V 5/7 případů jsme provedli molekulárně-genetické vyšetření u nepostižených prvostupňových příbuzných. Později jsme od tohoto postupu upustili a příbuzným dle platných standardů doporučili kardiologickou dispenzarizaci s kardiologickým screeningo-

				Činnost při úmrtí								Obtíže před smrtí	
	Veřejné místo	Jinde	NZ	Běžná	Lehká	Středně náročná	Těžká	Spánek	Bdělý odpočinek	Jiná	NZ	Dlouho- dobé	Krátko- dobé
	2/0	1/0	2/0	7/1	1/0	1/0	0/0	4/0	3/0	1/0	4/0	12/1	8/1
	3	2	0	4	1	1	2	10	1	0	1	8	6
	0	1	0	0	0	0	0	7	0	0	0	6	1
	1	0	2	3	1	1	1	8	5	0	3	10	9
	5	0	2	1	3	0	3	3	1	0	1	6	6
	1	0	1	2	1	0	0	5	4	0	1	8	9
	0	0	0	0	0	0	0	0	1	0	0	0	0
	2	1	0	2	2	0	0	2	3	0	2	4	7
	0	1	2	0	0	1	0	2	1	0	3	2	4
	14	6	9	20	9	4	6	41	19	1	15	57	51

NZ – neznámý; RA – rodinná anamnéza náhlého úmrtí u prvostupňového nebo druhostupňového příbuzného; den definován jako doba od 6.00–22.00 h, noc od 22.00–6.00 h; úmrtí jinde – např. ve volné přírodě, osobním autě apod.; běžná činnost – zhruba definována jako práce v domácnosti, osobní hygiena, vaření; lehká zátěž – zhruba volná chůze, lehká fyzická práce; těžká zátěž – běh, těžší fyzická práce; bdělý odpočinek – sedící osoba; dlouhodobé obtíže > 1 den, spíše týdny až roky; krátkodobé obtíže nejčastěji v intervalu jednoho dne při úmrtí (neúměrná únava, dušnost, kašel, tlak na hrudi, bušení srdce, horečnatý infekt).

vým vyšetřením v pravidelných intervalech do 50.–60. roku života.^{5,15,16} Z této kohorty jsme vyšetřovali dva případy fibromuskulární dysplazie koronárních cév, tedy onemocnění zatím s neznámou genetickou příčinou.¹⁷ S rodinami jsme se proto v obou případech dohodli pouze na jejich kardiologickém screeningovém vyšetření. *Post mortem* molekulárně-genetické vyšetření bylo nakonec provedeno a hodnoceno celkem ve 106 případech (obr. 3, tabulka 5).

Kardiologické screeningové vyšetření proběhlo u 328 přímých příbuzných formou klidového EKG a v případě vysloveného podezření na dědičnou kardiomyopatii u zemřelého pomocí transthorakální echokardiografie. Tato vyšetření byla doplněna ambulantní monitorací EKG a zátěžovým EKG testem, pokud bylo u zemřelého vysloveno podezření na dědičný arytmiický syndrom jako příčinu úmrtí (zejména případy SADS/SUDS). V případech *post mortem* podezření na ACM jsme dále doplnili vyšetření pozdních potenciálů. Příbuzní náhle zemřelých s akutní disekcí byli vyšetřeni echokardiograficky a aorta znázorněna v celém jejím průběhu pomocí výpočetní tomografie nebo magnetické rezonance (CT/MR). Pokud u vyšetřených byly nalezeny známky některého z dědičných kardiovaskulárních onemocnění, byla doplněna další vyšetření dle individuální diagnózy k lepšímu odhadu rizika život ohrožujících arytmii (LTVA) formou MR, programované stimulace komor nebo farmakologických záťažových testů dle platných mezinárodních doporučení.⁵

Výsledky

Po iniciální stratifikaci jsme komplexní kardiogenetické vyšetření případů SCD provedli u 115 případů SCD (34 žen, 81 mužů) ze 110 rodin. Z důvodů absence materiálu

nebo smysluplnosti molekulárně-genetického vyšetření byla laboratorní molekulárně-genetická analýza provedena ve 106 případech. Průměrný věk zemřelých byl 31,8 roku, při vyjmutí kategorie SIDS a SUDI dosáhl průměrný věk zemřelých 34,2 roku.

Vyhodnocení anamnestických dat (tabulka 5)

Rodinná anamnéza

V rodinách náhle zemřelých jsme zaznamenali náhlé úmrtí u prvostupňového nebo druhostupňového příbuzného ve 21/115 (18,2 %) případech. Ve vyšetřovaných rodinách byl ještě před zahájením kardiologického kaskádového screeningu jeden nebo více příbuzných v odborné péči pro onemocnění srdečního svalu ve 33/115 případů (28,6 %). Současné náhlé úmrtí a příbuzný s onemocněním byly zaznamenány v 5/115 (4,3 %) případech.

Osobní anamnéza

Z hlediska anamnestických údajů o náhle zemřelém byl údaj o dlouhodobých potížích (např. kolaps či synkopa, epilepsie, dlouhodobá nepřírozená únava, dušnost, palpitace apod.) dohledán v 57/115 případů (49,5 %). V 51/115 případů (42,6 %) náhle zemřelý jedinec dlouhodobými potížemi netrpěl, ale náhlému úmrtí předcházely obdobné obtíže v intervalu kratším než 24 hodin, v 7 případech nebyly tyto údaje dostupné. Horečnatý infekt předcházel úmrtí v 19/115 případů (16,5 %). Absence dlouhodobých i krátkodobých obtíží byla zaznamenána jen u 27/115 (23,5 %) případů (tabulka 5).

Denní doba

O úmrtí v denní době se jednalo v 59/115 případů (51,0 %), u 35/115 případů (30,4 %) šlo o úmrtí v noci a u 21/115 pří-

padů (18,2 %) nebyla denní doba známa či zjištělná. Ve všech kategoriích pitevních diagnóz kromě SIDS a disekce převyšoval počet úmrtí ve dne počet úmrtí v noci.

Místo úmrtí

Nejčastějším místem úmrtí byl domov, kde došlo k úmrtí celkem v 74/115 případech (64,3 %). Následovalo veřejné místo, kde došlo k úmrtí ve 14/115 případech (12,2 %). V lůžkovém zdravotnickém zařízení, na jiném neurčeném místě a kategorii „místo úmrtí neznámo“ naplnilo shodně vždy 6/115 případů (7,0 %). Na jiném blíže určeném místě, např. ve volné přírodě, došlo k úmrtí v 7 případech (6,1 %), v práci v 6 případech (5,2 %) (tabulka 5).

Denní činnost a fyzická aktivita

K úmrtí docházelo nejčastěji ve spánku, a to ve 41/115 případech (35,7 %). Ve 20/115 případech (17,4 %) došlo ke kolapsu či úmrtí při běžné denní činnosti, v 18 případech (15,7 %) při bdělém odpočinku, v 9 případech (8,7 %) při lehké fyzické aktivitě, v 6 případech (6,1 %) při těžké fyzické aktivitě (dlouhodobý běh, těžká fyzická práce), ve 4 případech (2,6 %) při středně těžké fyzické aktivitě a v 15 případech nebyly údaje o činnosti či aktivitě, během které došlo ke smrti, známy (tabulka 5).

Molekulárně-genetické vyšetření

Molekulárně-genetické vyšetření bylo provedeno přímo z izolované DNA náhlé zemřelého v 75/106 případech (70,8 %). Pro nekvalitní vzorek DNA byla u dalších 21/106 případů (19,8 %) provedena analýza NGS u jasně postiženého prvostupňového příbuzného a v 10/106 případech (9,4 %) u obou rodičů, kdy v případě nálezu suspektní varianty byla cíleně potvrzena u zemřelého. Vysoce pravděpodobná nebo jistá molekulární etiologie (klasifikace DNA 4 nebo 5) byla ze 106 molekulárně-geneticky vyšetřených případů SCD zjištěna ve 21/106 případech (19,8 %). V případě jasně postižených prvostupňových příbuzných (náhlé úmrtí v 21 rodinách, postižený nemocný ve 33 rodinách, ale rodiny s náhlým úmrtím i postiženým příbuzným 5) až ve 16/49 (32,6 %).

Kategorie úmrtí dle výsledků pitvy

Dle pitevních diagnóz jsme řešili celkem 22 případů SUDS/ SUDI, 20 případů SADS, 7 případů SIDS (2 ženy a 5 mužů), 12 případů HCM, 13 případů DCM, 22 případů ACM, 1 případ LVNC a celkem 11 případů náhlého úmrtí na disekci aorty nebo koronárních cév (obr. 2, tabulky 5 a 6).

SUDS + SUDI

Do této kategorie bylo zařazeno 22 případů, 7 žen a 15 mužů, jejichž průměrný věk byl 30,4 roku (2 měsíce – 54 let). Celkem 18 případů bylo dodáno z pracovišť soudního lékařství, ve 4 případech bylo vyšetření doporučeno ošetřujícím kardiologem. Na základě genetické analýzy byly zařazeny 4/22 (18 %) případů do klasifikace DNA 4 nebo 5 (geny *TTN*, *FLNC*, *RYR2* a *TNNT2*). Genetická stratifikace stanovila diagnózu DCM/ACM ve 3/22 případů (13,6 %), diagnózu katecholaminergní polymorfní komorové tachykardie (CPVT) v 1/22 případů (4,5 %). Vyšetřeno bylo celkem 67 příbuzných, přičemž u 20 z nich (33,3 %) byl zjištěn rizikový genotyp nebo fenotyp dědičného onemocnění a nabídnuta kardiolo-

gická dispenzarizace s individualizovanou péčí (tabulky 6 a 7).

SADS

Do kategorie SADS bylo zařazeno 20 případů, 8 žen a 12 mužů, jejichž průměrný věk byl 31 let (4–55 let). Celkem 15 případů bylo dodáno z pracovišť soudního lékařství, v jednom případě bylo vyšetření doporučeno ošetřujícím kardiologem a 4 případy byly zařazeny na základě zájmu rodiny po úmrtí v rodině. Ve 2/20 případů (10,0 %) byla identifikována varianta klasifikace DNA 4 nebo 5 v genu *KCNH2* a genu *RYR2*. Genetická stratifikace tedy stanovila diagnózu dědičného arytmiického syndromu typu dlouhého intervalu QT typu 2 (LQT2) v 1/20 případů (5,0 %) a CPVT v 1/20 případů (5,0 %). Vyšetřeno bylo celkem 62 příbuzných, přičemž u 13 z nich (20,6 %) byl zjištěn rizikový genotyp nebo fenotyp dědičného onemocnění a nabídnuta kardiologická dispenzarizace s individualizovanou péčí (tabulky 6 a 7).

HCM

Do kategorie HCM bylo zařazeno 12 případů. Celkem se jednalo o 1 ženu a 11 mužů, jejichž průměrný věk byl 37,8 roku (14–59 let). Celkem 7 případů bylo dodáno z pracovišť soudního lékařství, ve 3 případech doporučil vyšetření spádový kardiolog příbuzného a 2 případy byly zařazeny na základě zájmu rodiny po úmrtí v rodině. Na základě genetické analýzy byly zařazeny 4/12 (33 %) případů do klasifikace DNA 4 nebo 5 (geny *MYBPC3*, *FHL1*, *MYPN*, *GLA* – *KCNQ1*). U náhlého úmrtí ženy ve věku 59 let bylo dle genetické stratifikace zjištěno nerozeznávané stádové onemocnění typu sfingolipidózy, konkrétně Fabryho choroba (gen *GLA*). Současně měla i dědičný arytmiický syndrom typu dlouhého intervalu QT typu 1 (LQT1 – gen *KCNQ1*). Tato rodina se přihlásila sama, neboť se v ní udála dvě další náhlá úmrtí a sestra zemřelé měla dlouhodobé srdeční obtíže bez dosud přesně stanovené diagnózy. *Post mortem* vyšetření její sestry vedlo ke stanovení diagnózy u žijící příbuzné. Toto umožnilo nabídnout jí a dalším dvěma genotyp-pozitivním rodinným příslušníkům péči ve specializovaném centru, včetně enzymové substituční terapie tohoto onemocnění, jejíž efektivita je prokázána ve vícero studiích.^{18,19} Vyšetřeno bylo celkem 44 příbuzných, přičemž 16 z nich (37,2 %) má fenotyp dědičného kardiovaskulárního onemocnění, případně nese rizikový genotyp a byla jim nabídnuta kardiologická dispenzarizace s individualizovanou péčí (tabulky 6 a 7).

DCM + jeden případ LVNC

Do této kategorie bylo zařazeno 13 případů s pitevním obrazem DCM a jeden případ s morfologickým nálezem LVNC. Celkem se jednalo o 3 ženy a 11 (1 LVNC) mužů, jejichž průměrný věk byl 33,4 roku (8–48 let). Pět případů bylo dodáno z pracovišť soudního lékařství, dalších 5 vyšetření bylo na základě doporučení ošetřujícího kardiologa jednoho z žijících příbuzných a 4 případy byly zařazeny na základě zájmu rodiny po úmrtí v rodině. Celkem 5/14 (35,7 %) případů spadalo na základě genetické analýzy do klasifikace DNA 4 nebo 5 (geny *TTN* [třikrát], *FLNC stop*, *RBM20*). Všechny geny jsou rozeznávanými molekulárními příčinami DCM s rizikem významných poruch srdečního rytmu. Vyšetřeno bylo celkem 41 příbuzných,

přičemž u 11 z nich (29,7 %) byl zjištěn rizikový genotyp, případně fenotyp kardiomyopatie a byla jim nabídnuta kardiologická dispenzarizace s individualizovanou péčí (tabulky 6 a 7).

ACM

K diagnóze ACM bylo přiřazeno 22 případů, 10 žen a 12 mužů, jejichž průměrný věk byl 36,0 let (17–56 let). Celkem 14 případů bylo dodáno z pracovišť soudního lékařství, v jednom případě doporučil k vyšetření ošetřující kardiolog nemocného příbuzného a 8 případů bylo zařazeno na základě zájmu rodiny po úmrtí v rodině. Na základě genetické analýzy byly 2 případy zařazeny do klasifikace DNA 4 nebo 5 (pozitivita *SCN5A*, *FLNC* stop). Oba geny patří mezi rozeznávané molekulární příčiny arytmogenní kardiomyopatie s rizikem život ohrožujících arytmí. Vyšetřeno bylo celkem 73 příbuzných, z nichž u 11 (22,5 %) byl zjištěn rizikový genotyp a/nebo fenotyp dané kardiomyopatie a byla jim nabídnuta kardiologická dispenzarizace s individualizovanou péčí (tabulky 6 a 7).

Akutní disekce

Do této kategorie bylo zařazeno celkem 11 případů, přičemž ve 2 případech se jednalo o fibromuskulární dysplazii koronárních tepen (oba případy muži), v jednom případě o spontánní disekci koronární tepny (žena) a zby-

lých 8 případů připadlo na akutní disekci aorty. Celkem se jednalo o 1 ženu a 10 mužů, jejichž průměrný věk byl 33,3 roku (16–49 let). Pět případů bylo dodáno z pracovišť soudního lékařství, ve 3 případech doporučil vyšetření ošetřující kardiolog jednoho z příbuzných a 3 případy byly zařazeny na základě zájmu rodiny po úmrtí v rodině. Na základě genetické analýzy byly 3 případy zařazeny do klasifikace DNA 4 nebo 5 (geny *COL3A1* [dvakrát], *TGFBR1*). Genetická stratifikace určila tedy diagnózu vaskulárního Ehlersova–Danlosova syndromu (EDS) u dvou vyšetřených, náhle zemřelých mladých mužů, u třetího z nich diagnózu Loyesova–Dietzova syndromu typu 1 (LDS1). Vyšetřeno bylo celkem 31 příbuzných, přičemž 9 z nich (29,0 %) je v riziku akutní disekce nebo již s dilatací aorty a byla jim nabídnuta kardiologická dispenzarizace s individualizovanou péčí (tabulky 6 a 7).

SIDS

Do kategorie SIDS bylo zařazeno 7 případů. Celkem se jednalo o 2 dívky a 5 chlapců, jejichž průměrný věk byl 0,3 roku (3 týdny – 5 měsíců). Čtyři případy byly dodány z pracovišť soudního lékařství, zbylé případy byly zařazeny na základě zájmu rodiny po úmrtí v rodině a doporučení specializované ambulance. Jistá příčinná varianta nebyla v žádném z případů nalezena. V jedné rodině byla nalezena varianta nejasného významu, která souvisí s feno-

Tabulka 6 – Výsledky post mortem genetického vyšetření včetně kardiologického screeningového vyšetření příbuzných v riziku

Post mortem diagnóza	Nr.	Pohlaví	Věk (roky)	Nr. pozitivní výsledek (varianta DNA 4 nebo 5)	Gen	Nr. vyšetření příbuzní/ fenotyp nebo genotyp pozitivní případy
HCM	12	1 žena, 11 mužů	14–59	4/12 (33 %)	<i>MYBPC3</i> , <i>FHL1</i> , <i>MYPN</i> , <i>GLA</i> , <i>KCNQ1</i> (jako druhá DNA varianta)	44/15
DCM	13	3 ženy, 10 mužů	8–48	4/13 (31 %)	<i>TTN</i> (3×), <i>RBM 20</i> , <i>FLNC</i> (stop)	38/11
LVNC	1	1 muž	35	1/1	<i>TTN</i>	3/0
ARVC	22	10 žen, 12 mužů	17–56	2/22 (9 %)	<i>SCN5A</i> , <i>FLNC</i> (stop)	73/11
Akutní disekce	11	1 žena, 10 mužů*	16–49	3/9 (33 %)	<i>TGFBR1</i> , <i>Col3A1</i> (2×)	31/9
SIDS	7	2 ženy, 5 mužů	< 1	0/7		20/6
SADS	20	8 žen, 12 mužů	4–55	2/10 (20 %)	<i>KCNH2</i> , <i>RYR2</i>	62/13
SUDS/SUDI	22	7 žen, 15 mužů	0–56	4/22 (18 %)	<i>RYR2</i> , <i>TNNT2</i> , <i>TTN</i> , <i>FLNC</i> (stop)	67/20
Vyšetření nepostižených příbuzných [#]	7	4 ženy, 3 muži	4–38	0/5*		8/0

* 2 muži zemřeli na dg. fibromuskulární dysplazie koronárních cév, genetické vyšetření nebylo provedeno.

* 2 příbuzní byli vyšetřeni již jen klinicky, molekulárně-genetické vyšetření „naslepo“ nebylo doporučeno.

[#] Prvostupňoví příbuzní zemřeli na SUDS (2 případy), SADS (3 případy), HCM (1 případ), akutní disekce aorty (1 případ).

Tabulka 7 – Seznam nalezených variant DNA pravděpodobně a jisté příčinných (třídy 4 a 5)

Přívětní dg.	Gen	Omim Nr.	Onemocnění	Varianta	Třída	Klasifikace ACMG	Poznámka
SADS	KCNH2	* 152427	LQT2	NM_000238.4 (KCNH2):c.43del (p.Leu15Trpfs*45)	5	PVS1, PM2, PP1	
	RYR2	* 180902	CPVT	NM_001035.3 (RYR2):c.7202G>A p.(Arg2401His)	5	PS2, PM2, PM5, PP3, PP5	
SUD/SUDI	TTN	* 188840	Arytmogenní kardiomyopatie	NM_001256850.1(TTN):c.98437del p.(Glu32813Asnfs*3)	5	PVS1, PM2, PP5	
	TNNT2	* 191045	Dilatační kardiomyopatie	NM_000364.3(TNNT2):c.40G>T p.(Glu14*)	5	PVS1, PM2, PP3	
	FLNC	* 102565	Arytmogenní kardiomyopatie	NM_001458.5(FLNC):c.3070C>T p.(Gln1024*)	5	PVS1, PM2, PP3	
	RYR2	* 180902	CPVT	NM_001035.3 (RYR2):c.1197G>A p.(Met399Ile)	4	PM1 PM2, PP1, PP3	
	MYBPC3	* 600958	Sarkomerická varianta HCM	NM_000256.3 MYBPC3:c.1227-13G>A	4	PM2, PP3, PS1, PS3, PM2	
HCM	FHL1	* 300163	Chromozom X vázaná muskulární dystrofie s rizikem HCM a LTVA	NM_001449.4(FHL1):c.7G>T p.(Glu3*) HET	5	PVS1, PM2, PP3	
	GLA KCNQ1	* 300644 * 607542	Andersonova-Fabryho choroba	NM_000169.3(GLA):c.644A>G (p.Asn215Ser) HET NM_000218.2(KCNQ1):c.1781G>A p.(Arg594Gln) HET	5 5	PM1, PM2, PP3, PP5 PM1, PP2, PP3, PP5, PS3	
DCM	MYPN	* 608517	HCM	NM_032578.4 (MYPN):c.3263G>A (p.Arg1088His)	4	PM2, PP5, PP1	
	TTN	* 188840	DCM/ACM	NM_001256850.1(TTN):c.33260_33261del (p.Tyr11087Cysfs*3)	4	PVS1, PM2	
	TTN	* 188840	DCM/ACM	NM_001256850.1 (TTN):c.41745_41748del p.(Glu13916Profs*28)	4	PVS1, PM2	
	TTN	* 188840	DCM/ACM	NM_001256850.1(TTN):c.76201G>T p.(Glu25401*) HET	4	PVS1, PM2	
	RBM20	* 613171	DCM/ACM	NM_001134363.2(RBM20):c.1900C>T p.(Arg634Trp)	5	PM1, PM2, PM5, PP3, PP5	
ARVC	FLNC	* 102565	Arytmogenní kardiomyopatie	NM_001458.4 (FLNC):c.102G>A p.(Trp34Ter)	5	PVS1, PM2, PP3, PP5	
	FLNC	* 102565	Arytmogenní kardiomyopatie	NM_001458.5(FLNC):c.6406dup p.(Glu2136Glyfs*20)	5	PVS1, PM2, PP3	
	SCN5A	* 600163	Arytmogenní kardiomyopatie/ dědičný arytmiický syndrom	NM_000335.5(SCN5A):c.4219G>A (p.Gly1407Arg)	5	PS1, PM2, PP3, PP1	
Disekce	COL3A1	* 120180	Vaskulární Ehlersův-Danlosův syndrom	NM_000090.3(COL3A1):c.2654G>A (p.Gly885Asp)	4	PM1, PM2, PP2, PP3	
	COL3A1	* 120180	Vaskulární Ehlersův-Danlosův syndrom	NM_000090.3(COL3A1):c.1330G>A p.(Gly444Arg)	5	PS1, PS2, PM1, PM2	
	TGFBR1	* 190181	Loyesův-Dietzův syndrom typu 1	NM_004612.3(TGFBR1):c.1460G>A (p.Arg487Gln) het	5	PM1, PM2, PM5, PP2, PP3, PP5	
	KCNE1	* 176261	LQT5 lite	NM_000219.5(KCNE1):c.253G>A p.(Asp85Asn)	RF		

Tabulka 8 – Nalezené DNA varianty nejasného významu (VUS)

Přítvň dg.	Gen	Omim Nr.	Onemocnění	Variant	Třída	Klasifikace ACMG	Poznámka
HCM	MYH7	* 160760	HCM	NM_000257.4 (MYH7):c.2908G>T (p.Ala970Ser)	3	PM2, PP2	
	MYBPC3	* 600958	HCM	NM_000256.3 (MYBPC3):c.844C>T (p.Arg282Trp)	3	PM2, PP3	Kumulativní efekt mutací?
	ANK2	* 106410	LQT4	NM_001148.5 (ANK2):c.6100G>A (p.Gly2034Arg)	3	PM2, PP3	
	PRKAG2	* 602743	Střádavé onemocnění, glykogenóza	NM_016203.4 (PRKAG2):c.593dupC (p.Asp199GlyfsTer74)	3	PM2, PP3	
	SCN10A	* 604427	Dědičný arytmičtý syndrom/syndrom epizodické bolesti	(SCN10A):c.472T>G p.(Tyr158Asp)	3	PM2, PP3	
DCM	DES	* 125660	DCM/ACM	(DES):c.976C>T (p.His326Tyr)	3	PM2, PP2, PP3	Souhlasí segregace
	ELN	* 130160	Dědičné onemocnění pojiva	NM_000501.3 (ELN):c.1315+1G>A	3		
	FLNA	* 300017		NM_001110556.1 (FLNA):c.875A>G p.(Glu292Gly)	3		
ARVC	SLC4A3	* 106195	DCM	NM_005070.4 (SLC4A3):c.2909G>A p.(Trp970*)	3	PM2, PP3	
	TTN	* 18884	DCM	NM_001256850.1 (TTN):c.91142_91144del p.(Lys30381del)	3	PM2, PP3	
	FLNC	* 102565	DCM/ARVC	(FLNC):c.1732G>T (p.Gly578Cys)	3	PM2, PP3	
	LMNA/C	* 150330	DCM/ARVC	NM_170707.4 (LMNA):c.1660G>A (p.Glu554Lys)	3	PM2, PP2, BP4	Souhlasí segregace ve více generacích
	LMNA/C	* 150330	DCM/ARVC	NM_170707.4 (LMNA):c.1489-4C>T	3	PM2	
SUD	DSP	* 125647	ARVC	NM_004415.3 (DSP):c.4558A>G p.(Ser1520Gly)	3	PM2, PP3	Souhlasí segregace ve více generacích
	DES	* 125660	ARVC/DCM	NM_001927.4 (DES):c.641A>C p.(Asp214Ala)	3	PM2, PP2, PP3	
	SCN5A	* 600163	ARVC/LQT3 apod.	NM_001160161.1 (SCN5A):c.246C>A (p.Asp82Glu)	3	PM2, PP2, PP3	
	CTNNA3	* 607667	ARVC	NM_013266.4 (CTNNA3):c.592C>A (p.Pro198Thr)	3	PM2, BP4	
	RYR2	* 180902	CPVT	NM_001035.2 (RYR2):c.836C>T (p.Thr279Met)	3	PP2, PP3, PM2	
SADS	NEBL	* 605491	DCM	NM_006393.2 (NEBL):c.2149-1G>A HET	3	BS1, PM2	Kumulativní efekt mutací?
	PRKAG2	* 602861	HCM	NM_001304527.1 (PRKAG2):c.68G>A p.(Arg23His)	3	PM2	
	MYH6	* 602743		NM_002471.3 (MYH6):c.365G>T p.(Cys122Phe)	3	PM2, PP3	
	CSRP	* 123876	HCM	(CSRP3):c.10T>C p.(Trp4Arg)	3		
	SCN10A	* 604427	Dědičný arytmičtý syndrom/syndrom epizodické bolesti	NM_001293306.2 (SCN10A):c.3784C>T p.(Arg1262*)	3	PM2, PP3	
SIDS	MYLK2	* 606566	HCM	(MYLK2):c.1754_1755insTCC p.(Ile585_Ser586insPro)	3	PM2, PM4, PP3	Kumulativní efekt mutací?
	KCNH2	* 152427	LQT2	NM_000238.3 (KCNH2):c.1717A>G (p.Asn573Asp)	3		
	CACNA1C	* 114205	LQT8	NM_199460.2 (CACNA1C):c.202G>A (p.Ala68Thr)	3	PM2, PP3	Kumulativní efekt mutací?
SIDS	DPP	* 126141	Familiární komorová fibrilace	NM_130797.4 (DPP6):c.2350T>A p.(Phe784Ile)	3	PM2, PP3	
	DSP	* 125647	ARVC	NM_004415.2 (DSP):c.3616T>A (p.Leu1206Ile)	3	PM2, PP3	
	KCNT1	* 608167	Noční frontální epilepsie s rizikem apnoe	NM_001272003.1 (KCNT1):c.2017G>A p.(Asp673Asn)	3	PM2, PP1, BP6	Souhlasí segregace v rodině

typem a v rodině u 5 klinicky postižených, prvo- i druhostupňových příbuzných segreguje s klinickým postižením. Tato varianta je popsána v kapitole věnované variantám nejasného významu (VUS) níže v textu (tabulky 6 a 8).

Vyšetření zdravých potomků náhle zemřelých

Molekulárně-genetické vyšetření s cílem vyloučit známé formy dědičného onemocnění u prvostupňových příbuzných – zdravých potomků, kteří nevykazovali žádné jisté známky dědičného kardiovaskulárního onemocnění, nepřineslo nález žádné jisté příčinné varianty DNA (tabulka 6). V těchto případech se jednalo o pitevní diagnózu HCM nebo akutní disekce aorty, v dalších 2 případech se dle pitevní zprávy jednalo o SUDS a ve 3 případech o SADS prvostupňového příbuzného.

LQT5 lite

Ve skupinách SUDS, SADS, ARVC a DCM jsme vždy u jednoho zemřelého identifikovali známou rizikovou variantu DNA v genu pro draslíkový kanál: NM_000219.5(KCNE1): c.253G>A p.(Asp85Asn). Přítomnost této varianty definuje diagnózu syndromu dlouhého intervalu QT typu 5 s lehkým průběhem a neúplnou penetrancí.^{20,21}

Varianty DNA neznámého významu (VUS, klasifikace 3)

V rámci molekulárně-genetického vyšetření jsme našli 29/106 (27,3 %) variant nejasného významu. Jednalo se o varianty DNA v genech, jejichž změny jsou rozeznatelnou příčinou jednotlivých kardiomyopatií či dědičných arytmiických syndromů. Nicméně i přesto, že dle kritérií ACMG jde o varianty velmi vzácné (kritérium PM2) a dle funkčních programů významně měnící funkci genového produktu (kritérium PP3), dle uznaných diagnostických kritérií jsou stále variantami nejasného významu (VUS) (tabulka 8). Tuto klasifikaci nepozměnil ani fakt, že některé z nich segregovaly s onemocněním u prvo- i druhostupňových příbuzných (kritérium PP1) dle ACMG: Genetic Variant Interpretation Tool University of Maryland School of Medicine (umaryland.edu).¹⁴ V případě náhlého úmrtí novorozence jsme našli variantu neznámého významu v genu *KCNJ71*, která ale v rozsáhlé rodině segregovala s fenotypem, který souvisí s popisovanými projevy onemocnění v literatuře²² (tabulka 8). Protože se jedná o onemocnění, které je dle literatury možné specificky léčit, tuto variantu jsme rodině oznámili a odkázali je na specializované pracoviště.

Kardiogenetické vyšetření příbuzných

Z 328 vyšetřených příbuzných mělo pozitivní genotyp nebo fenotyp dědičného kardiovaskulárního onemocnění celkem 83 vyšetřených příbuzných (25,3 %). Tento počet zahrnuje i příbuzné, kteří nesou variantu VUS a současně mají známky dědičného onemocnění. V jednom případě byl na základě kardiologické rizikové stratifikace implantován kardioverter-defibrilátor (ICD). V případě syndromu LDS1 podstoupila sestra zemřelého v rámci primární prevence akutní disekce kardiokirurgickou náhradu ascendentní aorty. V ostatních případech obdrželi příbuzní se známkami dědičného onemocnění s klinickými příznaky nebo jasným rizikovým genotypem odpovídající doporučení pro úpravu životního stylu, případně terapii v rámci primár-

ní prevence náhlého úmrtí. Dále jsme příbuzným nabídli dlouhodobou kardiologickou dispenzarizaci. Pravidelná kardiologická vyšetření jsme doporučili všem prvostupňovým rodinným příslušníkům, kde aktuálně nebyl nalezen jasný fenotyp ani genotyp dle současných doporučení.^{5,14}

Diskuse

Tato práce přináší doposud nejrozsáhlejší studii molekulárních příčin náhlého úmrtí v České republice. Její hlavní výsledky lze shrnout následovně: 1) Většina postižených rodin v ČR má zájem o *post mortem* analýzu a vlastní kardiologické screeningové vyšetření. 2) Záchyt příčinných DNA variant v naší kohortě je v 19,8 % případů, což zcela odpovídá publikovaným zahraničním výstupům. 3) Ve 28,6 % rodin byl prvostupňový příbuzný v kardiologické péči pro srdeční selhání či arytmiu a lze předpokládat, že části náhlých úmrtí by bylo možné zabránit pomocí kaskádového rodinného screeningu. 4) V rámci této studie jsme odhalili 83 příbuzných v riziku onemocnění a jeho závažných komplikací.

Multidisciplinární spolupráce

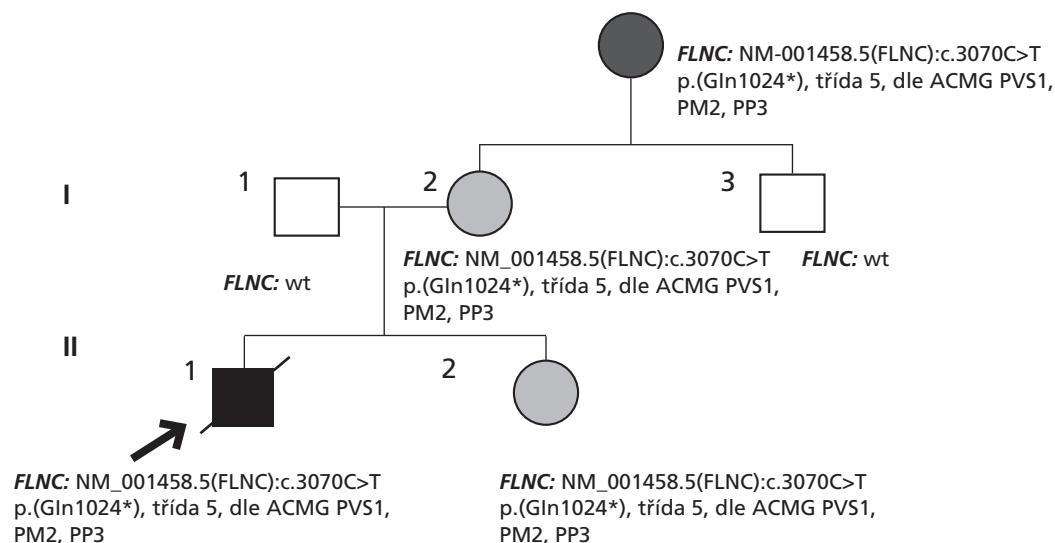
Jedním z důležitých dopadů studie bylo postupné rozšíření spolupráce mezi různými subjekty. Projekt byl zpočátku omezen na fakultní pracoviště v Praze a Olomouci. Stavbou přednáškovou činností a komunikací se podařilo postupně významně rozšířit povědomí o této problematice nejen v kardiologické, ale i soudnělékařské společnosti v ČR (tabulka 3). Tím se velmi navýšil počet spolupracujících odborníků a následně i počet vyšetřených případů oprávněných k tomuto typu diagnostiky. Velkou výhodou vidíme v centralizaci molekulárně-genetického vyšetření, čímž jsme zajistili jednotné metodické postupy a v neposlední řadě i posuzování identifikovaných variant DNA se standardizovaným přidělením odpovídajících diagnostických kritérií dle ACMG, která se jinak mohou v molekulárně-genetické praxi lišit mezi jednotlivými laboratořemi.

Charakteristika řešených případů náhlé kardiální smrti včetně anamnestických dat

Naprostá většina náhlých úmrtí se udála ve dne a v domácím prostředí při běžné činnosti nebo ve spánku, což odpovídá mezinárodním studiím.²³ Pouze 6,1 % zemřelých zemřelo při intenzivní sportovní nebo fyzické aktivitě. Do studie nebyl zařazen ani jeden případ náhlého úmrtí vrcholového sportovce. Muži tvořili v našem souboru většinu případů náhlých úmrtí. Studie ověřila, že naprostá většina rodin (120/133, 90,2 %) má zájem o vyšetření příčiny úmrtí u jejich příbuzného i o kardiologické screeningové vyšetření dospělých i nezletilých potomků.

Molekulárně-genetické výstupy

Celkové výsledky molekulárně-genetického vyšetření u zemřelých, včetně nálezů v jednotlivých podskupinách dle pitevní diagnózy v naší studii odpovídají publikovaným mezinárodním studiím obdobného rozsahu.^{4,24-26} Na základě našich zkušeností a v souladu s mezinárodními studiemi lze tedy očekávat, že genetická stratifikace vede k odhalení jednoznačně dědičného onemocnění u zhruba 20 %, tedy u přibližně jednoho z pěti případů.



Obr. 4 – Příklad náhle zemřelého nezletilého chlapce a neúplná penetrance příčinné varianty DNA u příbuzných žen v rodině.

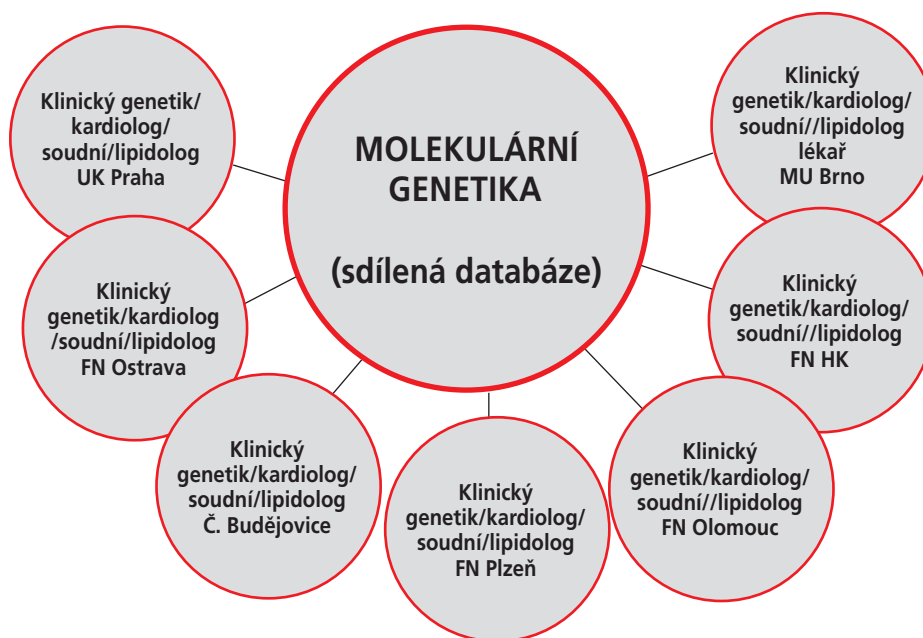
Popis: 13letý chlapec, který zemřel náhle během distanční výuky doma. Před smrtí si opakovaně stěžoval na rychle bušení srdce, nikdy ale neupadl do bezvědomí. Protože i starší sestra zemřelého měla palpitace, v minulosti diagnostikované jako život neohrožující supraventrikulárního charakteru a podstoupila její úspěšnou radiofrekvenční ablacii, nepřikládali rodiče obtížím takovou závažnost a chlapce nenechali časné vyšetřit. Genetické vyšetření nakonec prokázalo příčinnou trunkující variantu v genu pro FLNC, kterou nesla sestra, matka a její matka. Podrobné kardiologické screeningové vyšetření u žijících příbuzných žen neprokázalo žádnou jistou formu strukturálního onemocnění, opakovaně nebyly v dlouhodobé monitoraci a při zátěži prokázány významné poruchy srdečního rytmu. Sestra i matka dostaly preventivně beta-blokátory, byla jim nabídnuta dlouhodobá kardiologická dispenzarizace, zatím nebyl implantován defibrilátor (ICD) pro převyšující rizika implantačního výkonu a jeho přítomnosti nad rizikem arytmií

V rámci molekulárně-genetické analýzy jsme potvrdili výrazné proarytmické působení trunkujících variant v genu pro filamin C (*FLNC*) zejména u mužského pohlaví.²⁷ V naší studii jsme ji identifikovali jako jasnou molekulární příčinu u tří jedinců ze skupiny SUDS, DCM a ACM. Různorodé pitevní nálezy korelují s popsánými klinickými projevy genu *FLNC* a ukazují také na známý fakt, že arytmiické komplikace mohou předcházet rozvoji jednoznačných strukturálních změn srdečního svaly.^{28,29} Rozdíly v závažnosti průběhu kardiomyopatií i počtu náhlých úmrtí mužů byly opakovaně popisovány^{30,31} a v našem souboru vícekrát pozorovány, zejména pro příčinné varianty v genu titin (*TTN*) a filamin C (*FLNC*). Jako názorný příklad uvádíme případ náhlé zemřelého 13letého chlapce, který zemřel během distanční výuky doma. Před smrtí si opakovaně stěžoval na rychlé bušení srdce, nikdy ale neupadl do bezvědomí. Protože i starší sestra zemřelého měla palpitace, v minulosti diagnostikované jako život neohrožující supraventrikulární arytmie, a podstoupila úspěšnou radiofrekvenční ablacii, nepřikládali rodiče obtížím takovou závažnost a chlapce nenechali časně vyšetřit. Genetické vyšetření nakonec prokázalo příčinnou trunkující variantu v genu pro *FLNC*, kterou nesla sestra, matka a její matka. Podrobné kardiologické screeningové vyšetření u žijících příbuzných žen neprokázalo žádnou jistou formu strukturálního onemocnění, opakovaně nebyly v dlouhodobé monitoraci a při zátěži prokázány významné poruchy srdečního rytmu. Sestra i matka dostaly preventivně beta-blokátory, byla jim nabídnuta dlouhodobá kardiologická dispenzarizace a prozatím jim nebyl implantován defibrilátor (ICD) pro převyšující rizika implantačního výkonu a jeho přítomnosti nad rizikem arytmií¹⁰ (obr. 4).

Na druhou stranu se mohou kardiomyopatie u genotyp-pozitivních žen projevit až ve věku nad 50 let,³² a proto je vhodné zvažovat kaskádový rodinný screening nebo *post mortem* genetické vyšetření i v těchto případech. V rámci studie jsme tuto zkušenost ověřili v případě náhle zemřelé 59leté ženy s HCM a geneticky určenou Fabryho chorobou nebo v případě 56leté ženy s *post mortem* diagnózou fibrózy srdce a geneticky určenou familiární DCM s defektem v genu pro titin (*TTN*). V obou případech vedl k *post mortem* vyšetření zájem příbuzných při výskytu náhlých úmrtí a onemocnění srdce u více rodinných příslušníků. Riziko pro LTVA je v případě syndromu dlouhého intervalu QT identické pro obě pohlaví, ale liší se výskytem v určitých věkových skupinách.³³

Ve srovnání s výsledky molekulárně-genetického vyšetření u žijících jedinců s identickou diagnózou dědičného kardiovaskulárního onemocnění byl v případech HCM, DCM a akutní disekce téměř identický záchyt příčinných variant.^{32,34–36} *Post mortem* případy SADS a SUDS by odpovídaly souboru pacientů po přežití srdeční zástavě, kteří byli úspěšně resuscitováni a nebyla u nich diagnostikována jednoznačná příčina, tedy stanovena diagnóza tzv. idiopatické fibrilace komor (iVF). Záchyt příčinných variant je téměř identický v souboru zemřelých (SADS a SUDS) a přeživších.³⁶

Naopak v souboru *post mortem* diagnózy ACM jsou míra detekce jistých příčinných variant i spektrum genů zásadně odlišné – výrazně nižší než u žijících jedinců s touto diagnózou.³⁷ Není vyloučeno, že skutečné příčiny náhlého úmrtí jsou jiné než příčiny ACM u žijících/preživších pacientů. Pravděpodobnějším vysvětlením je však spíše nespolehlivost diagnózy *post mortem*, která se zakládá



Obr. 5 – Návrh multidisciplinární péče v jednotlivých centrech

na detekci tukové degenerace a fibrózy myokardu pravé komory. Tyto nálezy mohou být zkresleny kvůli obecné tendenci k nadváze u současné populace. Pro spolehlivé zhodnocení by bylo nutné analyzovat tělesnou hmotnost a výšku u této kohorty náhle zemřelých, avšak tyto údaje nebyly k dispozici zdaleka u všech případů pro nejednotné postupy na různých pracovištích soudního lékařství.

Syndrom dlouhého intervalu QTc typu 5, lehký (KCNE5 lite)

Nález časté varianty v genu pro draslíkový kanál *KCNE1* definující dědičný arytmiický syndrom LQT5 lite je obtížně interpretovatelný u zemřelých i žijících. Na základě dostupné literatury jsme jej neoznačili jako jednoznačnou molekulární příčinu náhlého úmrtí.^{21,38} Rodinám jsme ale nález sdělili, detekovaným nosičům varianty doporučili beta-blokátory v maximálně tolerované dávce a upozornili na další úpravy životosprávy, které jsou důležité pro prevenci významných poruch srdečního rytmu (např. vyhnout se výkyvům minerálů, vyhnout se lékům uvedeným v seznamu na www.crediblemeds.org).¹⁰

DNA varianty nejasného významu

Limitace molekulárně-genetických metod lze spatřovat v průkazu DNA variant nejasného významu (klasifikace DNA 3, tzv. VUS) u významné skupiny SCD, v našem souboru u 30/106 případů (28 %). Vzhledem k současně nejednoznačné pitevní morfologii se ani kombinace obou metod nezdá být dostatečná ke stanovení jednoznačné příčiny smrti. V několika případech jsme u zemřelých našli i více variant nejasného významu a není vyloučen jejich kumulativní efekt. Vliv je ale nejasný a za současných podmínek neprokazatelný. Tento fenomén byl popsán i jinými autory.³⁹ Významným interpretačním problémem je vztah tohoto molekulárně-genetického nálezu k mož-

nostem prevence u přímých příbuzných. Východiskem je dlouhodobá kardiologická dispenzarizace rodinných příslušníků a reevaluace nalezených variant v pravidelných časových intervalech.^{40,41}

Někteří autoři diskutují výskyt větších genomových inzercí a delecí u genů pro kardiomyopatie nebo dědičné arytmiické syndromy a jejich limitní detekční možnosti.⁴² Nicméně námi zvolená molekulárně genetická metoda sekvenování NGS od firmy Sophia Genetics zaručuje spolehlivou detekci právě těchto změn, které raritně nacházíme (vlastní nepublikovaná data).

Smysluplnost genetického testování u nepostižených příbuzných

V rámci studie jsme nabídli molekulárně-genetické vyšetření pěti prvostupňovým příbuzným bez jistých známek dědičného onemocnění, kde tkáň z náhle zemřelého nebo jeho obou rodičů nebyla dostupná. Tato diagnostika nepřinesla žádný výsledek, který ale v principu přítomnost genetického onemocnění u vyšetřených nevylučuje. Dle našich zkušeností je pravděpodobně racionální těmto rodinným příslušníkům nabídnout kardiologickou dispenzarizaci do 50.–60. roku života.¹⁵ Molekulárně-genetické vyšetření je oprávněné provést až v případě přítomnosti jasných známek určitého dědičného onemocnění (jasného fenotypu).

Rodinná anamnéza a kaskádový rodinný screening

Důležité je, že až v 42 % případů se náhlá smrt udála v rodinách s předchozími případy náhlého úmrtí nebo s příbuznými, kteří již byli ve specializované kardiologické péči. Tento fakt podporuje indikaci kaskádového rodinného screeningu u pacientů s jinak nevysvětlitelným srdečním selháním s redukovanou i zachovanou systolicou funkcí, závažnými poruchami srdečního rytmu nebo

rozšířením aorty bez anamnézy hyperlipoproteinemie nebo dlouhodobě neléčené arteriální hypertenze. Při screeningovém vyšetření jsme prokázali, že až jedna třetina příbuzných má známky dědičného kardiovaskulárního onemocnění, a je tedy v principu v riziku náhlého úmrtí, bereme-li v úvahu různou penetranci a expresivitu jednotlivých genových variant. Individualizovaná kontinuální péče v těchto případech přispěje k primární prevenci závažných poruch srdečního rytmu u často mladých, ekonomicky aktivních jedinců. V některých, obzvláště závažných případech s vysokou penetrancí v rodině se postižené rodiny rozhodují o primární prevenci onemocnění u potomků formou asistované reprodukce a preimplantační diagnostiky. Tím mohou zamezit dalšímu šíření tohoto konkrétního onemocnění do budoucích generací.

Post mortem vyšetření i v případě oddáleného úmrtí na jednotkách intenzivní péče

Na základě mezinárodních doporučení³ by měl být uvedený diagnostický postup aplikován i u případů náhlé srdeční zástavy s úspěšnou resuscitací a oddáleným úmrtím pacienta během hospitalizace. Interval mezi zástavou a úmrtím se může pohybovat od několika hodin až po několik dnů až týdnů. S ohledem na indikace pitev dle aktuálně platného zákona o zdravotních službách se mohou někteří takto postižení pacienti dostat na patologicko-anatomickou pitvu na ústavy a oddělení patologie. V té souvislosti je třeba vyslovit apel na provedení pitvy i u těchto zemřelých, ať už v režimu patologicko-anatomické pitvy, či po dohodě se soudnělékařským pracovištěm v režimu zdravotní pitvy (dle zvyklostí zdravotnického zařízení) a zajištění materiálů k *post mortem* diagnostice i u těchto případů.

Multidisciplinární týmy

Pro zlepšení komunikace mezi jednotlivými profesemi navrhujeme dle obecných doporučení evropských kardiologických, patologických a genetických společností^{3,5,12} sestavení lokálních multidisciplinárních týmů, které se pravidelně scházejí (obr. 5). Tyto týmy se potom mohou na národní úrovni setkávat, vyměňovat si zkušenosti a sdílet data v rámci pravidelných národních kongresů jednotlivých odborných společností. Molekulárně-genetická analýza by měla být nicméně sjednocena do jednoho, maximálně dvou specializovaných center (obr. 5).

Závěr

Studie ukázala, že centralizovaná molekulárně-genetická analýza umožňuje získat spolehlivé výsledky i v rámci ČR zhruba u jedné pětiny všech případů. Významná část případů náhlé srdeční smrti (42 %) měla pozitivní rodinnou anamnézu, což zdůrazňuje vhodnost provádění kaskádového rodinného screeningu u rodinných příslušníků pacientů s kardiomyopatií a/nebo komorovými arytmiemi nejasné etiologie v běžné kardiologické praxi za účelem primární prevence náhlé srdeční smrti u příbuzných. Pozůstali jsou ochotni podstoupit genetickou a kardiologickou péči ve většině případů. Tento postup vede k primární prevenci náhlého úmrtí až u jedné třetiny příbuzných, v naprosté většině v produktivním věku.

Post mortem genetická analýza při náhlé srdeční smrti (SCD) představuje důležitý diagnostický nástroj pro primární prevenci srdeční zástavy u příbuzných obětí a vyžaduje multicentrickou a multidisciplinární spolupráci. Dostupné informace a shrnutí možností *post mortem* diagnostiky jsou nově uvedeny na www.nahleumrti.cz.

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Coronary artery bypass grafting after iatrogenic coronary artery dissection: A single center eight years' experience

Mehmet Ali Yeşiltaş, Ali Aycan Kavala, Saygin Turkyilmaz, Yusuf Kuserli, Hasan Toz, Onur Emre Satılmış

Department of Cardiovascular Surgery, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey

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SOUHRN

Kontext: Iatrogenní disekce koronární tepny během diagnostické nebo terapeutické katetrizace představuje vzácnou a smrtelnou komplikaci, která může vést k rozvoji dalšího infarktu myokardu. Cílem této studie je podělit se o výsledky léčby koronárním bypassesem (coronary artery bypass grafting, CABG) u pacientů s iatrogenní disekcí koronární tepny po koronarografickém vyšetření (coronary angiography, CAG) na naší klinice.

Metody: Retrospektivně byly analyzovány údaje všech pacientů, u nichž byla v období mezi lednem 2014 a prosincem 2021 v naší nemocnici provedena CAG nebo perkutánní koronární intervence (PCI); do studie byli zahrnuti i pacienti s CABG po iatrogenní disekcí koronární tepny. Disekce se hodnotila pomocí klasifikace National Heart, Lung and Blood Institute (NHLBI).

Výsledky: Během uvedených osmi let byla CAG provedena u 20 398 pacientů a PCI u 9 583 pacientů. Koronární bypass pro iatrogenní disekci koronární tepny bylo nutno provést u 17 pacientů (0,06 %). K disekcí kmene levé věnčité tepny došlo u 6 (35,3 %) pacientů, přední sestupné větve u 6 (35,3 %), circumflex tepny u 2 (11,8 %) a pravé věnčité tepny u 3 (17,6 %). U 3 pacientů (17,6 %) překročila doba intubace 48 hodin. Jeden z těchto pacientů nedávno předtím prodělal onemocnění covid. U dalšího pacienta došlo k rozvoji otoku plic. Jiný pacient zemřel 4 dny po operaci v důsledku nízkého srdečního výdeje. Doba pobytu na jednotce intenzivní péče činila 2 (min.: 1 – max.: 13) dní; celkově v nemocnici 6 (min.: 4 – max.: 20) dní.

Závěr: Vývoj kritického klinického stavu před chirurgickým výkonem těsně souvisí s vyšší pravděpodobností úmrtí v časně a pozdní pooperační době. Z toho jasně vyplývá, že jakákoli léčba v každém období před operací, během ní a po ní představuje nejdůležitější determinantu konečného výsledku.

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ABSTRACT

Background: Iatrogenic coronary artery dissection during diagnostic or therapeutic catheterization is a rare and mortal complication that may result in a newly developed myocardial infarction. In this study, we aimed to share the results of CABG treatment of patients with iatrogenic coronary artery dissection after coronary angiography (CAG) in our clinic.

Methods: All patients who underwent CAG or percutaneous coronary intervention (PCI) in our hospital between January 2014 and December 2021 were analyzed retrospectively and patients who underwent CABG after iatrogenic coronary artery dissection were included in the study. The dissection classification was achieved according to the National Heart, Lung and Blood Institute (NHLBI) classification.

Results: During the eight years, CAG was applied to 20,398 patients and PCI to 9583 patients. Needed to treat CABG in iatrogenic coronary artery dissection developed in 17 of the patients (0.06%). LMCA was dissected in 6 (35.3%) patients and LAD in 6 (35.3%), CX in 2 (11.8%) and RCA dissection in 3 (17.6%). 3 patients (17.6%) had an intubation time longer than 48 hours. One of them has recently had a COVID infection. Another was suffering from pulmonary edema. The other patient died on the 4th postoperative day due to low cardiac output. The length of stay in the intensive care unit was 2 (min: 1 – max: 13) days. The hospital stay was 6 (min: 4 – max: 20) days.

Conclusion: The development of a critical clinical condition prior to surgery is strongly associated with a higher probability of early and late postoperative death. For this reason, it is clear that the treatments applied at every stage of the pre-, per-, and postoperative period are the most important determinants of the results.

Address: Mehmet Ali Yeşiltaş, Department of Cardiovascular Surgery, S.B.Ü. Bakırköy Dr. Sadi Konuk E.A.H., Zuhuratbaba Mah. Dr. Tevfik Sağlam Cad. No:11, e-mail: dr.maliyes@gmail.com
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Introduction

Iatrogenic coronary artery dissection during diagnostic or therapeutic catheterization is a rare and mortal complication that may result in newly developed myocardial infarction (MI).¹ The frequency of iatrogenic left main coronary artery (LMCA) dissection during coronary angiography has been reported as <0.1%. Depending on the size of the dissection flap and luminal occlusion, the clinical presentation may vary from an asymptomatic angiographic finding to hemodynamic deterioration.² Therefore, after the complication, conservative treatment could be enough or a patient may require treatment with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Complications following percutaneous coronary intervention are usually successfully managed in the catheterization laboratory, but some complications may require immediate surgical intervention.^{3,4} In such patients, myocardial infarction (MI) develops during the procedure, and as a result, they may need high-dose inotropic agent support, intra-aortic balloon pump (IABP), and extra corporeal membrane oxygenation (ECMO) to correct hemodynamic deterioration. Although emergency CABG is the most common treatment strategy in such cases where hemodynamic stability is not achieved but the 30-day mortality rate following a successful CABG remains at a high level of 26%.⁵ In this study, we aimed to share the results of CABG treatment of patients with iatrogenic coronary artery dissection after coronary angiography (CAG) in our clinic.

Methods

In our study, all patients who underwent CAG or PCI in our hospital between January 2014 and December 2021

were analyzed retrospectively and patients who underwent CABG after iatrogenic coronary artery dissection were included in the study. The dissection classification was achieved according to the National Heart, Lung and Blood Institute (NHLBI) classification.² Patients who are followed up or underwent PCI or died without undergoing CABG after coronary dissection were excluded from the study. If the patients had previous CABG or need an additional valve surgery were also excluded from the study (Fig. 1).

The information of the patients included in the study was obtained from the hospital data system and patients files. Baseline patients characteristics (age, hypertension, diabetes mellitus, previous PCI, chronic kidney failure), preoperative and postoperative ejection fraction (EF%), preoperative CABG time, number of vessels applied, postoperative death, stroke, MI, renal failure, intensive care unit stay and hospital stay were evaluated.

Definition of NHLBI and indication of CABG

According to NHLBI coronary artery dissection classification, Type C dissections appear as contrast outside the coronary lumen ("extra luminal cap") with persistence of contrast after dye has cleared from the lumen. Type D occurs as spiral ("barbershop pole") luminal filling defects, often with excessive contrast staining of the false lumen. Type E represents as new, persistent filling defects within the coronary lumen. Type F occurs those that lead to total occlusion of the lumen without distal antegrade flow. Patients with Type C–F were treated with balloon angioplasty or PCI in the same session. When residual stenosis was less than 30% and if the thrombosis in myocardial infarction (TIMI) 3 flows maintained procedure is considered successful. The patients who did not succeed in the interventional procedure were referred to CABG.

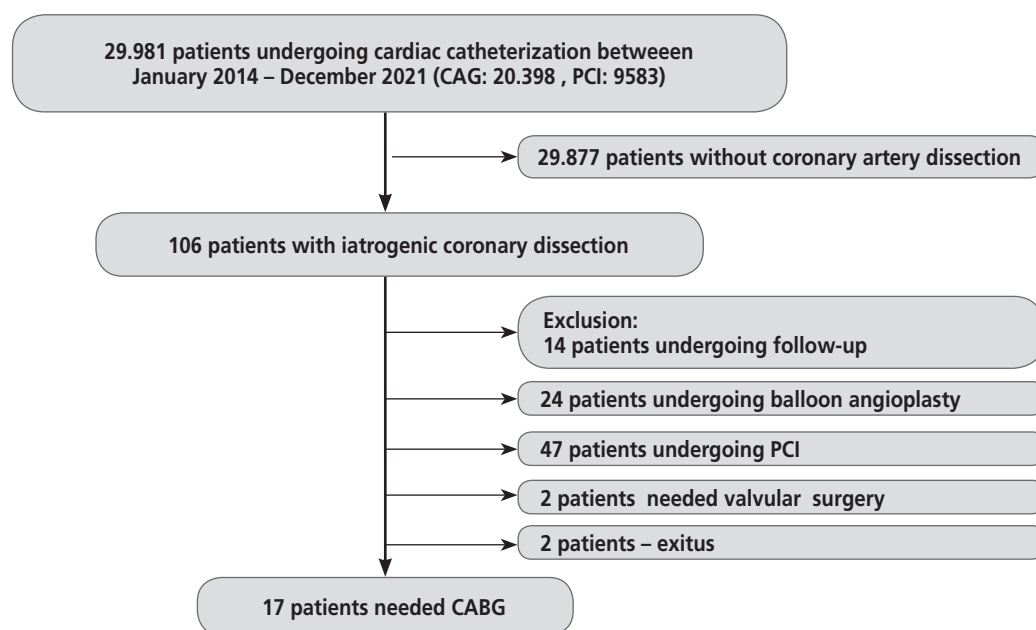


Fig. 1 – Study flow chart. CAG – coronary angiography; PCI – percutaneous coronary intervention.

In addition, if there is an indication for CABG according to the ESC Guidelines in patients who developed coronary artery dissection during diagnostic CAG, these patients were also referred to CABG.

The patients are treated with on-/off-pump CABG, depending on the patient's hemodynamic status and the surgeon's preference. Our clinical preference is off-pump CABG in hemodynamically stable patients and beating heart on pump or conventional CABG in unstable patients.

Procedure of CABG

All operations were performed with median sternotomy. Standard cannulation has been performed if it was an on-pump CABG surgery by placing arterial cannula in the ascending aorta and two-stage cannula in the right atrium. 100 IU/kg of heparin was administered intravenously to start extracorporeal circulation. A membrane oxygenator, a roller pump therefore a non pulsatile flow were used during cardiopulmonary bypass. We aim to achieve a nasopharyngeal temperature of 32 °C (mild hypothermia) and a hematocrit value of 22–24% (moderate hemodilution). During cardiopulmonary bypass, mean blood pressure of a patient was maintained over 60 mmHg and a pump flow at 2.4 l/m²/min. Cardiac arrest was achieved with antegrade (and also with retrograde if it is needed) potassium blood cardioplegia (10 ml/kg) to preserve the myocardium after cross-clamping. If the left internal mammary artery was a suitable graft it used as the last distal anastomosis on the left anterior descending artery. After taking cross clamp off, proximal anastomoses were performed under side clamping on the beating heart in all operations.

If it is an off-pump surgery, we still harvested the left internal mammary artery and 100 IU/kg heparin to achieve adequate anticoagulation (activated coagulation time of >250 s). The pericardium was dissected widely for proper cardiac positioning. Also a deep pericardial traction suture was placed in two thirds of the posterior pericardium to be able to elevate the base of heart by avoiding any injury to the phrenic nerve, the esophagus or the pulmonary lobe. The pericardium in the right aspect was incised widely to position the heart into the pleural space. To achieve the optimal visualization of the target vessels especially in the lateral and inferior aspect, the operating table was placed in the right decubitus Trendelenburg position. We prefer a cardiac positioning system that allows lifting the heart with preserved functional geometry without pushing the apex of the heart (Maquet ACROBAT stabilizer and XPOSE positioner; Maquet GMBH & Co, Rastatt, Germany). To be able to achieve a clean surgical field we routinely use a CO₂ insufflator. After a short waiting time after heparinization we perform arteriotomy and place an intracoronary shunt into the artery (Medtronic Inc., MN, USA). We perform the anastomosis using interrupted 7-0 Prolene sutures and remove the shunt from the coronary artery just prior to the completion of anastomosis. When all distal anastomoses were completed we suture proximal anastomoses onto the aorta using 6-0 Prolene sutures under a side-biting clamp. Total opera-

tion time, target arteries, and number of anastomosis are recorded. After the surgery is completed, we transfer all patients to the intensive care unit (ICU) with intubation.

Statistical analysis

The data were analyzed with SPSS v21. Descriptive statistical categorical variables were expressed in frequency (n) and percentage (%), while numerical variables were expressed in mean standard deviation.

Results

During the period of study, CAG was applied to 20,398 patients and PCI to 9583 patients. A need to treat CABG in iatrogenic coronary artery dissection developed in 17 of the patients (0.06%). Thirteen (76.4%) of these patients were male. In 12 (70.6%), hypertension was accompanied. Eight (47%) of these patients had a previous history of PCI. Dissection has developed during diagnostic angiography in 2 (11.8%) patients and during performing PCI in 15 (88.2%) patients. The dissection classification of these patients was done according to the NHLBI. Type C dissection was seen in 1 (5.9%) patient, Type D lesion in 2 (11.8%), Type D dissection in 6 (35.3%), Type E dissection in 8 (47%) patients. LMCA was dissected in 6 (35.3%) patients and LAD in 6 (35.3%), CX in 2 (11.8%) and RCA dissection was carried out in 3 (17.6%) (Table 1).

Considering the clinical condition of the patients and the type of dissection, the timing of the operation also varied. 9 patients (52.9%) were operated on urgently, 8 patients (47%) were operated as an emergency. The procedure was performed as off-pump CABG in 10 patients (58.8%), and as on-pump CABG in 7 patients (41.2%). 5 vessel CABG was applied to 1 patient (5.9%), 4 vessels to 2 patients (11.8%), and 3 vessels to 4 patients (23.5%). On-pump CABG was applied to 1 patient with 5 vessels, 2 patients with 4 vessels, 2 patients with 3 vessels, and 2 patients with 2 vessels. Intra-aortic balloon pump was needed in 7 of the patients (41.2 %). 4 (23.5%) of them were applied preoperatively and 3 (17.6%) were applied per-operatively (Table 2).

In the postoperative period, 1 patient (5.9%) was re-operated on the same day due to bleeding. There was bleeding caused by the incision of the aortic cannula and it was repaired. No complications developed afterwards. 3 patients (17.6%) had an intubation time longer than 48 hours. One of them has recently had a COVID infection. Another patient suffered from pulmonary edema. The other patient died on the 4th postoperative day due to low cardiac output. The length of stay in the intensive care unit was 2 (min: 1 – max: 13) days. The hospital stay was 6 (min: 4 – max: 20) days. Patients came to the routine postoperative controls on the 14th day and it was observed that one patient had no ventilation sounds in the left lung during auscultation. The patient was hospitalized and the left lung was drained with pleurocan. Another patient applied to the emergency room with dyspnea in the 3rd month postoperatively. It was observed that patients had low EF and non-adherence to medica-

Table 1 – Baseline demographics

Patients	Median (min–max)	Mean ± SD	n (%)
Age (years)		68.7±10.5	
Male			13 (76.4)
Hypertension			12 (70.6)
Diabetes mellitus			6 (35.3)
Insulin-treated diabetes			3 (17.6)
Smoking			11 (64.7)
Hyperlipidemia			8 (47)
Renal insufficiency			4 (23.5)
Hemodialysis			1 (5.9)
Prior MI			7 (41.2)
Prior CVE			1 (5.9)
Prior PCI			8 (47)
PVD			3 (17.6)
COPD			3 (17.6)
EF (%)	30 (20–60)		
Procedure type			
Diagnostic CAG			2 (11.8)
PCI			15 (88.2)
Vascular access			
Radial			5 (29.4)
Femoral			12 (70.6)
Dissection vessel			
LMCA			6 (35.3)
LAD			6 (35.3)
CX			2 (11.8)
RCA			3 (17.6)
Dissection type (NHLBI classification)			
C			1 (5.9)
D			2 (11.8)
E			6 (35.3)
F			8 (47)

CAG – coronary angiography; COPD – chronic obstructive pulmonary disease; CVE – cerebrovascular event; CX – circumflex artery; EF – ejection fraction; LAD – left anterior descending artery; LMCA – left main coronary artery; MI – myocardial infarction; NHLBI – National Heart, Lung and Blood Institute; PCI – percutaneous coronary intervention; PVD – peripheral vascular disease; RCA – right coronary artery.

tion. The patient was rehospitalized and discharged on the 3rd day with adequate diuretic therapy. Acute renal failure developed in 3 patients. 1 patient required hemodialysis and another one required hemofiltration. The patient who needed hemofiltration was discharged with normal renal functions. 4 patients (23.5%) had POAF and 2 of them returned to sinus rhythm with medication and 1 with cardioversion. One patient was discharged with AF after no hemodynamic problems were found. In the 2nd

Table 2 – Perioperative data

Patients	Median (min–max)	Mean ± SD	n (%)
Urgent			9 (52.9)
Emergency			8 (47)
CPB			
On-pump			7 (41.2)
Off-pump			10 (58.8)
Need for inotropic agent			11 (64.7)
Blood transfusion (ES)	2 (0–8)	1±0.7	
IABP			7 (41.2)
Preoperative using			4 (23.5)
Perioperative using			3 (17.6)
Total CPB time	53 (24–87)	Mean ± SD	
Cross clamp time	23 (9–38)	Mean ± SD	
Number of grafts			
One vessel			4 (23.5)
Two vessels			6 (35.3)
Three vessels			4 (23.5)
Four vessels			2 (11.8)
Five vessels			1 (5.9)

CPB – cardiopulmonary bypass; ES – erythrocyte suspension; IABP – intra-aortic balloon pump.

Table 3 – Postoperative data

Patients	Median (min–max)	Mean ± SD	n (%)
Reoperation for bleeding			1 (5.9)
On ventilator ≥48 h			3 (17.6)
Postoperative EF (%)			
In-hospital	35 (20–60)		
After 90 days	42 (25–60)		
Length of ICU stay (days)	2 (1–13)		
Length of hospital stay (days)	6 (4–20)		
Re-hospitalization			2 (11.8)
Postoperative AKI			3 (17.6)
New-onset dialysis-dependent			2 (11.8)
Postoperative AF			4 (23.5)
Postoperative stroke			1 (5.9)
Postoperative MI			0
Postoperative PCI			0
Re-CABG			0
Postoperative mortality			
In-hospital mortality			2 (11.8)
In 30 days			2 (11.8)
In 180 days			2 (11.8)

AF – atrial fibrillation; AKI – acute kidney injury; CABG – coronary artery bypass grafting; EF – ejection fraction; ICU – intensive care unit; MI – myocardial infarction; PCI – percutaneous coronary intervention.

month follow-ups, it was observed that this patient was also in sinus rhythm. 1 patient (5.9%) had a transient ischemic attack. It was observed that there was also a loss of strength (4/5) in the right upper extremity. This patient was operated on urgently. It was observed that he had a carotid lesion in the postoperative carotid doppler imaging. 2 patients died postoperatively due to low cardiac output as a result of diffuse anterior myocardial infarction on postoperative day 1 and day 4 (Table 3).

Discussion

Coronary artery dissection may rarely develop during diagnostic or therapeutic interventional procedures.⁶ While it may be sufficient to just follow up a patient with a coronary artery dissection without any intervention, CABG is needed in some patients.⁷ Although it is the type of CADx that determines such a difference in terms of indications, the clinical conditions and hemodynamics of the patients are also the main determinants. While there are many studies about the cause of iatrogenic coronary artery dissection or the interventional treatment, there are not enough studies on the surgical treatment.^{4,5,8–10} In this study, we shared the management, treatment planning, and results of patients with CABG after coronary artery dissection during coronary angiography.

There are some studies that it was thought the catheter selection and how these catheters are used is related with coronary artery dissection. Considering the results of these studies, it was stated that choosing the right catheter to be used according to the angle of the ostium of coronary artery with the aorta is important. In addition, it has been observed that the diameter of the catheter must be in accordance with the ostial diameter of the coronary artery, the catheter should not advance too far towards the ostium during imaging or intervention. It should be placed in the right axis and the catheter should not be dampened, or contrast injection must not be given with high pressure.¹¹ After all, we think that the patient's coronary ostium diameters should play a role in the selection of the catheter and that having enough experience in the use of catheters is also required. In addition, we believe that it would be more accurate to use automatic devices to give contrast injection instead of trying to adjust pressure manually.

In a study, it was seen that there is no difference in radial or femoral access as a risk factor.¹² The reason for the proportional difference with the access site in the studies was that the clinic performing the catheterization has an approach priority depending on their experience. In our study, the femoral artery was used in 12 (70.6%) patients and the radial artery was used in 5 patients (29.4%). We do not think that the proportional difference here is due to the access region. Since the femoral approach is mostly preferred as a catheterization site, it was concluded that there was a proportionately higher rate of femoral artery access.

In most studies, iatrogenic LMCA dissection appears to be <1%.⁷ As a result of diagnostic or therapeutic catheterization, the rate of dissection in LMCA and RCA was 0.14%. In the same study, approximately 90% of dissec-

tions occurred during PCI and it was approximately 20 times more likely to occur during PCI compared to CABG.¹³ In our study, 15 (88.2%) of the iatrogenic coronary artery dissection patients who needed CABG occurred during PCI and 2 (11.8%) during CABG. Overall, the risk of developing coronary artery dissection while performing PCI was 15 times higher than CABG in our study.

When planning CABG after coronary artery dissection, the clinical condition and symptoms of the patient are kept in consideration. However, there is no clear treatment algorithm determined by the guidelines. Therefore, the dissection level of the patients was defined according to NHLBI.^{2,12} According to these classifications, Type A and B dissections are more stable. Type C–F coronary dissections carry the risk of acute myocardial infarction. Therefore, intervention is recommended for these patient groups.¹² CABG is a good option in unstable patients, especially in patients whose true lumen cannot be fully defined. Since emergency intervention is an important issue in these cases, it is important that the cardiac surgery team is ready beforehand. In some centers, because the team gets ready, there is a tendency to perform PCI to provide hemodynamic stability.¹⁴ Although there is no study in the literature to determine whether there is an advantage in patients who underwent PCI and CABG, the short term results were found to be acceptable with patients who underwent PCI.¹² Coronary artery dissection developed in 106 patients, and CABG was applied in 17 of them in our study. The main reason for this low rate is that the dissection has occurred in CX and RCA in most of the patients. These patient groups were treated with interventional methods or followed up if they are asymptomatic. CABG has been a priority in LMCA and LAD dissections, especially in patients with long segment dissections.

Timing of surgery is an important factor in patients who need CABG. In general, in cases of acute MI, there is a tendency to take CABG after cardiac enzymes have normalized if hemodynamics and patient clinic allow.^{15,16} However, considering the symptoms of patients, it is obvious that there is an urgent need for intervention. In other studies, prolonged ischemia time was associated with MI and mortality in patients not admitted to emergency CABG.² In our study, 9 patients (52.9%) were taken to urgent CABG, while 8 patients (47.1%) were taken to emergency CABG. In order to undergo CABG operation under elective conditions after coronary artery dissection, it may be considered that the type of coronary dissection may be more asymptomatic, such as C–D, but even in these cases, the need for an emergency operation may arise. During the preoperative evaluation of the patients, IABP can be used to protect the hemodynamics of the patients and to reduce the myocardial burden.¹³ In our study, we used IABP in 4 (23.5%) of the patients to be taken for emergency operation. Considering the patients who were taken to the emergency operation, IABP was used in one of every two patients.

Off-pump CABG was preferred in patients with CADx if they had a suitable vascular structure, stable hemodynamics for positioning, suitable diameters with the target vessel.^{17,18} CPB triggers the formation of systemic inflammatory response syndrome (SIRS) through many

pathways such as the complement system, cytokines, coagulation-fibrinolysis cascade, endothelium and cellular immune system. Surgical procedure, contact of blood elements with the inner surface of the pump system in cardiopulmonary bypass, ischemia/reperfusion injury, hypothermia, endotoxemia, surgical stress and anesthesia are the causes of SIRS.¹⁹ This inflammatory response may occur in the postoperative period with myocardial dysfunction, respiratory failure, renal and neurological disorders. It may be associated with complications such as bleeding diathesis, liver dysfunction, and even multiple organ failure (MOF).^{20,21} At the same time, a cardiac-stunned heart may have difficulty with weaning from CPB. Therefore, in our study, 7 patients (41.2%) had on-pump surgery and 10 (58.8%) had off-pump. In our preference, we mostly decided according to the number of vessels to be bypassed and also depending on the primary surgeons decision. When we look at the patients who underwent on-pump, 1 patient (5.9%) had 5-vessel CABG, 2 patients (11.8%) 4-vessel CABG, 2 patients (11.8%) 3-vessel CABG, 2 patients (11.8%) 2-vessel CABG. According to our result, we observed that Cx which is the most difficult accessible coronary in off-pump surgery is in the common cluster.

Myocardial stunning (MS) is defined as a reversible myocardial damage, however, post-ischemic mechanical dysfunction can persist despite the adequate revascularization. So no matter how quickly we intervene, the probability of encountering a stunning situation after acute MI is high enough. It may take days or even weeks for the ventricle to return to normal function.²² Considering our patients, since iatrogenic coronary artery dissection can cause unexpected myocardial infarction, the treatment of these patients is similar to the management of myocardial stunning process in addition to surgery. Therefore, inotropic support is indicated for these patient groups.^{23,24,25}

The most commonly used and recommended vasoactive drugs as first-line therapy in the treatment of circulatory shock are dopamine and norepinephrine. These drugs act on both alpha and beta adrenergic receptors to varying degrees. Therefore, the effects of these drugs on cardiac output, another organ perfusion, peripheral circulation and cardiac contractility can be different.^{26,27} These important agents used in cardiac surgery sometimes adversely affect the cardiac process by triggering arrhythmia. Therefore, the use of dopamine at low cardiac output after cardiac surgery triggered arrhythmia more compared to noradrenalin, necessitating additional protocols in the cardiac process and prolonged intensive care processes.²⁸ All of our patients needed inotropes. In inotropic treatment, dopamine, noradrenaline, and adrenaline were used, respectively. In our patients, atrial fibrillation developed in 4 patients during the intensive care stays. Three of these 4 patients were receiving both dopamine and noradrenaline infusions.

In addition to the support of inotropic agents in these patient groups, IABP should be considered at the appropriate time to minimize myocardial damage. Both bypass and myocardial ischemic times are also associated with increased dependence on inotropic support.²⁸ In our study, there were 11 patients (64.7%) receiving inotropic sup-

port which is a significantly high rate. When we focus on the subgroups of these patients, we discovered that there are hemodynamically compromised patients with advanced types of dissection and acute MI. 4 (23.5%) of these patients had IABP placed preoperatively. IABP was placed in 3 patients (17.6%) because of difficulty of weaning from CPB. In 2 patients who received IABP preoperatively, they were needed taken into the operation urgently due to the continuation of angina while they were receiving IABP support and maximum medical treatment.

While most patients are treated with percutaneous interventions after iatrogenic coronary artery dissection, we observed that patients with severe mortality are often treated with CABG. In patients undergoing CABG, the management of the surgical process is of great importance. After the development of coronary artery dissection, if percutaneous treatments are evaluated or even tried, the duration of myocardial ischemia is significantly prolonged. In this process, CABG planning should be done as quickly as possible according to both the hemodynamic and clinical conditions of the patients, and even inotropic agents and IABP may be required to protect hemodynamics. In the slightest hemodynamic instability or in the presence of any clinical complaints, an inotropic agent or IABP should not be hesitated to start, and the patient should be operated on as soon as possible. Preferring off-pump CABG during the operation to avoid myocardial ischemia and systemic inflammatory response brought about by CPB will yield better results in terms of patient clinic and cardiac function. On-pump CABG can be applied in patients who cannot tolerate off-pump surgery hemodynamically. We think that the use of IABP is beneficial to reduce cardiac preload and increase coronary nutrition at any stage. To terminate inotropic medication, IABP or mechanical ventilator support, the hemodynamic status of the patient should be considered carefully and rapid decisions should be avoided. While planning the medical treatment of the patients during discharge, the necessary medical treatment of heart failure should be added. It has been observed that especially in patients with low EF, if there is non-compliance with medical treatment, patients return to the hospital with complaints of pulmonary failure and diffuse edema. These results showed us that diuretics should be included in medical treatment. In addition, in the control echocardiogram of the patients postoperatively, it was observed that there was an increase in EF after surgery, although it was not statistically significant. Therefore, in patients in the acute stage, early CABG prevented myocardial ischemia and increased cardiac function by allowing the correction of EF.

When it comes to limitations of the study, our work is retrospective in nature and therefore susceptible to all its inherent weaknesses. However, our institute policy is to treat all patients with iatrogenic lesions, regardless of age and comorbidities, thereby greatly reducing selection bias. Although the sample size was relatively small, it is probably the largest study to include the patient undergoing corrective cardiac surgery for complications occurring during PCI. It is a descriptive study without a control group.

Conclusion

Iatrogenic coronary artery injuries requiring CABG after PCI or diagnostic angiography are associated with high operative mortality and prolonged hospital stays despite urgent surgical treatment. Patients who develop acute coronary occlusion during PCI have a poor long-term prognosis. The development of a critical clinical condition prior to surgery is strongly associated with a higher probability of early and late postoperative death. For this reason, it is clear that the treatments applied at every stage of the pre-, per-, and postoperative period are the most important determinants of the results.

Conflict of interest

No conflict of interest was declared by the authors.

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Ethical statement

Ethics committee approval was received.

Informed consent

Informed consent was obtained from the participants.

Authors' contribution

All authors read and approved the final version of the manuscript. All authors contributed equally.

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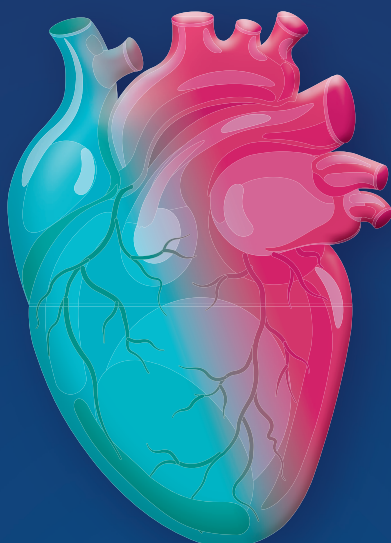
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Zkrácená informace o léčivém přípravku: Ylpio 80 mg / 2,5 mg tablety: Složení: Telmisartanum 80 mg a indapamidum 2,5 mg v 1 tabletě. **Indikace:** Substituční terapie esenciální hypertenze u dospělých pacientů, jejichž krevní tlak je kontrolován kombinací telmisartanu a indapamidu podávanými současně ve stejných dávkách, jako jsou v kombinaci. **Kontraindikace:** Hypersenzitivita na léčivé látky, sulfonamidy nebo pomocné látky, těžká porucha funkce jater nebo jaterní encefalopatie, těžká porucha funkce ledvin, hypokalemie, obstrukční poruchy žlučových cest. **Kontraindikace** během druhého a třetího trimestru těhotenství. Léčba přípravkem se během kojení nedoporučuje. Současné užívání telmisartanu s přípravky obsahujícími aliskiren je kontraindikováno u pacientů s diabetes mellitus nebo poruchou funkce ledvin (GFR < 60 ml/min/1,73 m²). **Nežádoucí účinky:** *Související s telmisartanem:* Infekce močových cest nebo horních cest dýchacích, hyperkalemie, synkopa, vertigo, bradykardie, kašel, průjem, dyspepsie, zvracení, pruritus, zvýšené pocení, kožní vyrážka, myalgie, poškození ledvin včetně akutního renálního selhání, bolesti na hrudi, astenie, zvýšení hladiny kreatininu v krvi. *Související s indapamidem:* Hypokalemie, únava, závratě, bolest hlavy, parestezie, nauzea, zvracení, zácpa, sucho v ústech, hypersenzitivní reakce, makulopapulární vyrážky, purpura, fotosenzitivita. **Interakce:** Kombinace telmisartanu s digoxinem může zvýšit hladinu digoxinu. Telmisartan může vyvolat hyperkalemii. Riziko se zvyšuje při kombinaci s dalšími látkami vyvolávajícími hyperkalemii (např. kalium šetřící diuretika, ACE inhibitory, NSAID, heparin, cyklosporin, takrolimus a trimethoprim). **Kombinace, které nejsou doporučeny:** Podání s draslíky šetřícími diuretiky nebo přípravky obsahujícími draslík (např. spironolakton, amilorid, triamteren, náhražky soli obsahující draslík). Při nezbytnosti současného podávání je nutno často kontrolovat kalemii, případně EKG. Přípravek může zvyšovat plazmatickou koncentraci lithia. **Kombinace vyžadující zvýšenou opatrnost:** Nesteroidní protizánětlivé léky (NSAID) a kyselina salicylová (≥ 3 g/den) mohou snižovat antihypertenzní účinek. Při oslabené funkci ledvin může kombinace telmisartanu a přípravků blokujících cyklooxygenázu vést až k akutnímu selhání ledvin. U dehydratovaných pacientů hrozí riziko akutního renálního selhání. Předchozí léčba vysokými dávkami diuretik vede k riziku hypotenze po zahájení léčby telmisartanem. Kombinace s léčivými vyvolávajícími *torsade de pointes* (např. antiarytmika, některá antipsychotika, bepridil, erythromycin i.v., pentamidin, moxifloxacin, vinkamin i.v.) zvyšuje riziko ventrikulárních arytmií, zvláště *torsade de pointes*. Je tedy třeba sledovat a korigovat hypokalemii a monitorovat elektrolyty a EKG. Doporučuje se používat látky, u kterých při hypokalemii nehrozí riziko *torsade de pointes*. Jiná léčiva způsobující pokles hladiny draslíku (např. i.v. amfotericin B, kortikosteroidy, tetrakosaktid, stimulační laxativa) zvyšují riziko hypokalemie (kalemie se má sledovat a korigovat). Hypokalemie predisponuje k toxickým účinkům digitalisu a při současném léčbě se doporučuje monitorování kalemie a EKG. Zvýšené opatrnosti je třeba rovněž dbát při kombinaci s ACE inhibitory (zejména v počátcích léčby a při depleci sodíku nebo při městnavém srdečním selhání) a je třeba brát v úvahu, že se nedoporučuje duální blokáda RAAS pomocí kombinovaného užívání inhibitorů ACE, blokátorů receptorů pro angiotenzin II nebo aliskirenu. Dále je třeba dbát zvýšené opatrnosti při kombinaci s baklofenem a alopurinolem. **Kombinace, jež je nutno vzít v úvahu:** Jiné antihypertenzní léky, imipraminová antidepresiva, neuroleptika, baklofen a amifostin mohou zvýšit antihypertenzní účinek. Ortostatická hypotenze může být potencionována alkoholem, barbituráty, narkotiky nebo antidepresivy. Opatrnosti je dále třeba při kombinaci s metforminem (riziko laktátové acidózy), jodovanými kontrastními látkami, vápníkem, cyklosporínem, takrolimem a kortikosteroidy. **Upozornění:** Léčba nesmí být zahájena během těhotenství. Jestliže je zjištěno těhotenství, musí být léčba přípravkem ihned ukončena. Pacientům s oboustrannou stenózou renální arterie nebo se stenózou arterie zásobující jedinou funkční ledvinu hrozí během léčby zvýšené riziko těžké hypotenze a renální nedostatečnosti. Thiazidům podobná diuretika jsou plně účinná pouze při normální nebo minimálně snížené funkci ledvin. U pacientů s poruchou renálních funkcí užívajících telmisartan se doporučuje sledování kalemie a kreatininemie. U pacientů s primárním aldosteronismem se léčba telmisartanem nedoporučuje. Je třeba věnovat zvýšenou pozornost pacientům trpícím stenózami aortální nebo mitrální chlopně nebo obstrukční hypertrofickou kardiomyopatií. Pravidelné sledování hladiny glukózy v krvi je důležité u diabetiků. U pacientů, jejichž cévní tonus a renální funkce závisí převážně na aktivitě RAAS (např. u pacientů se závažným městnavým srdečním selháním nebo u pacientů s průvodním onemocněním ledvin, včetně stenózy renální arterie), může být léčba spojena s akutní hypotenzí, hyperazotémií, oligurií nebo vzácněji i s akutním selháním ledvin. U pacientů s poklesem intravaskulárního objemu nebo koncentrace sodíku (např. v důsledku diuretické terapie, omezování soli v dietě, průjmů nebo zvracení) se zejména po první dávce telmisartanu/indapamidu může objevit symptomatická hypotenze. Natřemii je nutno stanovit před zahájením léčby a pravidelně kontrolovat, častěji u starších pacientů a u pacientů s cirhózou jater. U rizikových pacientů z hlediska hyperkalemie se doporučuje kalemii monitorovat. Je třeba zabránit vzniku hypokalemie, zejména u vysoce rizikových skupin pacientů, tj. u starších pacientů, podvyživených pacientů a/nebo nemocných osob, užívajících řadu léků současně, u cirhotiků s otoky a ascitem, u pacientů s onemocněním koronárních tepen, pacientů se srdečním selháním a osob s dlouhým QT intervalem. V těchto případech je třeba častěji kontrolovat a korigovat kalemii, stejně jako u pacientů užívajících srdeční glykosidy nebo látky způsobující *torsade de pointes*. Přípravek může způsobit přechodné zvýšení hladiny vápníku v plazmě. Skutečná hyperkalemie může být výsledkem nerozpoznané hyperparatyreózy. U nemocných se zvýšenou hladinou kyseliny močové hrozí záchvat dny. Sulfonamidy nebo deriváty sulfonamidů mohou způsobit idiosynkratickou reakci vedoucí k choroidální efuzi s defektem zorného pole, přechodné myopii a akutnímu glaukomu s uzavřeným úhlem. Při nadměrném snížení krevního tlaku u pacientů s ischemickou kardiopatií nebo s ischemickou chorobou srdeční může dojít k infarktu myokardu nebo k cévní mozkové příhodě. **Dávkování a způsob podání:** Doporučená dávka je jedna tableta denně. Při těžké poruše funkce ledvin (clearance kreatininu pod 30 ml/min), u hemodialyzovaných pacientů a při těžké poruše funkce jater je přípravek kontraindikován. U pacientů s lehkou až středně těžkou poruchou funkce jater je nutná úprava dávkování a dávka telmisartanu nemá překročit 40 mg telmisartanu denně. Tablety se užívají před jídlem, během jídla nebo po jídle s trochou tekutiny. **Zvláštní opatření pro uchovávání:** Uchovávejte v původním obalu, aby byl přípravek chráněn před světlem. **Balení:** 30 tablet po 80 mg / 2,5 mg. **Datum revize textu:** 30. 8. 2022. S podrobnějšími informacemi o přípravku se seznámte v SPC. Přípravek je vázán na lékařský předpis a je hrazen z prostředků zdravotního pojištění. **Výrobce a držitel rozhodnutí o registraci:** PRO.MED.CS Praha a.s., Telčská 377/1, Michle, 140 00 Praha 4, Česká republika.

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New onset of atrial fibrillation in acute coronary syndromes

Helder Santos, Mariana Santos, Margarida Gancho Figueiredo, Mariana Caetano Coelho, Samuel Almeida, Lurdes Almeida, Sofia B. Paula, on behalf of the Portuguese Registry of Acute Coronary Syndromes

Serviço de Cardiologia, Centro Hospitalar Barreiro-Montijo EPE, Barreiro, Portugal

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Nově vzniklá fibrilace síní

SOUHRN

Kontext: S akutními koronárními syndromy (AKS) a s fibrilací síní (FS) se lze v portugalské populaci setkat často. V některých případech může první epizoda FS proběhnout v rámci AKS. Zdá se přitom, že nově vzniklá FS (nFS) v přítomnosti AKS je spojena s nepříznivou prognózou.

Cíle: Popsat různé charakteristiky pacientů s nFS při AKS a posoudit prediktory nFS.

Metody: Multicentrická prospektivní studie používající údaje portugalského Národního registru akutních koronárních syndromů získané od 29 851 pacientů přijatých pro AKS v období od 1. října 2010 do 4. září 2019 a klasifikovaných podle přítomnosti nebo nepřítomnosti nFS během hospitalizace. Pacienti s dřívějšími epizodami FS nebyli do studie zařazeni.

Výsledky: K nFS došlo u 1 067 pacientů (4,1 %), většinou starších osob, s několika komorbiditami jiné než kardiovaskulární etiologie, se sníženou ejekční frakcí levé komory (EF LK) a s komplexnějším postižením koronárních tepen. U pacientů s nFS se častěji prováděla antiarytmická terapie, avšak pouze 21,5 % jich užívalo trojkombinaci antitrombotik a 30,3 % duální antitrombotickou léčbu. Tato skupina vykazovala i vysoký výskyt komplikací a úmrtí během hospitalizace. Podle vícečetné logistické regrese byly prediktory nFS v přítomnosti AKS věk nad 75 let, prodělaná cévní mozková příhoda, vysoká třída klasifikace podle Killipa a Kimballa, hemoglobin < 12 g/dl a EF LK < 50 %. Při kontrolním vyšetření po jednom roce predikovalo skóre CHA₂DS₂-VASc nový vznik FS v rámci AKS (poměr šancí 2,07; $p < 0,001$), opětovný příjem do nemocnice z kardiovaskulárních příčin ($p < 0,001$) a opětovnou hospitalizaci z jakýchkoli příčin ($p < 0,001$).

Závěr: Prognóza pacientů s nFS v přítomnosti AKS je nepříznivější než prognóza pacientů se sinusovým rytmem. Ukázalo se, že skóre CHA₂DS₂-VASc použité pro hodnocení rizika vzniku tromboembolie představuje středně spolehlivý prediktor nFS.

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ABSTRACT

Background: Acute coronary syndrome (ACS) and atrial fibrillation (AF) are common in the Portuguese population. In some cases, AF first episode can occur in ACS context. Nevertheless, the impact of new-onset AF (nAF) in the setting of ACS seems to be associated with a poor prognosis.

Objectives: To understand different characteristic in nAF patients with ACS and to evaluate the predictors of nAF.

Methods: Multicenter retrospective study based on the Acute Coronary Syndrome Portuguese National Registry, including 29 851 patients admitted for ACS between 1/10/2010–4/09/2019, classified according to the presence or absence of nAF during the hospitalization. Patients with previous AF were excluded.

Results: nAF was identified in 1067 patients (4.1%), mostly older, presenting more non-cardiovascular comorbidities, decreased left ventricular ejection fraction (LVEF) and a more complex coronary disease. nAF patients received more anti-arrhythmic therapy, but just 21.5% had triple anti-thrombotic therapy and 30.3% had dual anti-thrombotic therapy. This group also presented high rates of in-hospital complications and death. Multiple logistic regression revealed that age >75 years old, previous stroke, higher Killip–Kimball class, haemoglobin <12g/dL and LVEF <50% were predictors of nAF in the setting of ACS. CHA₂DS₂-VASc score was a predictor of nAF in the setting of ACS (odds ratio 2.07, $p < 0.001$), of cardiovascular re-admission ($p < 0.001$) and all-cause of re-admission ($p < 0.001$) at one year follow-up.

Conclusions: Patients with nAF in the setting of ACS have a worse prognosis when compared to sinus rhythm patients. CHA₂DS₂-VASc score used for thromboembolic risk assessment was noted to be a moderate predictor of nAF.

Keywords:

Acute coronary syndromes

CHA₂DS₂-VASc

Mortality

New-onset atrial fibrillation

Address: Helder Santos, Cardiology Department, Centro Hospitalar Barreiro-Montijo EPE, Avenida Movimento das Forças Armadas, 2834-003 Barreiro, Portugal, e-mail: helder33689@gmail.com

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting over 30 million people in developed countries. It has been estimated that the prevalence of AF will double over the next 50 years.¹ AF reduces quality of life and is associated with higher hospitalization and mortality rates, especially cardiovascular mortalities due to sudden death, heart failure or stroke.¹

The presence of AF in patients admitted with acute coronary syndrome (ACS) is common. Nevertheless, the AF type, namely permanent or paroxysmal, pre-existing or new-onset, may have a different impact on the patients, especially when associated with ACS.^{2,3} The management and implications regarding the approach of AF in ACS are a challenge since no randomized trials were designed for this population and all the available evidence is based on subgroup analyses.

Several mechanisms can explain an increased occurrence of AF in ACS, such as ischemia and reduction on the atrial blood flow, higher left ventricle end-diastolic and left atrial pressure, diastolic dysfunction and autonomic nervous system disorders. Other mechanisms, such as neurohormonal activation and inflammation may also be involved. Different studies reported the AF in ACS incidence, with values ranging between 2 to 25%, and its incidence increases with the severity of myocardial infarction.⁴ Other potential risk factors are older age, tachycardia, and heart failure signs.⁵ It is yet to be clarified if the occurrence of AF on the setting of ACS is a prognostic marker of ACS or related to other comorbidities.⁶ The presence of permanent AF in the setting of ACS is a direct predictor of mortality in the short and the long term,²⁻⁴ and new-onset AF (nAF) may have a worse prognosis comparing with history of permanent AF in the setting of ACS.^{4,7} A fact that this work pretends clarify. The main goal of this study was to analyse the rate, clinical features, therapeutic approach, complications and in-hospital mortality of nAF in the setting of ACS in a real-world scenario using data from the Portuguese Registry of Acute Coronary Syndromes.

Methods

Pro-ACS registry design

The Portuguese Registry of Acute Coronary Syndromes (Pro-ACS – ClinicalTrials.gov NCT 0162329) is a continuous, nationwide, prospective, observational registry launched in 2002. Data is uploaded by participating centres and managed by the Portuguese Society of Cardiology. All ACS patients older than 18 years are eligible for inclusion. ACS episodes are adjudicated according to current guidelines and based on electrocardiogram, myocardial necrosis biomarkers and clinical status.⁸ Data collected include patient demographics, baseline characteristics, presenting symptoms, biochemical, electro- and echocardiography findings, clinical evolution, medical treatment (background, in-hospital, and post-discharge), coronary anatomy, revascularization procedures, and clinical outcomes. Outcome data were collected after hospital discharge and after a 1-year of follow-up.

Definition of new-onset AF

The nAF is defined as the first episode of AF that has not been diagnosed before, regardless of the arrhythmia's duration or the presence and severity of AF-related symptoms. AF identification cannot represent its first occurrence, as sometimes episodes of silent AF have occurred before. Nonetheless, in this study the first recorded AF episode was characterized as nAF. We defined two groups: patients that presented nAF during hospitalization and patients without AF.

Study population

A total of 29 851 validated episodes in the Pro-ACS registry between 1 October 2010 and 4 September 2019 were accessed; 1 067 were defined as nAF (4.1%) in ACS context. Each patient might have more than one episode of ACS. Patients with missing data regarding the ACS type and the rhythm at admission and during hospitalization were excluded. The nAF was analysed according to the ACS presentation, as STEMI or NSTEMI. Patients with previous AF documented were also excluded.

Statistical analysis

All statistical analyses were performed by a professional statistician within the National Centre for Data Collection in Cardiology (CNCDC), using SPSS software (SPSS Inc., Chicago, IL, USA) for Windows XP (version 20.0). Continuous variables are described as mean and standard deviation (SD) if normally distributed, or median and interquartile range (IQR) in case of skewed distribution. Categorical variables are described as absolute and relative frequencies. Hypothesis testing for differences between nAF and sinus rhythm was performed using odds ratios (OR) and 95% confidence intervals (95% CI), as well as independent-samples t-test for continuous variables and chi-square test for categorical variables. Chi-square and Fisher exact tests, as well as univariate logistic regression, were used to assess in-hospital outcomes (categorical variables) as appropriate. Survival analysis for 1-year outcomes was performed using Kaplan-Meier curves and log-rank test. *p*-values are two-sided, and a threshold of 0.05 indicates statistical significance in all tests.

Ethical approval

Participation in the registry must be approved by the review board at each institution, the local ethics committee and by the Portuguese Data Protection Authority (no. 3140/2010).⁹ This way, ensuring the protection of human rights in Portugal, the confidential and anonymous information of every patient, in compliance with the Declaration of Helsinki. Informed consent was obtained to all the participants.

Results

Population clinical features

A total of 1 067 patients were categorized as having a nAF in the setting of ACS. Patients with nAF were old, with a low body mass index and a high prevalence of cardiovascular conditions and other comorbidities, including previous heart failure history, valvular heart disease, pe-

ipheral arterial disease, chronic obstructive pulmonary disease, dementia and previous stroke (Table 1). Previous medications are represented in Table 1.

Patients with nAF were more frequently admitted directly to the catheterization laboratory, while sinus rhythm patients to the emergency room. Other patterns of hospital admission were similar (Supplemental Table 1). Patients with nAF had similar symptoms onset to first medical contact time ($p = 0.379$) but had a shorter first medical contact to admission time ($p = 0.006$). Table 2 illustrates the clinical presentation features. Sinus rhythm patients frequently presented chest pain as the main symptom. As expected, Killip–Kimball (KK) class at admission was higher in nAF patients nevertheless, just 18.1% with KK $\geq$ II presented nAF at admission. Furthermore, nAF patients had high left or right-bundle branch block patterns, ST-segment depression and ST-segment elevations, and had less frequently normal ST-segment. Additionally, nAF presented increased brain natriuretic peptide (BNP), glycated haemoglobin and creatinine levels, as well as decreased haemoglobin levels.

Table 3 depicts clinical management features. nAF patients had a poor left ventricular ejection fraction (LVEF) ($p < 0.001$). On the other hand, the complex coronary disease was common in nAF patients, including left main and two- and three-vessel disease. Curiously, the left anterior descending artery was the most frequently revascularized vessel in nAF patients. No differences were found between groups regarding the performance of percutaneous coronary intervention (PCI) (odds ratio [OR]: 1.06, $p < 0.001$, confidence interval [CI] 0.93–1.21), nevertheless, nAF patients were less likely to have planned revascularization (OR: 0.47, $p < 0.001$, CI 0.37–0.58). Concerning the planned revascularization strategy, coronary artery bypass grafting (CABG) was

Supplement table 1 – Admission, laboratory, and electrocardiogram characteristics regarding the rhythm, in percentage

	SR	AF	<i>p</i>
Admission emergency room	57.3	51.3	<0.001
Admitted directly to cath lab	10.4	18.8	<0.001
Admission for intensive care unit	31.5	29.0	0.088
Symptoms onset to first medical contact time	380±157	423±161	0.379
First medical contact to admission time	263±132	202±100	0.006
Left bundle branch block	3.6	6.4	<0.001
Right bundle branch block	5.2	9.8	<0.001
ST elevation	39.2	52.9	<0.001
ST depression	16.8	20.4	<0.001
Normal ST	23.5	10.8	<0.001
Haemoglobin	13.8±1.9	13.2±2.0	<0.001
HbA _{1c}	6.6±1.6	7.1±2.1	0.201
BNP	412±718	979±1309	<0.001

SR in acute coronary syndrome (ACS) – sinus rhythm; atrial fibrillation (AF) – new onset of AF in the setting of ACS.

Table 1 – Population characteristics regarding the rhythm, in percentage

	SR	AF	<i>p</i>
Smoking	27.0	17.8	<0.001
Arterial hypertension	70.4	75.6	<0.001
Diabetes mellitus	31.4	34.6	0.029
Dyslipidaemia	61.8	56.4	<0.001
Familiar cardiovascular history	7.7	2.5	<0.001
Angina	28.7	24.0	<0.001
Previous acs	20.6	18.2	0.062
Valvular pathology	3.7	5.7	<0.001
Previous heart failure	5.7	11.5	<0.001
Previous stroke	7.0	11.3	<0.001
Peripheral arterial disease	5.4	8.1	<0.001
Chronic kidney disease	7.1	4.7	0.001
Neoplasia	4.9	5.6	0.327
Chronic obstructive pulmonary disease	4.2	9.1	<0.001
Dementia	1.6	4.5	<0.001
Haemorrhage	1.5	1.5	0.833
Acid acetylsalicylic	30.8	33.9	0.033
Other antiplatelet	14.2	13.3	0.439
Beta block	25.2	27.2	0.159
Angiotensin converting enzyme inhibitors/angiotensin ii receptors blockers	47.2	51.9	0.003
Statin	39.1	39.8	0.642
Calcium channel blockers	18.9	20.5	0.181
Ivabradine	1.4	2.4	0.009
Mineralocorticoid receptor antagonists	2.1	3.0	0.039
Diuretic	24.2	32.6	<0.001
Anti-arrhythmic therapy	1.5	2.0	0.176
Insulin	7.7	8.5	0.327
Oral antidiabetic drugs	21.3	23.3	0.114

SR in acute coronary syndrome (ACS) – sinus rhythm; atrial fibrillation (AF) – new onset of AF in the setting of ACS.

Table 2 – Clinical presentation characteristics regarding the rhythm, in percentage

	SR	AF	<i>p</i>
Chest pain	92.9	81.9	<0.001
Dyspnoea	3.2	9.2	<0.001
Syncope	1.4	2.8	<0.001
Cardiac arrest	0.5	1.0	0.007
Killip–Kimball class >I	14.3	35.6	<0.001
AF at admission	0	78.2	<0.001

SR in acute coronary syndrome (ACS) – sinus rhythm; atrial fibrillation (AF) – new onset of AF in the setting of ACS.

Table 3 – Clinical management, angiography, and revascularization characteristics regarding the rhythm

	SR	AF	p
Left ventricular ejection fraction (LVEF)	51±12	46±13	<0.001
Quantification of LVEF	93.3%	96.5%	<0.001
Angiography	84.5%	82.7%	0.101
Radial access	69.7%	69.0%	0.658
Multivessel disease	51.5%	56%	0.001
Culprit lesion: anterior descending artery	37.2%	40.9%	0.045
Culprit lesion: unknown	16.8%	11.7%	<0.001
Percutaneous coronary intervention	70.2%	79.5%	<0.001
Coronary artery bypass grafting	8%	7.4%	0.554
Hybrid strategy	0.7%	2.1%	<0.001

SR in acute coronary syndrome (ACS) – sinus rhythm; atrial fibrillation (AF) – new onset of AF in the setting of ACS.

Table 4 – In-hospital complications according to the rhythm, in percentage

	SR	AF	p
Mortality	3.4	11.0	<0.001
Reinfarction	0.8	2.5	<0.001
Heart failure	14.3	45.7	<0.001
Cardiogenic shock	3.6	16.1	<0.001
Mechanical complication	0.6	1.8	<0.001
Complete atrioventricular block	2.2	8.0	<0.001
Sustained ventricular tachycardia	1.1	7.8	<0.001
Cardiac arrest	2.4	9.2	<0.001
Stroke	0.6	1.9	<0.001
Major haemorrhagic events	1.4	4.2	<0.001

SR in acute coronary syndrome (ACS) – sinus rhythm; atrial fibrillation (AF) – new onset of AF in the setting of ACS.

planned irrespective of the rhythm, although a hybrid revascularization strategy (PCI + CABG) was chosen more frequently in nAF patients. No differences were found regarding success rates.

Therapy

No differences were found regarding therapy with P2Y12 blockers or GP IIb/IIIa receptor inhibitors, as well as dual-antiplatelet therapy. nAF patients were more frequently given aspirin, any heparin/heparin-related-agent, enoxaparin, and vitamin K antagonists. Nonetheless, they were likely to receive less in-hospital beta-blockers and angiotensin converting enzyme inhibitors (ACEI)/angiotensin II receptors blockers (ARB). nAF patients were more frequently given ivabradine, mineralocorticoid receptor antagonists, diuretics, amiodarone, digoxin, others antiarrhythmic drugs and inotropes.

At discharge, nAF patients were less frequently prescribed with aspirin or ticagrelor, but the rates of clopidogrel prescription were higher. As expected, nAF patients had high prescription of vitamin K antagonists or any of the new anticoagulants. Interestingly, in the nAF group, just 21.5% of the patients had prescribed triple antithrombotic therapy and 30.3% had dual antithrombotic therapy. Nonetheless, nAF patients receive high percentage of mineralocorticoid receptor antagonists, diuretics, amiodarone, digoxin and other antiarrhythmic drugs.

Concerning patients discharged with triple antithrombotic therapy, follow-up at one year (32.5% of all the patients had follow at one year) revealed no statistical significance in mortality rates ($p = 0.578$), re-admission for cardiovascular causes ($p = 0.301$) and re-admission for all causes ($p = 0.431$).

Prognosis

Patients with nAF in the setting of ACS had increased in-hospital all-cause of death (OR: 3.47 [2.83–4.25], $p < 0.001$), as well as higher rates of re-infarction, congestive heart failure, cardiogenic shock, mechanical complications, AV block, sustained ventricular tachycardia, aborted cardiac arrest, stroke and major bleeding ($p < 0.001$ for all comparisons) (Table 4). nAF patients also exhibited longer in-hospital stay ($p < 0.001$). nAF patients had high rates at 1-year of re-admission for all-cause, as well as cardiovascular hospitalization and all-cause of death.

Multiple logistic regression revealed age > 75 years old (odds ratio [OR] 2.07, $p < 0.001$, confidence interval [CI] 1.74–2.47), previous stroke (OR 1.40, $p = 0.019$, CI 1.06–1.85), KK > 1 (OR 2.10, $p < 0.001$, CI 1.72–0.56), haemoglobin < 12 g/dL (OR 1.29, $p = 0.018$, CI 1.04–1.59), admission glycemia (OR 1.84, $p < 0.001$, CI 1.52–2.22) and LVEF $< 50\%$ (OR 1.91, $p < 0.001$, CI 1.60–2.27) as the predictors of nAF in ACS.

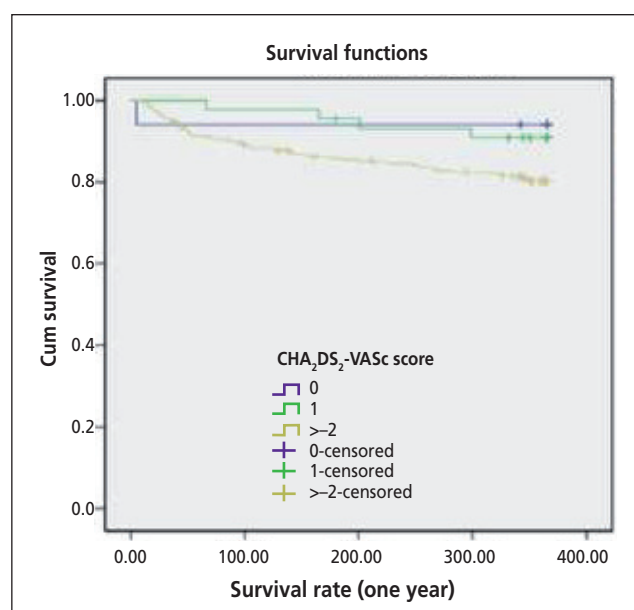


Fig. 1 – Representation with the Kaplan–Meier test of survival rates at one year of follow-up according to CHA₂DS₂-VASc punctuation, 0, 1, and ≥ 2 .

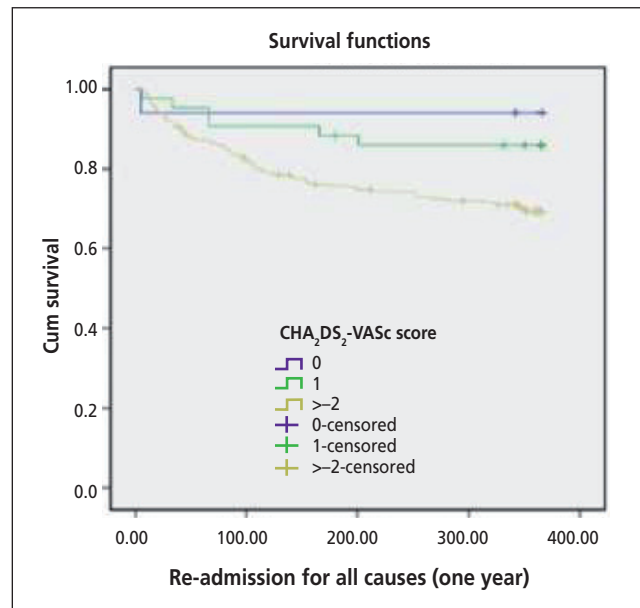


Fig. 2 – Representation with the Kaplan–Meier test of re-admission for all causes at one year of follow-up according to CHA₂DS₂-VASc punctuation, 0, 1, and ≥ 2.

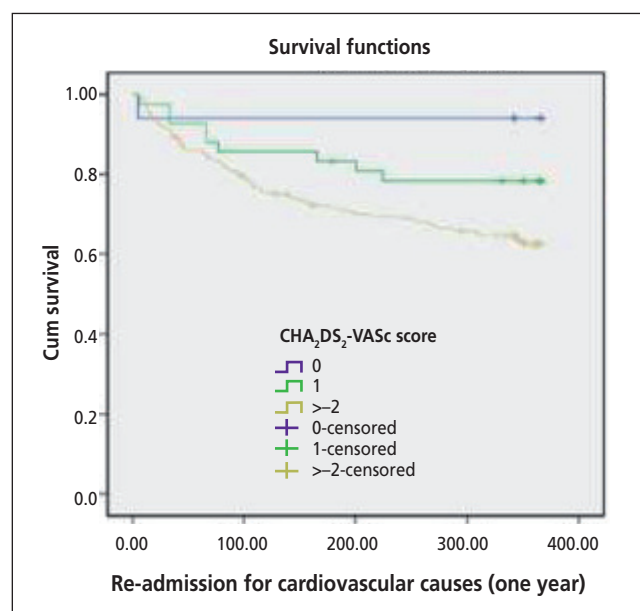


Fig. 3 – Representation with the Kaplan–Meier test of re-admission for cardiovascular causes at one year of follow-up according to CHA₂DS₂-VASc punctuation, 0, 1, and ≥ 2.

CHA₂DS₂-VASc score

Logistic regression analysis revealed that the CHA₂DS₂-VASc score was a median predictor of nAF in ACS (OR: 2.07, $p < 0.001$, CI 1.74–2.47; Area Under Curve: 0.642, CI 0.625–0.659), with a 66.7% sensibility and 55.1% specificity. Mortality analysis at one year of follow up revealed higher mortality rates associated with higher CHA₂DS₂-VASc punctuation, although this association did not achieve statistical significance, $p = 0.099$ (Fig. 1). On the other hand, the score exhibited a statistically significant

value ($p = 0.016$), at the re-admission for all causes (Fig. 2), according to its punctuation of 0, 1 or ≥2. Regarding re-admission for cardiovascular causes (Fig. 3), higher rates of readmission at 1-year follow-up were associated with a higher score classification, with a Kaplan–Meier test of $p = 0.013$.

Discussion

nAF is a frequent finding in ACS, and the ACS can be considered as a trigger to arrhythmias.¹⁰ Our study reveals that nAF in the setting of ACS reflects several clinical characteristics and therapeutic implications and represents one of the largest analysis of nAF in the setting of ACS.

Patients with nAF, in general, have a higher prevalence of cardiovascular risk factors, coronary disease, chronic kidney disease and heart failure. This group has also low percentages of evidence-based medical therapies,¹¹ which is in line with our findings, suggesting that the identification of nAF in the setting of ACS is frequently in patients with more comorbidities, which have more propensity to arrhythmia's development.

The arrhythmia contributes to several hemodynamic alterations, like fast ventricular rates, hypoxia, hypotension or hypertension, adrenergic discharge, the loss of atrial contraction and atrioventricular synchrony (which promote an imbalance between myocardial oxygen supply and demand). All of these hemodynamic alterations can be associated with exacerbation of acute ischemia and heart failure.⁷ Therefore, and according to some authors,⁷ the presence of AF should be interpreted as a sign or at least a trigger of hemodynamic compromise. Our results showed that patients with nAF presented higher Killip–Kimball (KK) class, less time until the first medical contact, worst left ventricular function, and were referred more frequently to the catheterization laboratory, which proves the direct hemodynamic impact the arrhythmia, being in agreement with the previous study. On the other hand, it was expected that patients admitted with STEMI presented higher hemodynamic compromise, thus presenting higher rates of nAF when compared to NSTEMI patients, which was not proved in our findings.

Curiously, the anatomical location of the infarction seems not to be related to the prevalence of AF in the setting of ACS, and patients with undefined ACS location had a higher prevalence of AF.¹² nAF patients, in our results, had a more complex multivessel and critical anatomical coronary disease, a finding very frequently in patients diagnosed with undefined ACS location.

Another problematic issue in patients with AF in the setting of ACS is the need of a percutaneous coronary intervention, which may imply the necessity of triple therapy with oral anticoagulation in patients with CHA₂DS₂-VASc scores ≥2 and dual anti-aggregation in patients submitted to percutaneous coronary intervention (PCI).¹³ Triple therapy is associated with a higher haemorrhagic risk and more difficult therapy management.^{2,13} In our study, only 21.5% of the patients with nAF in the setting of ACS received triple therapy during hospitalization, and even considering that some may not have anticoagulation.

on criteria, a very significant percentage of patients did not receive the recommended therapy.

A study including over 69 000 patients¹⁴ found that less than half of the patients received triple therapy because of the haemorrhagic risk associated. In another report, older patients were prescribed with dual antiplatelet therapy without anticoagulation,¹⁵ for the same reason. Thus, the high rate of haemorrhagic incidents during the hospitalization in our patients may have influenced the physicians' decision on whether prescribing triple therapy.

In dual therapy (an anticoagulant and one antiplatelet), clopidogrel is preferred to other antiplatelet agents, because it has a lower haemorrhagic risk, explaining the higher prescription of clopidogrel and less acetylsalicylic acid in our group of nAF patients. A very curious finding in our study is the absence of prognostic significance of triple therapy in mortality and readmission rates at 1 year follow-up, contrary the major literature described,¹⁴ a fact that maybe justify the physicians' decision on double therapy.

Beta-blockers were less used during hospitalization, probably due to the increased KK class in the ACS presentation, being nAF patients more frequently submitted to anti-arrhythmic therapy. Interestingly, we observed a diminished use of beta-blockers at discharge in the AF group, which can be justified by the arrhythmia presence. In fact, the nAF patients demonstrated a frequent left ventricular dysfunction and would consequently benefit from beta-blockers therapy. However, in our study, this did not occur requiring further investigation.

Considering that ivabradine is recommended in sinus rhythm patients only, an interesting result was the higher prescription of this medication to nAF patients. These last two arguments, prove the difficult and a complex therapeutic approach in nAF patients.

Lopes RD et al.³ did not find an association between nAF in the setting of ACS and short-term mortality; despite that, higher rates of in hospital complications such as heart failure, acute mitral regurgitation, sustained hypotension, cardiogenic shock and strokes were found. Several studies concluded that the presence of nAF, comparing to sinus rhythm, is associated with a higher in-hospital and long term follow up mortalities.^{16,17} These conclusions seem to be independent of AF onset (paroxysmal, chronic or new-onset).^{2,17} These findings are in line with our results that confirmed that nAF patients had worse short-term prognosis (considering the complications during hospitalization) as well as mortality rates compared to sinus rhythm in the setting of ACS. On the other hand, other results^{6,18} did not report that nAF in the setting of ACS was an independent predictor of mortality.

Nonetheless, for the majority of authors, it was not clear if the arrhythmia was a direct complication of the ACS or a risk marker of severity.² Some authors identified the following characteristics as risk factors to nAF in the setting of ACS: female gender, higher Killip-Kimball class, worse renal function, higher BNP and CK-MB, electrocardiogram and echocardiogram alterations.^{19,20} Our results are in agreement that a higher KK class, age, and echocardiogram alterations are predictors of nAF. On the other hand, it suggests that a previous stroke, lower haemoglobin levels and higher glycaemic levels are also

significant predictors of arrhythmia. Then it is imperative to identify risk factors to predict the development of AF during the hospitalization and therefore, develop preventive measures. The role of revascularization in nAF in the setting of ACS is not completely clarified.⁷

CHA₂DS₂-VASc score is used to estimate the stroke or thromboembolic risk in patients with AF and to decide the introduction of anticoagulant therapy. As so, this score was not developed to predict mortality, nevertheless the practical utility of this simple's score may be applied in the risk stratification of other clinical diseases. For example, CHA₂DS₂-VASc score was used in the general population to predict AF.²¹ When analysing the score, we identified several cardiovascular risk factors, like hypertension, diabetes, heart failure, age, all of them significantly associated with worse outcomes in the follow up of ACS.²² There are limited evidence on the use of the CHA₂DS₂-VASc score as a prognostic tool in ACS²³ being associated with long-term cardiovascular events prediction and as a good predictor of STEMI occurrence.²⁴ Our results are in line with these findings, suggesting that the CHA₂DS₂-VASc score is also able to predict re-admissions of nAF hospitalized for ACS.

To the best of the authors' knowledge, there are no publications that use the CHA₂DS₂-VASc score as a prognostic tool to identify patients at risk of developing nAF in the setting of ACS. Considering that the CHA₂DS₂-VASc score is easily calculated, it may be useful to evaluate the risk of nAF in patients presenting with ACS, allowing the physicians to prevent the occurrence of AF and/or to provide a faster response to the arrhythmia.

Limitations

There are several limitations to be considered in the study interpretation. This was observational and non-randomized study, which can have associated confounders that can influence the outcomes. Some of the patients could have misclassified characteristics or incomplete records. Analysis of differences between patients with and without the combined endpoint was performed with univariable, non-adjusted models without correction of multiple inferential tests. Other complications, namely non-cardiovascular complications, can interfere in the patient's prognosis, but there were not considered in the registry. Even considering the high number of patients in the registry, just a few patients had a documented follow-up after the hospitalization. Another potential limitation might be that the ProACS registry just allows considered the follow-up events as cardiovascular or all-cause readmission/mortality, lacking some detail regarding the events.

Conclusion

Our results are in accordance with several publications that suggested that nAF is a major complication of ACS with an important clinical impact. It should be considered a prognostic marker, and an active approach and therapy must be performed in these patients. Despite the di-

different characteristics between the groups, our analysis suggested that the presence of comorbidities favours the occurrence of nAF in the setting of ACS and that there is a bidirectional relationship between AF and ACS. Further investigation should focus on the determination of whether nAF can be considered a risk marker of prognosis or a direct mortality factor. The CHA₂DS₂-VASc score may be a useful tool to predict the occurrence of nAF in the setting of ACS, allowing a better approach to patients with increased risk.

Conflict of interest

The authors declare that there is no conflict of interest.

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- Superiorita v prevenci CMP a SE vs. warfarin¹
- Superiorita ve snížení rizika výskytu závažného krvácení vs. warfarin¹

Zkrácená informace o přípravku: ELIQUIS® 2,5 mg a 5 mg potahované tablety. Složení: Léčivá látka apixabanum 2,5 mg nebo 5 mg v jedné potahované tabletě; pomocné látky se známým účinkem: 102,86/51,43 mg laktosy (tableta 5/2,5 mg); a další pomocné látky. **Indikace:** Prevence žilních tromboembolických příhod (VTE) u dospělých pacientů, kteří podstoupili elektivní náhradu kyčelního nebo kolenního kloubu. Prevence cévní mozkové příhody (CMP) a systémové embolie (SE) u dospělých pacientů s nevalvulární fibrilací síní (NVAf) a s jedním nebo více rizikovými faktory, jako jsou předchozí cévní mozková příhoda nebo tranzitorní ischemická ataka (TIA); věk > 75 let; hypertenze; diabetes mellitus; symptomatické srdeční selhání (třída NYHA > II). Léčba hluboké žilní trombózy (DVT) a plicní embolie (PE), a prevence rekurentní DVT a PE u dospělých. **Dávkování a způsob podání:** Prevence VTE: 2,5 mg perorálně 2x denně. Počáteční dávka by měla být užita 12 až 24 hod po operaci. Doporučená délka léčby je 32 až 38 dní (náhrada kyčelního kloubu) a 10 až 14 dní (náhrada kolenního kloubu). Prevence CMP a SE u dospělých pacientů s NVAf: 5 mg perorálně 2x denně, snížená dávka 2,5 mg perorálně 2x denně při splnění kritérií pro redukci dávky dle SPC. Pacienti podstupující kardioverzi mohou užít jednorázovou nasycovací dávku 10mg nejmeně 2 hod před výkonem. Léčba akutní DVT a léčba PE: 10 mg perorálně 2x denně prvních 7 dní; poté 5 mg perorálně 2x denně. Prevence rekurentní DVT a PE: 2,5 mg perorálně 2x denně po dokončení 6-ti měsíční léčby apixabanem nebo jiným antikoagulem. Tablety přípravku Eliquis se zapíjejí vodou, užívají se bez závislosti na jídle a lze je také podat rozdrcené a rozmíchané v tekutině či v jablečném protlaku. Podrobnosti viz SPC. **Kontraindikace:** hypersenzitivita na léčivou látku nebo na kteroukoli pomocnou látku, klinicky významné aktivní krvácení, jaterní onemocnění spojené s koagulopatií a klinicky relevantním rizikem krvácení, léze nebo stav s významným rizikem závažného krvácení, souběžná léčba jinými antikoagulemi vyjma specifických případů viz SPC. **Zvláštní upozornění:** Doporučuje se, aby byl přípravek Eliquis používán s opatrností v podmínkách vyššího rizika krvácení. Podávání přípravku Eliquis se musí přerušit, jestliže se vyskytne závažné krvácení. Podrobnosti vysazení před elektivním výkonem viz SPC. Souběžné užívání přípravku Eliquis s antiagregancií zvyšuje riziko krvácení; při souběžné léčbě NSAID (včetně ASA) a SSRI/SNRI je třeba dbát zvýšené opatrnosti. Podrobnosti k podání u poruch ledvin a jater a hemodynamicky nestabilních pacientů viz SPC. Eliquis není doporučen u pacientů s trombózou v anamnéze, u nichž byl diagnostikován antifosfolipidový syndrom. Je-li u pacientů s nádorovým onemocněním zvažován apixaban k léčbě DVT nebo PE, je třeba pečlivě vyhodnotit přínosy léčby oproti jejím rizikům. **Interakce:** Užívání se nedoporučuje u pacientů, kteří současně užívají systémové silné inhibitory CYP3A4 a P-gp, jakými jsou např. azolová antimykotika a inhibitory HIV proteázy. Při současném podávání se slabšími inhibitory CYP3A4 a/nebo P-gp není nutná úprava dávky apixabanu. Při současném podávání apixabanu se silnými induktory CYP3A4 a P-gp není nutná žádná úprava dávky apixabanu, avšak silné induktory CYP3A4 a P-gp by se měly současně podávat s opatrností. **Fertilita, těhotenství a kojení:** Užívání apixabanu v průběhu těhotenství se nedoporučuje. **Nežádoucí účinky:** Časté: krvácení (oční, z dásní, z úst, gastrointestinální, rektální, abnormální vaginální a urogenitální), hematomy, epistaxe, hematurie, kontuze, anémie, nauzea, kožní vyrážka, trombocytopenie, hypotenze, zvýšení gamaglutamyltransferázy a alaninaminotransferázy. **Předávkování:** Předávkování apixabanem může způsobit vyšší riziko krvácení. Je k dispozici látka ke zvracení aktivity apixabanu proti faktoru Xa. **Uchovávání:** Žádné zvláštní podmínky uchovávání. **Balení:** Eliquis 2,5 mg: mimo jiné - 20, 60, 60x1 nebo 168 potahovaných tablet v blistru. Eliquis 5 mg: 28, 60 nebo 168 potahovaných tablet v blistru. **Jméno a adresa držitele rozhodnutí o registraci:** Bristol-Myers Squibb/Pfizer EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Irsko. **Registrační číslo:** mj. EU/1/11/691/002-4,9,11,13,14. **Datum poslední revize textu:** 16.2.2022 Výdej léčivého přípravku je vázán na lékařský předpis. Přípravek je částečně hrazen z prostředků veřejného zdravotního pojištění. Před předepsáním se prosím seznámte s úplnou informací o přípravku.

CMP – cévní mozková příhoda, SE – systémová embolie

Reference: 1. Granger CB et al. N Engl J Med. 2011; 365: 981–992

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Pfizer, spol. s r. o., Stroupežnického 17, 150 00 Praha 3
tel.: +420 283 004 111, fax: +420 251 610 270, www.pfizer.cz



The Effect of Exercise-Based Cardiac Rehabilitation on Neutrophil to Lymphocyte Ratio in Patients with Coronary Artery Disease

Faruk Kara, Ahmet Özderya, Gülay Uzun, Ezgi Kalaycıoğlu, Muhammet Raşit Sayın, Turhan Turan

Department of Cardiology, University of Health Sciences Trabzon Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital, Trabzon, Turkey

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Poměr počtu neutrofilů
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Zátěžová kardiorehabilitace

SOUHRN

Cíl: Vliv zátěžové kardiorehabilitace (cardiac rehabilitation, KR) na systémový zánět dosud nebyl u pacientů s ischemickou chorobou srdeční (ICHS) podrobněji zkoumán. Jako nový marker zánětu byl navržen poměr počtu neutrofilů a lymfocytů (N/L), přičemž se ukázalo, že jeho zvýšené hodnoty jsou u pacientů s ICHS spojeny s nepříznivějším výsledným klinickým stavem. Dalším nezávislým prediktorem morbidit a mortality je u pacientů s ICHS nízká kvalita života v souvislosti se zdravím (health-related quality of life, HRQL). Cílem této studie bylo zjistit vliv zátěžové KR na poměr N/L a na HRQL u pacientů s ICHS.

Metody: Do studie jsme zařadili 200 ambulantních pacientů se stabilní ICHS indikovaných svými lékaři k absolvování III. fáze programu KR (skupina KR). Tuto skupinu jsme srovnali se skupinou 100 ambulantních pacientů se stabilní ICHS bez přístupu ke KR pro velkou dojezdovou vzdálenost nebo komorbidit omezující možnost zátěže (skupina bez KR).

Výsledky: Nebyl nalezen žádný statisticky významný rozdíl mezi skupinami ve vstupních klinických a biochemických charakteristikách. I když poměr N/L a hodnoty CRP po programu KR byly nižší než poměr N/L a hodnoty CRP před absolvováním programu KR ve skupinách KR a bez KR ($p < 0,001$ a $p < 0,007$, resp. $p < 0,001$ a $p < 0,001$), byl poměr V/L a hodnoty CRP ve skupině KR po absolvování programu KR nižší než ve skupině bez KR ($p < 0,001$ a $p < 0,001$, resp. $p < 0,001$ a $p < 0,001$). Celková skóre HRQL v dotazníku MacNew byla po absolvování KR vyšší ve skupině bez KR ($p < 0,001$).

Závěry: Program zátěžové KR zlepšuje u pacientů se stabilní ICHS poměr N/L a zvyšuje HRQL. Protože léčba tlumící systémový zánět pozitivně ovlivňuje výsledný stav pacientů s ICHS, mohou být naše zjištění potenciálně významná pro klinickou praxi.

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ABSTRACT

Objective: The effect of exercise-based cardiac rehabilitation (CR) on systemic inflammation was not well established in patients with coronary artery disease (CAD). Neutrophil/lymphocyte (N/L) ratio has emerged as a new inflammation marker and elevated levels were found to be associated with worse clinical outcome in patients with CAD. Also, poor impaired health-related quality of life (HRQL) is an independent predictor of morbi-mortality in patients with CAD. The purpose of this study is to determine the effect of exercise-based CR on N/L ratio and HRQL in patients with CAD.

Methods: We enrolled 200 stable CAD out-patients referred for Phase III CR program by their physicians (CR group). We compared them with 100 stable CAD out-patients who did not have access to CR because of travel distance or comorbid conditions that limited exercise (non-CR group).

Results: There was not a statistically significant difference in the baseline clinical and biochemical characteristics between the groups. Although N/L ratio-post and CRP-post values were lower than the N/L ratio-pre and CRP-pre in CR & non-CR groups ($p < 0,001$ & $p < 0,007$ and $p < 0,001$ & $p < 0,001$), in the CR group N/L ratio-post and CRP-post values were lower than the non-CR group ($p < 0,001$ & $p < 0,001$ and $p < 0,001$ & $p < 0,001$). Mac-New HRQL total-postscores were higher in the non-CR group ($p < 0,001$).

Conclusions: Exercise-based CR program improves N/L ratio values and HRQL in patients with stable CAD. A therapy that improves systemic inflammation is important for good outcome in patients with CAD, therefore our results may have potentially significant clinical effects.

Keywords:
Exercise-based cardiac
rehabilitation
Neutrophil/lymphocyte ratio

Address: Ahmet Özderya, MD, Department of Cardiology, University of Health Sciences Trabzon Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital, Vatan St. Ortahisar/Trabzon, Turkey PK: 61000, e-mail: ahmetozderya@gmail.com

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Introduction

Inflammation plays an important role in the progression and destabilization of atherosclerosis.¹ White blood cells, particularly neutrophils, are useful inflammatory biomarkers associated with cardiovascular events.² On the other hand, low lymphocyte counts have been shown in acute coronary syndrome patients and associated with various complications.³ Recently, the absolute number of neutrophils to the number of lymphocytes (neutrophil/lymphocyte (N/L) ratio) has emerged as a new inflammation marker. Previous studies have shown that N/R ratio elevation was associated with the presence and the severity of coronary artery disease (CAD), poor prognosis in acute coronary syndromes and stable coronary heart diseases can be used in the risk stratification of patients with various cardiovascular (CV) diseases in addition to the traditionally used markers.³⁻⁵

Exercise-based cardiac rehabilitation (CR) is a comprehensive intervention including medically supervised exercise training, risk factor management, patient education, and psychosocial counseling.⁶ CR has been reported to be effective in improving exertional ischemic symptoms, exercise tolerance, and coronary risk factors in patients with CAD. Also, it was shown that exercise-based CR reduces total and CV mortality in ranging rate from 20% to 32% in patients with CAD.⁷ Although the anti-inflammatory effects of exercise training have been reported,⁸ the effect of this therapy on systemic inflammation was not well established in patients with CAD.

Patients with CAD are likely to have an impaired health-related quality of life (HRQL)⁹ and poor HRQL is an independent predictor of morbi-mortality in patients with CAD.¹⁰ So, the assessment of HRQL is increasingly important in evaluating the effectiveness of CAD treatment strategies.¹¹

The purpose of this study is to determine the effect of exercise-based CR program on N/L ratio, which is a new, inexpensive, easy obtain and widely available inflammation marker, in patients with stable CAD. Also, we analyzed the effect of CR program on HRQL in these patients. This study has potential important clinical implications as epidemiologic data strongly support the persistent low-level inflammation as an independent predictor of coronary heart diseases¹² and the identification of therapies that improves systemic inflammation is important for prevention of CV events.

The study protocol did approve by the local Ethics Committee of the University of Health Sciences Trabzon Kanuni Training and Research Hospital and the Republic of Turkey Ministry of Health. The study was conducted in concordance with the Helsinki Declaration and the International Conference on Good Clinical Practices Harmony, and written informed consent was obtained from all participants.

Methods

Study population

We enrolled 230 stable CAD out-patients referred for Phase III CR program by their physicians. 30 patients did

not complete the CR program due to personal reasons, so finally 200 stable CAD out-patients were included in the CR group. We compared them 100 stable CAD out-patients who did not have access to CR because of travel distance or comorbid conditions that limited exercise (non-CR group, standard pharmacological care alone). Study inclusion criteria were: age between 18–80 years; left ventricular ejection fraction >45%; coronary angiographic documentation of CAD which was defined as having more than 70% stenosis in at least one coronary artery. Patients with immunologic or inflammatory disease, hematological disease, sepsis, active local or systemic infections, chronic renal disease (creatinine >1.6 mg/dL), a history of recent infection (<3 months before the study) and a history of malignancy were excluded.

Patients' medical treatments were optimized before the participation and none had any medication changes throughout the study.

Blood measurements were made at baseline for non-CR group, one day before the CR program for CR-group and after 6 weeks for both groups. Total and differential leukocyte counts were measured using an automated hematology analyzer Advia 2120 (Siemens). Body mass index (BMI) was calculated as weight (kg)/height (m²).

CR program

A step incremental cycle ergometer test was performed before the CR program to determine the exercise capacity of the patients. After a 2-minute resting period, the workload was increased by 25 W every 2 minutes. With electrocardiogram monitoring heart rate and blood pressure were measured throughout the exercise. The maximum workload was determined as the maximal exercise capacity.

The CR program was performed on supervising of a multidisciplinary team including a cardiologist, an experienced physiotherapist as a coordinator and a physical therapy and rehabilitation specialist as a medical director. The rehabilitation program was performed in the CR center of our cardiology and cardiovascular surgery hospital.

Main part of the rehabilitation program was aerobic exercise training. According to the result of the exercise testing, the exercise prescription was scheduled individually. Patients continued the program for 5 days in a week, for a total of 6 weeks. Before aerobic exercise muscle training was performed by all patients. Each session lasted 30 minutes, which included a 8 warm-up of 5 minutes and a final 5 minute cool-down period. The aerobic exercise intensity was prescribed according to the individual's exercise capacity. Exercise intensity began at 40–50% of maximal heart rate reserve and gradually increased to 70–85% of maximal heart rate reserve. Heart rate reserve was evaluated by the Karvonen Formula ($HR_{train} = (HR_{max} - HR_{rest}) \times \text{Exercise Intensity} + HR_{rest}$).¹³ HR_{train} represents heart rate during the aerobic exercise, HR_{max} represents maximum heart rate reached thorough the cycle ergometer test, and HR_{rest} represents heart rate at rest. The Borg Scale of Rate of Perceived Exertion (RPE) was used; patients exercised at an RPE of 13–15. Electrocardiograms were continuously tele-monitored and blood pressures were measured every 5 minutes throughout the exercise. During study, pa-

tients were also directed to psychologist, dietitian, and smoking cessation clinic.

Quality of life measures

The Mac-New Heart Disease HRQL questionnaire, which is specifically designed to evaluate how daily activities and physical, emotional, and social functioning are affected by CAD and its treatment, was used in the current study. The-MacNew questionnaire consists of 27 items, which fall into 3 domains:¹ a 13-item scale in the physical limitations domain,² a 14-item scale in the emotional function domain, and³ a 13-item scale in the social function domain. There are 5 items that address the impact of symptoms: 1. angina/chest pain, 2. shortness of breath, 3. fatigue, 4. dizziness, and 5. aching legs. Scoring of the Mac New is straight-forward. The maximum possible score in any domain is 7 [high HRQL] and the minimum is 1 [poor HRQL].¹⁴ The time frame for the Mac-New is the previous two weeks. All study participants completed the questionnaire at baseline and after 6 weeks.

Statistical analysis

Statistical analyses were carried out using SPSS statistical software (version 21.0, SPSS, Chicago, IL, USA). Continuous variables are presented as mean and standard deviation. Categorical variables are presented as number and percentage. The Kolmogorov–Smirnov test was used to verify the normality of the distribution of continuous variables. The independent sample t test or the Mann–Whitney U test was used for the continuous variables and the chi-square test for categorical variables. The paired samples T test was used to compare variables before and after therapy. General linear model of repeated measurements test was used for the evaluation of differences in measurements before and after the treatment of patient groups. Pearson correlation analysis was performed to examine the relationship between continuous variables. A *p* value of <0.05 was considered statistically significant.

Results

The study population consisted of 300 stable CAD patients (200 patients in CR-group and 100 patients in non-CR group). There was not statistically significant difference in the baseline clinical and biochemical characteristics between the groups (Table 1). Majority of patients were hypertensive in both groups (CR-group 91%, non-CR group 85%; *p*: 0.178). 58% in the CR-group and 62% in the non-CR group had a history of percutaneous coronary intervention (*p*: 0.535). Changes of the values in CR and non-CR groups were shown in Table 2. Although LDL-cholesterol (mg/dl)-post, triglycerides(mg/dl)-post, N/L ratio-post and CRP (mg/l)-post values were lower than the LDL-cholesterol (mg/dl)-pre, triglycerides(mg/dl)-pre, N/L ratio-pre and CRP mg/l-pre in CR & non-CR groups (*p* <0.001 & *p* < 0.001, *p* <0.001 & *p* <0.001 & *p*: 0.007 and *p* <0.001 & *p* <0.001 respectively), in the CR group LDL-cholesterol (mg/dl)-post, triglycerides(mg/dl)-post, CRP(mg/l)-post and N/L ratio-post values were lower than in the non-CR group (*p* <0.001, for all measurements). Pre- and post-N/L ratio values in groups were shown in Figure 1.

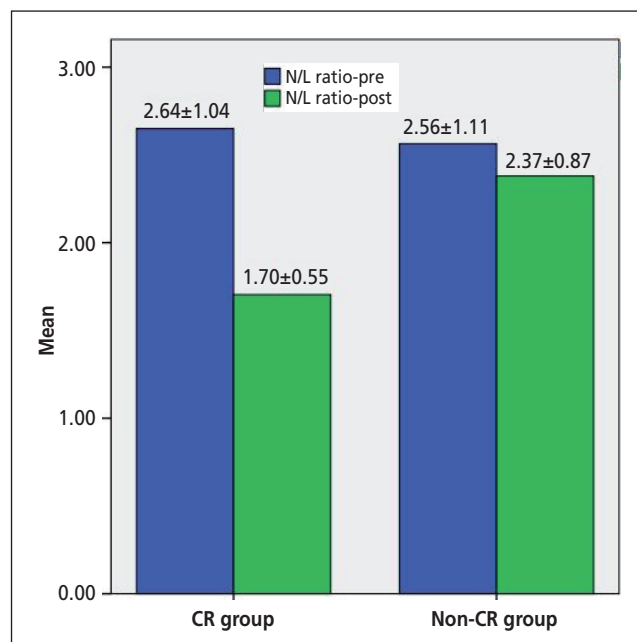


Fig. 1 – Pre- and post-N/L ratio values in groups.

Table 1 – Baseline clinical characteristics and laboratory findings of study participants

Variables	CR group (n: 200)	Non-CR group (n: 100)	p value
Age (years)	56.2±7.9	57.9±7.3	0.073
Sex, female (n, %)	44 (22%)	23 (23%)	0.883
BMI (kg/m ²)	28.3±3.9	28.2±3.1	0.853
Hypertension (n, %)	181 (91%)	85 (85%)	0.178
Diabetes mellitus (n, %)	55 (28%)	20 (20%)	0.203
Current smoker (n, %)	27 (14%)	11 (11%)	0.586
Fast plasma glucose (mg/dL)	107±34	102±27	0.116
Hemoglobin (g/dL)	13.6±1.1	13.4±1.0	0.114
Creatinine (mg/dL)	0.87±0.21	0.89±0.21	0.616
LV ejection fraction (%)	58±6	57±5	0.117
RAS inhibitors (n, %)	162 (81%)	83 (83%)	0.753
Beta-blockers (n, %)	155 (78%)	85 (85%)	0.168
Calcium-channel blockers (n, %)	90 (45%)	43 (43%)	0.806
Statins (n, %)	200 (100%)	100 (100%)	NA
By-pass surgery history (n, %)	37 (19%)	19 (19%)	0.917
PCI history (n, %)	116 (58%)	62 (62%)	0.535
ACS history (n, %)	49 (25%)	29 (29%)	0.406

ACS – acute coronary syndrome; BMI – body mass index; CR – cardiac rehabilitation; LV – left ventricle; PCI – percutaneous coronary intervention; RAS – renin-angiotensin inhibitors.

There was not statistically significant difference in the Mac-New HRQL social-pre, Mac-New HRQL physical-pre, Mac-New HRQL emotional-pre and Mac-New HRQL total-

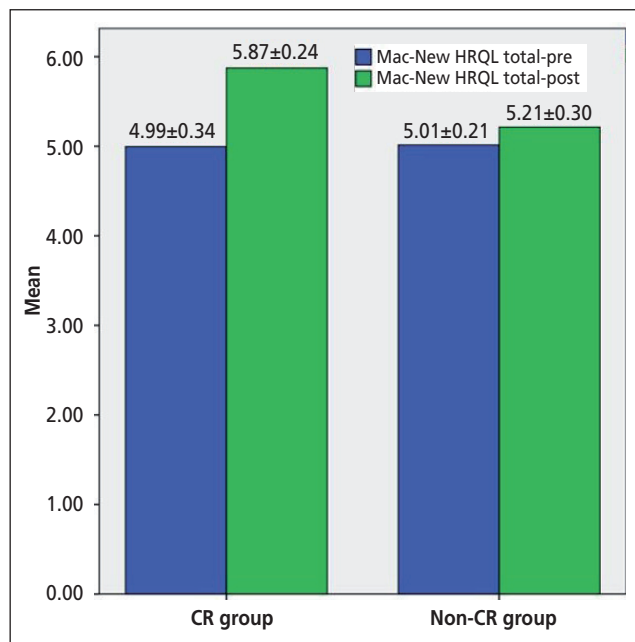
Table 2 – Changes of the values in the CR and non-CR groups

Variables	CR group (n: 200)	non-CR group (n: 100)	p value
LDL-cholesterol (mg/dL)-pre	120±36	117±31	0.835
LDL-cholesterol (mg/dL)-post	92±25	112±25	<0.001
p value	<0.001*	<0.001*	<0.001#
HDL-cholesterol (mg/dL)-pre	35±6	35±5	0.329
HDL-cholesterol (mg/dL)-post	39±6	36±5	<0.001
p value	<0.001*	<0.001*	<0.001#
Triglycerides (mg/dL)-pre	158±62	147±39	0.668
Triglycerides (mg/dL)-post	121±43	137±34	<0.001
p value	<0.001*	<0.001*	<0.001#
WBC count, × 10 ⁹ /L -pre	7.56±1.34	7.40±1.03	0.252
WBC count, × 10 ⁹ /L -post	6.65±1.30	7.32±1.06	<0.001
p value	<0.001*	0.903*	<0.001#
Neutrophil count, × 10 ⁹ /L -pre	4.66±1.17	4.83±1.26	0.475
Neutrophil count, × 10 ⁹ /L -post	3.67±0.97	4.56±1.14	<0.001
p value	<0.001*	<0.001*	<0.001#
Lymphocyte count, × 10 ⁹ /L -pre	1.94±0.69	2.06±0.58	0.140
Lymphocyte count, × 10 ⁹ /L -post	2.28±0.67	2.02±0.50	0.002
p value	<0.001*	<0.429*	<0.001#
N/L ratio-pre	2.64±1.04	2.56±1.11	0.256
N/L ratio-post	1.70±0.55	2.37±0.87	<0.001
p value	<0.001*	0.007*	<0.001#
CRP (mg/L) -pre	3.44±1.32	3.40±1.26	0.792
CRP (mg/L) -post	2.26±0.81	3.33±1.19	<0.001
p value	<0.001*	<0.001*	<0.001#
Mac-New HRQL social-pre	5.14±0.48	5.17±0.51	0.547
Mac-New HRQL social-post	5.87±0.33	5.31±0.50	<0.001
p value	<0.001*	<0.001*	<0.001#
Mac-New HRQL physical-pre	4.99±0.47	4.93±0.41	0.449
Mac-New HRQL physical-post	5.85±0.36	5.08±0.46	<0.001
p value	<0.001*	<0.001*	<0.001#
Mac-New HRQL emotional-pre	4.99±0.48	5.08±0.35	0.070
Mac-New HRQL emotional-post	6.05±0.44	5.18±0.37	<0.001
p value	<0.001*	<0.001*	<0.001#
Mac-New HRQL total-pre	4.99±0.34	5.01±0.21	0.158
Mac-New HRQL total-post	5.87±0.24	5.21±0.30	<0.001
p value	<0.001*	<0.001*	<0.001#

p* value – p value within groups (paired samples T test); p# value – general linear model repeated measures test.

CR – cardiac rehabilitation; CRP – C-reactive protein; HDL – high density lipoprotein; HRQL – health-related quality of life; LDL – low density lipoprotein; WBC – white blood cell.

pre scores between CR and non-CR groups (p : 0.547, p : 0.449, p : 0.070 and p : 0.158, respectively). Although Mac-New HRQL social-post, Mac-New HRQL physical-post, Mac-New HRQL emotional-post and Mac-New HRQL total-post

**Fig. 2 – Pre- and post-Mac-New HRQL total score values in groups.**

scores were higher in the CR & non-CR groups (p < 0.001 & p < 0.001 for all measurements), in the CR group Mac-New HRQL social-post, Mac-New HRQL physical-post, Mac-New HRQL emotional-post and Mac-New HRQL total-post scores were higher in the CR-group than in the non-CR group (p < 0.001 for all measurements). Pre- and post Mac-New HRQL total score values in groups were shown in Figure 2. In the general linear model of repeated measurements test, the change in the parameters in the cardiac rehabilitation group was statistically larger than the group not included in the cardiac rehabilitation (p < 0.001).

We also analyzed the correlation of decrement in N/L ratio (Δ N/L ratio) with decrement in CRP (Δ CRP) in CR group. Correlation analyses showed that Δ N/L ratio significantly correlated with Δ CRP (r : 0.529, p < 0.001).

Discussion

We have demonstrated a significant decrease in N/L ratio values in patients with CAD after participating in an exercise-based CR program compared to those treated with medical therapy alone. This study supports a potential beneficial effect of participation in CR program on lowering N/L ratio levels in patients with CAD. Participation in exercise-based CR program was also found to be associated with improvement in HRQL in these patients.

N/L ratio has recently emerged as a potential new biomarker which singles out individuals at risk for future CV events after controlling for all the currently accepted risk factors and commonly used biomarkers.³ An observational study in a cohort of patients with CAD demonstrated that atherosclerosis progression correlated with increased N/L ratio values.¹⁵ Arbel et al. demonstrated that N/L ratio > 3 was an independent predictor of CAD severity and worse clinical outcome with 3-year follow-up in 3005 patients and these results were found to be independent of

clinical presentation (acute coronary syndrome status, diabetes status, statin use).³ In a study of 186 patients who presented with stable angina pectoris, the N/L ratio >2.7 was found to be correlated with high SYNTAX score.¹⁶ At another study the N/L ratio found to be good predictor of a high Gensini score and the N/L ratio >2.04 highly predicted the presence of CAD.¹⁵ In our study the N/L ratio was 2.64 in the CR group and 2.56 in the non-CR group. Although there was not standard N/L ratio cut-off value for predicting CAD, our study population had high N/L ratio values in concordance with previous studies.

Previous research provides evidence that a physically active lifestyle is associated with lower whole-body inflammatory biomarkers but a number of researchers report minimal or no anti-inflammatory effect.⁸ It was shown that participation in CR appears to independently decrease the level of high sensitive C-reactive protein (HCRP) regardless of gender, age or presence of metabolic syndrome in patients with coronary heart disease.¹² Milani et al. analyzed the effect of 3-month exercise-based CR on HCRP in patients with CAD.¹⁷ They demonstrated a 41% median reduction in levels of HSCRIP independent of statin therapy and weight reduction. They speculated that this reduction was of similar or greater magnitude to that observed in multiple studies using statin therapy, where median reduction in HSCRIP was reported to be between 15% and 20%.¹⁷ CRP is a well-studied inflammation marker and elevated levels were associated with adverse CV events/poor prognosis in patients with CAD.¹² In this study we also analyzed the effect of exercise-based CR program on CRP values. In concordance with previous studies we found that patients who participated CR had lower CRP levels than those treated with medical therapy alone. We demonstrated 34.6% reduction in N/L ratio values and 34.3% reduction in CRP values in patients who participated CR program. Our study population was under statin treatment. So we showed the additive anti-inflammatory effect of exercise-based CR program on the well-proven benefits of statin therapy.

Also N/L ratio-post and CRP-post values were found to be lower than N/L ratio-pre and CRP-pre values in both groups. This may be explained by the fact that participants medical treatments were optimized before being included in the study. But between CR and non-CR groups N/L ratio-post and CRP-post values were found to be significantly lower in the CR-group.

We implemented the CR program for 5 days a week for a total of 6 weeks. Wang et al. showed in their study that participants exhibited a significant decrease in N/L ratio values with 4-week exercise training, which was shorter than our program, in 43 overweight male adolescents.¹⁸ Although previously it was shown that the anti-inflammatory effect of exercise training was evident as little as 2 to 12 weeks of supervised exercise,⁸ if we used 3-month program we may had lesser N/L ratio values.

Neuro-inflammation plays an important role in depression, anxiety, irritability, and mood instability.^{19,20} Previously it was shown that aerobic exercise improves quality of life, psychological well-being, and systemic inflammation in subjects with Alzheimer's disease.²⁰ Peixoto et al.²¹ demonstrated that exercise based-CR improves HRQL in

45 patients with acute myocardial infarction. Johnson et al.¹⁰ showed in their multi-center study that CR improves HRQL in women CAD patients. Our study population was larger than in these studies and we analyzed patients with stable CAD. In concordance with these studies we showed that exercise based-CR improves HRQL in patients with stable CAD that may be related with anti-inflammatory effect of CR. We used Mac-New HRQL questionnaire, because it has already been demonstrated to be valid, reliable and responsive in patients with CAD.²²

Our results are in agreement with other studies that have shown that exercise-based CR program reduces LDL-cholesterol, triglyceride levels, and increased HDL-cholesterol levels.^{7,23}

CR program composed of structured exercise training and comprehensive education addressing cardiac risk. Participation has been shown to reduce CV mortality, need for re-hospitalization and re-vascularization procedures and lead to improve functional status when compared with usual care.^{24–26} Currently the major problem with exercise based-CR is its underutilization by physicians. On the other hand, although data supporting the benefits of CR are highly regarded, they lack the support of large, appropriately powered clinical trials.²⁷ Therefore randomized controlled trials are needed to assess the impact of CR in CAD patients with a higher risk and patients with SAP.²⁸ By showing the positive effect of exercise-based CR program on systemic inflammation and HRQL, we think that our study can provide a significant contribution to the literature.

Study limitations

This study has several limitations. Our study was not randomized, raising the possibility of selection bias; particularly the control population chose not to attend the exercise-based cardiac rehabilitation program. We implemented the CR program for 5 days a week for a total of 6 weeks. We could implement a longer CR program, but there is no clear exercise duration or exercise intensity recommended in previous studies or reviews. Since our results are positive, we think this period is enough. We do not use spiroergometry.

Conclusion

In conclusion, this study provides new data on the effect of exercise-based CR program on the N/L ratio values. We showed that exercise-based CR program improves N/L ratio values and HRQL in patients with stable CAD. N/L ratio, an inflammatory biomarker, can be of predictive and prognostic factor for CV events and therapies that improves systemic inflammation is important for good outcome in patients with CAD.

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Conflicts of interest

None declared.

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Evaluation of Complications Predictors in the Performance of Coronary Artery Bypass Grafting Surgery in the Cardiac Surgery Clinic "Bicard"

Damir Osmonov^a, Asan Nazarov^a, Mustafa Unal^a, Ishenbai Moldotashev^b, Nazaraly Usabaliev^c, Alexander Sorokin^d, Dmitry Lezhnin^b

^a Private cardiac surgery clinic "Bicard", Bishkek, Kyrgyz Republic

^b Department of Family Medicine, I.K. Akhunbaev Kyrgyz State Medical Academy, Bishkek, Kyrgyz Republic

^c Department of Therapy, International High School of Medicine, Bishkek, Kyrgyz Republic

^d Department of Physics, Medical Informatics and Biology, Faculty of Medicine, Kyrgyz-Russian Slavic University, Bishkek, Kyrgyz Republic

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HIGHLIGHTS

- Acute myocardial infarction in anamnesis is the main factor complications occurrence after coronary artery bypass grafting
- Predictors are also named low left ventricular ejection fraction (less than 40%), left ventricular diastolic dysfunction of and duration of procedure of artificial circulation
- Left ventricular diastolic dysfunction is the most specific predictor

SOUHRN

Hlavním cílem práce byl komplexní výzkum a stratifikace klinických, funkčních a chirurgických rizikových faktorů z hlediska vzniku komplikací koronárního bypassu v předoperačním období.

Materiály a metody: Byly analyzovány údaje 97 pacientů ve věku 31–84 let (průměrný věk $62,9 \pm 8,4$) s ischemickou chorobou srdeční po koronárním bypassu (v mimotělním oběhu). Za prognostická kritéria posloužil věk pacienta, přítomnost akutního infarktu myokardu v anamnéze, délka hospitalizace, počet zkratů, délka komprese aorty i trvání mimotělního oběhu. Mezi sledované parametry patřily rozměry levé komory na konci diastoly a systoly, anteroposteriorní rozměr levé síně, tloušťka mezikomorového septa a spodní stěny levé komory, ejekční frakce levé komory, přítomnost a rozsah mitrální regurgitace a dysfunkce levé komory v diastole.

Výsledky: Sledování klinických, funkčních a chirurgických rizikových faktorů pro rozvoj komplikací koronárního bypassu prokázalo nejvyšší senzitivitu akutního infarktu myokardu (v anamnéze i těsně před výkonem) a nejvyšší specifitu diastolické dysfunkce levé komory.

Závěr: Jako nejvýznamnější prediktory vzniku komplikací koronárního bypassu v pooperačním období byly identifikovány akutní infarkt myokardu, ejekční frakce levé komory $< 40\%$, přítomnost diastolické dysfunkce levé komory a délka použití mimotělního oběhu.

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ABSTRACT

The main aim of the research was to do the complex research and stratification of clinical, functional, and surgical risk factors for coronary artery bypass grafting complications development in the preoperative period.

Materials and methods: Data of 97 patients with coronary heart disease aged 31–84 (the mean age 62.9 ± 8.4) after coronary artery bypass grafting (with the artificial circulation) have been analyzed. As prognostic criteria were analyzed the patient's age, a history of the acute myocardial infarction, hospitalization time, number of the placed shunts, aortic compression duration, as well as the duration of the artificial circulation

Address: Prof. Ishenbai Moldotashev, MD, 92, Akhunbaev St, 720020, Bishkek, Kyrgyz Republic, e-mail: moldotashev53@mail.ru
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system, using. End diastolic and end systolic dimensions of the left ventricle, anteroposterior dimension of left atrium, thickness of interventricular septum and posterior wall of the left ventricle, left ventricular ejection fraction, presence and extent of mitral regurgitation, left ventricular diastolic dysfunction were studied. **Results:** Studies of the clinical, functional, and surgical risk factors of coronary artery bypass grafting complications development have shown the highest sensitivity for acute myocardial infarction (both history and immediately before surgery), and the highest specificity for the presence of left ventricular diastolic dysfunction.

Conclusion: Acute myocardial infarction, left ventricular ejection fraction less than 40%, presence of left ventricular diastolic dysfunction, and the duration of application of the artificial circulation system were fixed as the most important predictors of coronary artery bypass grafting complications development in the postoperative period.

Introduction

Currently coronary artery bypass grafting (CABG) surgery became one of the most effective methods of treatment of coronary heart disease (CHD). Volume of these interventions is increasing each year, including the Kyrgyz Republic.¹⁻³ Increasing of the number of such operations is accompanied by the increase in the frequency of complications in preoperative period due to increase in the number of elderly and senile patients often admitted to surgery with severe comorbidities.^{4,5} Moreover, the most frequent complications are the development of acute heart failure (AHF), renal dysfunction, long-term invasive ventilation, hemodynamic instability, and various heart's rhythm disorders.⁶⁻⁸

The results of vascularization, identification, and stratification of predictors of complications development are extremely important for improvement. Based on the obtained data the risk of complications occurrence can be predicted. This allows the creation of a system of preventive measures.

Despite a large number of research works, estimating risk factors of different complications, their results remain quite contradictory. In our opinion, the main reason for such discrepancies is differentiation in the level of equipment, and the difference in the number of patients involved in the researches, the difference in the qualifications of specialists conducting operation interventions (including CABG). Therefore it remains relevant to identify and stratify predictors of the development of complications during the preoperative period of CABG specifically for each medical establishment.

The aim of this study was to study and stratify clinical, functional, and surgical risk factors for complications in the preoperative period of CABG in order to develop measures to reduce the number of complications in a private cardiology clinic.

Material and methods

The research has been based on materials of the 97 patients with CHD at the age from 31 to 84 years old (the average age is 62.9 ± 8.4 years). Among patients prevailed males (86.6%); the number of women was significantly inferior 13 patients (13.4%). The CABG surgery was performed to all patients in the conditions of artificial circulation (AC) according to the generally accepted method. All actions of the conducted research have been considered

at the meeting of the Bioethics Committee. Protocol 13 from November 2 2021 declared that current research has been conducted according to the ethical principles for medical research involving human subjects (Helsinki, June 1964, with later amendments till October 2008).

In order to control the treatment process, Echocardiographic (EchoCG) examination was performed with use of VIVID 7 apparatus; M-, B-modes and dopplerography were also used.

Patient's age, presence of previous acute myocardial infarction (AMI), length of hospitalization, placed shunts number, duration of aortic compression, and duration of Artificial Circulation were studied as prognostic criteria. Left ventricular end diastolic dimension (LVEDd) and left ventricular chamber diameter at end systole (LVDS), anteroposterior size of left atrial (LA), thickness of interventricular septum (IVS), and posterior wall (PW) of the left ventricle, left ventricular ejection fraction (LVEF), presence and stage of mitral regurgitation (MR), and diastolic dysfunction of the left ventricle (DDLV) were used following EchoCG indicators.

Statistical analysis

Statistical processing was performed using the statistical package SPSS Version 16. Mean and standard deviations were calculated as descriptive statistics. The odds ratio and 95% confidence interval were calculated to assess the association of the presumed predictor and the occurrence of complications. For the main predictors, values of sensitivity (Se), specificity (Sp), prognostic predictive value (Ppv) and negative predictive value (Npv). The level of statistical significance was taken $p = 0.05$.

Results

Clinical characteristics of patients

All patients prior to operation were diagnosed with stenocardia of 11-1V Functional Class (FC) according to the Classification of Canadian Association of Cardiologists. 62 patients (63.9%) suffered from AIM. And in anamnesis this pathology was detected during the preoperative period remotely in 82.3% (51), immediately before AIM intervention 11 patients (17.7%) came through. CABG surgery was not performed to anyone of the patients enrolled in the research previously.

Clinical signs of chronic heart failure (CHF FC 1-111 Stage according to the New York Heart Association Classification) were detected in 87.6% ill people (85 people).

Co-existing arterial hypertension was detected in 79 (81.4%) people. Was analyzed the body mass index (BMI) of patients. BMI was $30.2 \pm 3.0 \text{ kg/m}^2$. Has been indicated the presence of overweight in most patients.

Hypercholesterolemia has been diagnosed in patients (85.6%), in this case the total cholesterol was $>4.5 \text{ mmol/L}$. Performing EchoCG volume LVEF ranged from 25% to 65%, averaging $44.8 \pm 8.7\%$. In 29 people (29.9%) LVEF was recorded less than 40%. Signs of postinfarction aneurysm of LV were diagnosed in 9 (9.1%) people. Volumes of LA ranged from 28 mm to 61 mm (average $40.4 \pm 6 \text{ mm}$), and volumes of LV – EDD from 43 to 74 mm (average $62.9 \pm 8.4 \text{ mm}$), ESD from 20 to 63 mm (average $39.6 \pm 6.7 \text{ mm}$). LVDD was detected in 32 patients (33%) and MR in 31 ill people (32%).

Treadmill test before surgery was performed in 53 patients (54.6%). Its result was positive for everyone. Multivessel disease of coronary arteries was observed according coronarography data of all patients.

In performing the CABG the duration of AC was from 56 to 270 min (average $131.9 \pm 53 \text{ min}$), and the duration of aortic compression was from 14 to 180 min (average $65.7 \pm 41 \text{ min}$). The average number of shunts per one patient was 2.8 ± 0.4 (from 1 to 5).

The average hospitalization time was 7.5 ± 3.7 days. The total hospital mortality was 3.4%. And this is comparable to the world standards. In the world practice, hospital mortality in this case does not exceed 1–3%.⁹ In the same time the mortality of patients with low LVEF ($>40\%$) was 9.1% (3 cases out of 33 patients).

Evaluation of predictors of post-operative complications

Our research has demonstrated that acute heart failure (AHF) had developed (or progressed) in the intraoperative and early postoperative periods in 31 patients out of 97. At the same time, it was manifested by pulmonary edema, cardiac asthma, cardiogenic shock, acute heart rhythm disorders in the form of ventricular tachycardia with the transition to ventricular fibrillation, flickering and fluttering of the atria. Study of clinical, functional, and surgical risk factors of complications development in the intraoperative and early postoperative periods of CABG showed the following results (Table 1).

We have not found a significant dependence of the complications occurring and the age of the treated patients (Table 1). And the length of AC period and aortic compression time have not shown a statistically significant effect on the development of the cardiac complications in our research. So more, the number of applied shunts was not also closely connected with complications development in our research. But the myocardial infarction has demonstrated the dependence. So, AMI in anamnesis and immediately prior to CABG were the factors of the highest risk of postoperative complications development in our research.

If we consider the length of hospitalization as an indicator of the complicated course of postoperative period, we have not found such dependence.

We have taken as the base that echocardiographic indicators such as LVEF, DDLV stage, and MR are of the closest dependence related to cardiac complications. And

current observation has approved this but other echocardiographic indicators, like heart size, IVS thickness, and LVPW, didn't show such dependence. Moreover, length of the artificial circulation period, aortic compression time as the length of the artificial circulation period and aortic compression time had no the significant influence on the development of the post-surgery complications in cardiac surgical patients. The most significant predictors of mortality were hemodynamic instability and renal dysfunction according to our observation. And the LVEF had great connection with post-surgery complications development.

Table 1 – Data on odds ratio for studied parameters

Parameters	Odds ratio 95% CI	p
Acute myocardial infarction	11.194 (2.457–50.993)	0.000
Age	2.240 (0.992–5.445)	0.996
Diastolic dysfunction of left ventricular	2.593 (1.048–6.415)	0.147
Left ventricular ejection fraction	6.175 (2.391–15.948)	0.004
Left ventricular end diastolic dimension	0.922 (0.371–2.295)	0.315
Left ventricular chamber diameter at end systole	0.557 (0.225–1.380)	0.154
Interventricular septum thickness	1.955 (0.591–6.464)	0.968
Thickness of left ventricular posterior wall	1.504 (0.478–3.559)	0.673
Mitral regurgitation	0.627 (0.232–1.696)	0.223
Length of hospital stay	0.134 (0.029–0.621)	0.002
Anteroposterior volume of the left ventricle	0.615 (0.097–3.905)	0.418
Number of shunts	0.459 (0.120–1.751)	0.246
Length of aortic compression	0.593 (0.122–2.887)	0.516
Length of AC period	0.889 (0.186–4.244)	0.883

Table 2 – Predictive ability estimations of the major predictors

Parameters	Sensitivity value	Specificity value	Positive predictive value	Negative predictive value
Acute myocardial infarction	0.92	0.46	41.9	93.9
Left ventricular ejection fraction	0.86	0.51	43.1	89.7
Diastolic dysfunction of left ventricle	0.48	0.73	43.7	76.9

So, this research has confirmed the results we had previously obtained, in this case, LVEF had the greatest connection with complications development. For the purpose of estimating predictive value, sensitivity and specificity levels were determined for each of the prognostic parameters. As a result of performed analyses, AMI was determined as having the highest sensitivity (0.92), and the presence of LVDD of the heart presented the highest specificity (0.73) (Table 2).

So we have noted that the presence and severity stage of MR remains one of the important predictors of complications development in the early CABG post-operative period.

Discussion

According to the numerous researches data, the main cause of death in patients having undergone myocardial revascularization is AHF, due to systolic or diastolic myocardial dysfunction.¹⁰ So, according to Ushakov⁵ perioperative predictors of acute heart failure development are: 1) value of the scale of the complex evaluation of age degree of wear (AHF = 1.2; $p = 0.001$); 2) Systolic LV dysfunction in the presence of EF less than 50% (AHF = 9.0; $p = 0.001$); 3) AC using (AHF = 1.1; $p = 0.036$).

Some authors have demonstrated the dependence of the development of the complications on age,¹¹ but this is not the single opinion. Sumin et al. haven't found such dependence.¹² We have noted that the age of patients did not have significant impact on the development of AHF during the intraoperative and early postoperative periods. However, the most number of authors tend to conclude the older people (especially those older than 80 years) had a higher risk of death and serious complications.¹³ Like the research of Gratti et al.⁶ They have declared the hospital mortality in the period of 62±4 years was 5.3%. Fretschnier et al.⁸ have observed 1013 after CABG surgery and noted that women older than 60 years, patients who suffered two or more myocardial infarctions, who had previously been in intensive care, had oxygen saturation of less than 70%, and needed three or more shunts for complete revascularization had the highest risk of lethal outcome development.

If we are looking for echocardiographic indicators we can say about AMI in anamnesis and immediately prior to CABG were the factors of the highest risk of postoperative complications. Our data is supported also by researches of other authors.^{14–16} The risk of complications development in case of CABG increases if the AIM has been presented in anamnesis, an intraoperative connection of intra-aortic balloon counterpulsation has been conducted; the artificial circulation has been used for more than 120 min, and aortic compression has been introduced for more than 90 min.¹²

We have got data opposite¹⁷ to the one declared by Nadeem et al. and Ortiz et al. that length of the artificial circulation period and aortic compression time are the predictors of postoperative complications development in cardiac surgical patients.^{18,19}

Our research has shown there is no significant influence of the number of applied shunts on the compli-

cations development. Other researchers demonstrated the number of bypass shunts (of two or more) is a risk factor of complications development in patients after CABG.²⁰

The hospitalization length is considered by the number of researchers as an indicator of complicated course of postoperative period.²¹ But we have not found such dependence.

As our earlier researches showed, LVEF, DDLV stage, and MR out of echocardiographic indicators had the closest dependence related to cardiac complications development.²² Other echocardiographic indicators, like heart size, IVS thickness, and LVPW, didn't show such dependence.

Vic Kneson et al.⁷ performed retrospective analyses of 346 patients (2015–2019) with low LVEF ($\leq 30\%$). Results of observations have showed patients with significant LV dysfunction, subjected to CABG, were satisfactory for a month. The most significant predictors of mortality were hemodynamic instability and renal dysfunction. Khaled et al.²³ have shown patients with diabetes mellitus, with significant diastolic LV dysfunction, and after using the intra-aortic counterpulsation in surgery had increased risk of hospital lethality.

Conducted research has confirmed the results we had previously obtained, in this case, LVEF had the greatest connection with complications development. Data of literature have also shown that LVEF is the most significant risk factor of serious complications developed during the early postoperative period.^{9,16}

Gratti et al.⁶ studied 4383 cases after CABG performed because of multiple coronary artery lesions (January 1999–September 2014; the average age of 300 studied patients – 66.1 ± 9.6 years). The most frequent postoperative complications were prolonged invasive ventilation (17.7%) and acute renal failure (14.7%).

Data of other researchers showed²⁴ that people who had undergone CABG surgery complicated by CF, have increased mortality risk developing in the late (within a year) postoperative period. Risk of AHF development after CABG is increasing with coronary artery lesions (more than 4 coronary arteries), long time of surgery, and reconstruction of LV cavity in the case of its aneurysm.²⁰ The risk of CABG complications development increased if:

- 1) MI with unstable hemodynamics/shock up to 24 hours;
- 2) acute coronary syndrome is present;
- 3) the stenosis of the left coronary artery trunk has been diagnosed;
- 4) LVEF was $\leq 35\%$.¹²

The most frequent development of threatening perioperative complications (pulmonary artery thromboembolism, acute cerebral circulation disorder, AHF, ventricular fibrillation, intraoperative MI) occurs when performing CABG up to 10 days from the moment of AMI development.²⁵

In recent years LVDD has received greater attention. It has been proved that during the post-perfusion period LVDD can be due to ischemic and reperfusion damage, hypothermia, metabolic disorders, or myocardial edema and is the independent factor in

the development of difficulties in excommunicating the patient from AC, using high doses of inotropic support and increased risk of complications development.¹⁰ LVDD has been shown to be powerful, predisposing factor in the development of postoperative atrial fibrillation. It was established, LVDD increases preoperative mortality in patients with cardiac surgical profiles.²⁵ LVDD has also been shown as an independent risk factor for postoperative CF, atrial fibrillation, and fatal outcome.²⁶

MR presence together with IHD significantly increases mortality of such patients. So more than 40% of ill people with combined IHD and MR of severe stage die during the first year from the moment of MR.²⁷ If the combination of IHD and MR (moderate stage) is present, mortality is about 15–18%; if MR is in the mild stage 8–11%. At the same time, the mortality of patients with IHD without MR is 5% approximately.²⁸ It has been shown convincingly that moderate ischemic MR had affected the increased risk of mortality from cardiovascular diseases, including patients with CF.²⁹ Our data confirm that presence and severity stage of MR remains one of the important predictors of complications development in the early CABG post-operative period.

Study limitations

All conducted observations were made in conditions of the private cardiology clinic. The observation results can depend on the current condition of the certain conditions of the hospital and surgeons' qualifications and the number of surgeries for the year. So, each clinic has to have its own research on the occurrence of the complications' predictors.

Conclusions

Results of our researches, performed in the current conditions of the private clinic, showed that, unlike data from other clinics, such parameters as age of patients, length of artificial circulation period, and the time of aortic compression, as well as the number of applied shunts did not show the statistically significant effect on the development of complications. This supports our proposal to identify predictors of the development of complications following coronary artery bypass grafting surgery in each separate clinic.

The closest connection of complications development during the intraoperative and early postoperative periods in the considered clinic was revealed with acute myocardial infarction, with low left ventricular ejection fraction, and the presence of diastolic dysfunction of left ventricular. In this case acute myocardial infarction had the most sensitivity on development, and the presence of diastolic dysfunction of left ventricular had the greatest specificity.

Conflict of interest

There are no conflicts of interest in the presented research.

Funding

There is no financial special relationship with the organization the research has been conducted.

Authors' information and contribution

Damir Osmonov, PhD in Medicine (0000-0001-6715-722X), collected the study results and created Discussion section; **Asan Nazarov**, Head of the Cardiothoracic Surgery and Resuscitation Department, (0000-0002-6949-2678), collected and analyzed (processed) research data; **Mustafa Unal**, Cardiac Surgeon, (0000-0002-1622-6923), collected the study results and created Discussion section; **Ishenbai Moldotashev**, Doctor in Medicine, Professor, (0000-0001-5525-3599), was the author of the study design, created Discussion section, and formed the conclusions of the research; **Nazaraly Usabaliev**, PhD in Medicine, Associate Professor, (0000-0002-8571-6803), created the Introduction and Discussion sections and formed the final article; **Alexander Sorokin**, PhD in Biology, (0000-0002-9682-8085), conducted and interpreted the results of statistical analysis, formed the Materials and Methods and Results parts of the Paper; **Dmitry Lezhnin**, Cardiac Surgeon, (0000-0001-9705-2891) has a part in data processing and results analyzing.

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Non-invasive assessment of ventricular-arterial coupling: correlation between myocardial work and the pulse wave velocity parameters

Antonio Parlavecchio^a, Rodolfo Caminiti^a, Giampaolo Vetta^a,
Michele Magnocavallo^b, Domenico Giovanni Della Rocca^{c,d}, Rosario Foti^e,
Manuela Ajello^a, Pasquale Crea^a, Giuseppe Dattilo^a, Massimo Siviglia^f,
Stefano Postorino^f, Antonio Pangallo^f, Francesco Antonio Benedetto^f,
Concetta Zito^a, Scipione Carerj^a

^a Cardiology Unit, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

^b Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatric Sciences, "Sapienza" University of Rome, Policlinico Umberto I, Rome, Italy

^c Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, USA

^d Heart Rhythm Management Centre, Postgraduate Program in Cardiac Electrophysiology and Pacing, Universitair Ziekenhuis Brussel-Vrije Universiteit Brussel, European Reference Networks Guard-Heart, Brussels, Belgium

^e Cardiology Unit, San Vincenzo Hospital, Taormina, Italy

^f Cardiology Unit, Department of Cardiology, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

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Tuhost

SOUHRN

Úvod: Měření práce myokardu (myocardial work, MW) představuje novou echokardiografickou metodu založenou na sledování smyčky tlak-deformace srdeční komory, což umožňuje kvantifikovat výkonnost srdce. Na druhé straně rychlost pulsní vlny (pulse wave velocity, PWV) určuje tuhost tepen na základě poznatku, že se zvyšující se tuhostí tepny se zvyšuje i rychlost anterográdního a retrográdního přenosu sfygmické vlny.

Cíl: Cílem této studie bylo stanovit korelaci mezi parametry MW a PWV.

Metody: Do studie jsme zařazovali všechny po sobě následující pacienty bez kardiovaskulárního onemocnění, kteří v období mezi červnem 2021 a červencem 2022 absolvovali transtorakální dopplerovské echokardiografické vyšetření. Hodnoty MW byly vypočítány ze smyčky tlak-deformace srdeční komory, do níž byly začleněny hodnoty neinvazivního vyšetření tepenného tlaku podle doporučení pro standardní echokardiografické vyšetření metodou „speckle tracking“. Hodnota PWV se měřila tonometrem na úrovni společné karotidy a společné femorální tepny.

Výsledky: Celkem bylo do studie zařazeno 66 pacientů průměrného věku $30,7 \pm 8,6$ roku. Byla nalezena statisticky významná negativní korelace mezi PWV a celkovou zbytečně vynaloženou energií (global wasted energy, GWE) ($r = -0,317$; $p < 0,01$) při korelaci s celkovou zbytečně vynaloženou prací (global wasted work, GWW) ($r = 0,324$; $p < 0,01$). Statisticky významná korelace přetrvávala v podskupinách žen i mužů u GWE (ženy: $r = -0,280$; $p < 0,05$; muži: $r = -0,362$; $p < 0,05$) i u GWW (ženy: $r = 0,359$; $p < 0,05$; muži: $r = 0,359$; $p < 0,05$).

Závěr: Vztah mezi MW a PWV jako projev součinnosti mezi levou komorou a velkými tepnami může potenciálně představovat užitečný nástroj pročasné odhalení subklinické dysfunkce kardiovaskulárního systému.

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ABSTRACT

Introduction: The myocardial work (MW) is a new echocardiographic method, based on the pressure-strain loop, which allows quantifying the cardiac performance. On the other hand, the pulse wave velocity (PWV) evaluates arterial stiffness, knowing that as the stiffness of an artery increases, the transmission velocity of the antegrade and the retrograde sphygm wave increases.

Address: Rodolfo Caminiti, MD, Cardiology Unit, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy,
e-mail: rudycaminiti@gmail.com.

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Keywords:

Myocardial work
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Purpose: The aim of the study is to evaluate the correlation between MW and PWV parameters.

Methods: We enrolled consecutively all patients without cardiovascular disease who underwent transthoracic Doppler echocardiography between June 2021 and July 2022. The MW parameters were derived from the strain-pressure loop, including in its calculation the measurement non-invasive arterial pressure, according to standard speckle tracking echocardiography recommendations. The PWV measurement was obtained by tonometry at the level of the common carotid artery and the common femoral artery.

Results: We enrolled 66 patients (mean age: 30.7 ± 8.6 years). There was a significant inversely proportional correlation between PWV and GWE ($r = -0.317$; $p < 0.01$) meanwhile there was a directly proportional correlation with GWW ($r = 0.324$; $p < 0.01$). The statistically significant correlation remained in the female and male subgroups for GWE (female: $r = -0.280$; $p < 0.05$; male: $r = -0.362$; $p < 0.05$) and GWW (female: $r = 0.359$; $p < 0.05$; male: $r = 0.359$; $p < 0.05$).

Conclusion: The relationship between MW and PWV as a demonstration of ventricular arterial coupling may potentially be a useful tool in the early recognition of subclinical cardiovascular dysfunction.

Introduction

Cardiovascular disease is the leading cause of the global burden of morbidity and mortality. The latest evidence has shown that to anticipate atherosclerosis there are other phenomena involving the remodeling of the arteries such as increased thickness and stiffness: the "arteriosclerosis". Vessel remodeling is a pathophysiological process that occurs with advancing age.¹ However, although the classic cardiovascular risk factors – smoking, hypertension, diabetes, dyslipidemia, obesity – may be a factor accelerating arteriosclerosis, vessel remodeling now seems to be confirmed as an independent risk factor for future cardiovascular events and all causes of mortality.^{2,3}

In the evaluation of arterial stiffness as an independent risk factor, it would be interesting to evaluate together the performance data of the left ventricle as a constitutive element of the ventricular-arterial coupling (VAC).⁴

VAC is defined as the interaction of the heart with the systemic circulation, playing a key role in cardiovascular performance, influencing both the magnitude and efficiency of left ventricular (LV) stroke work transfer to the circulation.⁵

In deed, it is well known how heart and vessels are mutually influenced and the deterioration of the function of one affects the other.^{6,7}

In optimal coupling conditions, in fact, a maximum cardiac work, efficiency, of the left ventricle is achieved while maintaining arterial pressure values in the normal range.

The assessment of arterial stiffness is obtained by measuring the velocity of the antegrade aortic sphygmoc wave (PWV) with tonometry, regarded as the gold standard.⁸

Among the devices currently in use for the assessment of arterial stiffness, the SphygmoCor Xcel system (AtCor Medical, Sydney, NSW, Australia) is a well-validated and widely used device.⁹

The SphygmoCor Xcel device measures Augmentation Index using a partially inflated brachial cuff and PWV using a partially inflated femoral cuff together with carotid applanation tonometry.

The non-invasive myocardial work (MW) is a newly implemented tool that evaluates global and regional myocardial performance derived from the non-invasive stress-pressure loop. This measurement is obtained from

2D strain data and non-invasive brachial artery pressure, being less dependent of preload and afterload.¹⁰

The aim of our study was to assess in healthy patients the PWV and the MW indices as the evaluation of the ventricular-artery coupling.

Methods

Study population

We enrolled consecutively outpatients who underwent transthoracic Doppler echocardiography (TTE) in the Echo-lab of Cardiology Institute of the Policlinico Universitario "G. Martino" of Messina between June 2021 and July 2022.

We included patients older than 18 years in the study and we excluded patients suffering from cardiovascular disease (CVD) and cardiovascular risk factors or poor acoustic window. All patients underwent cardiological examination, electrocardiogram, and complete echocardiogram colour-Doppler with the assessment of 2D strain, MW indices and PWV analysis. The Institutional Review Board of Policlinico Universitario "G. Martino" approved the study. Our study complies with the Helsinki declaration for investigations in human patients.

Cardiovascular disease and risk factors definition

CVD and risk factors were defined according to Guidelines on Cardiovascular Disease Prevention of the European Society of Cardiology.

CVD included previous acute myocardial infarction, acute coronary syndrome, coronary revascularization and other arterial revascularization procedures, stroke and transient ischemic attack, aortic aneurysm, peripheral artery disease, cardiomyopathies and genetic syndromes. It does not include some increase in continuous imaging parameters such as intima-media thickness of the carotid artery. Risk factors for CVD included: family history of premature CVD, smoking, arterial hypertension, diabetes mellitus, raised lipid level, obesity and chronic kidney disease.

Pulse wave velocity analysis

PWV analysis was performed with SphygmoCor XCEL System v1 technology (AtCor Medical Pty Ltd., Sydney, Australia) and software (SphygmoCor XCEL Software Versi-

on: 1.2). PWV analysis was performed according to the consensus document and measurement was performed at the level of the right carotid artery and right femoral artery. Measurement sites for the PWV analysis were the right carotid artery and right femoral artery.⁸ We marked the level where the carotid pulse was strongest, and a femoral cuff was placed at the level of the right thigh. The distance between the carotid artery mark and the upper edge of the femoral cuff was recorded into the SphygmoCor software. The 'femoral to cuff' length is automatically subtracted from the 'carotid to cuff' length to indicate the carotid-femoral distance which is used in the PWV calculation.

The brachial blood pressure was registered, and the time of the acquisition was chosen in the SphygmoCor software. For standardisation of registrations the device was placed on the marked carotid artery position, configured to record automatically and the pulse wave was recorded after high quality waveforms during the specified capture time.

The measurement quality was assessed automatically by the SphygmoCor software (based on consistent pulse peaks, troughs and amplitude), and were indicated with either a green "quality controlled" tick, or a red cross indicating a lower quality measure.¹¹ All data for inclusion in this research project were required to have a quality-controlled tick.

Echocardiographic analysis

Images were acquired with resting patients in the left lateral decubitus position with a commercially available ultrasound system in the parasternal and apical views (Vivid E9 and E95, GE Vingmed Ultrasound, Horten, Norway). M-mode and 2D, colour, pulsed wave and continuous wave Doppler images were obtained. Data were analysed offline using EchoPAC version 204 software (GE Vingmed Ultrasound, Horten, Norway). LV end-diastolic volume (LVEDV), LV end-systolic volume and LV ejection fraction (LVEF) were assessed in apical four- and two-chamber views using Simpson's biplane method.¹² In order to assess LV global longitudinal strain (GLS), 2D-speckle tracking analyses were carried out offline in images acquired from apical views at four, two and three axes as previously described.¹³

Myocardial work analysis

The LVMW calculation from non-invasive LV pressure-strain analysis has been described previously.^{10,14} LVMW indices were computed with the latest vendor-specific module (EchoPAC version 204 software, GE Medical Systems, Horten, Norway) combining LV GLS and a non-invasively measured blood pressure. LV GLS was evaluated with 2D speckle tracking echocardiography drawing manually the endocardial rim in four-, two-, and long-axis apical views. The non-invasive LV pressure curve was assessed by measuring the time of valvular events by echocardiography and adjusting the standard LV pressure curve to the duration of isovolumic contraction, LV ejection, and isovolumic relaxation. In order to calibrate the curve amplitude, blood pressure records from the patient's brachial cuff were recorded at baseline echocardiography and were used instead of the peak LV pressure. The

software then processed a non-invasive LV pressure-strain curve using a combination of LV GLS data from the entire heart cycle and the instant LV pressure. Cardiac work was calculated as a function of time throughout the cardiac cycle. The following LVMW indices were derived: global work index (GWI) defined as total work within the area of the LV pressure-strain loops calculated from mitral valve closure to mitral valve opening; global constructive work (GCW) defined as work performed during shortening in systole adding work during lengthening in isovolumic relaxation; global wasted work (GWW) defined as work performed during lengthening in systole adding work performed during shortening in isovolumetric relaxation and global work efficiency (GWE) calculated as the sum of constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments. GWI, GCW, and GWW were expressed as mmHg% and GWE as a percentage.¹⁵

Statistical analysis

Categorical data were summarized as percentages and continuous data as mean $\pm$ standard deviation (SD). T-test for independent samples was used to compare the means of continuous variables and χ^2 test for qualitative variables. We used the Kolmogorov-Smirnov test for normality in order to evaluate the assumption of t-test. The correlation between MW indices and PWV in the entire population and in subgroups according to gender was assessed using Spearman's rank correlation. A p value less than 0.05 was considered significant. All the statistical analyses were performed using IBM SPSS Statistics v26 software.

Results

Study population and clinical characteristics

In our study, 66 patients without cardiovascular disease were enrolled. The patients had a mean age of 30.73 ± 8.56 years, body mass index (BMI) of 23.54 ± 4.18 kg/m², body surface area (BSA) of 1.76 ± 0.20 m², systolic blood pressure (SBP) 119.94 ± 9.30 mmHg and diastolic blood pressure (DBP) 72.42 ± 9.10 mmHg, as seen in Table 1. The patients had mean LVEF of 60.36 ± 5.21 %, GLS -20.27 ± 1.70 %, GWI 1815 ± 196.20 mmHg%, GCW 2171.45 ± 255.52 mmHg%, GWE 95.82 ± 1.39 % and GWW 81.73 ± 32.59 mmHg%, as seen in Table 2. In the comparison between the female and male subgroups, there were no statistically significant differences in clinical and echocardiographic characteristics, as reported in Tables 1 and 2.

Correlation between pulse wave velocity and myocardial work indices

Figure 1 shows the correlations of PWV with MW indices. There was a significant inversely proportional correlation between PWV and GWE ($r = -0.317$; $p < 0.01$) meanwhile there was a directly proportional correlation with GWW ($r = 0.324$; $p < 0.01$). GWI ($r = 0.201$; $p = 0.16$) and GCW ($r = 0.236$; $p = 0.98$) did not show a statistically significant correlation with PWV. The statistically significant correlation remained in the female and male subgroups for GWE (female: $r = -0.280$; $p < 0.05$; male: $r = -0.362$; $p < 0.05$) and

Table 1 – Baseline clinical characteristics of population

	All patients (66)	Female (22)	Male (44)	p value
Age, years	30.73±8.56	30.82±4.49	30.68±10.04	0.952
BSA	1.75±0.19	1.58±0.09	1.84±4.49	0.265
BMI	23.55±4.18	21.65±3.40	24.49±4.25	0.008
SAP, mmHg	119.94±9.92	116.00±7.67	121.91±10.41	0.021
DAP, mmHg	72.42±9.02	72.91±7.76	72.18±9.66	0.760
HR, bpm	69.97±12.51	76.73±12.17	66.59±11.37	0.001
Sex (male), %	66.7			

BMI – body mass index; BSA – body surface area; DAP – diastolic artery pressure; HR – heart rate; SAP – systolic artery pressure.

Table 2 – Echocardiographic characteristics of population

	All patients (66)	Female (22)	Male (44)	p value
FE, %	60.36±8.56	30.82±4.49	30.68±10.05	0.692
EDVi, mL/m ²	50.67±10.45	47.30±10.19	52.34±10.28	0.64
ESVi, mL/m ²	20.55±6.37	19.91±7.03	20.88±6.06	0.564
E/E'	6.08±2.67	5.44±1.07	6.52±3.32	0.193
S', cm/s	10.67±1.82	10.27±1.66	6.52±3.33	0.243
LAVi, mL/m ²	15.24±10.46	14.25±9.72	15.73±10.88	0.592
PAPS, mmHg	21.57±5.70	21.60±5.14	21.56±6.13	0.985
GLS, %	-20.27±1.7	21.27±1.80	19.77±1.42	0.001
GWI, mmHg%	1815±196.20	1875±157.78	1785±208.02	0.079
GCW, mmHg%	2171.45±255.52	2268.27±213.26	2123.05±263.23	0.028
GWW, mmHg%	81.73±32.60	85.64±31.13	79.77±33.48	0.495
GWE, %	95.82±1.39	95.82±1.22	95.82±1.48	1.000
PWV, m/s	7.56±1.12	7.46±1.10	7.62±1.14	0.601
Pulse pressure, mmHg	34.09±8.18	30.27±5.18	36±8.76	0.006
AIX, %	16.15±15.05	18.27±18.11	15.09±13.36	0.422

AIX – central augmentation index; EDVi – end diastolic volume index; EF – ejection fraction; ESVi – end systolic volume index; GCW – global constructive work; GLS – global longitudinal strain; GWE – global work efficiency; GWI – global work index; GWW – global wasted work; LAVi – left atrial volume index; PAPS – pulmonary artery systolic pressure; PWV – pulse wave velocity.

GWW (female: $r = 0.359$; $p < 0.05$; male: $r = 0.359$; $p < 0.05$), as reported in Figure 2.

Discussion

The results obtained from our study confirm the close link between heart and vessels, but even more they show how through non-invasive methods it is possible to assess the status of one in relation to the other. MW in this scenario was found to be useful in assessing myocardial performance by demonstrating better sensitivity than traditional LV performance assessment methods.¹⁰ GWW is a parameter that represents wasted work, a quota of work that does not contribute to the building of LV ejection. The increase in GWW can be caused by several scenarios, first ischemia, but also chronic damage or congenital alterations, or even in the context of hypertensive heart disease.¹⁴

The worsening of LV function can be recognized in an imbalance between GWW and GCW. GWE is the parameter that best describes the relationship between GCW and GWW and is expressed as a percentage.¹⁶ A high value of efficiency is clear to indicate a maximal cardiac work in which the waste (GWW) is low. LV efficiency is therefore affected by increased outflow resistance, increased afterload and by arteriosclerosis.⁶ In fact, in healthy subjects both parameters GWW and GWE correlated with PWV with high significance.

PWV is the speed of the anterograde sphygmocardi wave inside the vessel; it is generated by systole and ends with the end of the cardiac cycle: its propagation on the walls of the arteries generates many reflex waves that are added to the anterograde wave in the diastolic phase and lead to an increase in pressure in the peripheral territories.^{17,18} The sum of these two wavefronts is assessed by the AI parameter. When arteriosclerosis is present, it is clear how both parameters (PWV and AI) are increment-

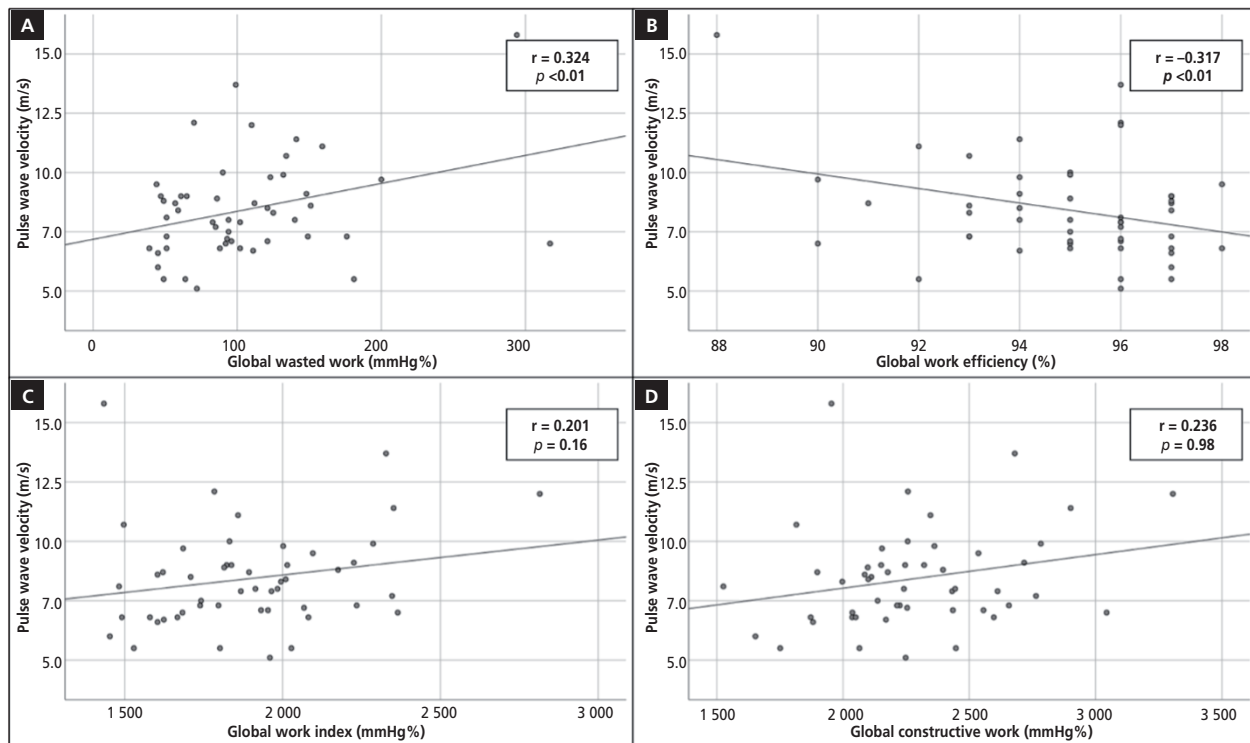


Fig. 1 – Scatterplot of the relationship between pulse wave velocity and GWW (A), GWE (B), GWI (C) and GCW (D).

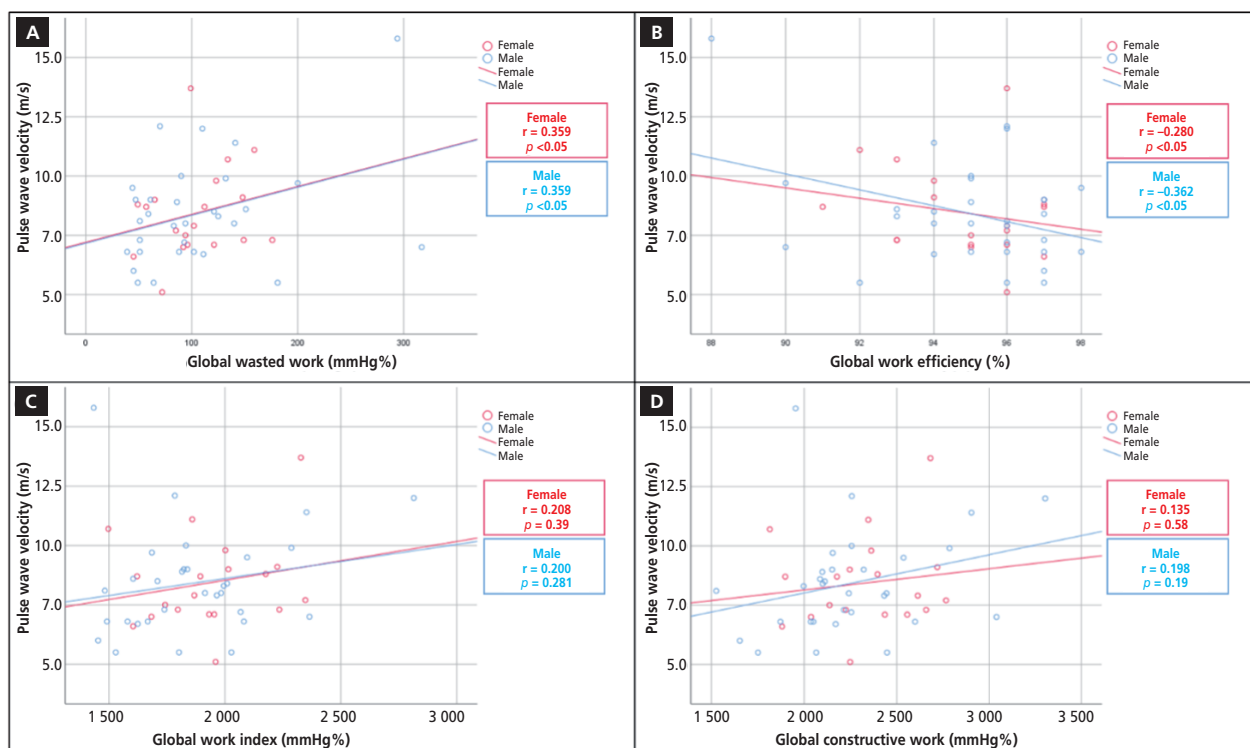


Fig. 2 – Scatterplot of the relationship between pulse wave velocity and GWW (A), GWE (B), GWI (C) and GCW (D) in female and male sub-groups.

ed. Increased vessel resistance and decreased vessel distensibility can enhance sphygmocardi wave velocity, resulting in mistiming with the cardiac cycle, conflicting with the

reflex waves just before the end of systole: as a result, the pressure rises in the systolic phase, leading to an afterload increase.¹⁹

The afterload causes an increase of the systolic pressure of the left ventricle; consequently we will have an increased wall stress that results in a worsening of the efficiency of the left ventricle and with the generation of wasted work. However, the same mechanism, resulting in increased afterload, leads to premature closure of the aortic valve, increasing the wasted work.²⁰

Analyzing the function of the MW, the assessment of wasted work is provided by the deformation of the left ventricle following the closure of the aortic valve: fibre-shortening does not occur during systole but at its end ("post-systolic deformation").^{14,21}

Our study also found the same correlation by analyzing both male and female groups.

In summary, VAC assessment represents a promising tool for early detection of cardiovascular disease. The MW and PWV are closely related, studying the correlation between them may reveal new perspectives in the detection of "primum movens" and in therapeutic management of cardiovascular disease. A larger study is required to prove VAC alteration in patients with risk factors or cardiovascular disease.

Conclusion

The relationship between MW and PWV as a demonstration of ventricular arterial coupling may potentially be a useful tool in the early recognition of cardiovascular dysfunction. Further studies will be needed to investigate the feasibility of these two methods in daily practice.

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Matrix metalloproteinase-9 prognostic role in STEMI patients after percutaneous coronary intervention (PCI) in one-year follow-up period

Mykola Kopytsya^a, Yaroslava Hilova^a, Iulia Rodionova^a, Anton Bilchenko^a, Inna Kutia^a, Borys Shelest^b

^a Government Institution "L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine", Kharkiv, Ukraine

^b Kharkiv National Medical University, Department of Internal and Occupational Diseases, Kharkiv, Ukraine

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SOUHRN

Cíl: Použití matrixové metaloproteinázy-9 (MMP-9) u pacientů s akutním infarktem myokardu s elevací úseku ST (STEMI) po perkutánní koronární intervenci (PCI) jako prognostického indikátoru má mnoho mezer a lékařská komunita s tím má velmi omezené zkušenosti. Cílem studie bylo zhodnotit prognostickou roli MMP-9 u pacientů se STEMI po úspěšné revaskularizaci během 12měsíčního období sledování.

Materiál a metoda: Do studie bylo zařazeno 88 pacientů, kteří splnili kritéria pro zařazení a neměli žádná vylučovací kritéria, jimž byl diagnostikován STEMI a podstoupili primární PCI. Mužů bylo 66 (75,0 %), s průměrným věkem $60,84 \pm 9,68$ roku. Doba sledování činila 12 měsíců. Byl použit složený cílový ukazatel, který zahrnoval výskyt srdečního selhání, které si vyžádalo hospitalizaci, úmrtí z kardiovaskulárních příčin, recidivující infarkt myokardu, akutní cerebrovaskulární příhodu. Koncentrace MMP-9 byla stanovena pomocí ELISA.

Výsledky: Kaplanova-Meierova analýza křivek ukázala významnou souvislost mezi zvýšenou MMP-9 a studovaným složeným cílovým ukazatelem, $p = 0,0229$. Pacienti s koncentracemi MMP-9 $> 201,7$ ng/ml měli signifikantně více cílových ukazatelů. Jednorozměrná regresní analýza zjistila, že MMP-9 byla indikována jako nezávislá proměnná pro nepříznivý výsledek s poměrem šancí (OR): 1,017, 95% interval spolehlivosti (CI): 1,001–1,033, $p = 0,037$. Multivariační logistická regresní analýza ukázala, že MMP-9 (OR: 1,019; 95% CI: 1,005–1,033; $p = 0,009$) spolu s glukózou nalačno (OR: 1,246; 95% CI: 1,010–1,538; $p = 0,040$) a leukocyty (OR: 0,751; 95% CI: 0,558–1,011; $p = 0,057$) zůstaly významnými nezávislými prediktory složeného cílového ukazatele u studovaných subjektů po úpravě dalších zkoumaných zkreslujících faktorů, věku, pohlaví, indexu tělesné hmotnosti, lipidových a glukózových profilů.

Závěr: U pacientů se STEMI po PCI existuje významný vztah mezi nežádoucími účinky a zvýšenými koncentracemi MMP-9. MMP-9 se během ročního sledování prokázala jako vysoce citlivý marker pro predikci nepříznivého průběhu onemocnění u pacientů se STEMI.

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ABSTRACT

Objective: The use of matrix metalloproteinase-9 (MMP-9) in patients with acute myocardial infarction with ST-segment elevation (STEMI) after percutaneous coronary intervention (PCI) as a prognostic indicator has a lot of gaps and the medical community has very limited experience with it. The study aimed to evaluate the prognostic role of MMP-9 in STEMI patients after successful revascularization within a 12-month follow-up period.

Material and method: 88 patients met the inclusion criteria and had no exclusion criteria diagnosed with STEMI who underwent primary PCI were enrolled in the study. 66 (75.0%) were men, with a mean age of 60.84 ± 9.68 years. A follow-up period was 12 months. The combined endpoint was used and it included the occurrence of heart failure, which required hospitalization, cardiovascular death, recurrent myocardial infarction, acute cerebrovascular event. The level of MMP-9 was determined by ELISA.

Address: Borys Shelest, MD, 6, Trinklera street, 61022 Kharkiv, Ukraine, e-mail: borisshelestt@gmail.com

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Results: Kaplan–Meier curves analysis showed significant association between increased MMP-9 and studied combined endpoint, $p = 0.0229$. The patients with MMP-9 levels over 201.7 ng/ml had significantly more endpoints. Univariate regression analysis found that MMP-9 was indicated as independent variable for unfavorable outcome with odds ratio (OR): 1.017, 95 confidence interval (CI) %: 1.001–1.033, $p = 0.037$. The multivariate logistic regression analysis showed that MMP-9 (OR: 1.019; 95% CI: 1.005–1.033; $p = 0.009$) together with fasting glucose (OR: 1.246; 95% CI: 1.010–1.538; $p = 0.040$) and leucocytes (OR: 0.751; 95% CI: 0.558–1.011; $p = 0.057$) remained significant independent predictors of combined endpoint in the studied subjects after adjusting other investigated confounders, age, sex, BMI, lipid and glucose profiles.

Conclusion: There is a significant relationship between adverse events and elevated MMP-9 levels in STEMI patients after PCI. MMP-9 was evinced as a highly sensitive marker for predicting the adverse course of the disease in patients with STEMI during the one-year follow-up.

Introduction

The discovery and further implementation of new evidence-based treatments for patients with acute myocardial infarction (AMI) with ST-segment elevation (STEMI) in recent decades have led to a sharp reduction in the risk of recurrent cardiovascular events and a significant improvement in prognosis.^{1–3} However, there is still an increased risk of future cardiovascular events, and it stimulates further searches for ways to optimize the prognosis for each patient who underwent AMI with ST-segment elevation and additional novel biomarkers have been intensively studied in recent years.^{4,5}

Identification of biomarkers that have prognostic value is necessary for a better risk stratification in ST-segment elevation AMI. There is evidence that ST-segment elevation AMI is predicted by a variety of factors, such as dyslipidemia, smoking, hypertension, diabetes, age, male gender, and plasma levels of natriuretic peptide (NUP) and possibly by the level of matrix metalloproteinase-9 (MMP-9).⁶ Among the studied biomarkers MMP-9 is unique because it is closely related to the development of atherosclerosis and plaque instability and ACS consequently.⁷ Moreover, MMP-9 plays a key role in heart attack healing, tissue repair, and remodeling of the extracellular matrix after AMI with ST-segment elevation.⁸

The search for new biomarkers continues in STEMI, although in recent years the spread of new prognostic biomarkers in acute coronary syndrome has been impressive, only a few have convincingly proven their clinical value. Only some of them are promising in this regard, their role in clinical decisions has not yet been determined, in particular, treatment decisions.⁹

At the same time, very limited experience has been accumulated on the possibility of clinical use of MMP-9 in patients with STEMI after percutaneous coronary intervention (PCI) as a prognostic marker (indicator) in a one-year perspective. While this issue is very important in terms of the management of such patients and improving their survival and post-infarction recovery. Accumulated preliminary data allow us to hypothesize that the level of MMP-9 may be a significant predictor of the course of the disease and the post STEMI patient's condition after PCI.

The study aimed to evaluate the prognostic role of MMP-9 in STEMI patients after successful revascularization within a 12-month follow-up period.

Methods

Study design

130 patients diagnosed with STEMI were enrolled in the study. Patients were hospitalized in the intensive care unit of the Government Institution “L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine” (GI “L.T.Mala NIT NAMSU”) during the first two days after PCI stenting of the infarct-dependent coronary artery, which was held at the Government Institution “V.T. Zaycev Institute of General and Urgent Surgery NAMSU”. 88 patients met the inclusion criteria and had no exclusion criteria out of 130 enrolled patients. Among these 88 subjects, 66 (75.0%) were men and 22 (25.0%) were women, with a mean age of 60.84 ± 9.68 years.

Patients were under supervision in a 12-month follow-up period. The combined endpoint was used and it included the occurrence of heart failure (HF), which required hospitalization, cardiovascular death, recurrent myocardial infarction, acute cerebrovascular event. The complicated course of the disease (STEMI) in the acute period was assessed by the severity of acute HF (II–III) according to Killip grade, cardiac arrhythmias (paroxysms of atrial fibrillation, ventricular tachycardia, transient atrio-ventricular block II–III). The diagnosis of STEMI was established in accordance with the guidelines of the European Society of Cardiology (2018).¹⁰ The diagnosis of HF was established according to current ESC Guidelines.¹¹ The diagnosis of arterial hypertension was established in accordance with the current recommendations of the 2018 ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension.¹²

Ethical disclosure

The research was conducted in accordance with the provisions of the Declaration of Helsinki, and the protocol of the study was agreed with the GI “L.T.Mala NIT NAMSU” Commission on Ethics and Deontology (Protocol № 6 of 30.05.2017). All patients signed informed consent to participate in the study accordingly to the latest GMP ICH procedures.

Inclusion and exclusion criteria

Criteria for inclusion in the study were: established AMI with ST-segment elevation, age >35 years, no contraindications to PCI, written informed consent to participate in the study, and restore coronary blood flow at the level

of TIMI III. Exclusion criteria were age >80, severe concomitant chronic diseases (anemia, chronic obstructive pulmonary disease, bronchial asthma, liver cirrhosis, chronic kidney disease with glomerular filtration rate <35 ml/min/1.73 m², bleeding), known malignancy, cancer, inability to understand the study and informed consent and vulnerable segments of the population.

Patient management

Patients underwent primary PCI using a bare-metal coronary stent (BMS). The TIMI scale was used to assess the restoration of blood flow in the infarct-dependent coronary artery. 88 patients were able to restore coronary blood flow at the level of TIMI III, they were selected for further study. All patients received drug therapy in accordance with current recommendations: enoxaparin in a therapeutic dose of 0.1 mg/kg body weight twice a day, acetylsalicylic acid 100 mg once a day, ticagrelor 90 mg twice a day, rosuvastatin 40 mg or atorvastatin 80 mg once a day, β -blockers (bisoprolol or nebivolol), ACE inhibitors (ramipril or enalapril).

Ultrasound examination of patients was performed within 48 hours after hospitalization using the Toshiba Aplio 500, model TUS-A500, with the evaluation of next parameters: end-diastolic volume (EDV) of the left ventricle (LV) and end-systolic volume (ESV) of the left ventricle, myocardial mass LV (MMLV), LV ejection fraction (EF), left atrial volume (LAV), LV diastolic dysfunction – maximum early diastolic filling rate E (m/s), maximum atrial diastolic filling rate A (m/s), their E/A ratio.

Determination of troponin I, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) was carried out by the enzymatic method. The level of MMP-9 was determined by enzyme-linked immunosorbent assay using a set of Human MMP reagents – ELISA KIT, Invitrogen, Austria. Blood for determination of MMP-9 in serum was taken on day 3 after STEMI beginning.

Statistical processing of the normality of the distribution was done by Kolmogorov–Smirnov and Lilliefors tests. Normally distributed variables are presented in the form of mean (M) and standard deviation (SD) and were compared using the Student's t-test, otherwise, variables with not normal distribution are presented as medians and interquartile ranges and compared using the Mann–Whitney test and qualitative variables are presented as percentages and compared by the chi-square test (χ^2). Multivariate analysis was used to indicate the factors associated with adverse events (combined endpoint). Univariate analysis was performed for the measured variables. Predictor variables that were statistically significant when evaluated individually against a combined endpoint were included in the forward stepwise multiple logistic analysis. The results were calculated and presented as β -coefficient, standard errors (SE), odds ratio (OR), and 95% confidence interval (CI) for each factor. The level of statistical significance was set to a $p < 0.05$. Statistical analysis was performed using the software package Statistica 8.0 (StatSoft Inc, USA), and MedCalc Statistical Software version 20.111 (Belgium).

Results

All studied patients were divided into two groups depending on the level of MMP-9 (median 201.7 ng/ml). The first group 1 included 44 patients with MMP-9 ≥ 201.7 ng/ml. The second one was with MMP-9 <201.7 ng/ml and included the same number of patients. The main clinical, socio-demographic, anamnestic, cardiac instrumental and laboratory parameters of these groups are presented in Table 1.

The participant subjects were predominantly male (75.0%) with a median age of 60.84 ± 9.68 years, with coexistent commonplace risk factor for STEMI like increased blood pressure/arterial hypertension (HTN) (86.4%), followed by smoking (48.9%). On the other hand type 2 diabetes mellitus (2TDM) and increased body mass index (BMI) (>30 kg/m²) were present only in 23.9% and 26.1% of patients consequently. It is essential to point out that all investigated indicators – age, blood pressure, glucose and lipid metabolic balance, smoking, HbA_{1c}, serum creatinine and echocardiographic parameters were not significantly different between the groups with higher MMP-9 and the lower MMP-9 one. The differences in the concentration of the studied biomarker –MMP-9 indicate the activation of MMP-9 synthesis due to acute myocardial damage, $p = 0.0001$. Comparing the localization of infarction and atherosclerotic vascular lesions in the groups, no statistically significant differences were found.

To identify the MMP-9 role in the development of adverse cardiovascular events (combined endpoint) and the relationship between the course of the disease and the concentration of MMP-9, a cumulative

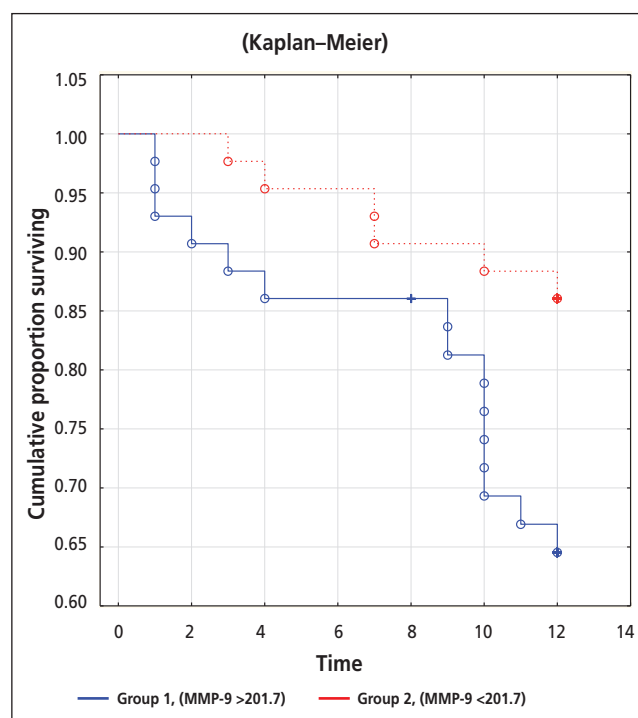


Fig. 1 – Kaplan–Meier curves showing the development of a combined endpoint in STEMI patients in a 12-month follow-up period depending on MMP-9 concentration.

Table 1 – Baseline characteristics of patients with STEMI depending on the level of MMP-9

Parameters	All patients (n = 88)	Group 1 MMP-9 $\geq$ median (n = 44)	Group 2 MMP-9 < median (n = 44)	χ^2 , p
Age, years (SD)	60.84 $\pm$ 9.68	60.68 $\pm$ 9.02	61.00 $\pm$ 10.39	0.878
Males, n (%)	66 (75.0)	32 (72.7)	34 (77.3)	0.623
Females, n (%)	22 (25.0)	12 (27.3)	10 (22.7)	
HTN, n (%)	76 (86.4)	38 (86.4)	38 (86.4)	1.0
2TDM, n (%)	21 (23.9)	12 (27.3)	9 (20.5)	0.617
HbA _{1c}	6.71 $\pm$ 2.01	6.89 $\pm$ 1.78	6.51 $\pm$ 1.99	0.678
Smoking, n (%)	43 (48.9)	20 (45.5)	23 (52.3)	0.522
BMI >30 kg/m ² , n (%)	23 (26.1)	8 (18.2)	15 (34.1)	0.0895
EDV LV, ml	123.40 $\pm$ 24.74	121.66 $\pm$ 26.02	125.01 $\pm$ 23.70	0.551
LVEF, %	46.63 $\pm$ 5.50	46.62 $\pm$ 4.64	46.63 $\pm$ 6.33	0.990
LAV	35.95 $\pm$ 9.26	35.81 $\pm$ 10.35	36.09 $\pm$ 8.17	0.896
E/E'	13.72 $\pm$ 4.89	12.67 $\pm$ 4.28	14.70 $\pm$ 5.29	0.120
TnI, ng/mL	7.56 [2.17–9.20]	7.45 [2.75–9.54]	6.81 [3.35–8.80]	0.362
TC, mmol/l	4.67 $\pm$ 1.23	4.70 $\pm$ 1.15	4.64 $\pm$ 1.31	0.844
HDL-C, mmol/l	1.03 $\pm$ 0.29	1.06 $\pm$ 0.37	1.00 $\pm$ 0.19	0.397
LDL-C, mmol/l	2.57 $\pm$ 1.08	2.69 $\pm$ 1.05	2.46 $\pm$ 1.11	0.358
TG, mmol/l	1.99 $\pm$ 1.11	1.81 $\pm$ 0.86	2.15 $\pm$ 1.28	0.164
Creatinine clearance, ml/min	77.08 $\pm$ 28.94	77.71 $\pm$ 29.08	76.46 $\pm$ 29.14	0.846
MMP-9, ng/ml	193.09 $\pm$ 59.32	238.25 $\pm$ 31.29	147.93 $\pm$ 44.34	0.0001

2TDM – type 2 diabetes mellitus; BMI – body mass index; E/E' – ratio between early mitral inflow velocity and mitral annular early diastolic velocity; EDV LV – end-diastolic volume of the left ventricle; HDL-C – high-density lipoprotein cholesterol; HTN – arterial hypertension; LAV – left atrium volume; LDL-C – low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; MMP-9 – matrix metalloproteinase 9; TC – total cholesterol; TG – triglycerides; TnI – troponin I.

Table 2 – Univariate and multivariate logistic analysis of factors influencing the development of adverse events after AMI with ST segment elevation

Parameter	β -coefficient	OR	95% CI	p
Univariate logistic analysis				
MMP-9, ng/ml	0.017	1.017	1.001–1.033	0.037
SAP, mm Hg	0.007	1.007	0.974–1.041	0.684
DAP, mm Hg	0.0113	1.011	0.936–1.093	0.775
BMI, kg/m ²	–0.138	0.871	0.716–1.060	0.168
Complications in the acute period	0.829	2.293	0.211–24.893	0.495
2TDM	0.883	2.419	0.310–18.867	0.399
Fasting glucose, mmol/l	0.193	1.213	0.927–1.586	0.159
EDV LV, ml	0.007	1.007	0.970–1.046	0.702
Leucocytes, $\times 10^9/l$	–0.299	0.741	0.524–1.049	0.091
TC, mmol/l	0.282	1.326	0.689–2.549	0.398
TG, mmol/l	–0.617	0.539	0.161–1.805	0.317
Creatinine, mmol/l	0.0163	1.016	0.998–1.041	0.177
Multivariate logistic analysis				
MMP-9, ng/ml	0.018	1.019	1.005–1.033	0.009
Fasting glucose, mmol/l	0.220	1.246	1.010–1.538	0.040
Leucocytes, $\times 10^9/l$	–0.287	0.751	0.558–1.011	0.057
Creatinine, mmol/l	0.012	1.012	0.997–1.029	0.180

2TDM – type 2 diabetes mellitus; BMI – body mass index; DAP – diastolic arterial pressure; EDV LV – end-diastolic volume of the left ventricle; MMP-9 – matrix metalloproteinase 9; SAP – systolic arterial pressure; TC – total cholesterol; TG – triglycerides.

Kaplan–Meier curves analysis was performed. And it showed significant association between increased MMP-9 and studied endpoint, F-criteria Cox, $F(12.30) = 2.848$, $p = 0.0099$ and Log-rank criteria, $p = 0.0229$ (Fig. 1). Significantly more endpoints were recorded in the patients with MMP-9 levels over 201.7 ng/ml, the vast majority of which were HF decompensation, which required hospitalization. Thus wise, increased MMP-9 concentrations showed a significant direct influence on unfavorable one-year prognosis in STEMI patients after PCI (Fig. 1).

Univariate with consequent multivariate logistic regression analyses were performed to investigate independent predictors of the adverse outcome presented as reaching the combined endpoint. After providing the univariate regression analysis it was found that MMP-9 was indicated as independent variable for unfavorable outcome OR: 1.017, 95 CI%: 1.001–1.033, $p = 0.037$. The multivariate logistic regression analysis showed that MMP-9 (OR: 1.019; 95% CI: 1.005–1.033; $p = 0.009$) together with fasting glucose (OR: 1.246; 95% CI: 1.010–1.538; $p = 0.040$) and leucocytes (OR: 0.751; 95% CI: 0.558–1.011; $p = 0.057$) remained significant independent predictors of combined endpoint (bad prognosis in patients with STEMI) in the studied subjects after adjusting other confounders as is shown in Table 2.

Discussion

We consider it important to point out that our investigation was focused on the MMP-9 role in prognosis in STEMI patients who underwent PCI and this issue was not previously fully described. It was established in our work that increased level of MMP-9 at admission in those patients is an important marker for further prognosis and a concentration of this enzyme over 201.7 ng/ml is prognostically unfavorable for the post-infarction one-year follow-up period. There are some works that presented the close results with accordant patients.^{13–15}

Even though MMP-9 belongs to the family of metalloproteinase and is considered to be widely studied, researchers continue to study the role of this enzyme in atherosclerosis, ACS, MI and other cardiovascular diseases (CVD).^{16–19}

The most recent studies continue to investigate the MMP-9 role as a player in pathways of myocardial injury and its place in the field of prognostic markers in cardiovascular pathology.^{20–23} And its role is under investigation not only in cardiovascular pathology, but also in chronic Chagas disease, ocular pathology, ischemic stroke, in diabetes.^{24–28} It is worth mentioning the work studying MMP-9 in renal diseases. For example, O. Zakiyanov et al. examined the dynamics of MMPs in patients with kidney disease.²⁹ The authors state that metalloproteinases are one of the key players in a variety of acute and chronic variants of kidney diseases. In their review, the authors argue that a deeper understanding of the MMPs' role in the development of renal pathology will open novel ideas for advanced therapeutic approaches. And we

consider that such a statement can be extrapolated to patients with CVD.

MMP-9 is regarded as a new effective marker and a possible therapeutic target for diseases based on atherosclerosis.^{30,31} In addition, MMP-9 also has potential as an indicator of the early stages of atherosclerotic damage, since an increase in the level of this substance most likely evidences destabilization of the atherosclerotic plaque and destruction of myocardial tissue, and also MMP-9 shows a significant prognostic value.¹⁴ MMP-9 levels increased in patients with acute myocardial infarction with ST-segment elevation and MMP-9 appeared to be a significant biomarker for the diagnosis of acute myocardial infarction with ST-segment elevation.³²

MMP-9 levels have been studied as a possible predictor of risk in patients with acute coronary syndrome (ACS) by G.M. Hamed and M.F. Fattah.³³ These investigators also took into account smoking status, blood pressure levels, lipid and glucose balance, markers of myocardial necrosis, and instrumental data. These authors showed that MMP-9 levels were higher in patients with ACS than in the stable CAD group. Importantly, this study demonstrated that STEMI has the highest levels of MMP-9. And this correlates with our data, that is, the MMP-9 values were significantly higher in patients who had an unfavorable outcome of the disease (recurrent ischemic attacks, congestive heart failure or death). However, their data pointed to an MMP-9 cut-off value of 3100 pg/mL as an indicator of the difference between MI and unstable angina (UA). Such a difference in numbers is most likely due to the various reagents that were used in the study, while the influence of the time of taking the material for the study is not excluded. This may suggest that further research is needed to elucidate the timing of peak MMP-9 levels in MI. The authors argue that MMP-9 can serve as an early marker that differentiates MI from UA, which we did not investigate in our work. At the same time, this work, like our study, showed the importance of MMP-9 as a predictor of an unfavorable outcome of MI.

Another recent work by D. Opincariu et al. dedicated to the role of MMP-9 in CVD showed the importance of the mentioned enzyme in predicting the course of STEMI.³⁴ At the same time, the MACE indicator for 1 year was chosen as the endpoint in their work. Authors showed that the most significant predictive indicators of MACE were elevated levels of MMP-9 along with I-CAM, V-CAM at 1-year follow-up. Interestingly, none of the other investigated parameters was found to be significant in this trial. The data by Opincariu et al. also correlate with our results. In general, D. Opincariu et al. emphasized that inflammatory biomarkers are more important and significant predictors for MACE than instrumental parameters such as LVEF. Noteworthy is their conclusion that a high level of MMP-9 (greater than 1155 ng/mL, AUC –0.786, $p < 0.001$) was the strongest predictor of STEMI recurrence even after adjusting for left ventricular ejection fraction, diabetes mellitus, acute phase complications, and other inflammatory biomarkers.

The recent work by H. Kook et al. from Korea in 2020 confirmed that MMP-9 is an important prognostic

marker in ACS.³⁵ However, in this paper, the authors improved the prediction model by adding soluble lectin-like oxidized low-density lipoprotein receptor-1, MMP-9, leukocyte levels, and peak levels of CK-MB to the discriminative model. They showed that such a complex model predicts plaque destabilization more effectively than single biomarkers in patients with ACS. However, their study was focused less on the long-term prognosis after STEMI and predominantly on the prognosis of plaque rupture in ACS, which distinguished this work from ours. However, in terms of studying the effect of MMP-9 on the pathogenesis of ACS, this work cannot be overestimated and it provides additional important information about the nature of the MMP-9 effects on the prognosis in STEMI patients. Their ROC analysis showed that MMP-9 ($p = 0.0274$) was a significant independent marker for separating the group with plaque rupture from the group without plaque rupture.³⁵ The mentioned work from Korea estimated that MMP-9, as an inflammatory biomarker, is actively involved in the process of destabilization of atherosclerotic plaques, and this is the basis for the development of both acute coronary syndrome and the development of subsequent adverse consequences in the post-infarction period.

Another important basic work for understanding our results can be considered a recent review by T. Li et al.³⁶ The authors note that increased production of MMP-9 most likely accentuates the destruction of the extracellular matrix and leads to destabilization of atherosclerotic plaques. Their work showed that high MMP-9 values are associated with greater plaque vulnerability. This review demonstrates that MMP-9 may be a predictor of destabilization of atherosclerotic plaques, and the further course of cardiovascular disease, that is in concordance with our results. The accumulated data make it possible to state that in addition to the fact that MMP-9 is a significant prognostic marker for predicting the course of atherosclerotic changes, this enzyme should also be investigated as a therapeutic target to improve the management and prognosis of such patients. It is also important that T. Li et al. noted the need to take into account the influence of additional factors on the relationship between MMP-9 and atherosclerotic lesions, such as ethnicity, MMP-9 gene polymorphism, and comorbidities.³⁶ Further large-scale works are still required to improve our understanding of the role and place of MMP-9 in CVD.

The work of G. Jordakieva et al. is newsworthy since it is somewhat similar in general meaning to our study.³⁷ The authors showed that the MMP-9 values are significant in the prediction of short-term (30-day) mortality, and this was applied more specifically to patients with heart disease. However, their study design had 120 patients who were examined in the intensive care unit of the internal medicine department, which, in addition to cardiac essential patients, also included other critically ill patients. This was very different from our work since we investigated only STEMI patients after PCI. At the same time, G. Jordakieva et al. obtained results also showed that high MMP-9 values may be important prognostic markers, as well as potential therapeutic targets in systemic inflammation and the intensive care unit setting.³⁷

This testifies in favor of the fact that the increased MMP-9 expression is an important pathogenetic link in various critical conditions and especially in acute cardiovascular conditions, such as STEMI or ACS.

There are several possible explanations for the association between elevated MMP-9 levels and subsequent adverse events after STEMI. Coronary atherosclerotic plaques are the pathological basis of coronary heart disease. From these considerations, we assume that the key reason is that MMP-9 is closely associated with the rupture of atherosclerotic plaques. An increased level of this enzyme reduces the fibrous cover of the plaque due to the degradation of the matrix of the fibrous cover of the atheromatous plaque, which leads to the formation and rupture of unstable plaques and the next clinical cardiovascular events. We consider that the increased synthesis of MMP-9 in the lesions in patients with STEMI is likely to suppress the rate of formation of a stable plaque and this is what affects the further course of the disease and the development of adverse events. High levels of MMP-9 support low gradient inflammation, which is the pathogenetic basis for the presence of unstable plaques in post-infarction patients.

The presented study had several limitations. First, it is worth mentioning that the study had the compact sample size to state definitive conclusions. Second, there were no series of measurements of MMP-9, to estimate the evolution of its minimum – maximum ranges. In addition, only one clinical site was involved. Also, the limitation is that predominantly males were among the investigated subjects. Additionally, we evaluated only exactly STEMI patients after PCI without any other treatment, on the other hand, this narrow target group together with appropriate statistical methods doing our best to avoid these possible biases. It can be considered as a limitation that we used a combined (composite) endpoint as an outcome, including some conditions but not an exact firm (primary) endpoint. Therewithal, the relationship between the obtained 12-month treatment and MMP-9 levels and the final outcome was not assessed. At the same time, we consider a trial's strength that it was carried out under conditions of routine clinical practice and granted us to gain real relevant data.

Our consideration is that further studies are required on the role of MMP-9 in the after PCI STEMI patients' prognosis and its pathogenetic role needs more deep investigations. Further sizable, multicenter trials are needed to confirm obtained relation between MMP-9 and prognosis in STEMI patients.

Conclusion

Based on the studied data, it can be assumed that there is a significant relationship between adverse events and elevated MMP-9 levels in STEMI patients after PCI. MMP-9 was evinced as a highly sensitive marker for predicting the adverse course of the disease in patients with STEMI during the one-year follow-up. Future investigations are needed to estimate whether MMP-9 is associated with myocardial infarction pathogenesis

and prognosis, revealed as a protective mechanism response, or unconcerned in the STEMI pathophysiological processes. Elucidating its exact and valid mechanism promisingly can lead to increasing in STEMI patients' survival and recovery and better management.

Conflict of interest

All authors declare that there is no conflict of interest.

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Ethical statement

The study was approved by the Ethics Committee of Government Institution "L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine", Kharkiv, Ukraine (Protocol № 6 of 30.05.2017).

Informed consent

Informed consent was signed by all participants accordingly to GMP ICH procedures, no vulnerable subjects were enrolled.

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Is the microRNA-221/222 Cluster Ushering in a New Age of Cardiovascular Diseases?

Lutfu Askin, Okan Tanriverdi

Department of Cardiology, Adiyaman Education and Research Hospital, Adiyaman, Turkey

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SOUHRN

Kromě regulace genové exprese regulují krátké nekódující molekuly RNA (microR, miR) rychlost degradace a translace informační RNA (messenger RNA). Krátké nekódující molekuly miR vykazují vysokou expresi v kardiovaskulárním (KV) systému, což ukazuje na jejich významnou úlohu ve vaskulárním zdraví. Proces vzniku a rozvoje aterosklerózy je dáván do souvislosti s miR-221 a -222. Krátké nekódující molekuly miR-221/222 působí proti vzniku stenóz a mohou potenciálně sloužit jako marker remodelace myokardu. Přesto ještě potrvá dlouho, než bude možno považovat molekuly miR-221/222 jako možný cíl léčby. Identifikace, ověření a poznání funkcí genových cílů, všechny tyto procesy jsou nesmírně důležité.

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ABSTRACT

In addition to regulating gene expression, microRNAs (MiRs) regulate messenger RNA degradation and translation rates. MiRs have a high expression in the cardiovascular (CV) system, indicating an important role in vascular health. The atherosclerotic process has been related to miRs-221 and -222. MiRs-221/222 possess anti-stenotic activity. MiR-221/222 may potentially serve as a marker for myocardial remodeling. There is still a long way yet before miRs-221/222 can be recognized as a potential therapeutic target. Identification, validation, and understanding of the function of gene targets are all critical.

Introduction

MicroRNAs (miRs) are endogenous non-coding RNAs that influence gene expression via regulating messenger RNA degradation and translation.¹ So far, over 1,000 miRs have been identified and described.² Some miRs impact the production of other miRs, leading in the establishment of complex regulatory networks. MiRs encode most mammalian proteins, and more genes may be regulated indirectly. As a result, it's unsurprising that miRs may play a critical role in a variety of biological activities at the molecular level.³ This review aims to investigate the link between miR-221/222 and cardiovascular diseases (CVDs).

Vascular system and miR-221/222

The high level of miRs directly affects the vascular system.³⁻⁶ Ordinary conditions, the endothelium is responsible for maintaining vascular homeostasis. Endothelial dysfunction is a critical threshold for atherosclerosis.⁷

Almost all of the coagulation cascades are associated with miRs. MiRs have been linked to pro-atherogenic pathways.^{8,9} Blood vessel homeostasis requires angiogenesis, which is involved in atherosclerosis. Several miRs appear to be angiogenic or anti-angiogenic.¹⁰

MiRs-221/222 play a vital role in maintaining vascular homeostasis.¹¹ For the miRs-221/222, Celic et al. summarized the known evidence on their characteristics and possible clinical applications.¹² Clinically, it is critical to evaluate the possibility that miR 221/222 may be therapeutic in cardiovascular disease and cancer.

Obesity and diabetes result in decreased miR 221 levels,¹³ while severely obese patients had higher levels of both miRs.¹⁴ MiR-221 was shown to be overexpressed in the serum of diabetics with microvascular problems.¹⁵ Those with metabolic syndrome had higher circulating miR-221 levels.¹⁶ Low miR-221 levels are caused by strokes and atherosclerosis.¹⁷ In diabetics with coronary artery bypass grafts, serum miR-221 was elevated and corrected by metformin.¹⁸ Carotid atherosclerosis patients also showed higher miR-221 levels.¹⁹ In contrast, atherosclero-

Address: Lutfu Askin, MD, Adiyaman Education and Research Hospital Cardiology Department, 2230 Adiyaman, Turkey, e-mail: lutfuaskin23@gmail.com

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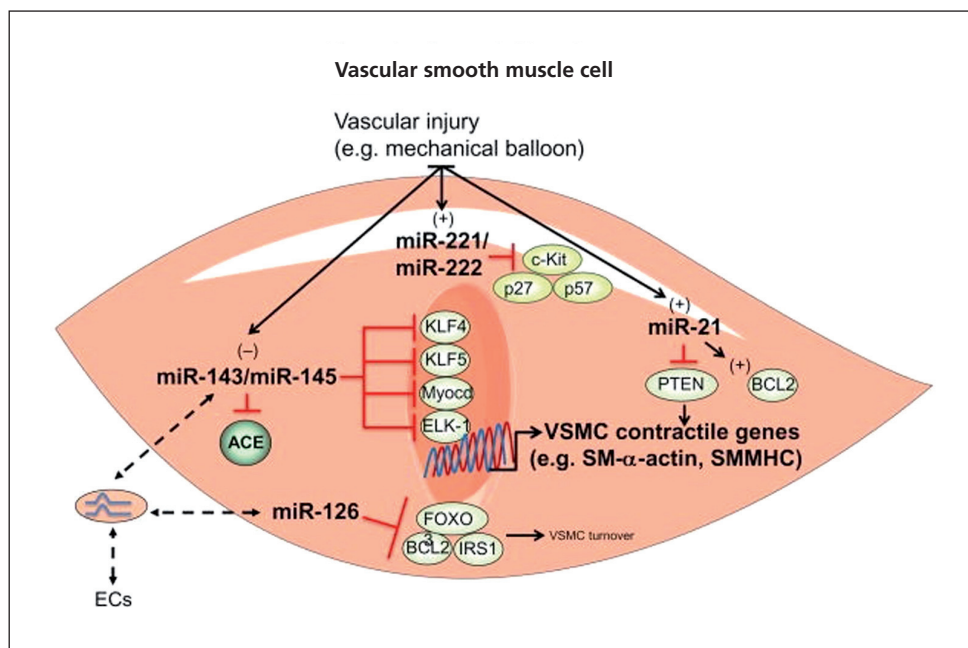


Fig. 1 – MiRs-221 and -222 and their role in atherosclerosis.

sis obliterans patients had lower serum miR-221.²⁰ Thus, miR-221/222 may be utilized to assess CV risk. But more research is needed to validate this.

MiRs-221 and -222 have been linked to the atherosclerotic processes (Fig. 1).^{21,22} Atherosclerotic lesions increase vascular calcification risk.^{23,24} As a result, alteration of miRs-221/222 activity may be helpful in illness follow-up.²⁵

Studies to halt the growth and migration of endothelial cells are continuing. The conflicting effects of this may be clinically relevant in patients with CAD.²⁶ Cardiomyocytes transduced with lentivirus precursors of miR-21, -24, and -221 lived substantially longer after transplantation in mice.²⁷ They control cardiac remodeling and the migration of progenitor cells.²⁸

Inhibitors or mimics of miRs may improve or raise miR activity in non-target tissues. The suppression of P27's antiproliferative action promotes cancer. For cell-specific interactions, adeno-associated viruses are preferred due to their inherent serotype diversity and organ-specific cell receptor tropism.²⁹

MicroRNA-221/222 in heart failure (HF)

MiR-221-3p and miR-222-3p (miR-221/222) are differentially regulated in human and mouse cardiomyopathies.³⁰ The miR-221/222 family has not been implicated in the pathophysiology of pressure overload-induced heart dysfunction. Studies on miR-221/222 in the heart have relied on cardiomyocyte-specific transgenic mice, which ignore endogenous miRNA levels and cell source(s).³¹ Other than the cardiac effect, miR-221 and miR-222 have been related to renal and liver fibrosis.³²

Recently, miR-221 and miR-222 were found upregulated in cardiac cells. HF is self-induced with increased fibrosis, reduced autophagy, and cardiomyocyte dysfunction in mice.³³ Mice with inducible cardiomyocyte miR-222

production were safeguarded against ischemia/reperfusion damage. Upregulation of miR-221 or miR-222 in cardiomyocytes causes cardiac remodeling, probably due to their impact on cardiomyocyte function and survival.³⁴

MiRNA-221/222 family is downregulated by TGF- β and pressure overload to enable fibroblast activation and fibrosis formation. In vivo administration of miRNA-221/222 mimics may restore TGF- β signaling in cardiac fibroblasts. Excessive miR-221/222 expression induces aberrant distribution in cardiac cells. MiR-221/222 may also be as an indicator of myocardial remodeling. A recent study indicates that decreased miR-222 plasma levels may be a risk of atrial fibrillation. Given that miR-221 is associated with myocardial collagen volume fraction in aortic valve stenosis patients, miR-221 and miR-222 may be used as biomarkers for myocardial fibrosis.³⁵

Other situations

Inflammatory reactions are controlled by the miR-221/222. As a result of its suppression, viral myocarditis is more likely to result in increased inflammation and cardiac damage.³⁶ In human umbilical vein endothelial cells (HUVECs), miR-221/222 inhibited Ets-1 and p21 expression. MiR-221/222 overexpression may protect HUVECs against ox-LDL-induced apoptosis. Qin et al.³⁷ thought that if miRNAs' functions in endothelial apoptosis and atherosclerosis are understood, they will be viable therapeutic targets.

Conclusion

MiRs-221/222 have diverse roles in many tissues. The evidence on their involvement in CVD origin and development is mounting. The current results support their

potential application as cardiac biomarkers. They may be useful for interfering with miRNA-regulated circuits. These may need cell-targeting. It will take time to establish miRs-221/222 as therapeutically relevant targets. Their gene targets need to be characterized and validated, and their roles understood.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Zkrácená informace • LEQVIO 284 mg injekční roztok v předplněné injekční stříkačce • **Složení:** Jedna předplněná injekční stříkačka obsahuje inkisiranum natricum odpovídající inkisiranum 284 mg v 1,5 ml roztoku. **Indikace:** Přípravek Leqvio je indikován u dospělých s primární hypercholesterolemií (heterozygotní familiární a nefamiliární) nebo smíšenou dyslipidemií jako doplněk k dietním opatřením: v kombinaci se statinem nebo statinem v kombinaci s jinými přípravky snižujícími hladinu lipidů u pacientů neschopných dosáhnout cílů pro LDL-C při maximální tolerované dávce statinu, nebo samostatně nebo v kombinaci s jinými přípravky snižujícími hladinu lipidů u pacientů trpících nesnášenlivostí statinu nebo u nichž je statin kontraindikován. **Dávkování:** Doporučená dávka je 284 mg inkisiranu podávaná jako jednorázová subkutánní injekce: počáteční dávka, další po 3 měsících a poté každých 6 měsíců. Pokud je plánovaná dávka opožděna o méně než 3 měsíce, má být inkisiran podán a dávkování má pokračovat podle pacientova původního schématu. Pokud je plánovaná dávka opožděna o více než 3 měsíce, má být zahájen nový dávkovací režim – má být podána počáteční dávka inkisiranu, další po 3 měsících a poté každých 6 měsíců. Inkisiran lze podávat okamžitě po poslední dávce monoklonální protilátky inhibující PCSK9. Pro udržení snížení LDL-C se doporučuje, aby byl inkisiran podán do 2 týdnů po poslední dávce monoklonální protilátky inhibující PCSK9. **Kontraindikace:** Hypersenzitivita na léčivou látku nebo na kteroukoli pomocnou látku. **Zvláštní upozornění/varování:** Účinek hemodialýzy na farmakokinetiku inkisiranu nebyl studován. Vzhledem k tomu, že inkisiran je vylučován ledvinami, nemá se hemodialýza provádět po dobu nejméně 72 hodin od podání inkisiranu. **Interakce:** Inkisiran není substrátem pro běžné transportéry léčiv, a přestože nebyly provedeny studie *in vitro*, nepředpokládá se, že bude substrátem pro cytochrom P450. Inkisiran není inhibítor nebo induktor enzymů cytochromu P450 nebo běžných transportérů léčiv. Proto se neočekává, že by inkisiran měl klinicky významné interakce s jinými léčivými přípravky. Na základě omezených dostupných údajů nejsou očekávány klinicky významné interakce s atorvastatinem, rosuvastatinem nebo jinými statiny. **Těhotenství a kojení:** Údaje o podávání inkisiranu těhotným ženám jsou omezené nebo nejsou k dispozici. Podávání inkisiranu v těhotenství se z preventivních důvodů nedoporučuje. Není známo, zda se inkisiran vylučuje do lidského mateřského mléka. Riziko pro kojené novorozence/děti nelze vyloučit. **Nežádoucí účinky:** Časté: Reakce v místě vpichu. **Podmínky uchovávání:** Chraňte před mrazem. **Dostupné lékové formy/velikosti balení:** 1,5 ml roztoku v předplněné injekční stříkačce (sklo třídy I) s pistovou zátkou (brombutyl, fluorotekem potažená pryž) s jehlou a pevným krytem jehly. Obsahuje jednu předplněnou injekční stříkačku. **Poznámka:** Dříve než lék předepíšete, přečtěte si pečlivě úplnou informaci o přípravku. **Reg. č.:** EU/1/20/1494/001 **Datum registrace:** 9.12.2020 **Datum poslední revize textu SPC:** 24.03.2022 **Držitel rozhodnutí o registraci:** Novartis Europharm Limited, Vista Building, Elm Park, Merion Road, Dublin 4, Irsko. *Výdej přípravku je vázán na lékařský předpis, přípravek není hrazen z prostředků veřejného zdravotního pojištění.*

LITERATURA: 1. SPC Leqvio 284 mg injekční roztok v předplněné injekční stříkačce, datum poslední revize 24.03.2022. 2. SUKL, www.sukl.cz.

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Inclisiran: new era of lipid-lowering therapy?

Jan Beneš

Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague

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SOUHRN

Dyslipidemie je nejčastější metabolickou poruchou v západní společnosti a hlavním rizikovým faktorem pro rozvoj ischemické choroby srdeční (ICHS). Léčba dyslipidemie je stále nedostatečná a doporučené cíle LDL cholesterolu jsou dosahovány jen u malé části pacientů. Nejdůležitější skupinou léků pro léčbu dyslipidemie jsou statiny. Ačkoli jde zřejmě o jednu z nejbezpečnějších lékových skupin vůbec, terapie statiny může vést ke svalovým bolestem a ke zvýšenému riziku rozvoje diabetes mellitus (DM). Přerušeni nebo ukončení léčby statiny je v klinické praxi časté, statiny jsou také často předmětem negativních sdělení v médiích. Inclisiran je modifikovaný oligonukleotid fungující na principu interference RNA. Inhibuje translaci mRNA pro protein konvertázu subtilisin/kexin typu 9 (PCSK9), což vede k dlouhodobému poklesu koncentrace LDL cholesterolu. Účinek inclisiranu se snižuje o přibližně 2 % měsíčně, takže efekt jediné dávky trvá zhruba dva roky. Při podávání jedenkrát za šest měsíců vede terapie tímto lékem k poklesu LDL cholesterolu o 50–55 %, u vybraných pacientů potom až o 65 %. Terapie inclisiranem není spojena se změnou počtu krevních destiček, lymfocytů, monocytů nebo neutrofilů, nevede ke změnám koncentrací cirkulujících cytokinů tumor nekrotizujícího faktoru alfa (TNF α) nebo interleukinu 6 (IL-6) a není spojena s indukcí tvorby protilátek proti tomuto léku. Nežádoucí reakce v místě vpichu tak zůstávají jediným relevantním nežádoucím účinkem této léčby. Inclisiran tak získává potenciál stát se široce preskribovaným lékem, který výrazně přispěje k léčbě dyslipidemie a v konečném důsledku povede ke snížení incidence a prevalence ICHS.

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ABSTRACT

Dyslipidemia is the most frequent metabolic abnormality in western world population and a major risk factor for coronary artery disease (CAD) development. Dyslipidemia treatment is still insufficient and achieving target LDL-level infrequent. Statins are a cornerstone of dyslipidemia management. Although statins are one of the safest drugs on the market, statin therapy can be associated with muscle symptoms and increased risk of DM development. Statin discontinuation is frequent, often driven by negative media coverage. Inclisiran is a therapeutic oligonucleotide that employs RNA interference and inhibits the translation of PCSK9-mRNA leading to long-lasting LDL-cholesterol lowering. LDL-cholesterol-lowering effect of inclisiran is reversed at the rate of approximately 2% per month, so the effect of a single dose persists up to approximately two years. When administered once every six months, inclisiran therapy decreases the level circulating LDL-cholesterol by 50–55% and up to 65% in selected patient populations.

Inclisiran therapy is not associated with alterations in platelet count, blood lymphocyte, monocyte or neutrophil count, does not cause alterations in blood TNF-alpha or IL-6 concentrations and does not induce relevant anti-drug antibodies. The only relevant side effect is an adverse reaction at the injection site. Inclisiran thus has the potential to become widely prescribed drug that will greatly contribute to dyslipidemia management and further decrease of CAD incidence.

Keywords:

Atherosclerosis

Coronary artery disease

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Inclisiran

LDL-cholesterol

Address: Jan Beneš, MD, Ph.D., Department of Cardiology, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, 140 21 Prague 4,

e-mail: jan.benes@ikem.cz

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Despite a significant decline in CAD incidence,^{1,2} CAD still remains a major public health issue and was (until the pandemic of covid-19) the most frequent cause of death.

Dyslipidemia

Dyslipidemia is a major risk factor for CAD development.³ Dyslipidemia (defined as total cholesterol ≥ 5 mmol/L or HDL-cholesterol < 1.0 mmol/L for males or < 1.2 mmol/L for females or LDL-cholesterol ≥ 3 mmol/L or triacylglycerols ≥ 1.7 mmol/L) was present in 81.0% of males and 70.6% of females with the increase with advancing age.⁴ In patients between 55–65 years, dyslipidemia was present in almost 90% of population. At the same time, only a small percentage of population (12.7% of males and 8.5% of females) was treated with lipid-lowering agents. ESC Guidelines for the management of dyslipidemias published and ESC Guidelines on cardiovascular disease prevention propose that in patients with established atherosclerotic cardiovascular disease (ASCVD) or at a very high risk, LDL-C reduction $\geq 50\%$ and a target level < 1.4 mmol/L are to be achieved.^{5,6} This is in sharp contrast with real-world evidence; according to latest EURASPIRE V study, 71% of patients after coronary event had LDL-C ≥ 1.8 mmol/L.⁷

These unsatisfactory results were further confirmed by recently published study showing that only 17% and 22% patients with a very high risk in primary and secondary prevention, respectively, met the new 2019 goals.⁸

Dyslipidemia treatment

Statins are cornerstone of dyslipidemia management. Statin therapy is extremely potent, a large meta-analysis of 26 statin trials showed that a reduction of 1 mmol/L in LDL-cholesterol over 5 years reduced major vascular events by 22%, CHD death by 20% and all-cause mortality by 10%.⁹ When ezetimibe and PCSK9-inhibitors were taken into account as well, each 1 mmol/L reduction in LDL-cholesterol was associated with a 19% relative risk (RR) reduction for major vascular events.¹⁰ Although statins are one of the safest drug groups, several issues remain. Statin-associated muscle symptoms (SAMS) are the most commonly reported adverse effects of statins (10–30% of patients in observational studies),¹¹ which is in sharp contrast with randomized trials that report only minimal differences in muscle symptoms occurrence.¹² Statin-induced necrotizing autoimmune myopathy (SINAM) is the most serious but fortunately extremely rare side effect of statin therapy that is independent of the type and duration of statin use.¹³ High-dose statin use is associated with higher risk of diabetes development; a finding first observed in the landmark JUPITER study (+25% increased risk for newly diagnosed diabetes compared to placebo)¹⁴ and further confirmed in other studies (12% increase in pooled risk).^{13,15–19} Importantly, the benefit of statin therapy exceeded the risk of new-onset DM. Nevertheless, statin discontinuation is high and is substantially driven by a negative media coverage about statins.²⁰ However, even in the primary prevention, a statin discontinuation is associated with markedly increased risk of admission for cardiovascular events.²¹

RNA interference

The fact that double-strand RNA (dsRNA) is able to induce post-transcriptional gene silencing was discovered in 1998.²² For this crucial discovery, Craig Mello and Andrew Fire received a Nobel Prize in 2006. DsRNA originate in the nucleus as primary microRNA (pri-miRNA). Pri-miRNA is cleaved by complex of two proteins (Drosha-DGCR8) to produced short hairpin RNAs (shRNAs) called pre-miRNA (about 30 bp long). Pre-miRNA is bound and transported into the cytoplasm by exportin-5. In cytoplasm, pre-miRNA binds with two other proteins Dicer and TAR RNA-binding protein (TRBP). Dicer cleaves the terminal loop of pre-miRNA and induces the formation of an RNA-induced silencing complex (RISC)-loading complex with other proteins called Argonaute (Ago1–Ago4) proteins. Double-strand RNA is disentangled and antisense guide strand is selected and loaded into Ago complex, passenger (sense) strand is discarded.

The mature RISC then regulates gene expression by inhibiting mRNA translation.

This naturally occurring process can be mimicked by artificially-delivered dsRNA – small interfering RNAs (siRNAs). They enter the cytosol by endocytosis and directly interact with cytosolic enzymes Dicer and TRBP, undergo strand selection, and produce mature RISC. The selective gene silencing is thus induced (Fig. 1). The loaded RISC has a remarkably long half-life and is extremely potent; as few as 100–200 loaded RISC complexes are able to sufficiently eliminate the expression of a target gene.

RNAi in clinical practice

First clinical trials with unmodified siRNAs resulted in immune-related toxicity, poor stability due to exonuclease, and endonuclease degradation and thus poor effect on RNA inhibition.²³ It took several years of further experiments before appropriate modifications were developed before siRNA became ready for clinical trials. RNAi drugs were introduced in routine clinical medicine on 10th August 2018 when US Food and Drug Administration (FDA) approved patisiran for the treatment of hereditary transthyretin amyloidosis (hATTR) with polyneuropathy.

Inclisiran

Inclisiran is a chemically modified dsRNA that targets 3'-UTR (untranslated region) of PCSK9 mRNA, which is degraded. This leads to lower amount of PCSK9 protein, an increase in the number of LDL-receptors and reduced LDL-cholesterol level (Fig. 2). Compared to native ds-mRNA, inclisiran underwent five modification of the molecule – three modifications are made in the guide strand (fosfothionate, 2'-fluoro-RNA, 2'-O-methyl-RNA), one modification of the passenger strand (2'-deoxythymidine) and the conjugation of 3'-end of the passenger strand to a triantennary N-acetylgalaktosamine (GalNAc, Fig. 3). The combination of the 2'-fluoro and 2'-O-methyl modification greatly improves dsRNA stability. Deoxythymidine

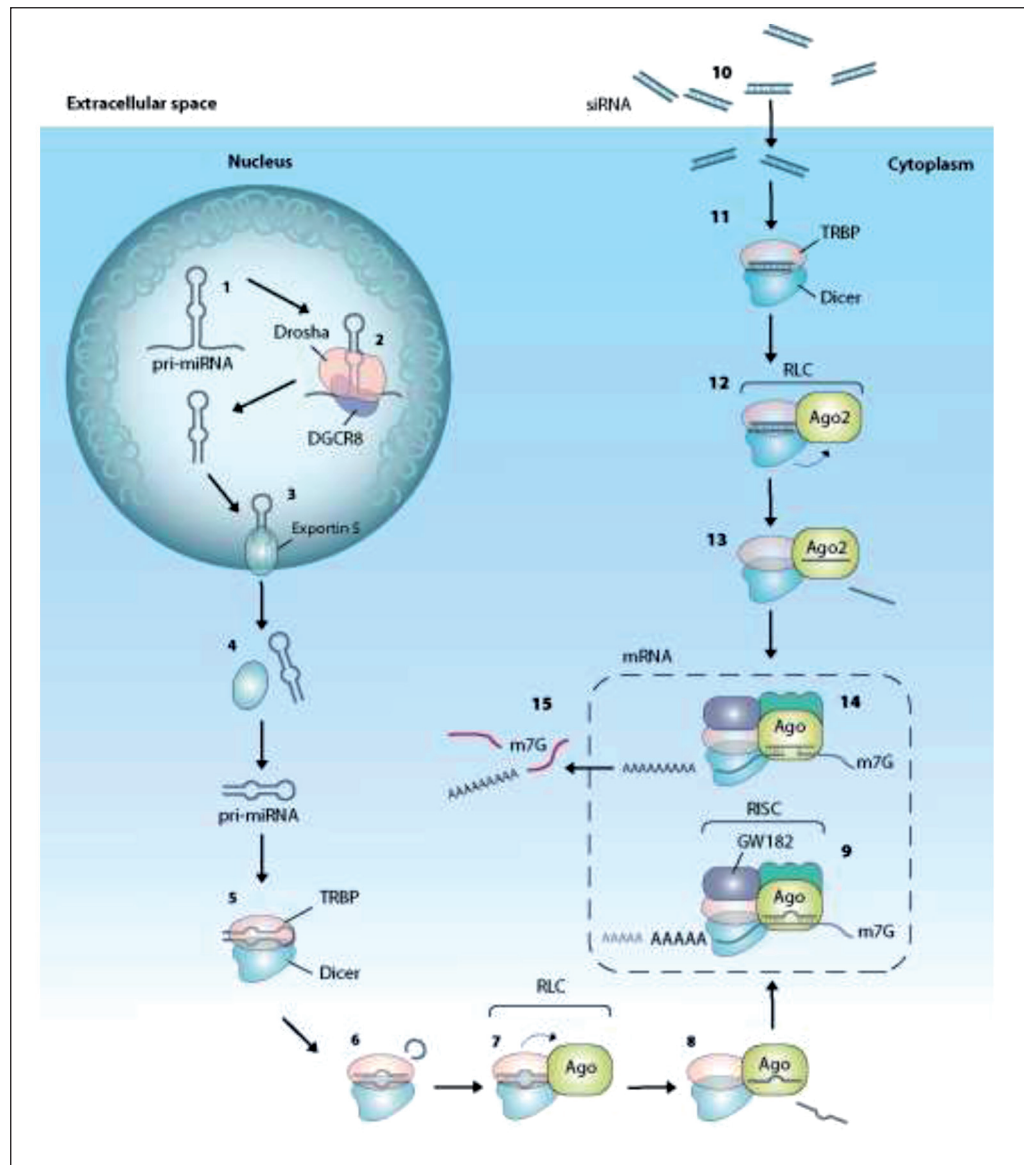


Fig. 1 – RNA silencing process. 1) Primary microRNA (miRNA) originate in the nucleus and (2) are cleaved by the Drosha-DGCR8 complex to produce pre-miRNA. (3) Pre-miRNA is bound by exportin-5 and transported into the cytoplasm (4) where it is released. (5) Subsequently, it is bound by proteins called Dicer and TAR RNA-binding protein (TRBP). (6) Dicer cleaves the terminal loop of pre-miRNA and (7) other protein (Ago1-Ago4) joins the pre-miRNA-Dicer-TRBP complex, which gives rise to RNA-induced silencing complex (RISC). (8) Antisense (guide) strand is selected and integrated within RISC, sense (passenger) strand is discarded. (9) The mature RISC regulates gene expression by inhibiting mRNA translation. Other proteins (GW182) are involved as well. The naturally occurring process can be mimicked by artificially delivered siRNAs. (10) Synthetic small interfering RNAs (siRNAs) enter the cell via endocytosis and (11) directly interacts with RNAi enzymes (Dicer and TRBP). (12) RISC-loading complex is created and (13) the proper (antisense) strand is selected giving rise to mature RISC. (14) siRNA guide strands have usually 100% complementarity to the target mRNA and thus induce long-lasting and selectively-targeted gene silencing. Adapted according to ³⁷.

incorporated in the middle of the sense strand improves guide-strand loading and accelerates the release and degradation of the passenger strand. Triantennary GalNAc attached to the 3'-end of the inclisiran molecule targets inclisiran to hepatocytes as this conjugate is specifically recognized by the asialoglycoprotein receptor (ASGPR) that is abundantly expressed on the surface of liver hepatocytes.

The majority of applied inclisiran is accumulated in hepatocytes, but only a relatively small fraction becomes immediately loaded into RISC and thus becomes biologi-

cally active. However, loaded RISC has a half-life of many weeks and inclisiran trapped intracellularly in endosomes function as intracellular depo of the drug. LDL cholesterol-lowering effect of inclisiran is reversed at the rate of approximately 2% per month, so it can persist up to approximately two years.^{24,25}

This mechanism of action is completely different than contemporarily used monoclonal antibodies (evolocumab, alirocumab). These drugs act extracellularly where they block existing and secreted PCSK9. On the contrary, inclisiran degrades mRNA for PCSK9

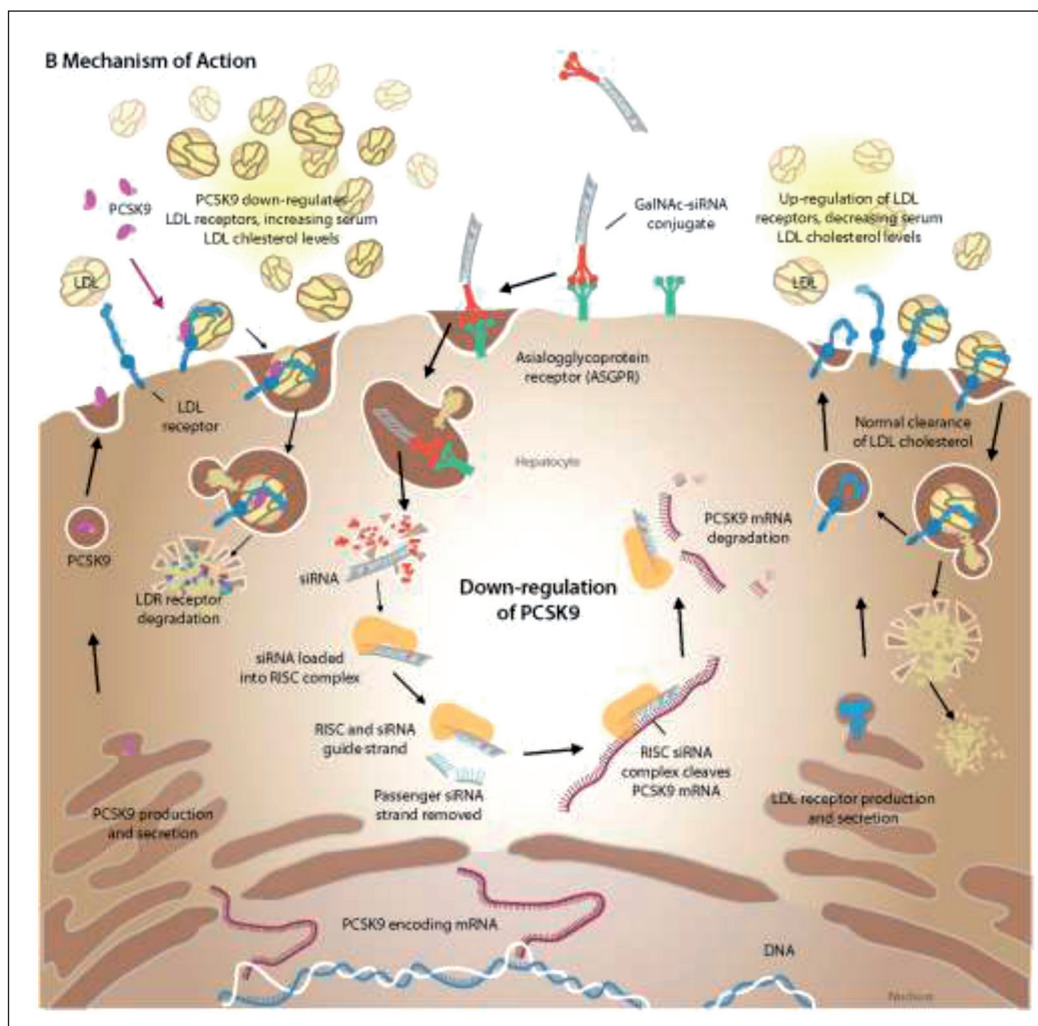


Fig. 2. – Inclisiran mechanism of action. Inclisiran targets 3'-untranslated region of PCSK9 mRNA resulting in its degradation. Lower amount of PCSK9 protein is produced leading to lower degradation of LDL-receptors. This ultimately leads to lower plasmatic LDL-cholesterol level.

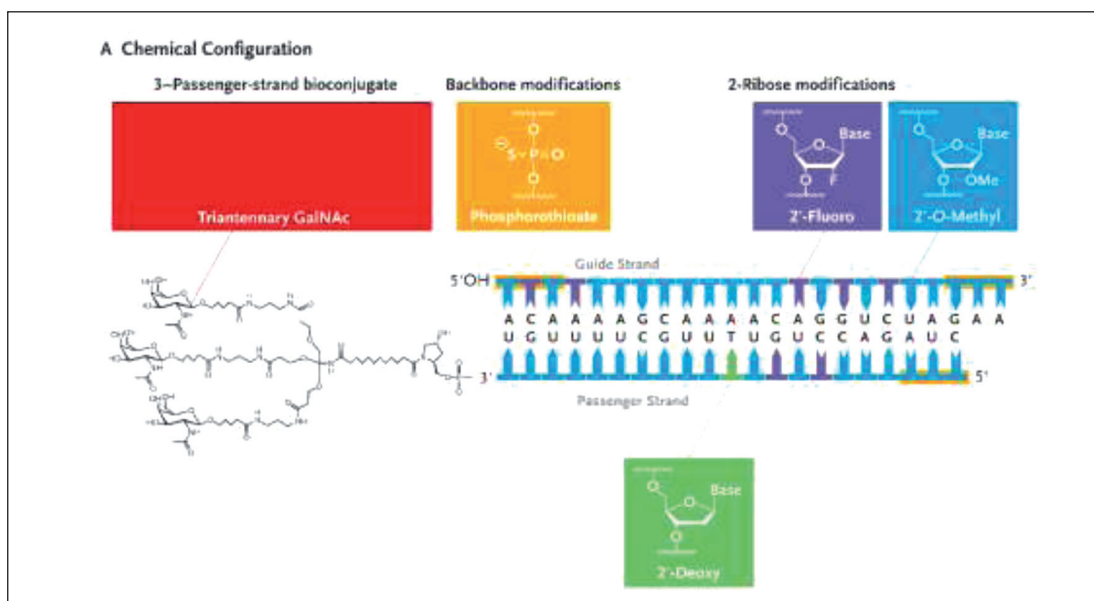


Fig. 3 – Inclisiran: modifications of native dsRNA molecule. Five modifications have been made in inclisiran molecule compared to the native ds-RNA. Three modifications have been made in the guide strand (fosfothionate, 2'-fluoro, 2'-O-methyl), one modification of the passenger strand (2'-deoxythimidine) and the conjugation of 3'-end of the passenger strand to a triantennary N-acetylglaktosamine (GalNAc).

Table 1 – Comparison of inclisiran and PCSK9-inhibitors

	PCSK9-inhibitor antibodies (alirocumab, evolocumab)	RNAi (inclisiran)
Site of action	Extracellularly	Intracellularly
Mechanism	Binds to PCSK9 on the cell surface and thus inhibits PCSK9-mediated degradation of LDL receptor	Inhibits translation of PCSK9 mRNA
Molecular size	Large, monoclonal antibody	Small, oligonucleotide
Dosage	Every 2–4 weeks	Once in 6 months
Efficacy	Decrease in LDL-cholesterol by 55–75%	Decrease in LDL-cholesterol by 50–55% (up to 65% in selected patient populations)
Side-effects	Nasopharyngitis (7.4%), upper respiratory tract infections (4.6%), backache (4.4%), arthralgia (3.9%), flu-like symptoms (3.2%), adverse reactions at the injection site (2.2%)	Adverse reactions at the injection site (8.4%)
Storage	Refrigerator (2–8 °C)	Room temperature
Who applies	Patient himself	Physician

According to Repatha³⁸, Praluent³⁹ and Leqvio³⁶ product characteristics.

and thus prevents the PCSK9 synthesis. Main differences between inclisiran and PCSK9i are summarized in Table 1.

Clinical trials with inclisiran

Inclisiran reduces the level of LDL-cholesterol in healthy volunteers²⁶ as well as in patients with high risk of cardiovascular disease with elevated LDL cholesterol.²⁴ The effect on PCSK9 and LDL cholesterol levels were dose-dependent, two doses of inclisiran 300 mg s.c. (given at day 1 and day 90) lead to 52.6% decrease in LDL-cholesterol at day 180. Serious adverse events were rare and unrelated to inclisiran application; injection-site reactions occurred in 5% of patients that received inclisiran. ORION-10 and ORION-11²⁷ are two largest studies with inclisiran published so far, these studies enrolled patients with established atherosclerotic cardiovascular disease (100% of patients in ORION-10 and 87% or patients in ORION-11) or atherosclerotic cardiovascular disease equivalent (13% of patients in ORION-11). In both these studies, 300 mg of inclisiran was administered on day 1, 90 and every 6 months thereafter over a period of 540 days. In both trials, LDL cholesterol was reduced by approximately 50% from day 90 until the end of study. Together with LDL reduction, inclisiran also lowered levels of triglycerides, lipoprotein(a) and increased HDL-cholesterol. Inclisiran therapy was not associated with any laboratory abnormality concerning liver and kidney function, C-reactive protein level and platelet count. Anti-drug antibodies were detected in 2.0 and 2.5% of the samples from inclisiran-treated patients. The frequency of positive samples was similar between pretreatment and post-treatment samples, was in low titer and was not associated with changes in any significant clinical or pharmacologic variable. Inclisiran treatment was not found to induce an anti-inclisiran antibody production. Adverse events concerning injection-site were slightly more frequent in patients treated with inclisiran. Although the study was not powered to detect the difference

in cardiovascular outcome, prespecified exploratory cardiovascular endpoints occurred in 7.4% and 7.8% of inclisiran-treated patients compared with 10.2% and 10.3% of patients treated with placebo. Similarly, inclisiran was found to reduce a LDL-cholesterol of about 50% in patients with familial hypercholesterolemia regardless of genotype.²⁸

Safety

As the therapy with inclisiran is extremely long-lasting (an effect of the drug persists up to 2 years)^{24,25} the safety issues are extremely important. Inclisiran does not exert any adverse effects on platelets count, blood lymphocyte, monocyte or neutrophil count, does not cause alterations in blood TNF-alpha or IL-6 concentrations and does not induce relevant anti-drug antibodies.²⁹ This is an important finding as treatment with single-strand antisense oligonucleotides (ASO) was associated with serious adverse events- treatment with both volanesorsen (apoC III inhibitor)³⁰ and inotersen (inhibitor of transthyretin protein production)³¹ were associated with significant thrombocytopenia. Although the underlying mechanism of ASO-induced thrombocytopenia is poorly understood, it is hypothesized that distinct motifs of the second-generation ASO can bind to platelet proteins (platelet collagen receptor glycoprotein VI) resulting in platelet activation.³²

However, inclisiran uses a different molecular principle (RNAi by double stranded siRNA) and is GalNAc-conjugated that specifically enhances hepatic uptake and plasma clearance.

The possibility of innate immune system activation with subsequent induction of inflammatory cytokines (TNF- α , IL-6) is another aspect of oligonucleotide therapeutic use.³³ The ability of oligonucleotide therapeutics to induce an immune responses seems to depend upon various factors including siRNA sequence as well as chemical modifications. Certain motifs (5'-UGU-3', 5'-UGUGU-3') may have potentially activate immune system and induce the production of inflammatory cytokines.³⁴ Toll-like recep-

tor (7/8)-dependent cytokine production may be attenuated by either replacement of uridine with adenosine or by modification of 2'-hydroxyl uridines with 2'-ribose, 2'-fluoro, 2'-O-methyl, or 2'-deoxy moieties.³⁵ Importantly, these modifications were performed during inclisiran development and no increase in inflammatory biomarker concentration was observed after inclisiran administration.²⁹

The summary of product characteristics of inclisiran (Leqvio) reports the only adverse side effect that is adverse reactions at the injection site occurring in 8.2% of patients.³⁶

Conclusion

Inclisiran decreases the level of circulating LDL-cholesterol by 50–55% and up to 65% in selected patient populations even when applied once in six months; it is the first therapeutic agent employing RNA interference that has the potential of becoming widely used.

Conflict of interest

The author has received speaker honoraria from Novartis, AstraZeneca and Swiix Biopharma.

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COSYREL®

bisoprolol fumarát + perindopril arginin

Spojení silných molekul pro kardioprotekci vašich pacientů

Zkrácená informace o přípravku COSYREL®: SLOŽENÍ: Cosyrel 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, 10 mg/10 mg, potahované tablety, obsahují bisoprolol fumaras (bis) 5 mg/, perindoprilum argininum (per) 5 mg, 5 mg bis/10 mg per, 10 mg bis/5 mg per, 10 mg bis/10 mg per. **INDIKACE:** Cosyrel je indikován k léčbě hypertenze a/nebo stabilní ischemické choroby srdce (u pacientů s infarktem myokardu a/nebo revaskularizací v anamnéze) a/nebo stabilního chronického srdečního selhání se sníženou systolickou funkcí levé komory (pouze Cosyrel 5 mg/5 mg a Cosyrel 10 mg/5 mg) jako substituční léčba u dospělých pacientů adekvátně kontrolovaných bisoprololem a perindopilem podáványi současně ve stejné dávce. **DAVKOVÁNÍ A ZPŮSOB PODÁNÍ:** Obvyklá dávka je jedna tableta jednou denně, nejlépe ráno a před jídlem. Pacienti musí být stabilizováni na léčbě bisoprololem a perindopilem ve stejné dávce po dobu nejméně 4 týdnů. Při kombinaci není vhodná k iniciální léčbě. U pacientů stabilizovaných na dávce bisoprololu 2,5 mg a perindoprilu 2,5 mg nebo bisoprololu 2,5 mg a perindoprilu 5 mg, při tabletách obsahujících 5 mg/5 mg nebo 5 mg/10 mg jednou denně. Je-li nutná změna dávkování, titraci je nutno provádět za použití jednotlivých složek samostatně. **Porucha funkce ledvin:** Doporučené dávkování podle clearance kreatininu. 5 mg/5 mg: Cl_{CR} ≥ 60 ml/min; 1 tableta; 30 < Cl_{CR} < 60 ml/min; 1/2 tablety; Cl_{CR} < 30; přípravek není vhodný, doporučená titrace dávky za použití jednotlivých složek samostatně. 5 mg/10 mg: Cl_{CR} ≥ 60 ml/min; 1/2 tablety; Cl_{CR} < 60; přípravek není vhodný. 10 mg/5 mg: Cl_{CR} ≥ 60; 1 tableta; Cl_{CR} < 60; přípravek není vhodný. 10 mg/10 mg: přípravek není vhodný. **Porucha funkce jater:** není nutná úprava dávkování. **Starší pacienti:** podávání podle renální funkce. **Pediatrická populace:** Bezpečnost a účinnost nebyla stanovena, použití u dětí a dospívajících se nedoporučuje. **KONTRAIKACE:** Hypersenzitivita na léčivé látky nebo na kteroukoliv pomocnou látku nebo na jiné inhibitory angiotenzin-konvertujícího enzymu (ACE); akutní srdeční selhání nebo probíhající epizody srdeční dekompenzace vyžadující i.v. inotropní terapii kardiogenní šok. AV blok druhého nebo třetího stupně (bez pacemakeru); sick sinus syndrom; sinoatriální blokáda; symptomatická bradykardie; symptomatická hypotenze; závažné bronchiální astma nebo chronická obstrukční plicní nemoc; závažné formy periferního arteriálního okluzečního onemocnění nebo Raynaudova syndromu; neléčený feochromocytom (viz bod Upozornění**); metabolická acidóza; anamnéza angioneurotického edému související s předchozí terapií inhibitory ACE; dědičný nebo idiopatický angioneurotický edém; 2. a 3. trimestr těhotenství (viz body Upozornění**); Těhotenství a kojení**), současné užívání s přípravky obsahujícími aliskiren u pacientů s diabetem mellitem nebo s poruchou funkce ledvin (GFR < 60 ml/min/1,73 m²) (viz body Upozornění**); Interakce* a Farmakodynamické vlastnosti*). Současné užívání se sakubitrilem/valsartanem, Cosyrel nesmí být nasazen dříve než 36 hodin po poslední dávce sakubitrilu/valsartanu** (viz bod Upozornění** a Interakce*), mimotělní léčba vedoucí ke kontaktu krve se záporně nabitým povrchem (viz bod Interakce*), signifikantní bilaterální stenóza renální arterie nebo stenóza renální arterie u jedné funkční ledviny (viz bod Upozornění**). **UPOZORNĚNÍ:** **Hypotenze:** u pacientů s poklesem objemu tělních tekutin, se symptomatickým srdečním selháním se současnou renální insuficiencí nebo bez ní, s ischemickou chorobou srdeční nebo cerebrovaskulárními chorobami je při zahájení léčby a změně dávky zapotřebí pečlivé monitorování. Náhlá hypotenze odpověď není kontraindikací pro podání dalších dávek, které mohou pacienti obvykle užívat bez obtíží, jakmile jim po doplnění objemu stoupne krevní tlak. **Hypersenzitivita (angioedém)/intestinální angioedém:** vysadit a zahájit monitorování až do úplného vymizení symptomů. Léčba betablockátorem musí pokračovat. Angioedém spojený s otokem hrtanu může být smrtelný. Současné užívání perindoprilu a sakubitrilu/valsartanu je kontraindikováno z důvodu zvýšeného rizika vzniku angioedému. Léčbu sakubitrilem/valsartanem nelze zahájit dříve než 36 hodin po poslední dávce perindoprilu. Pokud je léčba sakubitrilem/valsartanem ukončena, léčbu perindopilem nelze zahájit dříve než 36 hodin po poslední dávce sakubitrilu/valsartanu. Současné užívání inhibitory ACE s rasekadtrem, mTOR inhibitory (např. sirolimus, everolimus, temsirolimus) a gipitiny (např. inaglitin, saxagliptin, sitagliptin, vildagliptin) může vést ke zvýšenému riziku angioedému (např. otok dýchacích cest nebo jazyka spolu s poruchou dýchání nebo bez poruchy dýchání). U pacientů, kteří již užívají inhibitor ACE, je třeba opatrnosti při počátečním podání rasekadotrilu, mTOR inhibitory (např. sirolimus, everolimus, temsirolimus) a gipitiny (např. inaglitin, saxagliptin, sitagliptin, vildagliptin). **Selhání jater:** vzácně byly inhibitory ACE spojovány se syndromem, který začíná cholestátiou žloutenkou a progresuje ve fulminantní jaterní nekrózu a (někdy) v úmrtí. Ukončit léčbu v případě rozvoje žloutenky nebo výrazného zvýšení jaterních enzymů. **Černáská populace:** perindopril může být méně účinný a způsobit vyšší procento angioedému ve srovnání s jinými rasami. **Neprůduktivní kašel:** Hyperkalemie: časté monitorování koncentrace draslíku v krvi v případě renální insuficience, zhoršení renálních funkcí, věk > 70 let, diabetes mellitus, dehydratace, akutní srdeční nedostatečnost, metabolická acidóza a současné užívání draslík-šetřících diuretik, draslíkových doplňků, náhrad soli s obsahem draslíku, léčivých přípravků, které mohou způsobovat vzestup sérových koncentrací draslíku a zejména antagonistů aldosteronu nebo blokátory receptorů angiotenzinu**. U pacientů užívajících ACE inhibitory mají být proto kalium šetřící diuretika a blokátory receptorů angiotenzinu užívány opatrně a má být kontrolována hladina draslíku v séru a funkce ledvin**. **Kombinace s lithiem, s draslík-šetřícími diuretiky, draslíkovými doplňky nebo náhradami soli obsahujícími draslík, kaliovými antagonisty, antarytmiky třídy Ia centrálně působícími antihypertenzivy:** se obecně nedoporučuje. **Důležitá blokáda systému renin-angiotenzin-aldosteron (RAAS):** současné užívání inhibitory ACE, blokátory receptorů pro angiotenzin II nebo aliskiren zvyšuje riziko hypotenze, hyperkalemie a snížení funkce ledvin (včetně akutního selhání ledvin). Důležitá blokáda RAAS se proto nedoporučuje. Inhibitory ACE a blokátory receptorů pro angiotenzin II nemají být používány současně s diabetickou nefropatií. **Ukončení léčby:** nesmí být provedeno náhle ukončení léčby betablockátorem. Dávkování má být snižováno postupně pomocí jednotlivých složek, ideálně po dobu dvou týdnů. **Bradykardie:** při poklesu srdeční frekvence pod 50 – 55 tepů za minutu v průběhu léčby a pacientů postižených symptomy související s bradykardií, dávka má být snižována za použití jednotlivých složek s vhodnou dávkou bisoprololu. **AV blok prvního stupně, stenóza aortální a mitrální chlopně/hypertrofická kardiomyopatie, diabetici, stiskání jícnu:** podávat s opatrností. **Prizmatolová angina:** betablockátory mohou zvýšit počet a délku trvání epizod anginy pectoris. **Porucha funkce ledvin:** denní dávka má být upravena na základě clearance kreatininu. Monitorování draslíku a kreatininu. U pacientů s bilaterální stenózou renálních arterií nebo stenózou arterie solitární ledviny může dojít ke zvýšení sérových koncentrací urey a kreatininu. V případě renovaskulární hypertenze je riziko těžké hypotenze a renální insuficience zvýšené. **Renovaskulární hypertenze:** Pokud jsou pacienti s bilaterální stenózou renální arterie nebo stenózou renální arterie u jedné funkční ledviny léčeni inhibitory ACE, je zvýšené riziko závažné hypotenze a renálního selhání (viz bod Kontraindikace). Léčba diuretiky může být přispívající faktor. Ztráta renálních funkcí se může projevit pouze minimální změnou sérového kreatininu u pacientů s unilaterální stenózou renální arterie. **Transplantace ledvin, srdeční selhání s inzulin dependentním diabetem mellitem (typ II), těžkou poruchou funkce ledvin, těžkou poruchou funkce jater, restrikční kardiomyopatií, vrozeným srdečním onemocněním, hemodynamicky signifikantním onemocněním chlopní, infarktem myokardu v předchozích 3 měsících:** nejsou zkušenosti s podáváním. **Anafylaktoidní reakce během desenzibilizace:** dočasné vysadit léčbu před vyšetřeními. Tyto reakce se znovu objevily po náhodném opětovném vystavení. Bisoprolol může zvýšit senzitivitu vůči alergenům i závažnost anafylaktoidních reakcí. **Neutropenie/agranulocytóza/thrombocytopenie/anémie:** extrémní opatrnost u pacientů s kolagenovým vaskulárním onemocněním, s imunosupresivní léčbou, léčbou alopurinolem nebo prokainamidem, doporučuje se periodické monitorování počtu leukocytů. **Bronchospasmus (bronchiální astma, obstrukční onemocnění dýchacích cest):** souběžné podávání bronchodilatorní terapie. **Anestezie:** pokud je nutné betablockátory vysadit, je třeba to provádět postupně a ukončit 48 hodin před anestézií. **Pozor:** podání při zvažování přínosu a rizika. **Feochromocytom:** podávání bisoprololu vždy s blokátorem α_1 -receptorů. **Hyperkalemie:** symptomy mohou být maskovány. **Primární hyperaldosteronismus:** Pacienti s primárním hyperaldosteronismem obvykle neodpovídají na antihypertenzivní léčbu působící přes inhibici systému renin-angiotenzinu. Proto se užívání tohoto přípravku nedoporučuje. **Těhotenství:** zastavit léčbu. V případě nutnosti zahájit alternativní léčbu. Pomocné látky: bez sodku. **INTERAKCE:** **Kombinace kontraindikované:** aliskiren u pacientů s diabetem mellitem nebo poruchou funkce ledvin, mimotělní léčba, sakubitril/valsartan. **Nedoporučuje se současné užití:** centrálně působící antihypertenziva, např. klonidin a další (methyldopa, moxonidin, rilmenidin); antarytmika třídy I (chinidin, disopyramid, lidokain, fenytion, flekainid, propafenon); antagonisté kalcia typu verapamilu a v menší míře diltazemu; aliskiren a blokátory receptorů pro angiotenzin II; estramustin, hepariny, imunosupresiva jako cyklosporin nebo takrolimus, trimethoprim a kotrimoxazol (trimethoprim/sulfamethoxazol), draslík šetřící diuretika (triamteron, amilorid), draslík (soli); lithium. **Kombinace vyžadující zvláštní opatrnost:** antidiabetika (inzulín, perorální antidiabetika); nesteroïdní antilgostika (NSAID) včetně kyseliny acetylsalicylové ≥ 3 g/den; antihypertenziva a vaskulodilatancia; trikyklidická antidepresiva/antipsychotika/anestetika; sympatomimetika; antagonisté kalcia dihydropyridinového typu (felodipin, amlodipin); antarytmika třídy II (amiodaron); parasympatomimetika; lokální betablockátory (např. oční kapky k léčbě glaukomu); digitální glykosidy; baktérie; draslík šetřící diuretika (epiloron, spironolaktón); rasekadotril; inhibitory mTOR (např. sirolimus, everolimus, temsirolimus) a gipitiny (inaglitin, saxagliptin, sitagliptin, vildagliptin). **Kombinace vyžadující určitou opatrnost:** melifochin, inhibitory monoaminooxidázy (kromě inhibitorů MAO-B), žláto. **Léky vyvolávající hyperkalemii:** aliskiren, draslíkové soli, draslík-šetřící inhibitory ACE, antagonisté receptorů pro angiotenzin II, NSAID, hepariny, imunosupresiva jako cyklosporin nebo takrolimus, trimethoprim a kotrimoxazol (trimethoprim/sulfamethoxazol) **. **TĚHOTENSTVÍ A KOJENÍ:** Podávání není doporučeno v prvním trimestru těhotenství a během kojení. Podávání je kontraindikováno ve 2. a 3. trimestru těhotenství. **FERTILITA:** ÚČINNOST NA SCHOPOVNOST ŘÍDIT A OBSLUHOVAT STROJE: u některých pacientů se mohou vyskytnout individuální reakce související s nízkým krevním tlakem. V důsledku toho není vhodné řídit a obsluhovat stroje narušená. **NEŽÁDOUCÍ ÚČINKY:** **Velmi časté:** bradykardie. **Časté:** bolest hlavy, závratě, vertigo, dyspnoe, parestezie, porucha zraku, tinitus, zhoršení srdečního selhání, hypotenze a účinky související s hypotenzí, pocit chladu nebo znečištění/končet, kašel, dyspnoe, bolest břicha, zácpa, průjem, nauzea, zvracení, dyspepsie, vyrážka, pruritus, svalové křeče, astenie, únava. **Méně časté:** ezofagitida, hypoglykémie, hyperkalemie, hyponatremie, změny nády, poruchy spánku, deprese, somnolence, synkopa, palpitace, tachykardie, poruchy AV vedení, ortostatická hypotenze, vaskulitida, bronchospasmus, suchý ušlech, angioedém obličej, končetin, rtů, sliznic, jazyka, glottis a/nebo hrtanu, kopřivka, fotosenzitivní reakce, pemfigoid, hyperhidróza, svalová slabost, artralgie, myalgie, renální insuficience, erektilní dysfunkce, bolest na hrudi, malátnost, periferní edém, pyrexie, zvýšená hladina urey a kreatininu v krvi, pád. **Vzácné:** rinidita, noční můry, halucinace, snížená tvorba slz, poruchy sluchu, hepatitida cytolytického nebo cholestatického, hypersenzitivní reakce (svědění, zvracení, vyrážka), zhoršení psoriázy, poruchy potence, vzestup jaterních enzymů, zvýšená hladina bilirubinu v krvi, zvýšená hladina triglyceridů, syndrom nepřiměřené sekrece antidiuretického hormonu (SIADH) **, akutní renální selhání **, anurie/oligurie **, zvracení **, **Velmi vzácné:** agranulocytóza, pancytopenie, leukopenie, neutropenie, trombocytopenie, hemolytická anémie u pacientů s vrozeným deficitem G-6PDH, zmatenost, konjunktivitida, arytmie, angina pectoris, infarkt myokardu a cévní mozková příhoda, možné sekundární kadmerné hypotenze v vysoké rizikových pacientů, osinoftalmie pneumonie, pankreatitida, erythema multiforme, alopecie, betablockátory mohou způsobit nebo zhoršit psoriázu nebo způsobit vyrážku připomínající psoriázu, snížená hladina hemoglobinu a snížení hematokritu. **Není známo:** Raynaudův fenomén. **PŘEDÁVACÍ VLASTNOSTI:** Bisoprolol je vysoké beta 1-selektivní blokátor adrenergetických bez vnitřní sympatomimetické a membrány stabilizující aktivity. Perindopril je inhibitor enzymu, který konvertuje angiotenzin I na vazokonstrikční angiotenzin II (ACE). **BALENÍ:** Balení 30, 90 potahovaných tablet přípravku Cosyrel 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, 10 mg/10 mg. **Uchovávaní:** Žádné zvláštní podmínky uchovávaní ani zacházení. **Držitel rozhodnutí o registraci:** LES LABORATOIRES SERVIER, 50, rue Carnot, 92284 Suresnes cedex, Francie. Registrací číslo: 58/563-566/15-C. **Datum poslední revize textu:** 3. 1. 2022. Před předepsáním přípravku si přečtěte Souhrn údajů o přípravku. Přípravky jsou k dispozici v lékárnách a jsou na lékařský předpis. Přípravky jsou částečně hrazeny z veřejného zdravotního pojištění, viz Seznam cen a úhrad léčivých přípravků: <http://www.sukl.cz/sukl/seznam-leciv-az-uzk-hrazeny-ze-zdrav-pojisteni>. Další informace na adrese: Servier s.r.o., Na Florenci 2116/15, 110 00 Praha 1, tel: 222 118 111, www.servier.cz. * pro úplnou informaci si prosím přečtěte celý Souhrn údajů o přípravku. ** všimněte si prosím změn v informaci o léčivém přípravku Cosyrel

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Proč využít fixní kombinaci bisoprolol/perindopril u hypertoniků s ICHS?

(Why to use fixed dose perindopril, bisoprolol combination in hypertonics with CHD?)

Ondřej Petrák

Centrum pro výzkum, diagnostiku a léčbu arteriální hypertenze, III. interní klinika, 1. lékařská fakulta Univerzity Karlovy a Všeobecná fakultní nemocnice v Praze, Praha

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SOUHRN

Kardiovaskulární onemocnění jsou celosvětově nejčastější příčinou úmrtnosti. Arteriální hypertenze patří k ovlivnitelným rizikovým faktorům aterosklerózy a její časná léčebná intervence významně snižuje kardiovaskulární morbiditu a mortalitu. Léčbu musíme přizpůsobit jednotlivému pacientovi na míru dle závažnosti hypertenze a jeho kardiovaskulárnímu i metabolickému rizikovému profilu. Fixní kombinace má řadu výhod od lepšího a rychlejšího dosažení cílových hodnot krevního tlaku přes menší množství nežádoucích účinků až po zlepšení adherence k léčbě. Kombinace beta-blokátoru (bisoprololu) a inhibitoru angiotenzin konvertujícího enzymu (perindoprilu) má komplementární účinky na sympatický nervový systém a osu renin-angiotenzin-aldosteron. Kombinace těchto léků účinně snižuje krevní tlak i tepovou frekvenci, což zlepšuje kardiovaskulární prognózu vybraných nemocných. Článek je věnován indikacím těchto léků u pacientů jak v léčbě nekomplikované hypertenze, tak v sekundární prevenci u pacientů s ischemickou chorobou srdeční. Důraz je kladen zejména na postavení beta-blokátorů.

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SUMMARY

Cardiovascular disease is the leading cause of mortality worldwide. Arterial hypertension is one of the earliest risk factors of atherosclerosis and early intervention significantly reduces cardiovascular morbidity and mortality. We have to tailor the treatment to individual patients according to their hypertension subclass and their cardiovascular and metabolic risk profile. The fixed combination has a number of advantages, from better and faster achievement of blood pressure target values, through fewer side effects to improved adherence to treatment. The combination of a beta-blocker (bisoprolol) and an ACE inhibitor (perindopril) has complementary effects on the sympathetic nervous system and the renin-angiotensin-aldosterone axis. The combination of these drugs effectively reduces blood pressure and heart rate, which improves the cardiovascular prognosis of selected patients. The article is devoted to the indications of these drugs in patients both in the treatment of uncomplicated hypertension and in secondary prevention in patients with ischemic heart disease. The emphasis is placed especially on the position of beta-blockers.

Keywords:

Arterial hypertension

Bisoprolol

Ischemic heart disease

Fixed dose combination

Perindopril

Arteriální hypertenze a její kontrola

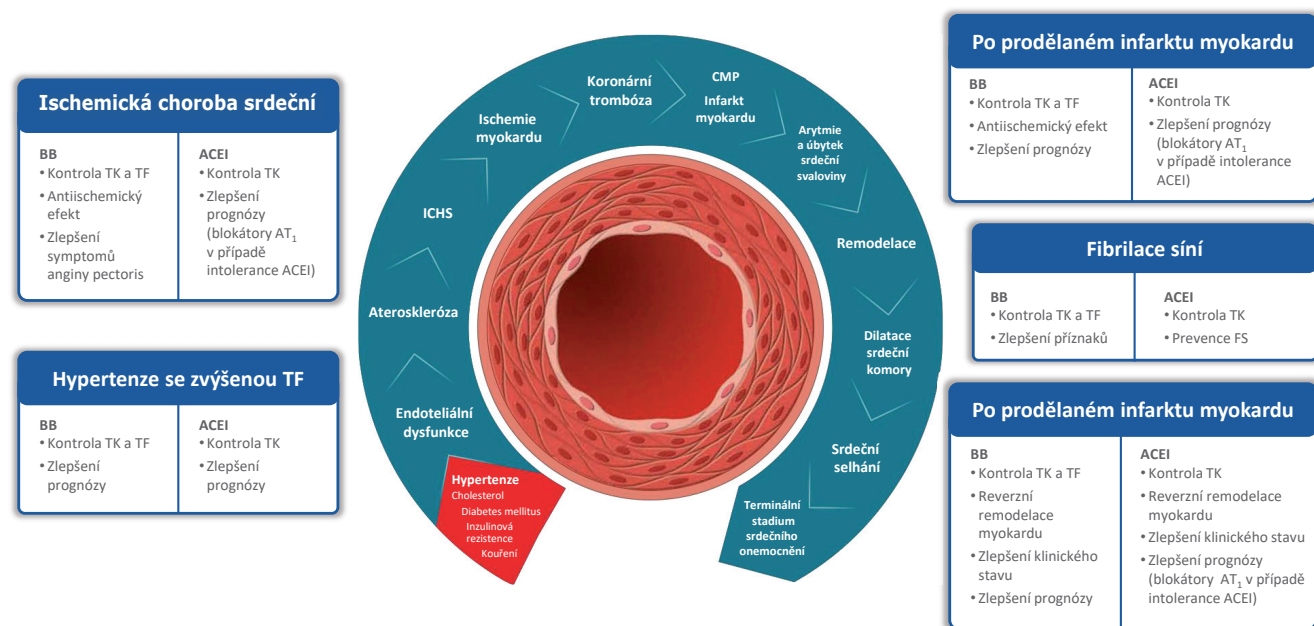
Arteriální hypertenze je časný a ovlivnitelný rizikový faktor aterosklerózy, a tedy i ischemické choroby srdeční. Vysoký krevní tlak je zcela počáteční fází tzv. kardiovaskulárního kontinua pro srdeční onemocnění (obr. 1). Časnou kontrolou krevního tlaku můžeme výrazně ovlivnit

kardiovaskulární prognózu našich pacientů. Současná doporučení určují jako cílové hodnoty klinického krevního tlaku hodnoty nižší než 140/90 mm Hg u všech hypertoniků a v případě vysoce rizikových nemocných se snahou o dosažení hodnot 130/80 mm Hg, a to nejlépe do tří měsíců od zahájení léčby.¹⁻³ I přes jasná doporučení však v reálné praxi bývá dosažení dobré kontroly krevního tlaku obtížné.⁴ Studie EUROASPIRE sledující asymp-

Adresa pro korespondenci: Doc. MUDr. Ondřej Petrák, Ph.D., Centrum pro výzkum, diagnostiku a léčbu arteriální hypertenze, III. interní klinika, 1. lékařská fakulta Univerzity Karlovy a Všeobecná fakultní nemocnice v Praze, U Nemocnice 499/2, 128 08 Praha 2, e-mail: Ondrej.Petrak@vfn.cz

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Obr. 1 – Kombinace beta-blokátoru a ACEI v průběhu kardiovaskulárního kontinua pro srdeční onemocnění. Převzato z ⁸. ACEI – inhibitor angiotenzin konvertujícího enzymu; BB – beta-blokátor; ICHS – ischemická choroba srdeční; TF – tepová frekvence; TK – krevní tlak.

tomatické jedince ve vysokém kardiovaskulárním (KV) riziku zjistila, že pouze u 42 % bylo dosaženo cílových hodnot krevního tlaku i přes užívanou antihypertenzní léčbu.⁵ Obdobné jsou i výsledky jiných výzkumů, např. 44 % léčených Američanů nemá krevní tlak pod kontrolou.⁶ A přitom nedostatečně léčená hypertenze je spojena s vyšší celkovou mortalitou i mortalitou z kardiovaskulárních příčin ve srovnání s normotonií.⁷ Evropský průměr úspěšné kontroly krevního tlaku u léčených hypertoniků je 49 % a v České republice je to 45 %.⁴

Fixní kombinační léčba

Dnes již víme, že se není nutno obávat kombinační terapie již od počátku léčby hypertenze. Spojení dvou léků s rozdílným mechanismem působení má řadu výhod, zejména výraznější vliv na pokles krevního tlaku,⁹ časnější ochranu před hypertenzí navozeným orgánovým poškozením,¹⁰ méně nežádoucích účinků, a tedy i lepší adherenci a v neposlední řadě i omezení lékařovy inercie.¹¹ V tomto smyslu hovoří všechna doporučení z posledních let, nicméně upozorňují i na výjimky, jako je nízkorizikový hypertonik 1. stupně nebo křehký senior, u nichž je lepší zahajovat léčbu monoterapií. Kombinace inhibitoru systému renin-angiotenzin (inhibitoru angiotenzin konvertujícího enzymu [ACEI] nebo sartanu) s beta-blokátorem má své specifické postavení v léčbě hypertenze, a to zejména u pacientů se známou ischemickou chorobou srdeční. Následující text je zaměřen na tuto kombinaci v léčbě hypertenze a ICHS. O benefitu ACEI bylo v léčbě napsáno mnoho a je všeobecně známo, i proto všechna odborná doporučení odborných společností po celém světě doporučují tyto léky jako první volbu v léčbě hypertenze. Jaké je však postavení beta-blokátorů?

Důkazy pro beta-blokátory v léčbě nekomplikované hypertenze

Beta-blokátory jsou současnými doporučeními pro léčbu hypertenze poněkud odsunuty na okraj. Přestože právem patří do hlavní třídy antihypertenziv, jsou v iniciační fázi léčby hypertenze doporučovány jen v indikovaných případech, kterými se rozumějí komorbidity jako ICHS, symptomatická angina pectoris, stavy po infarktu myokardu, srdeční selhání nebo fibrilace síní. Důvody, proč v léčbě hypertenze nepreferujeme beta-blokátory, jsou metabolické. Metaanalýza 12 studií popsala souvislost mezi užíváním beta-blokátoru a nově vzniklého diabetes mellitus 2. typu zejména u nemocných s již vyjádřeným metabolickým syndromem.¹² Na druhou stranu řada studií a metaanalýz potvrdila, že podávání beta-blokátorů ve srovnání s placebem je spojeno s nižším rizikem CMP, srdečního selhání a vážnými kardiovaskulárními příhodami. Pokud je srovnáván beta-blokátor s ostatními antihypertenzivy, je považován za stejně účinný v prevenci KV příhod. Jedinou výjimkou je cévní mozková příhoda (CMP), kde v rámci Cochraneovy analýzy byl popsán vyšší výskyt cerebrovaskulárních příhod u nemocných léčených beta-blokátorem ve srovnání s blokátorem renin-angiotenzinu či blokátorem kalciových kanálů.¹³ Na tento výsledek je však nutno nahlížet v kontextu hodnocených studií, což byly dominantně studie ASCOT¹⁴ a INVEST,¹⁵ ve kterých byl jako komparátor volen atenolol navíc podáván jen jednou denně s krátkým biologickým poločasem necelých šest hodin. Je tedy zřejmé, že tento lék není schopen ovlivnit noční a ranní vzestupy krevního tlaku, které bývají považovány za nejrizikovější pro vznik CMP.

Často je v souvislosti s beta-blokátory uváděna subanalýza studie ASCOT označovaná jako CAFÉ (Conduit Artery Functional Endpoint), která ukázala, že atenolol je méně účinný ve snižování centrálního systolického

krevního tlaku ve srovnání se skupinou léčenou perindopilem/amlodipinem.¹⁶ Nicméně beta-blokátory jsou velmi rozmanitou skupinou s rozdílnou farmakokinetikou a farmakodynamikou, a tedy jistě odlišným efektem na kardiovaskulární aparát. Například randomizovaná studie srovnávající efekt bisoprololu a atenololu u dosud neléčených hypertoniků ukázala identický vliv na snížení brachiálního krevního tlaku, ale jen bisoprolol významně snižoval centrální systolický a pulsní tlak.¹⁷ A tak lze konstatovat, že atenolol, svého času celosvětově nejpopulárnější antihypertenzivum, jistě nebyl vhodnou volbou pro srovnání s jinými třídami léků pro svou relativně krátkou dobu působení a malý účinek na centrální systolický tlak.

Můžeme tedy beta-blokátor použít v léčbě prosté hypertenze, bez dalších kardiovaskulárních komorbidit?

Ano, můžeme ho s výhodou využít u nemocných se zvýšenou sympatikotonií a hyperkinetickou cirkulací. Autonomní nervový systém se podílí na mnoha homeostatických funkcích včetně řízení energetické bilance a kontrole krevního tlaku. Pacienti s arteriální hypertenzí a tepovou frekvencí nad 80/min na podkladě zvýšené sympatikotonie mají vyšší kardiovaskulární riziko než jedinci s tepovou frekvencí (TF) nižší než 80/min.¹⁸ Například čím vyšší je tepová frekvence, tím větší je index hmotnosti levé komory.¹⁹ Ve studii VALUE zůstávalo vyšší kardiovaskulární riziko u jedinců se zvýšenou tepovou frekvencí, a to i přestože jejich krevní tlak byl dobře kontrolován.²⁰ Zdá se tedy, že k optimálnímu snížení kardiovaskulárního rizika je zapotřebí nejen dobrá kontrola krevního tlaku, ale i tepové frekvence, což otevírá prostor pro beta-blokátory, případně i non-dihydropyridinové blokátory kalciových kanálů.

Optimální kontrola hypertenze způsobené nadměrnou aktivací sympatiku tedy bude vyžadovat přidání beta-blokátoru do léčby. Volba selektivního beta₁-blokátoru povede k inhibici sympatiku v srdci a ledvinách, a přitom zachová vazodilataci zprostředkovanou beta₂-receptory a sníží riziko nežádoucích účinků způsobených blokádou beta₂-receptorů v plicích a periferních tkáních.

Léčba hypertenze u ischemické choroby srdeční

Ischemická choroba srdeční zůstává celosvětově nejčastější příčinou úmrtí.²¹ Cílem naší léčby je zabránit další ischemii, zlepšit kvalitu života a předcházet dalším kardiovaskulárním příhodám a předčasně smrti. To označujeme jako sekundární prevenci ICHS. Jestliže jsme v předchozí části v léčbě nekomplikované hypertenze váhali nad nasazením beta-blokátoru, tak v případě ICHS po prodělané kardiovaskulární příhodě je to naopak jeden z pilířů léčby.

Důkazy pro beta-blokátory v léčbě ICHS

Beta-blokátory se doporučují jako lék první volby pro jejich antiischemický efekt na myokard (negativní

chronotropní, inotropní, dromotropní a bathmotropní efekt) s tím, že cílová klidová tepová frekvence by měla být 55–60/min.²² Ve studii TIBBS (Total Ischemic Burden Bisoprolol Study) bylo 631 pacientů se stabilní anginou pectoris a EKG změnami při zátěži randomizováno na osm týdnů buď k terapii bisoprololem, nebo nifedipinem.²³ Bisoprolol se ukázal jako účinnější ve snížení počtu a trvání přechodných ischemických příhod. Dostatek silných důkazů o benefitu beta-blokátorů máme u osob po prodělaném infarktu myokardu a/nebo s chronickým srdečním selháním se sníženou ejekční frakcí, kde je léčba spojena s významným snížením úmrtnosti i dalších kardiovaskulárních příhod. Naopak nemáme dostatek studií, které by to samé potvrzovaly u nemocných s ICHS bez předchozího infarktu myokardu nebo srdečního selhání.²⁴

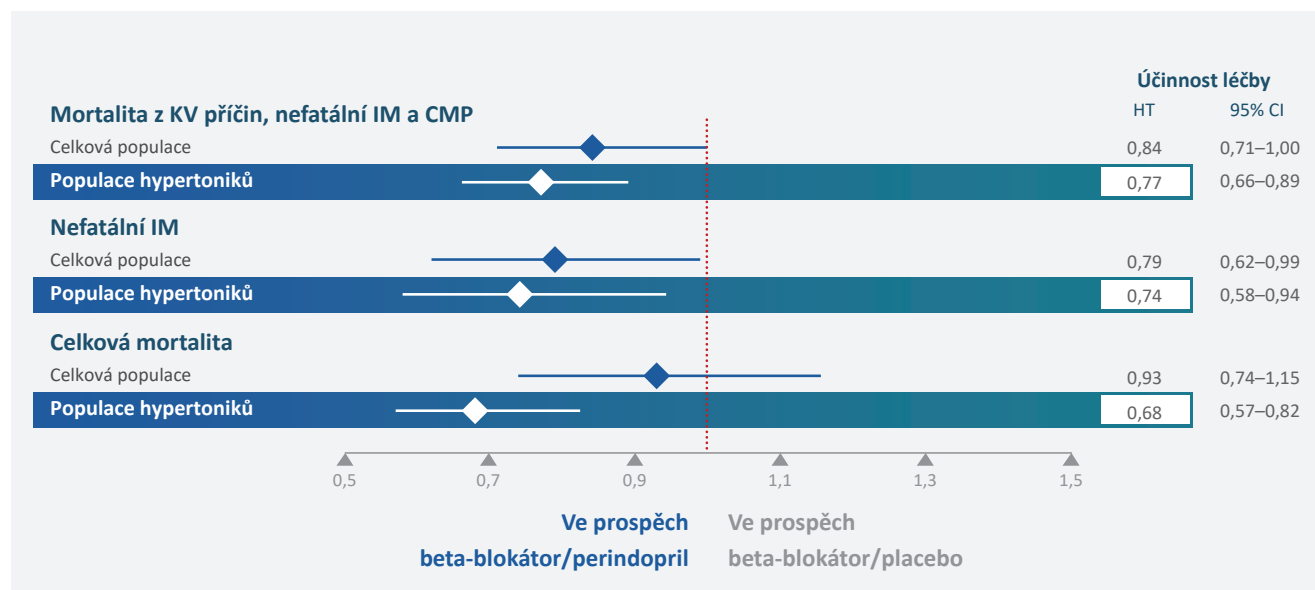
Nedávná analýza britského registru porovnávala incidenci a riziko úmrtí a kardiovaskulárních příhod u pacientů s anginou pectoris užívajících monoterapii bisoprololem oproti jiným beta-blokátorům anebo ostatním antihypertenzivům podaným v primární péči.²⁵ Výsledkem bylo zjištění, že nově zjištěná angina pectoris léčená bisoprololem byla spojena s významným snížením rizika úmrtí (o 50 %), kardiovaskulárních příhod (o 23 % anginy pectoris, o 55 % infarktu myokardu a o 39 % fibrilace síní) ve srovnání s ostatní léčbou. Bisoprolol je tak jistě vhodnou volbou v první linii.

V doporučeních Evropské kardiologické společnosti a Evropské společnosti pro hypertenzi pro léčbu arteriální hypertenze jsou beta-blokátory uvedeny jako třída důkazů I, úroveň A, pro použití u pacientů s hypertenzí a anamnézou infarktu myokardu, a to na základě metaanalýzy ze 147 randomizovaných studií s antihypertenzivy.¹ Tato analýza prokázala, že léčba beta-blokátory je spojena s 29% snížením ischemických příhod (relativní riziko 0,71, 95% CI 0,66–0,78), a to nad rámec efektu na krevní tlak.²⁶ Léčba jinými třídami léků bez ohledu na ICHS či podávání beta-blokátorů u osob bez ICHS vedla také k poklesu relativního rizika, ale méně významnému (o 15 %, $p < 0,001$). Nicméně tento efekt trvá jen několik let po prodělaném infarktu.

Synergická neuroendokrinní blokáda (kombinace beta-blokátoru a ACEI)

Podání beta-blokátoru a ACEI můžeme označit za komplexní neuroendokrinní blokádu. Beta-blokátor ovlivňuje autonomní nervový systém, zejména snížením srdečního výdeje přímým vlivem na beta-adrenergní receptory myokardu. ACEI zase prostřednictvím blokády systému renin-angiotenzin navozuje vazodilataci, čímž snižuje periferní cévní rezistenci.

Bisoprolol a perindopril mají komplementární mechanismus účinku a dobrou evidenci u některých vysoce rizikových skupin. Bisoprolol je kardioselektivní beta-blokátor s 19násobně vyšší afinitou k beta₁-receptoru než beta₂-receptoru a dostatečně dlouhý biologický poločas zajišťuje více než 24hodinové působení.²⁷ Z třídy ACEI má zase perindopril nejvyšší selektivitu pro bradykininová vazebná místa a také dostatečně dlouhé 24hodinové působení.²⁸ Důkazy o výhodách perindoprilu v kombi-



Obr. 2 – Údaje z retrospektivní souhrnné analýzy pacientů ze tří velkých výsledných studií perindoprilu, kteří dostávali perindopril nebo placebo a již byli léčeni beta-blokátorem. Přidání perindoprilu k léčbě beta-blokátory bylo spojeno se snížením rizika primárního kombinovaného cílového ukazatele (mortality z kardiovaskulárních příčin, nefatálního infarktu myokardu a cévní mozkové příhody), jakož i sekundárních cílových ukazatelů (nefatálního infarktu myokardu a mortality ze všech příčin).³¹ CMP – cévní mozková příhoda; IM – infarkt myokardu; KV – kardiovaskulární.

naci s beta-blokátorem pocházejí ze studie, kde 12 000 pacientů se stabilní ICHS po infarktu myokardu či s anginou pectoris bylo randomizováno na terapii perindoprilem nebo placebem.²⁹ V této skupině nemocných bylo 62 % pacientů již léčeno beta-blokátory a přidání perindoprilu u nich vedlo k 24 % snížení relativního rizika kombinovaného primárního cílového ukazatele (úmrtí z kardiovaskulárních příčin, nefatální infarkt myokardu a resuscitovaná srdeční zástava) ve srovnání se skupinou užívající beta-blokátor s placebem.³⁰ Tyto údaje byly rozšířeny o retrospektivní souhrnnou analýzu pacientů s vaskulárním onemocněním ze tří velkých studií, kteří užívali perindopril nebo placebo a již byli na terapii beta-blokátory. Výsledky potvrdily předchozí zjištění³¹ (obr. 2).

Fixní kombinace bisoprololu a perindoprilu

První fixní kombinace beta-blokátoru a ACEI je dostupná od roku 2017 a je indikována u arteriální hypertenze, stabilní ischemické choroby srdeční a/nebo srdečního selhání. Údaje podporující přínosy bisoprololu/perindoprilu podávaných ve fixní kombinaci pocházejí ze studie u 2 394 pacientů s ICHS, která sledovala ovlivnění tlaku a srdeční frekvence. Jednalo se o pacienty původně léčené bisoprololem, kterým byla předepsána fixní kombinace. Po čtyřtýdenní léčbě 85 % pacientů dosáhlo srdeční frekvence nižší než 70/min a 87 % pacientů krevního tlaku nižšího než 140/90 mm Hg. Fixní kombinace také snížila frekvenci anginosních obtíží a zlepšila adherenci k léčbě.⁸

Dále přidání stejné fixní kombinace pacientům po revaskularizaci myokardu pro akutní koronární syndrom (velmi vysoce riziková populace) vedlo k dosažení cílo-

vých hodnot TK a srdeční frekvence do jednoho měsíce od zahájení terapie a stabilizaci těchto hemodynamických hodnot a klinických příznaků po celou dobu sledování (tři měsíce). A díky tomu mohli být časněji zařazeni do kardiorehabilitačních programů.⁸

Adherence k terapii je zásadní

Fixní kombinace dnes patří k základní volbě v terapii jak arteriální hypertenze, tak všech jejích komplikací. Špatná compliance k terapii nemusí být nutně jen důsledkem odmítání léčby jako takové, ale příliš velké množství tablet může vést k chybám v dávkování, nechtěnému opomenutí některých léků apod. To potvrzuje i nedávno uvedená studie SECURE, která sledovala rozdíl v užití statinu, acetylsalicylové kyseliny a ACEI buď v jedné tabletě (polypill), nebo jako volné kombinace u nemocných s ICHS, po prodělaném infarktu myokardu v posledních šesti měsících. Cílem 36měsíčního sledování bylo srovnání kardiovaskulární morbidity a mortality.³² Užívání fixní kombinace v jedné tabletě bylo spojeno s významným snížením rizika KV komplikací (o 24 %) ve srovnání s volnou kombinací léků (HR 0,76; 95% CI 0,06–0,96; $p = 0,02$).

Závěr

Existují spolehlivé důkazy o výhodách použití beta-blokátoru a ACEI u pacientů s hypertenzí a zvýšenou srdeční frekvencí, ischemickou chorobou srdeční zejména po prodělaném akutním koronárním syndromu, fibrilací síní a chronickým systolickým srdečním selháním. Tyto dvě třídy ve společné kombinaci poskytují komplexní neuroendokrinní blokádu. Výhody kombinace bisoprolol/perin-

dopřil jsou podpořené studiemi potvrzujícími nejen dobrý efekt s dlouhodobým působením, ale i dobrou snášenlivostí. Každý z těchto léků má dlouhý eliminační poločas při podávání jednou denně. Dostupné údaje naznačují, že kombinace těchto látek v jedné tabletě umožňují rychleji dosáhnout cílové srdeční frekvence a krevního tlaku, a pomůže tak snížit riziko kardiovaskulární příhody.

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Myokarditidy u dětí

Kristina Rücklová^{a,b}, Jan David^{c,d}, Karel Koubský^e, Jan Pavlíček^f, Eva Klásková^g,
Vojtěch Šedivý^c, Sylvia Krupičková^h, Hana Malcová^{ch}, Jitka Komínová^b,
Pavel Vítⁱ, Peter Kubuš^e

^a Klinika dětí a dorostu, 3. lékařská fakulta Univerzity Karlovy a Fakultní nemocnice Královské Vinohrady, Praha

^b Klinika pediatrie a dědičných poruch metabolismu, 1. lékařská fakulta Univerzity Karlovy a Všeobecná fakultní nemocnice v Praze, Praha

^c Pediatrická klinika, 2. lékařská fakulta Univerzity Karlovy a Fakultní nemocnice Motol, Praha

^d Soukromá pediatrická a nutriční ambulance, Praha 4

^e Dětské kardiocentrum, 2. lékařská fakulta Univerzity Karlovy a Fakultní nemocnice Motol, Praha

^f Klinika dětského lékařství, Lékařská fakulta Ostravské univerzity a Fakultní nemocnice Ostrava, Ostrava

^g Dětská klinika, Lékařská fakulta Univerzity Palackého v Olomouci a Fakultní nemocnice Olomouc, Olomouc

^h Royal Brompton Hospital, Londýn, Velká Británie

^{ch} Oddělení revmatologie dětí a dospělých, Fakultní nemocnice Motol, Praha

ⁱ Pediatrická klinika, Lékařská fakulta Masarykovy univerzity a Fakultní nemocnice Brno, Brno

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SOUHRN

Myokarditida u dětí je poměrně vzácné a zároveň potenciálně závažné onemocnění. Často představuje diagnostické a terapeutické dilema, stejně tak volba diagnostických metod a jejich interpretace nemusí být vždy jednoznačná. V posledních letech stoupá význam magnetické rezonance, u které může být limitací její dostupnost. Variabilní přístup k dětem s myokarditidou je často patrný i v oblasti terapeutické. Významným příspěvkem je odborné stanovisko American Heart Association z roku 2021. Níže předkládaný přehledový článek představuje souhrn současných dostupných literárních dat.

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SUMMARY

Myocarditis in children is a relatively rare disease which often presents a dilemma that has to be faced not only by paediatric cardiologists but also paediatricians. The diagnosis often remains clinically suspected or probable. Only recent advancements in cardiac magnetic resonance have enabled us to confirm the diagnosis. However, it may not be readily available. Scientific statement of the American Heart Association on paediatric myocarditis was published in 2021 and provides useful support for treatment. Hence, this article is a result of published guidelines.

Adresa pro korespondenci: MUDr. Jan David, Ph.D., Soukromá pediatrická a nutriční ambulance, Podolská 1485/10a, 147 00 Praha 4,

e-mail: jan.david@centrum.cz

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Úvod

Myokarditida je zánětlivé onemocnění srdce, definované histologickým nebo imunohistochemickým nálezem, případně specifickým obrazem na magnetické rezonanci srdce (CMR). Incidence u dětí je uváděna 1,95/100 000 dětí do 15 let za rok s převahou chlapců (77 %).¹ Stanovení diagnózy vždy vyžaduje komplexní vyhodnocení anamnézy, klinických příznaků, laboratorních parametrů, elektrokardiografických (EKG) a echokardiografických nálezů. Vyšetřovací modalita je často nutná v kontextu klinického vývoje opakovat a sledovat jejich dynamiku. Výrazným posunem v diagnostice myokarditidy bylo zlepšení technických parametrů a interpretace nálezů CMR, která umožňuje potvrdit myokarditidu i bez endomyokardiální biopsie (EMB).²

Publikované postupy pro myokarditidu v dětském věku jsou prozatím na úrovni konsenzu expertů či stanovisek odborných společností. V řadě případů je nutný individuální přístup. Diagnostické i terapeutické (indikace podání imunoglobulinů, antivirotik) strategie, včetně dlouhodobého sledování po prodělaném onemocnění, se značně liší na všech úrovních, od primární až po terciární péči. Proto jsme se nedávno rozhodli uspořádat online setkání dětských kardiologů a pediatriů, jehož cílem bylo sdílení zkušeností, vzájemné obohacení vycházející z praxe a otevření sporných otázek. Záměrem článku je shrnout výstupy naší diskuse na pozadí dostupných literárních dat.

Etiologie

Spouštěče myokarditidy u dětí můžeme rozdělit na infekční a neinfekční.² Mezi infekčními příčinami v Evropě dominují viry. V minulosti při prokázaném infekčním agens převažovaly adenoviry a enteroviry, v současnosti jde spíše o parvovirus B19 a lidský herpes virus 6, recentně také nový koronavirus SARS-CoV-2. Celosvětově se významně jako infekční příčina uplatňuje *Trypanosoma cruzii*. S ostatními infekčními agens se v našich podmínkách setkáváme minimálně, celkový přehled je uveden v tabulce 1.^{2,3} Bakteriální původci jsou taktéž raritní, možná je například myokarditida při akutní salmonelové či kampylobakterové infekci (ústní sdělení).

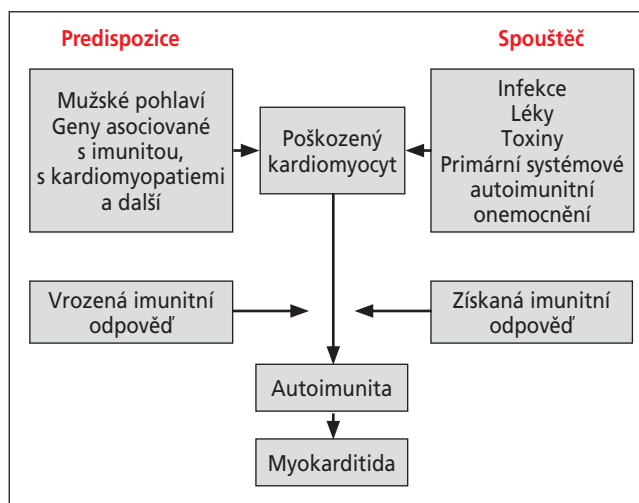
Vyjma onemocnění vlastního myokardu je u myokarditidy možné postižení převodního systému. *Borrelia burgdorferi* postihuje především bazální část mezikomorové přepážky, kde je lokalizován atrioventrikulární (AV) uzel, a proto se lymeská kardiitida typicky manifestuje AV bloádou.⁴ Myokarditida způsobená rickettsiemi nebo kvasinkami se může vyskytnout jako součást diseminované infekce, u hub převážně u imunokompromitovaných pacientů.^{5,6}

Myokarditida neinfekční etiologie je u dětí většinou součástí vaskulitid, především Kawasakiho nemoci nebo jiných autoimunitních onemocnění.⁷ Revmatická horečka je i v současné době příčinou nejčastějšího získaného onemocnění srdce v rozvojových zemích a nevymizela ani v Evropě či ve Spojených státech amerických.⁸ Izolované autoimunitní postižení srdce je příčinou závažné obrovskobuněčné myokarditidy.⁹ Autoimunitní mechanismus

se také předpokládá u myokarditid po mRNA vakcinaci proti covidu-19.¹⁰ Hyperinflamatorní stav u dětí po naze SARS-CoV-2, tzv. PIMS-TS – syndrom multisystémové zánětlivé odpovědi spojený s covidem-19 (Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2), může být asociován s imunitně podmíněnou myokarditidou přibližně v 18 % případů dle CMR.¹¹ Další neinfekční mechanismus mohou představovat hypersenzitivní reakce na léky, drogy, některá biologika nebo rejekce transplantovaného srdce. Drogy a léky však mohou srdeční sval poškodit i přímým toxickým účinkem, podobně jako katecholaminy při feochromocytomu.¹²

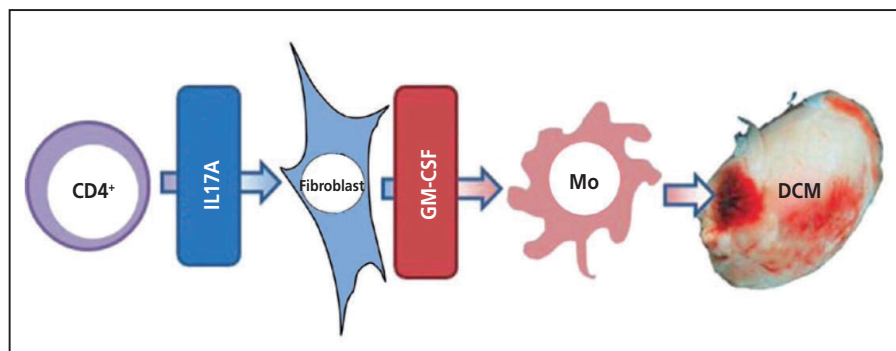
Patogeneze

Předpokládá se, že vznik myokarditidy je vždy výsledkem kombinace působení spouštěče u geneticky predisponovaného jedince a autoimunitní odpovědi (obr. 1).^{9,13}



Obr. 1 – Schéma patogeneze myokarditidy.^{9,13} Předpokládá se, že vznik myokarditidy je vždy výsledkem kombinace působení spouštěče u geneticky predisponovaného jedince a autoimunitní odpovědi.

Myší modely odhalily interakci mezi vrozenou a získanou imunitní odpovědí v patogenezi myokarditidy. U viróvé myokarditidy vstupuje virus díky virus-specifickým receptorům do kardiomyocytů, které poškozuje. Takto pozměněné kardiomyocyty aktivují systém vrozené (lymfoidní, NK buňky a mastocyty) a získané imunity, hlavně CD4 T lymfocyty. CD4 T lymfocyty produkují tumor nekrotizující faktor (TNF) alfa, interferon (IFN) gama a interleukin (IL) 17A. IL17A výrazně stimuluje srdeční fibroblasty k produkci růstových hormonů pro granulocytární řadu leukocytů a makrofágy (granulocyte macrophage colony-stimulating factor, GM-CSF). GM-CSF aktivuje kostní dřeň, ze které se uvolňují další zánětlivé buňky, především monocyty. Ty pak infiltrují srdce, poškozují ho a významně se podílejí na progresi do dilatační kardiomyopatie (obr. 2).⁹ CD4 T lymfocyty zároveň aktivují B lymfocyty tvořící autoprotilátky, které také přispívají k poškození myokardu.²



Obr. 2 – Schéma progresu myokarditidy do dilatační kardiomyopatie, publikováno se svolením autorů.⁹ Virem pozměněné kardiomyocyty aktivují mimo jiné CD4 T lymfocyty. Ty produkují interleukin (IL) 17A, který stimuluje srdeční fibroblasty k produkci GM-CSF (granulocyte-macrophage colony-stimulating factor). GM-CSF aktivuje kostní dřeň, ze které se uvolňují další zánětlivé buňky, především monocyty (Mo). Ty pak infiltrují srdce, poškozuji ho a významně se podílejí na progresi do dilatační kardiomyopatie (DCM).

Tabulka 1 – Příčiny myokarditid u dětí²

Infekční				
Viry	Bakterie	Spirochety	Houby	Rickettsie
Parvovirus B19	<i>Salmonella</i>	<i>Borrelia burgdorferi</i>	<i>Actinomyces</i>	<i>Coxiella burnetii</i>
Herpetické viry (HHV6, CMV, EBV)	<i>Brucella</i>	<i>Borrelia recurrentis</i>	<i>Aspergillus</i>	<i>Rickettsia prowazekii</i>
SARS-CoV-2	<i>Chlamydia</i>	<i>Leptospira</i>	<i>Blastomyces</i>	<i>Rickettsia rickettsii</i>
Adenovirus	<i>Clostridium</i>	<i>Treponema pallidum</i>	<i>Candida</i>	Protozoa
Enterovirus (Coxsackie A, B)	<i>Francisella tularensis</i>		<i>Coccidioides</i>	<i>Balantidium</i>
Influenza typu A, B	<i>Legionella</i>		<i>Cryptococcus</i>	<i>Entamoeba histolytica</i>
Hepatitida typu B, C	<i>Mycoplasma</i>		<i>Histoplasma</i>	<i>Leishmania</i>
RSV	<i>Mycobacterium tuberculosis</i>		<i>Nocardia</i>	<i>Plasmodium falciparum</i>
HIV	<i>Neisseria meningitidis</i>		<i>Sporothrix schenckii</i>	<i>Sarcocystis</i>
Příušnice	<i>Staphylococcus</i>		<i>Strongyloides stercoralis</i>	<i>Toxoplasma gondii</i>
	<i>Streptococcus A, pneumoniae</i>			<i>Trypanosoma brucei</i>
	<i>Vibrio cholerae</i>			<i>Trypanosoma cruzi</i>
Neinfekční				
Autoimunita/imunopatologie		Hypersenzitivita		
Součást vaskulitid	Kawasakiho nemoc	Léky	Antibiotika	Betalaktamy
	ANCA asociované vaskulitidy (EGPA, GPA)			Tetracykliny
PIMS-TS				Makrolidy
Součást autoimunitních onemocnění	SLE		Psychofarmaka	Benzodiazepiny
	JIA			TCA
	Zánětlivé myopatie (dermatomyozitida, polymyozitida)			Carbamazepin
	IBD			Fenytoin
	Systémová sklerodermie			
	Tyreotoxikóza			
	Myasthenia gravis	Drogy	Alkohol	
	Diabetes mellitus		Kokain	
	Revmatická horečka		Kanabis	
	Sarkoidóza	Toxiny		
Obrovskobuněčná myokarditida		Rejekce štěpu		
Myokarditida po mRNA vakcinaci proti covidu-19				

ANCA – antineutrofilní cytoplazmatické protilátky (anti-neutrophil cytoplasmic antibody); CMV – cytomegalovirus; EBV – virus Epstein-Barrův; EGPA – eozinofilní granulomatóza s polyangiitidou (eosinophilic granulomatosis with polyangiitis [syndrom Churgův-Straussův]); GPA – granulomatóza s polyangiitidou (granulomatosis with polyangiitis); HHV 6 – lidský herpes virus 6; HIV – virus lidské imunodeficiency; IBD – zánětlivé střevní onemocnění; JIA – juvenilní idiopatická artritida; PIMS-TS – syndrom multisystémové zánětlivé odpovědi spojený s covidem-19 (paediatric inflammatory multisystemic syndrome temporally associated with SARS-CoV-2); RSV – respirační syncytiální virus (respiratory syncytial virus); SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2; SLE – systémový lupus erythematosus; TCA – tricyklická antidepressiva.

Tabulka 2 – Anamnestické údaje, příznaky a jejich četnost při manifestaci myokarditidy u dětí²

Anamnéza (%)	Příznaky (%)	Fyzikální nález (%)
Prodromální virové příznaky (41–69)	Horečka (31–58)	Tachypnoe (52–60)
Dysrytmie (11–45)	Rýma (38–44)	Tachykardie (32–57)
Synkopa (4–10)	Kašel (17–44)	Hepatomegalie (21–50)
Náhlé úmrtí	Únava (25–70)	Šelest (26)
	Dušnost (35–69)	Cval (20)
	Zvracení a bolest břicha (28–48)	Nitkovité pulsy (16–21)
	Průjem (8)	Edém (7)
	Palpitace (16)	Cyanóza (2)
	Odmítání pití u kojenců	

Diagnostika

Symptomatologie

Diagnostiku myokarditidy znesnadňuje variabilní klinický obraz s nespecifickými příznaky, které mohou imitovat respirační nebo gastrointestinální onemocnění. Průběh pak může být velmi rozmanitý, od nenápadné tachykardie při virové infekci až po kardiogenní šok, nebo dokonce náhlé úmrtí. V novorozeneckém věku bývá průběh často fatální s těžkým srdečním selháním, naopak u adolescentů vidáme spíše obraz nekomplikované myokarditidy s bolestí na hrudi a elevací kardiálních enzymů, bez poruchy srdeční funkce a bez dysrytmií.¹⁴ Příznaky myokarditidy jsou jednak projevem daného infekčního nebo autoimunitního onemocnění a jednak důsledkem srdečního selhávání nebo dysrytmií (tabulka 2).²

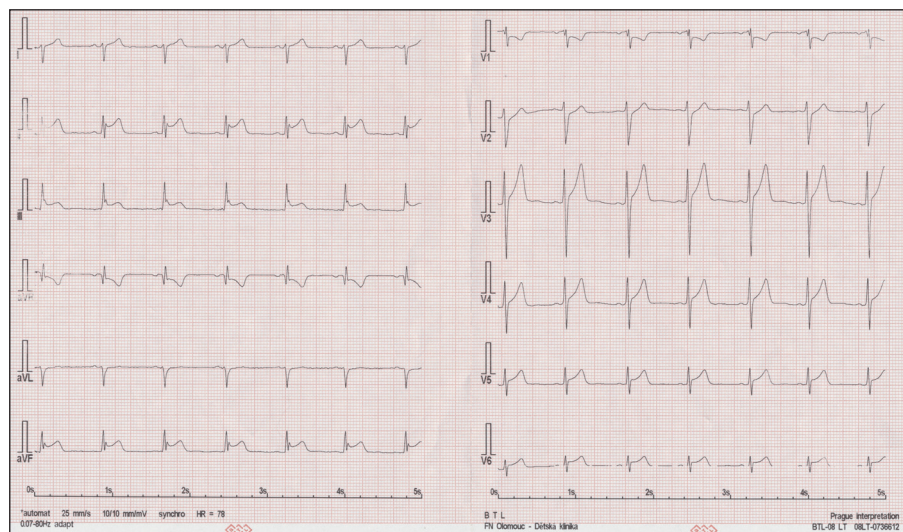
Laboratorní nálezy

U myokarditid zpravidla dochází k elevaci kardiálních enzymů. V současné době je běžně používán vysoce senzitivní (high sensitive, hs) troponin. Jeho zvýšení není specifické, stoupá u jakéhokoliv poškození myokardu, tedy nejen zánětem, ale i při kontuzi nebo ischemii srdce. Jeho koncentrace nekoreluje s prognózou myokarditidy.² Dal-

ším často využívaným parametrem je N-terminální fragment natriuretického propeptidu typu B (NT-proBNP), který koreluje se závažností srdečního selhání, odráží objemovou zátěž srdečních oddílů. Stoupá však i při systémových zánětech typu Kawasakiho nemoci nebo PIMS-TS, přestože je zachována myokardiální funkce. Při suspektní myokarditidě dále hodnotíme parametry zánětu, renální a jaterní funkce, koagulační parametry a chemické vyšetření moči. Při podezření na virovou myokarditidu se snažíme odhalit infekční agens metodou polymerázové řetězové reakce (PCR) z nazofaryngeálních stěrů, z krve nebo ze stolice (dle dané klinické situace). Výsledky nemusejí odpovídat virovému genomu v srdci, nicméně mohou pomoci vybrat antivirovou terapii. Vyšetření imunologických parametrů, včetně autoprotilátek, je indikováno cíleně při klinickém podezření na konkrétní autoimunitní systémové onemocnění. Pro úplnost se též iniciálně obvykle provádí skiagram hrudníku a ultrazvukové vyšetření břicha.

Elektrokardiogram

Při myokarditidě mohou být přítomny nejrůznější změny na EKG. Typicky se popisuje nízká voltáž, patologické vlny Q, změny úseků ST-T (obr. 3), nově vzniklé tachyarytmie,



Obr. 3 – Typické elektrokardiografické nálezy u akutní myokarditidy (změny úseků ST-T), zdroj vlastní (sedmnáctiletý chlapec s chlamydiovou myokarditidou)

komorové a síňové ektopie, prodloužené nitrokomorové vedení nebo AV blokády, případně sinusová tachykardie. EKG se v průběhu onemocnění mění a je třeba vyšetření provádět opakovaně.

Echokardiografie

Echokardiograficky můžeme zobrazit ztlustění stěny myokardu edémem. Může být patrná systolická nebo diastolická dysfunkce komor, případně regionální porucha kinetiky myokardu. Dilatace levé komory bývá většinou mírná, a pokud je výrazná, znamená horší prognózu. Dalším možným nálezem u myokarditidy je perikardiální výpotek, nově vzniklá mitrální nedomykavost či intrakardiální trombus.

Magnetická rezonance

CMR je schopna detekovat poškození tkáně ve smyslu edému, hyperemie a fibrózy. K dobrému posouzení přítomnosti myokarditidy a eventuálního odlišení od nezánettivé kardiomyopatie je potřeba použít kombinaci různých sekvencí (obr. 4). Konvenční kritéria, známá jako Lake Louise kritéria (LLC), byla původně stanovena pro neinvazivní diagnostiku myokardiálních změn ve všech stádiích myokarditidy. Časným syčením gadolini-

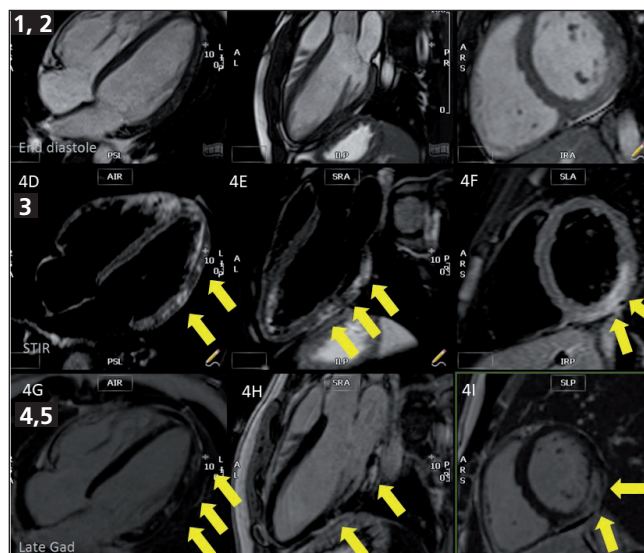
em (early gadolinium enhancement, EGE) v T1 vážených sekvencích lze detekovat intracelulární edém, hyperemii a kapilární únik, zatímco pozdní syčení gadoliniem (late gadolinium enhancement, LGE) identifikuje změny ireverzibilní. Nevýhodou LGE je vysoká citlivost na artefakty a neschopnost detekovat akutní změny u LGE (akutní zánět a intracelulární změny).¹⁵ Velikost srdce dítěte a rychlá srdeční frekvence jsou dalšími faktory, které ovlivňují kvalitu snímků. Navíc EGE a LGE vyžadují podání kontrastní látky a u menších dětí také nutnost celkové anestezie.

V posledních letech našlo parametrické zobrazování důležitou roli v kardiologii a používá se nejen jako marker srdečních onemocnění, ale také jako důležitý prognostický prediktor.¹⁶ T1 se prodlužuje s edémem a extracelulární expanzí (zánětem a fibrózou) a zůstává zvýšený, pokud se akutní zánět změní ve fibrózu, zatímco T2 primárně identifikuje obsah volné vody ve tkáních, a proto se normalizuje po odeznění akutních změn. Ačkoli je parametrické zobrazování spojeno s mnoha technickými složitostmi, dvě velké metaanalýzy prokázaly, že užití T1 a T2 mapování v akutní fázi je lepší než klasická LLC.^{17,18} Zejména T1 mapování, které se prodlužuje v přítomnosti edému a/nebo extracelulární expanze, má nejvyšší citlivost a specifitu u akutní myokarditidy (avšak méně v chronické fázi). S příznaky trvajících déle než dva týdny je T2 mapování jedinou možností, jak odlišit myokarditidu od nezánettivé kardiomyopatie.

Histologie

EMB je invazivní metoda, která je spojena s rizikem poranění srdce a u dětí i s riziky celkové anestezie. Důležitým momentem pro indikaci EMB je rozvaha o možnosti zachytu patologických změn myokardu, s čímž souvisí otázka lokalizace a počtu odebraných vzorků. EMB je v zásadě indikována pouze tehdy, pokud její výsledek může relevantně ovlivnit terapii a prognózu pacienta. Součástí vyšetření biotického vzorku musí být nejen histologie, ale i imunohistochemické vyšetření, které zlepšuje detekci zánětlivých buněk včetně jejich typizace, a PCR analýza k zachytu infekčního agens. Indikaci k EMB by mělo být podezření na eozinofilní či obrovskobuněčnou myokarditidu na základě klinického průběhu či laboratorních nálezů.^{14,19}

Diagnostický proces u myokarditidy je vždy založen na suspektní anamnéze a příznacích. Všichni pacienti s podezřením na myokarditidu by měli podstoupit opakované EKG, echokardiografické a laboratorní vyšetření kardiomarkerů. U hemodynamicky stabilních pacientů je vhodná CMR k potvrzení diagnózy. V případě těžkého průběhu s kardiogenním šokem a nedostatečnou odpovědí na inotropní podporu je prioritou zajištění pacienta v terciárním centru s dostupností mechanické podpory a extrakorporální membránové oxygenace (ECMO). V těchto případech je zpravidla indikována EMB, která může indikovat život zachraňující imunosupresivní léčbu, např. v případě potvrzení obrovskobuněčné nebo eozinofilní myokarditidy. U dětí s klinickým obrazem nebo anamnézou budící podezření na autoimunitní onemocnění nebo jiné imunopatologie indikujeme panel imunologických testů. U recidivujících



Obr. 4 – Srdeční magnetická rezonance (CMR) u třináctiletého pacienta s akutní myokarditidou, zdroj vlastní. 1. Normální indexované objemy levé komory s normální ejekční frakcí (EF = 61 %). Žádné regionální dyskineze. Levá komora bez hypertrofie. 2. Normální indexované objemy pravé komory s normální ejekční frakcí (EF = 55 %). Pravá komora bez hypertrofie. 3. Extenzivní myokardiální edém/zánět v bazální, inferiorní a inferolaterální stěně s přesahem apikálně do přední, septální a laterální stěny. Toto je patrné na: a) STIR zobrazeních; b) nativních T1 a T2 mapách, které prokázaly zesílený signál v bazální a střední části inferiorní a inferolaterální stěny. 4. Extenzivní nerovnoměrné subepikardiální fibrózy/nekrózy uprostřed stěny v bazální, inferiorní a inferolaterální stěně s přesahem do apikální části laterální stěny (spodní řada, pozdní syčení gadoliniem). 5. Normální tloušťka perikardu s minimálním perikardiálním výpotkem a lehkým perikardiálním syčením převážně kolem laterální stěny levé komory. Tyto nálezy jsou typické pro akutní myokarditidu/perimyokarditidu. Smyčky v prvním řádku (stejně jako echokardiografie) ukázaly normální nález. Avšak na zobrazeních s charakterizací tkáně (unikátní pro CMR) jsou patrné extenzivní změny kompatibilní s myokarditidou.

myokarditidy nebo familiárního výskytu je ke zvážení genetické vyšetření imunitních nebo neimunitních kandidátních genů.^{13,14}

Terapie

Léčba myokarditidy je zaměřena na zvládnutí komplikací, především srdečního selhání a dysrytmií. Pacient s myokarditidou by měl být hospitalizován na monitorovaném lůžku. Specifická léčba myokarditidy se zaměřuje na ovlivnění zánětu v srdci. Bohužel však jasný přínos těchto terapeutických možností (intravenózní imunoglobuliny, imunosuprese) nebyl prokázán. V akutní fázi by i pacienti s mírnou formou myokarditidy měli dodržovat klidový režim.

Poruchy srdečního rytmu jsou u pacientů s myokarditidou potenciálně život ohrožující. Ztráta sinusového rytmu může velmi rychle vést k nízkému srdečnímu výdeji – zvláště v kontextu snížené kontraktility. Přítomnost dysrytmií je rizikovým faktorem pro mortalitu a morbiditu. Tachyarytmie působící nestabilitu oběhu (supraventrikulární či komorová tachykardie nebo fibrilace) musí být vyřešena neprodleně elektrickou kardioverzí či defibrilací. Případy tachykardií na podkladě reentry okruhu terminovatelných adenosinem jsou u pacientů s myokarditidou vzácné. U recidivujících tachyarytmií (fokální síniová tachykardie, četná komorová ektopie či komorové tachykardie) je indikována antiarytmická léčba. Většina antiarytmik působí na myokard negativně inotropně a při jejich použití je třeba opatrnosti, protože mohou způsobit nestabilitu oběhu. Výběr konkrétního léku nemusí být jednoduchý a řídí se konkrétním pacientem a klinickou situací. Mezi používané léky patří např. amiodaron, beta-blokátory nebo lidokain. V případě výskytu závažné bradyarytmie, většinou na podkladě nově vzniklé pokročilé AV blokády v zánětlivém terénu, je indikována stimulace transvenózně zavedenou dočasnou elektrodou. Tyto převodní poruchy jsou většinou přechodné s dobrou šancí na zotavení AV převodu.²

Terapie srdečního selhání závisí na celkovém stavu pacienta. U pacientů v klinicky dobrém stavu a s echokardiograficky mírně sníženou ejekční frakcí je indikována léčba inhibitory angiotenzin konvertujícího enzymu (ACEI), případně beta-blokátory či digoxinem. Při závažnějším srdečním selhání s výraznější klinickou symptomatologií volíme převážně intravenózně podané léky a kompletní invazivní zajištění pacienta. Při známkách městnání (otoky, hepatomegalie, snížená kolapsibilita dolní duté žíly, přítomnost výpotků) podáváme diuretika, nejčastěji furosemid se suplementací draslíku. Při nízkém srdečním výdeji (chladná periferie, prodloužený kapilární návrat, hypotenze, oligurie) je často nutná inotropní podpora katecholaminy (dobutamin či dopamin, při nedostatečném efektu adrenalin) a tekutinová resuscitace. Inodilatátor milrinon má u dětí se srdečním selháním řadu příznivých účinků včetně plicní vazodilatace, kvůli jeho převažujícímu vazodilatačnímu efektu ho však nemusí akutně selhávající pacient tlakově tolerovat. Před jeho podáním je také nutno doplnit pacientovi cirkulující objem. Kalciový senzitizer levosimendan používáme u nejtěžších přípa-

dů. Podává se většinou v infuzi na 48 hodin a jeho aktivní metabolity poté přetrvávají v organismu více než jeden týden.²⁰

Zlepšit přísun kyslíku do tkání můžeme rovněž pomocí ventilačních manévrů. U pacientů ve stabilním stavu postačí oxygenoterapie, u těžších případů může být nutná neinvazivní nebo invazivní ventilace. Obecně má ventilace pozitivním přetlakem u pacientů se srdečním selháním příznivé účinky (snížení dechové práce, snížení afterloadu pro levou komoru). U pacientů s myokarditidou s fulminantním průběhem a srdečním selháním refrakterním na medikamentózní léčbu je možné využít některý typ mechanické podpory oběhu.²

Po odeznění akutní fáze onemocnění je při trvání myokardiální dysfunkce indikována perorální léčba srdečního selhání, především ACEI, betablokátory, digoxin, v případě městnání diuretika.

Antivirová léčba se v současné době doporučuje při známkách probíhající virové infekce a pozitivitě PCR konkrétního viru. Eliminuje se tak spouštěč, který dále potencuje imunitní odpověď pacienta a může zhoršovat poškození myokardu. Antivirová léčba je zatím v České republice spíše opomíjena. Je dostupná pro lidský herpes virus (aciclovir), cytomegalovirus (ganciclovir), chřipku (oseltamivir), SARS-CoV-2 (remdesivir, do 40 kg v režimu off-label), pro adenoviry (cidofovir od 18 let) a enteroviry (interferon-beta).^{2,21}

Podání intravenózních imunoglobulinů (IVIG) v dávce 2 g/kg (v infuzi během 24–48 h) je indikováno u dětí s akutní myokarditidou pro jejich imunomodulační účinek.²² Příznivý efekt na zlepšení srdeční funkce byl popsán na malých počtech pacientů a nebyl prokázán ve velkých studiích.²³ Obecně jsou většinou podávány u dětí s myokarditidou s komplikovaným průběhem, tedy se sníženou srdeční funkcí nebo arytmiemi. Výhodou je nízké riziko nežádoucích účinků a možnost podání i během akutní fáze v kontextu probíhající virové infekce, kdy kortikosteroidy zpravidla nezvažujeme.

Kortikosteroidy jako imunosupresivní terapie jsou jednoznačně indikovány u dětí s obrovskobuněčnou nebo eozinofilní myokarditidou a v rámci léčby systémových autoimunitních onemocnění.² U lymfocytární myokarditidy je použití imunosuprese diskutabilní, protože zlepšení prognózy pacientů nebylo jednoznačně prokázáno a nežádoucích účinků je řada. Cílem léčby je zmírnění autoimunitního zánětu v myokardu, kortikosteroidy se používají většinou v kombinaci s cyklosporinem A nebo azathioprinem. Na základě studií provedených u dospělých současná doporučení podmiňují zahájení imunosuprese průkazem myokarditidy v EMB a zároveň vyloučením přítomnosti virového genomu v myokardu.²¹

Většina pacientů s myokarditidou antikoagulační či antiagregační léčbu nevyžaduje. Zvažujeme ji u případů s velmi těžkou dysfunkcí levé komory s rizikem vzniku trombu. Jasná doporučení neexistují. Antikoagulační léčbou by měli být zajištěni pacienti se srdečním selháním v souvislosti s probíhajícím nebo proběhlým covidem-19, neboť v tomto případě se zároveň jedná o prokoagulační stav.

Shrnutí diagnostického a léčebného postupu dle stratifikace pacientů přináší obrázek 5.¹⁴

NEKOMPLIKOVANÁ MYOKARDITIDA		KOMPLIKOVANÁ MYOKARDITIDA	
	Akutní bolest na hrudi	Srdeční selhání/ synkopa	Hemodynamická nestabilita
Laboratoř	• ↑ Troponin	• ↑ Troponin	• ↑ Troponin
Echokardiografie	• Normální velikost a funkce LK, hemodynamicky stabilní	• Ejekční frakce < 50 %, normální velikost nebo mírná dilatace LK	• Těžká srdeční dysfunkce, LK dilatovaná, kardiogenní šok
EKG	• Bez dysrytmie, nebo ST-T patologie	• AV blokáda II–III, komorové dysrytmie	• Život ohrožující dysrytmie
TRVALÁ MONITORACE, OPAKOVANĚ LABORATOŘ, EKG A ECHOKARDIOGRAFIE, ANTIVIROTIKA PŘI PROKÁZANÉ AKUTNÍ INFEKCI			
Umístění pacienta	• Monitorované lůžko	• JIRP	• Terciární centrum
Další diagnostika	• CMR • Vyloučení autoimunitního onemocnění • Recidivy – genetické vyšetření	• CMR • Zvážit EMB • Vyloučení autoimunitního onemocnění	• EMB • CMR až po stabilizaci
Léčba	• Event. symptomatická léčba	• Léčba dysrytmií a srdečního selhání • IVIG	• Inotropika/mech. srdeční podpora • IVIG • Event. imunosupresivní léčba

Obr. 5 – Shrnutí diagnostického a léčebného postupu dle stratifikace pacientů, zdroj vlastní a upraveno dle ¹⁴. Pozn.: Indikace srdeční magnetické rezonance (CMR) u nekomplikované myokarditidy může být regionálně odlišná v závislosti na dostupnosti tohoto vyšetření.

Sledování a prognóza

Děti po prodělané myokarditidě zpravidla sledujeme do normalizace srdeční funkce a vymizení dysrytmií, minimálně však jeden rok po akutním onemocnění. Neomezený sport je povolen nejdříve za tři až šest měsíců za předpokladu normálního echokardiografického nálezu, nízkých kardiomarkerů a absence závažných dysrytmií při holterovském monitorování a ergometrii. Po podání IVIG se doporučuje očkování živou vakcínou nejdříve za 11 měsíců.²⁴ Diskutuje se také přínos kontrolní CMR s odstupem po akutní fázi. Zatím není jasné, zda by normální kontrolní CMR mohla být argumentem pro ukončení případné terapie ACEI, která má předcházet nepříznivé remodelaci srdce.²

Přežití u dětí s myokarditidou se pohybuje mezi 70–100 %, dvě třetiny dětí se zcela uzdraví. Negativním prognostickým faktorem je těžká dysfunkce levé komory s ejekční frakcí < 35 % a významná dilatace levé komory.²⁵ Z této podskupiny jedna třetina dospěje k transplantaci srdce a u poloviny se vyvine dilatační kardiomyopatie.²⁶

Akutní či fulminantní myokarditida ohrožuje pacienta na životě v počátku onemocnění a vždy vyžaduje intenzivní péči. Akutní zánět však většinou rychle vzniká a poté rychle ustupuje, a tak je dlouhodobá prognóza dobrá a šance na zotavení srdeční funkce vysoká, pokud pacient přežije akutní fázi onemocnění.²⁷ Naproti tomu chronický mírný zánět se nemusí dlouhou dobu projevit klinicky, ale způsobuje patologickou remodelaci myokardu a progresi do chronického srdečního selhání.

Závěr

Řada příčin myokarditidy uváděných v literatuře se v našich podmínkách vyskytuje minimálně. Téměř výhradně se setkáváme s viry, případně myokarditidami v rámci vaskulitid. V diagnostice je výrazným posunem CMR, která ale vyžaduje přesné nastavení přístroje, hodnocení kombinace různých sekvencí a velmi zkušeného radiologa. U laboratorních metod se objevuje tendence přece-

ňovat NT-proBNP, který má jistě svůj smysl vstupně a případně v dlouhodobém sledování u pacientů s progresí do dilatační kardiomyopatie. Dále je nutné si uvědomit, že u Kawasakiho nemoci nebo PIMS-TS výrazně stoupá i bez poruchy srdeční funkce. U těchto diagnóz může být NT-proBNP součástí diagnostických kritérií. V terapeutických postupech je opomíjeno použití antivirotik. V případě jejich dostupnosti, například pro chřipku, herpetické viry, apod., se přikláníme k jejich podání za předpokladu známek akutní infekce, a to i při průkazu viru pouze z periferních tkání. Většina pracovišť indikuje podání IVIG při komplikované myokarditidě, tedy při poruše funkce nebo nově vzniklých dysrytmích. Jejich podání při nekomplikované myokarditidě (tj. bez srdečního selhání) nepovažujeme za smysluplné.

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Prosthetic valve thrombosis: literature review and two case reports

Kotryna Druteikaitė^a, Simona Bėrontaitė^a, Gintarė Valterytė^b,
Gediminas Jaruševičius^{b,c}

^a Faculty of Medicine, Academy of Medicine, Lithuanian University of Health Sciences, Kaunas, Lithuania

^b Department of Cardiology, Lithuanian University of Health Sciences Kaunas Clinics, Kaunas, Lithuania

^c Cardiology Institute, Lithuanian University of Health Sciences, Kaunas, Lithuania

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SOUHRN

Trombóza umělé srdeční chlopně představuje jednu z nejzávažnějších komplikací implantace této chlopně. Zabránit vzniku této komplikace pomáhá řádné monitorování a péče o tyto pacienty. V případě trombózy je pro zhodnocení funkce umělé chlopně měřením úhlů otvírání a zavírání chlopně výhodné fluoroskopické vyšetření. Popisujeme dva případy trombózy mechanické aortální chlopně s různými mechanismy vzniku trombu. První případ se týkal 48leté ženy hospitalizované pro dušnost při minimální námaze a výrazně snížené toleranci zátěže. Vzhledem k přítomnosti revmatické choroby srdeční byly pacientce implantovány umělé aortální a mitrální chlopeň s podáváním warfarinu v terapeutických dávkách. Echokardiografické vyšetření prokázalo obstrukci mechanické aortální chlopně a těžkou regurgitaci trojicípe chlopně. U pacientky byla indikována operace aortálního kořene a implantace umělé trojicípe chlopně. Druhému pacientovi byla rovněž implantována mechanická aortální chlopeň pro těžkou aortální stenózu v důsledku revmatické choroby srdeční; ten se k lékaři dostavil s organizující pneumonií a progredujícím respiračním selháním jako komplikacemi onemocnění covid-19 a byl hospitalizován s dyspnoe, kašlem a celkovou slabostí. Přes optimální léčbu a terapeutickou hodnotu INR byla u pacienta stanovena diagnóza trombózy umělé aortální chlopně.

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ABSTRACT

Prosthetic heart valve thrombosis is one of the most dangerous prosthetic valve complications. Proper monitoring and management of these patients help to prevent this complication. Fluoroscopy is advantageous in cases of thrombosis to assess the function of the prosthetic valve by measuring opening and closing angles. We describe two cases of aortic mechanical valve thrombosis with different mechanisms of thrombus formation. The first case was a 48-year-old woman admitted to the hospital because of shortness of breath during minimal exertion and significantly reduced exercise tolerance. Due to rheumatic heart disease the patient underwent aortic and mitral mechanical prosthesis and has been using warfarin in therapeutic norms. During echocardiography aortic prosthesis obstruction and severe tricuspid valve regurgitation were observed. The patient was scheduled for aortic root and TV prosthesis surgery. The second patient also had aortic mechanical valve due to severe aortic stenosis caused by rheumatism and presented with organizing pneumonia and progressing respiratory failure as complications of the COVID-19 infection and was admitted with dyspnea, cough, and weakness. Aortic prosthetic valve thrombosis was diagnosed despite optimal treatment and therapeutic INR.

Keywords:

Aortic valve

Mechanical prosthesis

Prosthetic valve thrombosis

Address: Simona Bėrontaitė, MD, Faculty of Medicine, Academy of Medicine, Lithuanian University of Health Sciences, Kaunas, Lithuania,
e-mail: simun147@gmail.com

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Introduction

Prosthetic heart valve thrombosis (PVT) is an uncommon but usually life-threatening condition. PVT is a cause of valve prosthesis dysfunction and a complication of valve replacement surgery, occurring in any part of the heart valve prosthesis.¹ The exact rate of valve thrombosis is not known, but some authors estimate that incidence ranges from 0.5% to 6% per patient per year in the aortic and mitral position and up to 20% in the tricuspid position.² The main factors influencing the development of PVT are inappropriate treatment by anticoagulants, thrombogenicity of the valve and hemodynamics of the transprosthetic blood flow.³ Although thrombus formation is less frequent with new surgical techniques, the hemodynamic and physical properties of mechanical valves remain thrombogenic.⁴ The purpose of this article is to review the epidemiology, clinical features, diagnosis and updated management according to current guidelines of PVT.

Indications for aortic valve replacement, prosthetic valve thrombosis etiology, and risk factors

In Europe alone more than 13 million people are diagnosed with valvular heart disease (VHD) each year and 100 million worldwide.⁵ Aortic valve (AV) disease is the most common among valvular conditions (44.3% of all VHD)⁶ and surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) are the main treatment for this condition.⁷ Worldwide the number of AV replacement in 2003 was 290,000 and by 2050 is predicted to be 850,000.⁸ According to the latest ESC/EACTS guidelines, indications for AV replacement are severe symptomatic aortic regurgitation or asymptomatic aortic regurgitation in patients with left ventricular end-systolic diameter (LVESD) >50 mm or LVESD >25 mm/m² body surface area (BSA) in patients with small body size or resting left ventricular ejection fraction (LVEF) ≤50%. In case of aortic root or tubular ascending aortic aneurysm surgery is indicated in patients with Marfan syndrome who have aortic root disease with a maximal ascending aortic diameter ≥ 50mm or aortic dilation, if performed in experienced centers and durable results are expected. In addition to, AV replacement is recommended in symptomatic patients with severe, high-gradient aortic stenosis or in symptomatic severe low-flow, low-gradient aortic stenosis with LVEF <50% and evidence of flow (contractile) reserve.⁹ Each surgery has its own risks and one of the most common complications in valve replacement is PVT. Prosthetic valve dysfunction depends on the valve that has been implanted and on the procedure (SAVR or TAVI). Usually the suitable valve is selected based on the following risk factors: anticoagulant-related bleeding and valve deterioration. Antithrombotic therapy slows down but does not eliminate the risk of PVT, which also depends on the patient's lifestyle, metabolic profile or inflammatory status, especially in the case of TAVI.¹⁰ Predisposing factors for thrombosis include a high body mass index, male sex, bicuspid AV and a large aortic root requiring a large sized prosthesis.¹¹ There are several de-

scribed mechanisms causing PVT, one of them is surface-induced thrombosis, which is well described in mechanical valves and other medical devices. The exposure of valve prostheses to blood leads to a thrombogenic process that results in formation of thrombin, platelet activation, and the formation of platelet-fibrin networks on the surface of the prosthesis. Transcatheter aortic valves are also associated with pathological processes – thromboembolic events commonly found in the first 3 months after the procedure. One hypothesis is that, because the original valve is not removed during TAVI but left in place, the leaflets of native valves still contain high levels of tissue factor, which enhances platelet activation.¹²

Mechanical aortic valve thrombosis

Mechanical AV replacement is recommended for patients who are younger than 60 years and have no contraindications to long-term anticoagulation.¹³ Mechanical AV prostheses are characterized by their robust structure and a long service life. Monoleaflet valves are composed of a single disc with an opening angle relative to the valve annulus ranging from 60° to 80°, resulting in 2 different sized orifices. Bileaflet valves consist of 2 semilunar discs, the opening angle of the discs varies from 75° to 90° and the open valve consists of 3 orifices.¹⁴ When a mechanical valve is implanted, patients are at a high risk of stroke and valve thrombosis and require long-term anticoagulant treatment. The risk of PVT is higher for mechanical mitral valves (0.9% of cases per year) than for mechanical AV (0.5% of cases per year). Long-term anticoagulation reduces the annual risk of PVT from 1.8% to 0.4%.¹⁵ PVT is a serious complication occurring in 0.5–8% of mechanical mitral and AV prosthesis.¹⁶ Thrombus formation is more frequently observed in the mechanical valve than in the bioprosthetic, presumably due to inadequate anticoagulant use, and is associated with atrial fibrillation (AFib) and poor cardiac function.¹⁷ However, Maribas et al. reported that valve thrombosis is similarly frequent in patients with bioprosthetic valves and in those with mechanical valves who are consuming adequate anticoagulant therapy.¹⁸

Biological aortic valve thrombosis

The incidence of biological prostheses in middle-aged patients has increased in the last decade due to the improved durability of newer generation prosthesis, the reduced risk of reoperation for a degenerated aortic biological prosthesis, and emerging data on the unsuccessful outcome of TAVI in high-risk patients.¹⁹ Although biological prostheses do not require anticoagulant therapy, they are subject to structural valve degeneration, resulting in limited durability, which lasts between 10–15 years and exposes the patient to the risk of reintervention.²⁰ Surgical biological AV prostheses are made of biological tissue and can be xenogenic or allogenic as well as stented or stentless.²¹ Meta-analysis of aortic bioprosthesis estimates the incidence of PTV at 0.03 per 100 patients per year.²² Due to similar transvalvular flow gradients mechanical

and transcatheter valves are homogeneous in terms of thrombogenic potential while bioprosthesis remains the least thrombogenic prosthetic valve.²³

Transcatheter aortic valve thrombosis

Since first TAVI was performed in 2002, the rate of this procedure has raised enormously, with more than 50 000 having been performed worldwide, the vast majority of them in Europe.²⁴ In cases of severe aortic stenosis and appropriate heart anatomy, TAVI is the best treatment option.²⁵ Although current literature declares that SAVR is more likely to cause bleeding complications, acute kidney insufficiency and new arrhythmias,²⁶ TAVI is associated with higher rates of permanent pacemaker implantation, paravalvular regurgitation and vascular complications.²⁷

During the TAVI procedure, the tissue valve is implanted by balloon dilation or self-expansion. They are inserted percutaneously, using a transfemoral access in 90%²⁸ of cases, and the aortoventricular angle during the procedure must be $> 60^\circ$.²⁹ PVT after TAVI is rare, with an estimated incidence of approximately 0.61–2.8% based on echocardiography or cardiac CT angiography.³⁰ Risk factors for PVT include balloon-expandable valves, large valve prosthesis size, inappropriate valve expansion, patient-prosthesis mismatch and valve-in-valve TAVI.³¹ Researchers are currently attempting to prove that stasis in the neosinus between the native AV leaflets and the TAVI leaflets may be a major contributor to the formation of PVT, and quantification of stasis using patient-specific in vitro modeling has shown that it correlates with the extent of thrombosis.³² Bioprosthetic valves, both surgical and transcatheter, have better hemodynamic properties than mechanical valves, therefore the antithrombotic therapy is needed during the endothelialization process in the first 3–6 months after surgery. Although oral anticoagulants have been shown to reduce the incidence of leaflet thrombosis, the routine use of an oral anticoagulant after TAVI leads to excessive bleeding, and studies are currently underway to investigate whether the use of anticoagulants therapy will be demanded after TAVI in the future.³³

Indications for mitral valve replacement and risk factors

Based on 2020 ACC/AHA guidelines for the management of patients with VHD, mitral valve (MV) surgery is indicated for symptomatic severe primary mitral regurgitation (MR) when LVEF is above 30% and asymptomatic severe primary MR in patients with severe, chronic disease and left ventricular dysfunction with LVEF of 30% to 60%, or LVESD of at least 40 mm. For secondary MR valve replacement is indicated when patients do not have severe ventricular dysfunction and are symptomatic despite optimal medical therapy or while undergoing concomitant coronary artery bypass grafting.²⁰ Myllykangas' study in Finland that included 3684 patients shows that the annual prevalence rates of mitral surgery during the study period was 3.9/100 000. 62.4% of these procedures were

MV repairs and 37.6% were MV replacements. The mean age of MV surgery patients is 66.0 years and 33.4% of the patients were women.³⁴ The ideal time for MV surgery is when the patient's left ventricle approaches but has not yet reached the parameters that indicate systolic dysfunction (LVEF $\leq 60\%$ or LVESD ≥ 40 mm).³⁵ MV replacement is recommended for patients with moderate to severe mitral stenosis (mitral valve area ≤ 1.5 cm²) who have NYHA class III or IV symptoms, are not at high risk for surgery, and have an MV not amenable to either percutaneous mitral balloon commissurotomy or open commissurotomy/repair.²⁰ The opening and closing angles determined by 64-slice multidetector CT were 10.9 ± 0.6 and 131.1 ± 3.2 for the MV.³⁶ Main factors for development of mitral PVT are hemodynamic (local blood flow turbulences, relatively slow blood flow in case of AFib, atrial dilation or low LV output), hemostatic (tissue injury), surface (leaflet injury, prosthesis malposition, incomplete prosthesis endothelialization).³⁷

Mechanical mitral valve

Mitral PVT is two- to threetimes more common than aortic prosthetic thrombosis. The annual rate of PVT ranges from 0.1% to 5.7%, with higher rates in the early perioperative period and in association with subtherapeutic anticoagulation.³⁸ For patients undergoing prosthetic MV replacement surgery, the decision regarding the choice of prosthesis mechanical or bioprosthetic is based on the need for anticoagulation with mechanical valves, the belief of improved durability with current bioprostheses, and patient risks for reoperation.³⁹ Mortality rates of patients who receive a mechanical valve are equal to those of patients who receive a bioprosthetic valve. Mechanical prosthetic valves (MPV) are associated with lower risk of reoperation but increased risk of bleeding and stroke.⁴⁰ Lifelong anticoagulation using oral vitamin K antagonists (VKA) is required for all currently available mechanical MV prostheses. Newer anticoagulants have not shown to be safe or effective in patients with MPV. Anticoagulation with a VKA might be reached with an acceptable risk in most patients younger than 50 years, particularly if there is appropriate monitoring of INR levels. Mechanical valve in patients < 50 years of age is chosen more frequently due to more favorable balance between valve durability and risk of bleeding and thromboembolic events, unless anticoagulation is not desired, cannot be monitored, or is contraindicated.²⁰ The intensity of anticoagulation depends on the characteristics of prosthetic valve, e.g., bileaflet or tilting disc, and patient factors such as a history of thromboembolism, AFib, left atrial enlargement, left ventricular dysfunction with the target INR of 3.0 for modern bileaflet mechanical MV prostheses.⁴¹

Biological mitral valve

Biological heart valves should be chosen in patients with shorter anticipated survival or comorbidities that may lead to reoperations, and those who are at increased risk for bleeding. Bioprostheses are recommended for pati-

ents >70 years of age or those in whom life expectancy is shorter than the expected bioprosthetic valve durability. Thromboembolic complications are less frequent in pregnant women with biological bioprostheses than mechanical.⁴² Butnaru's case reported an incidence of 6% mitral bioprosthetic valve thrombosis out of 149 MV replacement surgeries over 10-year period, two thirds of whom showed resolution of symptoms.⁴³ A significant amount of implanted mitral bioprosthesis degenerate over time and need further treatment due to clinically significant prosthetic stenosis or regurgitation.⁴⁴ Between 60–70% of patients who undergo MV replacement surgery receive a bioprosthetic valve.³⁹ It was reported that patients between 40 to 69 years of age who receive a bioprosthetic MV have significantly higher 15-year mortality rates compared with those who received a mechanical MV.⁴⁵

Transcatheter mitral valve replacement

Together with developing transcatheter MV repair, investigators are improving methods for transcatheter MV replacement (TMVR).⁴⁶ Compared with transcatheter AV replacement, TMVR has been more challenging because of the size, location and anatomy of the MV, and the risk of left ventricular outflow tract obstruction.⁴⁷ TMVR for patients who have severe primary MR is a safe alternative when there are contraindications for surgery or operative risk is high.⁴⁸ As patients are carefully selected to avoid the failure of intervention, rejection rates for TMVR have been about 60% to 70%. Recent developments demonstrate the promise of increasing the population that could be treated, for example, using a transeptal or transapical approach. Procedure success rate was high but has some limitations due to intracardiac maneuverability and sheath sizes.⁴⁹ Advancing the development of TMVR is critical, as MR is the most common valvular lesion in the world, and substantial advances in treatment of heart failure (HF) has led to an aging population with MR who may be at either high or prohibitive risk for open surgery.⁵⁰

Mechanical tricuspid valve

According to 2020 ACC/AHA guidelines surgical treatment for tricuspid valve (TV) is an option for patients with tricuspid regurgitation (TR) at the time of surgery for left-sided valve lesions to treat symptomatic or asymptomatic severe regurgitation or to prevent further development of severe regurgitation. Surgical intervention should also be considered for selected patients with isolated TR in the absence of pulmonary hypertension (PH) or dilated cardiomyopathy. MPV are rarely implanted in the right heart, mainly because of their important thrombogenicity. TV replacement is needed when repair is unfeasible because of the marked leaflet tethering, complex primary TR with tricuspid annulus diameter >40 mm, or severe tricuspid stenosis with valve area ≤ 1.0 cm² with the manifesting symptoms of right ventricular malfunction, such as peripheral edema and ascites.⁵¹ The mean age of the surgery is 52.3±8.8 years and 66.7% are females.⁵²

Thrombosis is the most important and common complication of the prosthetic TV and is 20 times more likely in the tricuspid position (the reason is the lower pressure of the right system, the right ventricular morphology, and the low prostacyclin concentration of venous blood) during the first post-operative year compared with the AV and MV.⁵³ Mechanical valves have desirable hemodynamic properties, low gradients, low disturbances in flow, and long durability. The normal range of the opening angle is 60–80° for tilting disc valves and 73–90° for bileaflet valves.⁵⁴ MPV are preferred in younger age groups as well as patients with another mechanical valve.⁵⁵

Biological tricuspid valve

The advantage of the bioprosthetic valves is that they do not require long life anticoagulation in contrast to the mechanical valves and cause a higher risk for thromboembolism and hemorrhage.⁵⁶ Because of the lower risk of thromboembolism, many surgeons favor bioprosthetic valves but the choice of the type of prosthesis should be individual, considering the patient's age, condition, and concomitant cardiac or non-cardiac diseases.⁵⁷ Low pressure and stress in the right heart provides higher durability for the bioprosthesis compared to the left sided prosthetic valves and requires less reoperations compared with mechanic valve as well.⁵⁸ The average time for failure of tricuspid bioprosthesis is 7 years.⁵⁹ There are no differences between the mechanical and tissue valves in survival rate. Patients who receive bioprostheses must be carefully evaluated with periodic echocardiograms, especially after 7 to 10 years, for detecting clinical and subclinical signs of structural valve degeneration.⁶⁰

Clinical presentation and diagnosis

The clinical presence of PVT varies depending on whether there is an obstruction. Severe obstructive PVT (OPVT) is usually associated with HF, while a non-obstructive PVT (NOPVT) is often an accidental finding or presents as an embolic episode. When obstruction is partial it results in dyspnea, systemic embolism or fever. In the presence of fever diagnostic blood cultures should be performed to prevent or to diagnose infectious endocarditis early. Concentrations of D-dimers may be affected and increased. A detail physical examination should be performed, examining for the suppression or disappearance of prosthetic sounds and the occurrence of new regurgitating or obstructive murmurs, especially if PVT is suspected for the first time. The initial diagnostic tests are transthoracic echocardiogram (TTE) and cinefluoroscopy.⁶¹ Echocardiographic features that might help to suspect PVT are an acute increase in valve gradient of more than 50% over 5 years, thickening of the valve leaflet (>2 mm) downstream of the valve, decreased or limited leaflet mobility, and regress of echocardiographic abnormalities within 1–3 months of anticoagulant therapy. Cinefluoroscopy helps to assess the movement of the leaflets in mechanical valves. Nevertheless, for cinefluoroscopy a suitable patient position is required and this examination is time

consuming. Conversely, the valve can be reoriented in any CT plane. CT offers optimal visualization of valve profiles and it does not depend on valve position, neither patient physical characteristics. CT complements TTE and cinefluoroscopy by performing a functional and morphological evaluation of the mechanical valve as it combines the measured values of the opening and closing angles with other information like the size of the valve or the presence of a thrombus or pannus.⁶²

Thrombosis of prosthetic heart valves: treatment

Main therapeutic modalities considered when PVT is diagnosed: surgery, fibrinolysis, heparin treatment or optimization of anticoagulant and antiplatelet therapy. Treatment depends on the presence of obstruction and prosthesis location but prosthesis type does not have an importance in choosing a treatment.

Right-sided obstructive and non-obstructive PVT

Right-sided thrombosis is much more frequent than left-side. Although there are no formal prospective studies evaluating different treatment modalities, intensified anticoagulation should be the first choice of treatment in patients with right-sided NOPVT. Patients with obstructive TV thrombosis usually present with signs of right HF, such as peripheral edema and ascites, and the prosthetic valve click may be inaudible during the auscultation. TTE and transesophageal echocardiography (TEE) can reveal the increased echogenicity on the prosthesis, decreased movement of the disc, and an elevated prosthetic valve gradient. The treatment of choice in right-sided OPVT is thrombolytic therapy, fibrinolytic agents are associated with a high success rate and a low complication rate. Surgery should be reserved for cases of thrombolytic failure, and contraindication to thrombolysis. Replacement of the mechanical TV with a bioprosthesis can be considered in patients with failed thrombolysis, recurrent thrombosis, evidence of pannus or contraindications to thrombolytic therapy.⁶³

Non-obstructive left-sided PVT

Management can be divided according to the size of thrombus. Fibrinolysis has been performed with success for small non-obstructive thrombi, but also with a significant risk of systemic embolism. The prognosis is favorable with medical therapy by optimization of anticoagulant treatment (short-term intravenous unfractionated heparin followed by warfarin adjustment and aspirin addition) for small asymptomatic thrombi (length <10 mm). If thrombus size is increased or is complicated by embolism, thrombolytic therapy or surgery should be considered.⁶⁴ In all cases of PVT, anticoagulant treatment has to be optimally adjusted. Surgery is recommended for large (≥ 10 mm) NOPVT complicated by embolism or which persists

despite optimal anticoagulation.⁶⁵ Fibrinolysis should also be considered if surgery is at high risk.

Left-sided obstructive PVT

The treatment includes surgery (thrombectomy or valve replacement), thrombolytic therapy, and heparin. After a diagnosis has been made, heparin treatment should be started immediately. Surgery is recommended for patients in NYHA functional classes III–IV, unless it is at high risk. Surgery is also indicated for critically ill patients and restrict thrombolysis to patients with high surgical risk (thrombus area [2D TEE] >0.8 cm² and thrombus diameter 1.0 cm is associated with increased embolic risk and the rate of complications increases 2.4 times per 1.0 cm² increase in size, which makes surgery a better option.⁶⁶ Outcomes have been better with thrombolytic therapy, therefore it is suggested that thrombolytic therapy would be the treatment of choice in all cases except for patients with contraindications to these agents.

In hemodynamically unstable patients fibrinolysis should consist of recombinant tissue plasminogen activator (rtPA) 10 mg bolus + 90 mg in 90 min, or streptokinase 1 500 000 U in 60 min without heparin. While in hemodynamically stable patients: urokinase 4500 U/kg/h over a 12 h period, or 2000 U/kg/h + heparin over 24 h, streptokinase 500 000 IU in 20 min followed by 1 500 000 IU for 10 h without heparin or rtPA 10 mg bolus, 50 mg during the first hour, 20 mg during the second hour and 20 mg during the third hour.⁶¹

Prevention

Long-term anticoagulation is required to prevent thromboembolism after mechanical heart valve replacement, its value in patients receiving bioprostheses is uncertain.⁶⁷ Moderate-intensity anticoagulant therapy (INR of 1.5 to 2.0) was reported to be safe and feasible for preventing thromboembolic complications in high-risk surgical patients who are receiving long-term oral anticoagulant therapy. The study included 18% patients with a mechanical valve.⁶⁸ Patients with mechanical or bioprosthetic valves should receive antibiotic prophylaxis before some dental and surgical procedures to prevent endocarditis.⁶⁹ Nowadays, new generation of smart heart devices is capable of auto-detecting valve status and able to measure specific markers in plasma that could predict prosthetic HF. For bioprostheses, several markers have been identified as predictors of structural valve degeneration: the ratio apoB/apoA-I; lipoprotein-associated phospholipase A2 (Lp-PLA); the ratio of oxidized low-density lipoprotein and high-density lipoprotein (OxLDL/HDL); proprotein convertase subtilisin/kexin 9 (PCSK9) levels.⁷⁰ In addition, to solve geometry issues like patient-prosthesis mismatch latest technologies use stereolithographic 3D printing models based on X-ray CT scans of native valves.⁷¹ Using this technology it becomes possible to produce a tailor-made prosthetic valve, made of tissues or polymers that would mimic the native valve with a minimal error. In patients with suspected bioprosthetic

valve thrombosis who are hemodynamically stable, a trial of anticoagulation should be considered. It is also crucial to recognize the difference between structural valve degeneration and bioprosthetic valve thrombosis as a cause of prosthetic valve dysfunction as the treatment differ. Thrombolysis or secondary surgical intervention could be suggested in patients who do not respond to anticoagulation therapy or are hemodynamically unstable.⁷²

Case 1

A 48-year-old woman was referred to Lithuanian University of Health Sciences (LUHS) Kaunas Clinics, Department of Cardiology suffering shortness of breath during minimal exertion, significantly reduced exercise tolerance, swelling of the legs and recurrence of rhythm disorders. The patient has been suffering from the above complaints for the past year, shortness of breath and HF symptoms progressing during the last months. In 1999, the patient was diagnosed with a mixed rheumatic defect and underwent mechanical AV and MV prosthesis, since then she has been using warfarin in therapeutic norms. The patient had recurrent atrial flutter (AF) episodes since 2016 and had undergone radiofrequency catheter ablation 4 times but no positive effect was observed. VVI mode cardiac pacing was implanted in 2019, followed by recurrence of atypical AF episodes which was reversed with cordarone. During TTE severe TR was observed. For further investigation in the function of the mechanical prostheses, treatment of TR and clarification of the diagnosis, a decision to hospitalize the patient was obtained. Patient denied other chronic and infectious diseases. For outpatient treatment she has been using warfarin, cordarone, β -blockers, trimetazidine and diuretics.

Upon arrival in the cardiology department, clinical findings included: heart rate (HR) 83 b.p.m., blood pressure (BP) 120/70 mmHg, pulse oximetry 96%, normal mechanical valve clicks, and a II° systolic murmur at the apex of the heart, AV and Erb's point. Laboratory tests showed slightly elevated NT-proBNP (344.9 ng/l) and anticoagulation studies revealed an INR of 3.1, an aPTT of 45.1 s and a PT of 80.6 s. ECG showed normal cardiac pacing activity. 2D TTE showed impaired LVEF – 50%, elevated transprosthetic aortic Doppler peak velocity – 3.2 m/s, elevated peak transprosthetic gradient – 40.96 mmHg, I° intraprosthetic regurgitation. Signs of rheumatic damage to the TV were also observed, such as copulating leaflets, accelerated tricuspid peak velocity – 1.7 m/s, III–IV° TR. Chest x-ray showed mild pulmonary vascular congestion. Invasive hemodynamic tests were performed to differentiate possible causes of dyspnea and severe post-capillary PH with reduced cardiac output were found. TTE was repeated to monitor the dynamics – AV prosthesis peak velocity 3.8–4 m/s was recorded from the adaptive positions and assessed as prosthesis dysfunction (Fig. 1).

Patient's status worsened and the "heart team" consensus recommended reoperation of the AV and TV prosthesis surgery. In the department of cardiology lansoprazole and heparin, with dose titration according to aPPT, were added to the previous treatment. The patient was transferred to the cardiac surgery unit for further surgi-

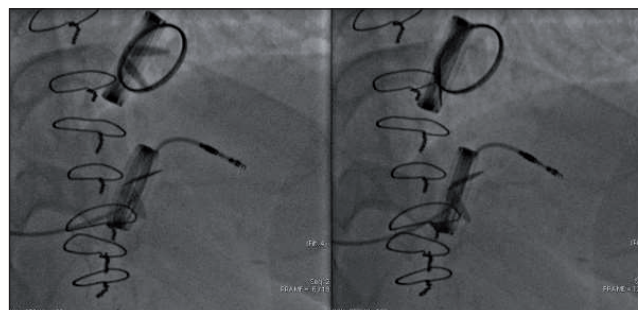


Fig. 1 – Fluoroscopic view of the mechanical prosthetic aortic valve thrombosis.

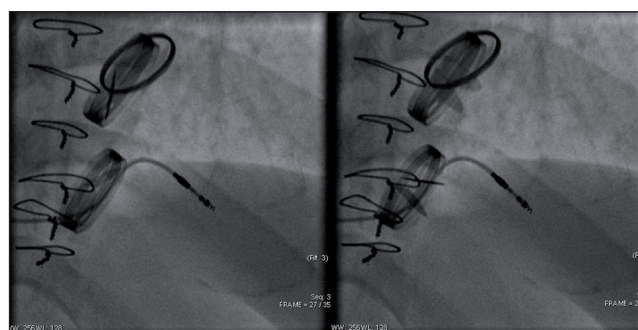


Fig. 2 – Fluoroscopic view of the prosthetic aortic valve replacement due to valve thrombosis and tricuspid valve prosthesis.

cal treatment – aortic root and TV prosthesis surgery in case of dysfunction of the mechanical AV prosthesis and severe TV regurgitation (Fig. 2).

PVT can still occur despite adequate anticoagulation and optimal INR values, so it is important to monitor patients at risk and identify complications as soon as possible.

Case 2

A 60-year-old man was referred to the LUHS Kaunas Clinics, Department of Cardiology with progressive dyspnea on minimal exertion and at rest, cough that produces hemoptysis and weakness. The previous medical history of the patient was a surgical closure of patent ductus arteriosus at the age of 8 and rheumatism in childhood. There is family history of rheumatism. A mechanical AV for severe aortic stenosis was implanted 15 years ago and the patient has been treated with acenocoumarol since then. Complaints lasted for a month, especially it has been intensifying during the last 2 weeks. In the regional hospital patient was treated for organizing pneumonia and progressing respiratory failure that were recognized as complications of the Covid-19 infection. He was treated with dexamethasone and cefuroxime but it was unsuccessful. There is past history of left middle cerebral artery infarct that was diagnosed in 2016, patient lost eyesight in one eye. Patient was admitted taking beta-blockers, angiotensin receptor-neprilysin inhibitors (ARNi), and loop diuretics due to HF, hypertension and permanent AFib. Hospitalization was required for the further investigation of progressing respiratory and HF.

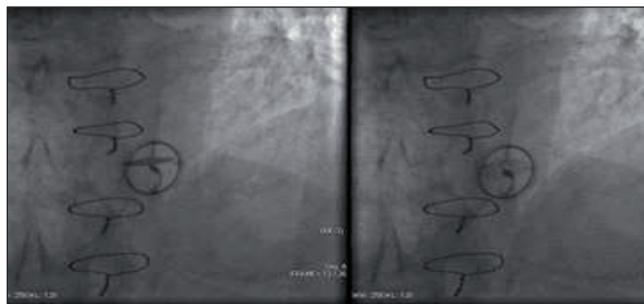


Fig. 3 – Fluoroscopic view of the mechanical prosthetic aortic valve leaflet with a 15° opening angle secondary to thrombus formation.

Upon arrival in the cardiology department, clinical findings included: HR 94 b.p.m., BP 116/54 mmHg, pulse oximetry 92% with 6 L/min oxygen mask, irregular heartbeats, both diastolic and systolic III° murmurs at the projection of the aortic, tricuspid valves, apex and Erb's point.

Laboratory results showed electrolytes in normal range, normal liver function and impaired renal function (creatinine 150.8 $\mu\text{mol/l}$, urea 20.7 mmol/l). Troponin I was 82 ng/L ($n < 14$ ng/L), NT-proBNP 18000 ng/L ($n < 300$ ng/L), D-dimers 2400 $\mu\text{g/L}$ ($n < 350$ $\mu\text{g/L}$). Abnormal coagulation test was observed with INR 2.7, PT 67.1 s, aPTT 41 s, ECG – AFib.

2D TTE showed reduced mobility of the one-leaflet mechanical aortic prosthesis with an image suggestive of thrombus ($V_{\text{max}} - 4.6$ m/s, $G_{\text{max}} - 73.96$ m/s, the mean transprosthetic gradient – 29 mmHg, effective orifice area – 0.97 cm^2) and reduced LVEF (44%) in the setting of AFib. Dilated left ventricle, moderate (II–III°) MV insufficiency, signs of severe PH – right ventricle systolic pressure – 89 mmHg.

Chest X-ray showed large bilateral non-homogenous infiltrations. The AV opening angle measured by the thoracic CT-scan was 15° (Fig. 3). Coronary artery angiography was performed to differentiate the cause of dyspnea but coronary artery stenoses were excluded and it confirmed the dysfunction of AV.

Despite the adequate treatment of HF, anticoagulation therapy, patient's condition was worsening due to venous congestion and hypotension, therefore urgent surgical treatment was recommended. Intravenous dopamine was given to the patient but cardiogenic shock was progressing and patient was transferred to the intensive care unit. Mechanical aortic prosthesis was surgically removed and changed with bioprosthetic valve. During the postoperative period patient's condition continued to worsen due to progressing respiratory failure, cardiogenic shock, acute renal failure, liver failure, urinary tract infection and metabolic acidosis. Patient vital functions were supported with veno-arterial extracorporeal membrane oxygenation, renal replacement therapy, mechanical ventilation, antibiotics were added to the treatment. On the 8th postoperative day patient died. Histopathological examination of AV showed thrombotic mass with the features of degeneration on the valve. Even though further investigations are needed because of the unclear mechanisms but it is suspected that the pro-inflammatory and pro-coagulant states of SARS-CoV-2 virus are related

to the risk of PVT despite therapeutic INR and optimal treatment.

Discussion

Prosthetic valve obstruction by pannus, thrombus, or both is one of the most life-threatening complications of mechanical prostheses.⁷³ Clinical presentation of the patient may vary from mild dyspnea to severe respiratory failure and rapid worsening of HF. Sudden increases in transvalvular gradients from baseline during TTE are indicative of valvular obstruction.⁷⁴ It is crucial to be aware of a possible acute decline in a clinical status and alert in case of an emergency intervention. Fibrinolytic therapy and surgical intervention remain main options in PVT management, even though it is still controversial and the choice is based on the clinical manifestations. The choice of the PVT treatment is reliant on the features of mechanical valve thrombosis.⁹ High-risk left-sided PVT features (NYHA functional class III to IV, mobility of the thrombus and the size > 0.8 cm^2) are in favor of surgical approach.

Thrombosis may present with acute manifestations while the pannus usually presents with chronic evolution, over several weeks or months. Prosthetic valve dysfunction at AV position is often caused by pannus formation which is an uncommon, but serious complication. Its incidence varies between 1.8% in tilting discs to 0.73% in bileaflet valves.⁷⁵ All types of available prosthetic valves can be affected by pannus formation. Pannus formation is a biological reaction to valve prostheses associated with factors such as surgical technique, thrombus formation due to inadequate anticoagulation and infection.⁷³

Rheumatic heart disease patients are usually treated with mechanical valve replacement surgery, owing to their durability and lower reoperation rates. However, these patients require lifelong oral anticoagulation therapy to prevent thromboembolic complications. Chronic anticoagulation has the risk of bleeding which necessitates close monitoring of INR. This complicates the lives of patients with mechanical prosthesis, thus inadequate anticoagulation therapy is the main reason for the development of PVT. A large meta-analysis of 1005 patients showed that up to 61% of patients with PVT had adequate anticoagulation so the cause of PVT in them remains unclear.⁷⁶ However, the INR can be falsely elevated in certain cases. Falsely elevated INR have been recorded in patients with lupus anticoagulant antibodies or dysfibrinogenemia and in those undergoing conversion from direct thrombin inhibitors.⁷⁷ Though the increase of INR may also result from the coagulation factors deficiency, liver dysfunction or vitamin K deficiency.⁷⁸ In our first case, the patient had sufficient anticoagulation but still developed prosthetic valve dysfunction. In this case, we need to remain alert and suspect other conditions that may be responsible for the high INR values.

Cardiac rheumatism may have played a role in our cases, especially considering that our first patient also developed TV rheumatic regurgitation. It is important to note that most of the previously reported cases of pannus formation at AV position were females as well as our first case. Differential diagnosis between thrombus

and pannus is made based on clinical, echocardiographic and morphopathological criteria and is essential because therapeutic approaches are different. If in thrombotic obstruction, thrombolysis can be considered, this is contraindicated in the case of pannus, where the only valid treatment is surgery – valve replacement or pannus removal.⁷⁹ In our case, chronic evolution and effective anticoagulation resembles the clinical picture of pannus formation rather than thrombosis. Since a TV prosthesis surgery was required, it was decided that the dysfunction of the AV prosthesis would be corrected during the same surgery.

Recently it was discovered that the pro-coagulant effect of the SARS-CoV-2 virus does not always protect patients from the risk of thrombosis, even under effective anticoagulation like it was observed in the second clinical case. In patients with mechanical valves receiving VKA treatment, high risk of thrombus formation remains.⁸⁰ The treatment is based on thrombolysis by therapeutic anticoagulation, fibrinolysis, or surgery and is selected depending on the size, composition of thrombus, and clinical status. In our case, due to the manifestation of organizing pneumonia as a late-phase Covid-19 infection complication and the rapidly worsening condition of the patient, the surgical treatment was required. Allione's study shows that the monitoring of D-dimer levels associated with the inflammation parameters (CRP and IL-6) might be useful for early recognition of prothrombotic pattern associated with SARS-CoV-2, despite therapeutic values of INR during warfarin treatment.⁸¹

Conclusions

Despite PVT being rare, it is a highly lethal condition that requires rapid diagnostic assessment. Diagnosis is based on the findings of the clinical examination, cinefluoroscopy and echocardiography. The role of TTE is fundamental, not only for accurate diagnosis but also to provide optimal treatment. Treatment depends on the presence of obstruction and prosthesis location and might be chosen as one of the following: surgery, fibrinolysis, heparin treatment or optimization of anticoagulant and antiplatelet therapy. Adequate anticoagulation remains the most important factor in the prevention of PVT in mechanical prosthesis.

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Is the Atherogenic Index of Plasma (AIP) a Cardiovascular Disease Marker?

Lutfu Askin^a, Okan Tanriverdi^b

^a Department of Cardiology, Gaziantep Islamic Science and Technology University, Gaziantep, Turkey

^b Department of Cardiology, Adiyaman University, Adiyaman, Turkey

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o vysoké hustotě

SOUHRN

V diagnostice a stanovování prognózy kardiovaskulárních onemocnění (KVO) již byla použita řada ukazatelů. Aterogenní index plazmy (AIP) se vypočítává jako logaritmus molárních koncentrací triglyceridu (TG) a lipoproteinů o vysoké hustotě (high-density lipoprotein, HDL). Vynikající predikční hodnota AIP je výsledkem těsného vztahu mezi AIP a velikostí lipoproteinových částic. AIP lze jednoduše vypočítat pomocí typického lipidového profilu. Jedná se o přesnější prediktor velikosti lipoproteinových částic než velikosti částic jednotlivých lipidů nebo poměru TG a HDL.

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ABSTRACT

Keywords:

Atherogenic index of plasma

Cardiovascular disease

Ratio of triglyceride to high-density lipoprotein

Numerous indicators have been used to diagnose and prognosticate cardiovascular disease (CVD). The atherogenic index of plasma (AIP) is a logarithmic conversion of triglyceride (TG) to high-density lipoprotein (HDL) molar concentrations. The close association between AIP and the size of lipoprotein particles may account for its excellent predictive value. AIP may be computed simply using a typical lipid profile. It is a better predictor of lipoprotein particle size than that of individual lipids or the ratio of TG to HDL.

Introduction

Cardiovascular disease (CVD) causes one third of fatalities globally, and the risk factors for CVD are growing.¹ The most fundamental effort in combating the CVD epidemic is preventing risk factors and understanding their interactions. Obesity, inactivity, poor nutrition, and smoking are major CVD risk factors.² Among them, the plasma lipid profile is the key CVD predictor.³

The LDL/HDL ratio is widely used to assess CV risk since there is a clear link between high LDL-C and low HDL-C.^{4,5} Conversely, elevated TG levels have been linked to increased LDL-C particles and CV risk.⁶ Thus, atherogenic

dyslipidemia (high LDL/HDL ratio and elevated TG) raises CV risk.⁷

Better atherogenic dyslipidemia indicators are replacing old rates.⁵ The atherogenic index of plasma (AIP) is

$$\text{Atherogenic index of plasma} = \log \frac{[\text{Triglyceride}]}{[\text{HDL cholesterol}]}$$

Fig. 1 – The AIP calculation.

Address: Assoc. Prof. Lutfu Askin, MD, Gaziantep Islamic Science and Technology University Cardiology Department, 2022 – Gaziantep, Turkey,

e-mail: lutfuaskin23@gmail.com

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a powerful predictor of atherosclerosis.^{8–10} AIP stands for protective and atherogenic lipoprotein interaction.¹¹ AIP is calculated as $\log(\text{TG}/\text{HDL-C})$ (Fig. 1).¹² AIP readings below 0.11 are related to a low risk of CVD, whereas those between 0.11 and 0.21 are associated with an intermediate and increasing risk.¹³ We conducted a review to assess the relationship between AIP and CVD.

A novel CV predictive biomarker

Regular exercise has been shown to reduce the risk of heart disease, stroke, hypertension, and diabetes.¹⁴ According to Tariq M. Ali Rajab et al., diabetes dyslipidemia is characterized by a rise in TG and a reduction in HDL-C.¹⁵ Another study indicated that hyperglycemia, aberrant lipid profiles, and HTN all contributed to atherosclerosis progression.¹⁶ Various studies have shown a high association between AIP and lipoprotein particle size, making AIP an indication of atherogenic lipoprotein status.¹²

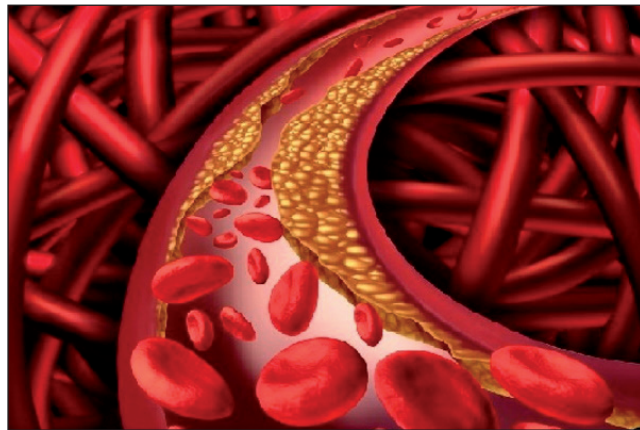


Fig. 2 – AIP may predict acute coronary events.

AIP may be used to evaluate CV risk factors and predict acute coronary events (Fig. 2).¹⁷ AIP may also be used as a screening technique when all atherogenic parameters are normal.⁵ The AIP index rises with changes in other CV risk factors. According to Niroumand et al., regular exercise and a balanced diet are suggested. AIP should be used regularly as a CVD indicator, especially in patients with high CV risk factors. It's a simple statistic to calculate, especially when other lipid levels are normal.¹⁸

For example, a study of 340 healthy women found a significant connection between AIP and the Framingham risk score (FRS), indicating an AIP involvement in early coronary artery disease (CAD) identification.¹⁹ A recent study of young individuals identified an association between AIP and CV risk factors.²⁰ A higher AIP value enhanced the incidence of CAD in HIV patients and RA/SLE women.^{21,22} The AIP value may better reflect metabolic dysfunction than a single metric like LDL-C. This subfraction of LDL-C is known as sdLDL.²³

Unsurprisingly, a higher AIP score may raise the risk of CAD in adults. It has to be replicated in a larger adult sample to determine the AIP's potential as a CAD risk predictor.²⁴ Fernández-Macias et al. show

that AIP may be used as a CVD biomarker in Mexico, because strong relationships were found between asymmetric dimethylarginine (ADMA) and adipocyte-fatty acid binding protein (FABP4) concentrations and AIP in people.²⁵

Cardiovascular diseases

The severity of OSA illness corresponds with AIP but not sleep quality or quantity. Although this was an experimental goal, AIP did not outperform other lipid measures in detecting dyslipidemia in OSA. The AIP value can vary drastically in OSA.²⁶ In OSA, the apnea-hypopnea index (AHI) is linked to AIP and the apoB/apoA1 ratio. According to Cao et al., the AIP and apoB/apoA1 ratio rose with OSA severity, perhaps contributing to the significant CVD risk in OSA.²⁷

AIP may be a reliable indicator of acute ischemic stroke, particularly the stroke subtype of large-artery atherosclerosis.²⁸ According to Kim et al., high AIP predicts IHD in non-diabetic Koreans. As an alternative to isolated TG levels or other lipid markers, AIP is increasingly used to stratify distinct cardiometabolic risks.²⁹ Research by Abacoglu et al. is significant in revealing that AIP is superior to TG/HDL-C and equal to stent length in predicting ST. It also proposes reducing LDL-C as well as serum TG and HDL levels to avoid ST. If AIP is found in regular lipid measurements, treatment choices may need to be changed or expanded.³⁰ AIP was related to angiographic progression of CAD irrespective of recognized risk factors.³¹

T2DM was linked to AIP transitions. Preventive measures are required to address T2DM at an early dyslipidemic stage.³² When it comes to AIP and coronary heart disease risk factors, Korean men are no exception. Obesity, diabetes, and lipid metabolic indices are all beneficial. Consumption of milk and dairy products was greater among those with low AIP. The AIP quartiles differed in total fat intake but not in saturated fat consumption. AIP recommends further research on the causal link between coronary heart disease risk factors and dietary intake. It is also vital to include both male and female genders in research for comparative analysis.³³

Based on a large-scale clinical experiment with 10,251 randomized T2DM patients, AIP is a strong predictor of CV events. Major adverse cardiovascular events (MACEs) were more common in diabetics with high AIP. The outcomes of this research helped design a unique MACE bio-indicator for use in high-risk populations.³⁴ AIP is better than normal lipid profiles in assessing CAD risk, and this finding may offer a theoretical foundation for successful CV prophylaxis in T2DM patients.³⁵

Due to its capacity to detect metabolic dysfunction, AIP may be used to predict poor outcomes in non-diabetic individuals following percutaneous coronary intervention (PCI). The HR-AIP index association seems J-shaped. The AIP index cutoff of 0.18 might be utilized to calculate hazard ratios (HRs) for non-diabetic patients following PCI. We need further multi-center research on non-diabetic individuals with metabolic dysfunction to confirm the AIP index's utility in this setting.³⁶

Adolescents from Spain had the highest AIP. The ROC AUC findings imply that all atherogenic indicators can predict MetS. More research is required to fully understand this forecasting ability.³⁷ The best diagnostic cutoff values for CAD and SS >23 were 2.035 and 2.23, respectively. Using AIP as a biomarker may help avoid CAD in Chinese patients. In clinical diagnosis and therapy, clinicians should consider patients' AIP values.³⁸

Conclusion

This review is noteworthy since it indicates that AIP is more predictive of CVD than TG or HDL-C. This also means that, in addition to LDL-C, serum TG and HDL levels must be examined while attempting to prevent CVD. If AIP is explored in conjunction with conventional lipid measurements, treatment techniques may need to be altered or increased. This review is important because it sheds light on multicenter, prospective studies with a lot of patients.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Pseudoaneurysma arteria radialis jako komplikace selektivní katetrizační koronarografie

(Pseudoaneurysm of radial artery as a complication of selective coronary catheterization)

Josef Laštůvka, Martin Porzer, Marian Branny, Leoš Pleva, Jan Mrózek, Pavel Kukla, Tomáš Grézl

Oddělení kardiiovaskulární, Interní a Kardiologická klinika, Fakultní nemocnice Ostrava, Ostrava

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Pseudoaneurysma

Radiální přístup

Selektivní katetrizační

koronarografie

SOUHRN

Selektivní koronarografie je běžně prováděné vyšetření s nízkým rizikem závažných komplikací.¹ V posledních letech se jako dominantní přístup vzhledem k nejmenšímu riziku lokálních komplikací a komfortu pacienta využívá transradiální cesta. Z lokálních komplikací tohoto přístupu se nejčastěji jedná o spasmus, okluzi radiální tepny (ORA) a neokluzivní poškození. Ve vzácných případech je to pak perforace cévy, pseudoaneurysma, arteriovenózní (AV) fistule, poškození nervu, tromboembolizace nebo větší krvácení.^{2,3} V naší kazuistice chceme ukázat na příklad, kdy došlo po několika letech k náhodnému objevení pseudoaneurysmatu radiální tepny jako iatrogenní komplikaci po předchozím invazivním katetrizačním vyšetření. Většina těchto cévních komplikací je oligo- až asymptomatická, nicméně může být i potenciálně riziková. Proto je stále nutné dbát na jasnou indikaci invazivního katetrizačního vyšetření a převyšující benefit nad případnými riziky pro pacienta.

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ABSTRACT

Selective coronary angiography is a routine examination with a low risk of serious complications.¹ In recent years, with regards to minimizing the risk of local complications and comfort of the patient, the transradial access has been used as the dominant approach. Among the local complications of this approach the most frequent are spasm, radial artery occlusion (ORA), and non-occlusive damage. In rare cases, it is a vessel perforation, pseudoaneurysm, AV fistula, nerve damage, thromboembolization or major bleeding.^{2,3} In our case study, we want to show an example where, after several years, a pseudoaneurysm of the radial artery occurred accidentally, as an iatrogenic complication after a previous invasive catheterization examination. Majority of these vascular complications are oligo- to asymptomatic, but can be also potentially risky. Therefore, it is still necessary to pay attention to a clear indication of an invasive catheterization examination and the necessity that benefit for the patient outweighs the possible risks.

Keywords:

Arteria radialis

Local complication

Selective coronary angiography

Transradial access

Úvod

Diagnosticke srdeční katetrizace s případnou navazující perkutánní koronární intervencí (PCI) je ve většině případů prováděna transradiálním či transfemorálním přístupem. Transradiální přístup byl poprvé k srdeční katetrizaci použit v roce 1989.⁴ Příčinou rozšíření tohoto typu přístupu bylo zejména snížení krvácivých komplikací, možnost zkrácení hospitalizace a preference pacienty.⁵ Více prací prokázalo snížení krvácivých a vaskulárních rizik také u pacientů s akutními koronárními syndromy.^{6,7}

Přestože zejména vaskulární komplikace jsou u radiálního přístupu významně méně četné ve srovnání s femorálním přístupem, mohou se vyskytovat.⁸ Jedná se zejména o spasmus radiální tepny, disekci a perforaci radiální tepny, lokální hematoma, AV fistuli, pseudoaneurysma a okluzi radiální tepny.^{7,8}

Perforace radiální či brachiální tepny je méně častou komplikací (0,07–0,9 %), ale potenciálně závažnou, s možnou tvorbou rozsáhlého hematoma a compartment syndromu.⁹ Pseudoaneurysma radiální či brachiální tepny vzniká penetrujícím poraněním stěny cévy, včetně poranění v místě vpichu, a následnou pulsuující extravazací do měkkých tkání. Incidence arteriálního pseudoaneurysmatu je u transradiálního přístupu nízká (0,03–0,2 %).^{7,10}

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Adresa pro korespondenci: MUDr. Josef Laštůvka, Oddělení kardiiovaskulární, Interní a Kardiologická klinika, Fakultní nemocnice Ostrava, 17. listopadu 1790/5, 708 52 Ostrava-Poruba, e-mail: lastuvka.josef@gmail.com

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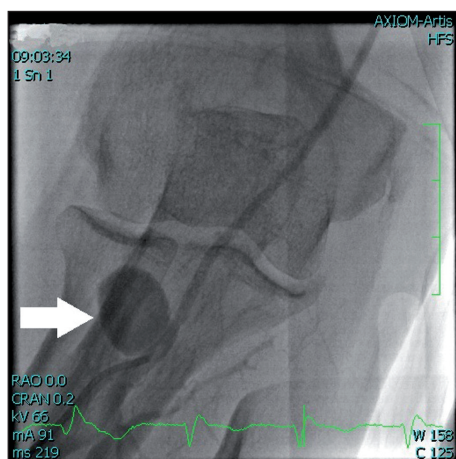
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Podle některých prací je riziko vzniku pseudoaneurysmatu radiální tepny (po kanylaci v intenzivní péči či při katetrizaci radiálním přístupem) vyšší u pacientů s fibrilací síní, hypertenzí a chronickou renální nedostatečností.¹¹

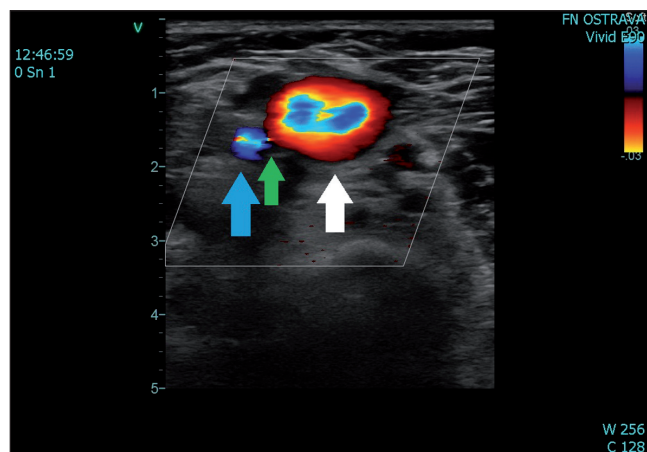
V následující kazuistice popisujeme přítomnost chronického pseudoaneurysmatu radiální tepny jako komplikaci předchozí katetrizace.

Popis případu

Čtyřiasemdesátiletý pacient již před lety po uzávěru defektu septa síní, po plastice trikuspidální chlopně (De Vega) pro významnou regurgitaci byl přijat plánovaně k provedení invazivní koronární angiografie. Ta byla indikována před zvážení reintervence na trikuspidální chlopní pro rekurenci symptomatické významné regurgitace. Při samotném vyšetření radiálním přístupem nebylo možné volně projít vodicím drátem dále než do kubitální oblasti, proto byla provedena angiografie horní končetiny prostřednictvím zavedeného sheathu. Bylo patrné plnicí se depo kontrastní látky po odstupu radiální tepny z tepny brachiální. Nebyl patrný leak, depo bylo elipsoidního tvaru s ostrou konturou, dominující jako možné



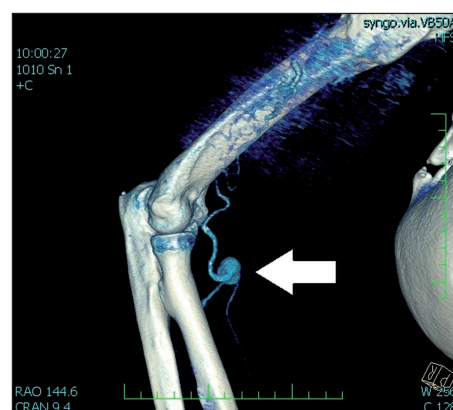
Obr. 1 – Selektivní nástřik a. radialis při koronografii a patrné pseudoaneurysma (bílá šipka)



Obr. 2 – Vyšetření duplexní sonografií. Vak pseudoaneurysmatu (bílá šipka), krček pseudoaneurysmatu (zelená šipka), nativní a. radialis (modrá šipka)



Obr. 3 – CT angiografie radiální tepny s pseudoaneurysmatem (bílá šipka)



Obr. 4 – 3D rekonstrukce pseudoaneurysmatu radiální tepny (bílá šipka)

pseudoaneurysma (obr. 1). Vzhledem k tomuto nálezu proběhla konverze na femorální přístup. Další vyšetření proběhlo standardně, během koronární angiografie nebylo zjištěno významnější aterosklerotické postižení věnčitých tepen. V druhé době jsme provedli duplexní ultrasonografické vyšetření (obr. 2) a následně i CT angiografii tepen pravé horní končetiny, která definitivně potvrdila suspekci na pseudoaneurysma radiální tepny velikosti 1,7 × 2 × 2,6 cm (obr. 3 a 4).

Vzhledem k potenciálnímu riziku vzniku trombózy a případné embolizace jsme u pacienta indikovali chirurgické řešení – resekci a cévní rekonstrukci.

Z kardiologického hlediska byla u pacienta indikována reintervence na trikuspidální chlopní, která byla provedena přednostně před cévním výkonem. Vzhledem ke složitosti výkonů jsme ustoupili od původně zvažovaného sdruženého výkonu na chlopních i cévách pravé horní končetiny.

Diskuse

Nechirurgické řešení pseudoaneurysmatu, vhodné u nálezů pod tři centimetry, spočívá v kompresi s následnou trombotizací vaku či podání trombinu do pseudoaneurys-

matu. Zatímco jsou dostatečné důkazy pro prospěšnost podání trombinu do pseudoaneurysmatu femorální tepny, data pro tento postup u řešení nálezu radiálních jsou limitována. Chirurgickou terapii považujeme za vhodnější u pseudoaneurysmat s průměrem nad tři centimetry, bez dostatečného „krčku vaku“ (obr. 2), přičemž „dostatečnost krčku“ není jasně definována. Selhání konzervativní terapie je pak také indikací k chirurgickému řešení.^{11,12}

Pozdní prezentace iatrogenního pseudoaneurysmatu radiální tepny jsou vzácné. Jsou dokumentovány případy opožděného vzniku.¹³

V případě námi prezentované kazuistiky se jedná velmi pravděpodobně o akutně vzniklou komplikaci následkem perforace radiální tepny vodičem při předchozí katetrizaci před více než deseti lety.

I když je v současné době pseudoaneurysma u pacienta zcela asymptomatické, domníváme se, že může být zdrojem distální embolizace a takto rizikem akutní končetinové ischemie, a proto budeme pacienta dále směřovat k chirurgickému řešení nálezu. Po tuto dobu ponecháme pacienta na antikoagulační terapii.

Závěr

Komplikace transradiálního přístupu k srdeční katetrizaci, resp. selektivní koronární angiografii, jsou méně časté ve srovnání s transfemorálním přístupem. Vznik pseudoaneurysmatu je komplikací vzácnou, nicméně vzhledem k velmi vysokému počtu vlastních katetrizací radiálním přístupem nikoliv zanedbatelnou. Absolutní většina může být řešena konzervativně, intravaskulárním podáním trombinu či chirurgicky. Při pozdním nálezu pseudoaneurysmatu tepen předloktí je nutno pomýšlet na iatrogenní etiologii v souvislosti s předchozí, byť velmi dávnou, srdeční katetrizací a nepoznanou perforací tepny.

Prohlášení autorů o možném střetu zájmů

Žádný střet zájmů.

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Katetrizační uzávěr perzistující Botallovy dučeje u pacienta po endovaskulární léčbě aortální disekce typu B

(Catheterizational Closure of a Persistent Botallo's Duct in a Patient After Endovascular Treatment of Aortic Dissection Type B)

Jan Švejda^a, Ladislav Pešl^a, Jiří Haniš^a, Aleš Mokráček^b

^a Kardiologické oddělení, Kardiocentrum, Nemocnice České Budějovice, a.s., České Budějovice

^b Kardiochirurgické oddělení, Kardiocentrum, Nemocnice České Budějovice, a.s., České Budějovice

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SOUHRN

U pacientů s akutní disekcí aorty typu B (dle Stanfordské klasifikace) s komplikovaným průběhem je rekonstrukce hrudní aorty endovaskulárním přístupem (thoracic endovascular aortic repair, TEVAR) léčbou první volby. Smyslem implantace stentgraftu je překrytí entry disekce provázené v ideálním případě následnou trombotizací falešného lumen v průběhu celého stentgraftu, čímž dochází ke stabilizaci stěny hrudní aorty. V námi popisované kazuistice k této žádoucí trombotizaci nedošlo. Důvodem byl zachovaný průtok falešným lumen při nediagnostikované perzistující Botallově dučeji. Řešením této komplikace bylo uzavření perzistujícího zkratu pomocí Amplatzerova síňového okluderu cestou falešného lumen disekované aorty.

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ABSTRACT

In patients diagnosed with an acute aortic dissection type B according to the Stanford classification, thoracic endovascular repair (TEVAR) is the primary recommended treatment in cases with a complicated course. The purpose of implanting a stent graft is to close the entry point of the dissection, thus hopefully causing a thrombus to fill the false lumen throughout the whole stent graft, stabilizing the thoracic aortic wall. In our case report, the thrombus unfortunately did not form, the reason being continuous flow through the false lumen due to an undiagnosed persisting Botallo's duct. The solution to this complication was closing the persisting shunt by implanting an Amplatzer septal occluder through the false lumen of the dissected aorta.

Úvod

Akutní aortální disekce patří mezi akutní aortální syndromy. Mezi vrozené rizikové faktory vzniku aortální disekce patří biskuspidální aortální chlopeň, koarktace aorty a defekty pojivové tkáně (Marfanův syndrom, Ehlersův–Danlosův syndrom). K získaným rizikovým faktorům řadíme arteriální hypertenzi, věk, autoimunitní vaskulitidy (Takayasuova arteriitida, obrovskobuněčná arteriitida) a aortitidy luetické, bakteriální či mykotické. Dále se může vyskytnout disekce aorty u žen v souvislosti s těhotenstvím, u pacientek bez přidruženého defektu pojivové tkáně se jedná však o onemocnění velmi vzácné. Iatrogeně způsobená disekce aorty vzniká v souvislosti s katetrizačním výkonem, použitím intraaortální balonkové kontrapulsace či poraně-

ním svorkou při kardiochirurgickém výkonu. V neposlední řadě může dojít k traumatické ruptuře aorty v souvislosti s deceleračním traumatem (autonehody, pád z výšky).

K disekci aorty dochází v důsledku disrupce vnitřní vrstvy (tunica intima) cévní stěny aorty a odtržením její různé velké části s následným tokem krve do svalové vrstvy (tunica media). V naprosté většině případů dojde distálně od entry k další perforaci vnitřní vrstvy – re-entry. Dochází tak ke vzniku dvou cévních lumen, pravého a nepravého, které je ohraničeno z velké části tenkou zevní vrstvou stěny aorty (tunica adventitia). Nepravé lumen může vést ke komplikacím odpovídajícím lokalizaci a rozsahu dané disekce. Dle Stanfordské klasifikace rozdělujeme aortální disekce na typ A, kde postižení aorty začíná ve vzestupné části hrudní aorty, a typ B, kde je postižení aorty lokalizo-

Adresa pro korespondenci: MUDr. Jan Švejda, Kardiocentrum, Nemocnice České Budějovice a.s., B. Němcové 585/54, 370 01 České Budějovice,

e-mail: svejda.jan92@gmail.com

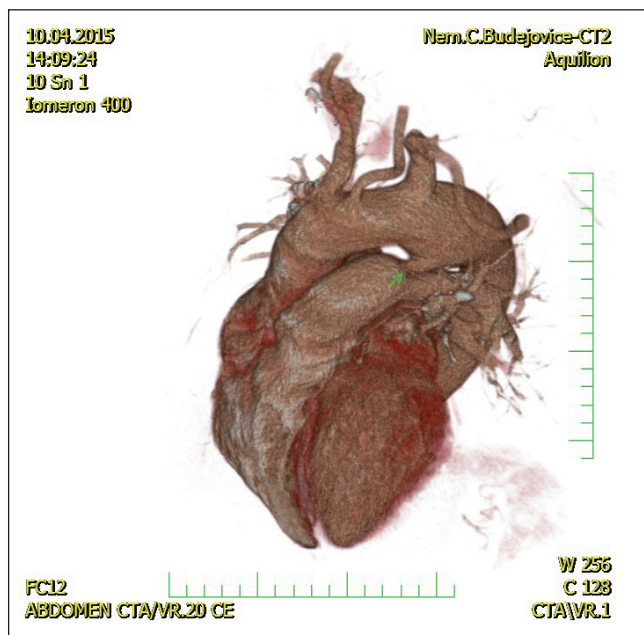
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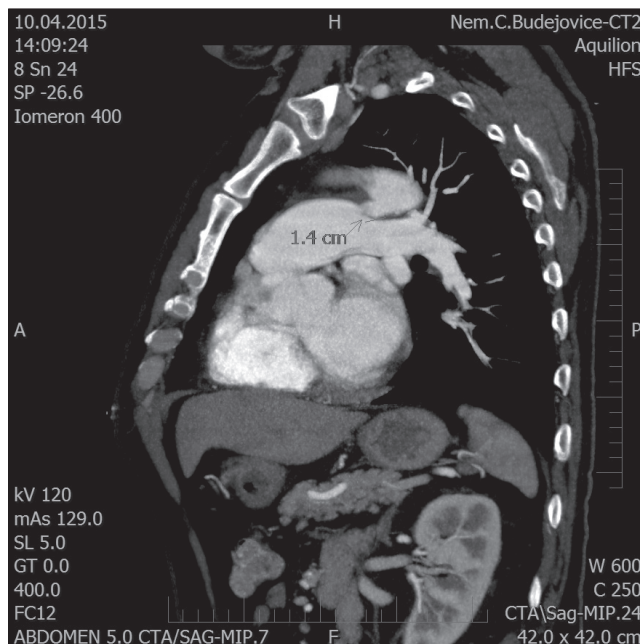
váno distálně od odstupe levé podklíčkové tepny. Distálně zůstávají oba typy disekce hrudní aorty bez ohraničení (abdominální aorta, pánevní tepny atd.). Toto praktické a jednoduché dělení je vhodné také pro základní selekci pacientů k následnému způsobu léčby. Standardem léčby disekce typu A je operační řešení, kdežto u komplikované disekce typu B je preferována endovaskulární léčba (TEVAR).

Popis případu

První hospitalizace 52letého pacienta proběhla na našem kardiologickém oddělení v roce 2015. Pacient byl přivezen na akutní kardiologickou ambulanci s anamnézou synkopy a odeznělé ataky bolesti na hrudi. V době přijetí na monitorované lůžko byl pacient již zcela bez potíží, hemodynamicky stabilní a byl zahájen standardní diferenciální diagnostický algoritmus vyšetření bolestí na hrudi. Na EKG byl přítomen sinusový rytmus s bloádou levého Tawarova raménka (LBBB) nejasné doby trvání. Laboratorně byly kardiopospecifické markery opakovaně negativní, ostatní laboratorní ukazatele se pohybovaly v mezích normy. Echokardiograficky byla přítomna excentrická hypertrofie LKS s ejekční frakcí 55 %, bez regionální poruchy kinetiky, bez významného poškození srdečních chlopní. Vedlejším nálezem byla dilatace průměru descendentní aorty na 50–55 mm. Z tohoto důvodu bylo doplněno CT angiografické (CTAG) vyšetření aorty, které vyloučilo její disekci, nicméně bylo potvrzeno aneurysmatické rozšíření descendentní části hrudní aorty na 50 mm. Na přechodu oblouku a sestupné části hrudní aorty byla patrna výchlupka směřující ke kmeni plicnice, bez patrné zkratové komunikace při náplni kontrastní látkou. Nález byl uzavřen jako rudiment po ductus arteriosus (obr. 1, 2). Během kontinuální monitorace EKG byly opakovaně zachyceny běhy nesetřvalé komorové tachykardie (NSKT). Na podkladě tohoto nálezu pacient podstoupil selektiv-



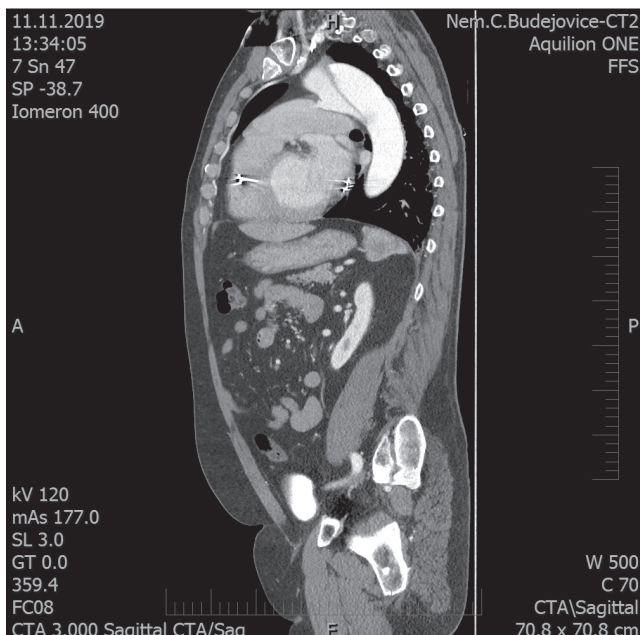
Obr. 1 – 3D rekonstrukce CTAG – rudiment po ductus arteriosus



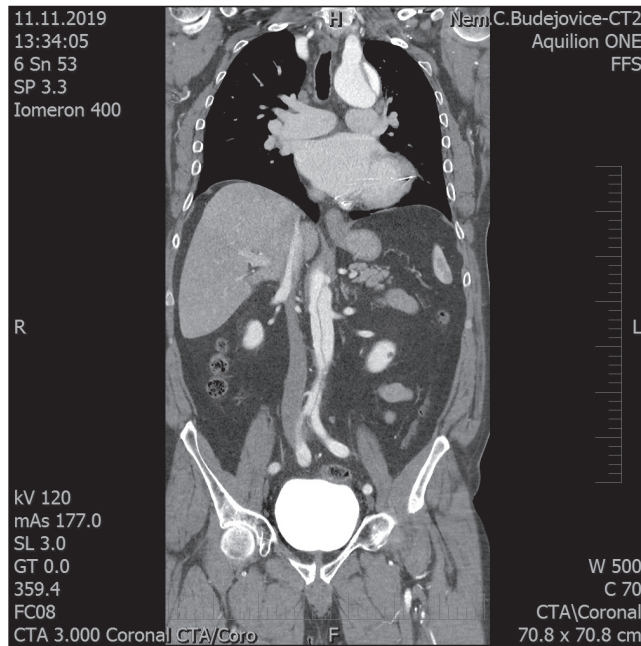
Obr. 2 – CTAG – výchlupka stěny descendentní hrudní aorty – rudiment po ductus arteriosus

ní koronarografii (SKG) s nálezem izolované významné stenózy proximální části ramus interventricularis anterior (RIA1, nemoc jedné tepny), která byla ošetřena implantací jednoho stentu. Z důvodu přetrvávání během NSKT i po provedené intervenci včetně maximální tolerované antiarytmické farmakoterapie bylo u pacienta indikováno elektrofyziologické vyšetření (EFV). Výsledkem byly opakovaně vyvolatelné komorové tachykardie a pacientovi byl implantován kardioverter-defibrilátor (ICD).

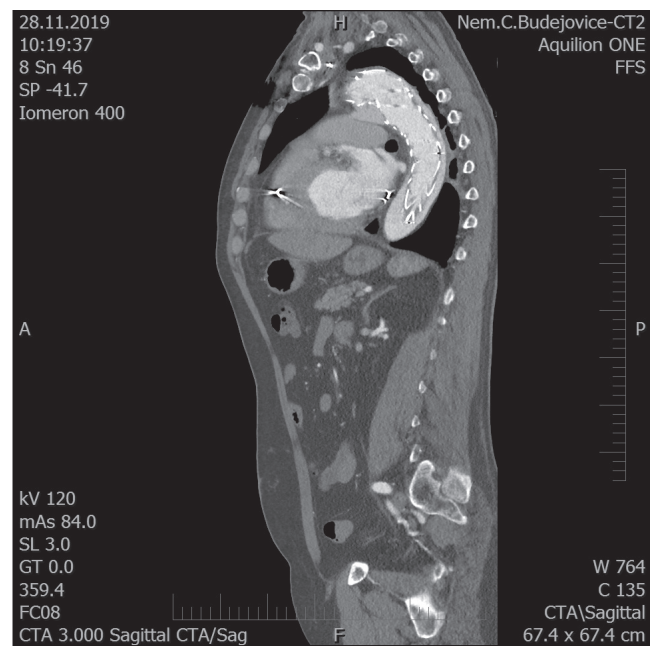
V následujících třech letech byl pravidelně echokardiograficky kontrolován a pro pokles ejekční frakce (EF) levé komory pod 35 % vlivem asynchronní kontrakce při LBBB u něj byla indikována srdeční resynchronizační léčba



Obr. 3 – CTAG – disekce aorty typu B



Obr. 4 – CTAG – disekce aorty typu B



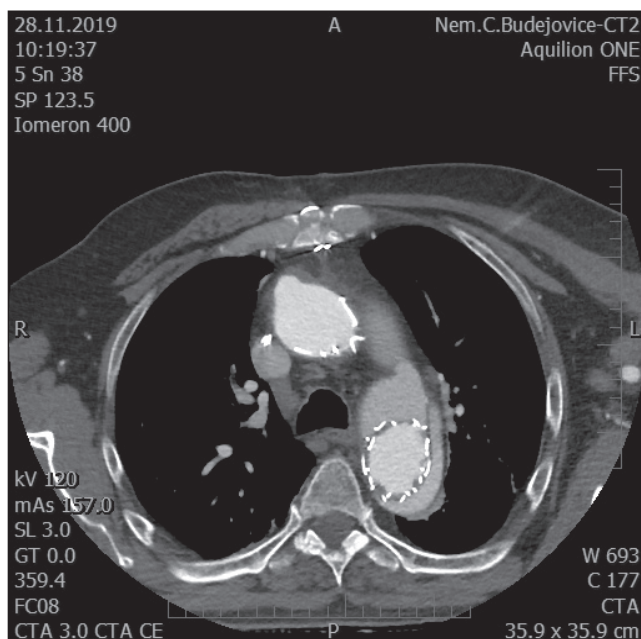
Obr. 6 – CTAG po debranchingu a implantaci stentgraftů

(biventrikulární ICD), což následně vedlo k restituci systolické funkce levé komory na EF 55 %. Zároveň podstoupil katérovou radiofrekvenční ablací (RFA) pro fibrilaci síní. Pacient absolvoval pravidelné CTAG kontroly aorty, na kterých nedocházelo k progresi dilatace hrudní aorty. Rovněž ani na jednom vyšetření nebyla patrna zkratová komunikace mezi aortou a plicnicí.

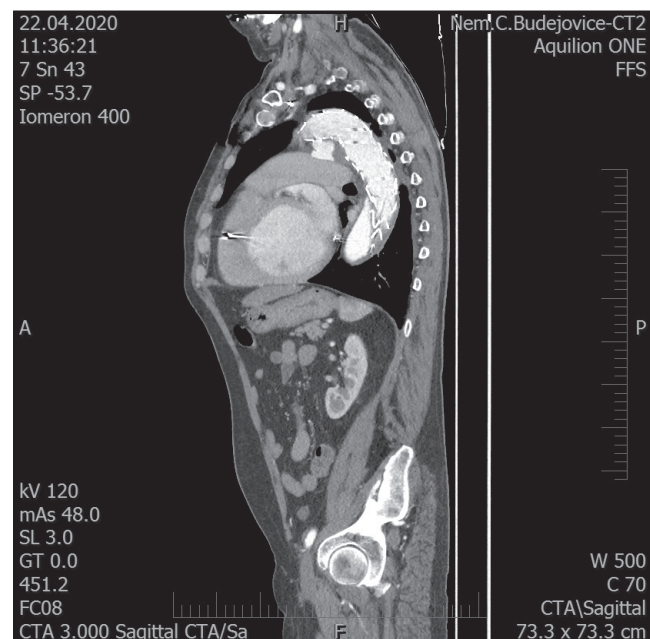
Koncem roku 2019 byl pacient akutně přijat pro náhle vzniklou bolest mezi lopatkami s následným průkazem akutní disekce aorty typu B (obr. 3, 4). Vzhledem k již výše zmíněné dilataci descendentní části hrudní aorty byly anatomické poměry poněkud odlišné. Levá podklíčková tepna odstupovala již z dilatovaného úseku aorty a spo-

lehlivé ukotvení proximální části stentgraftu by vedlo k překrytí levé společné krkavice. Proto, po společné konzultaci s kardiologem, pacient nejdříve podstoupil chirurgický debranching aortálního oblouku, při kterém mu byl našit aortosubklaviální a aortokarotický bypass vlevo. Následně absolvoval endovaskulární řešení disekce aorty, při kterém mu byly implantovány dva stentgrafty do oblouku a descendentní části hrudní aorty (obr. 5, 6) s překrytím proximálního entry disekce. Takto ošetřen byl pacient propuštěn a dále dispenzarizován.

První kontrolní CTAG vyšetření aorty v odstupu jednoho měsíce prokázalo stále se plnící nepravé lumen disekované části hrudní aorty (obr. 7, 8). Příčinou



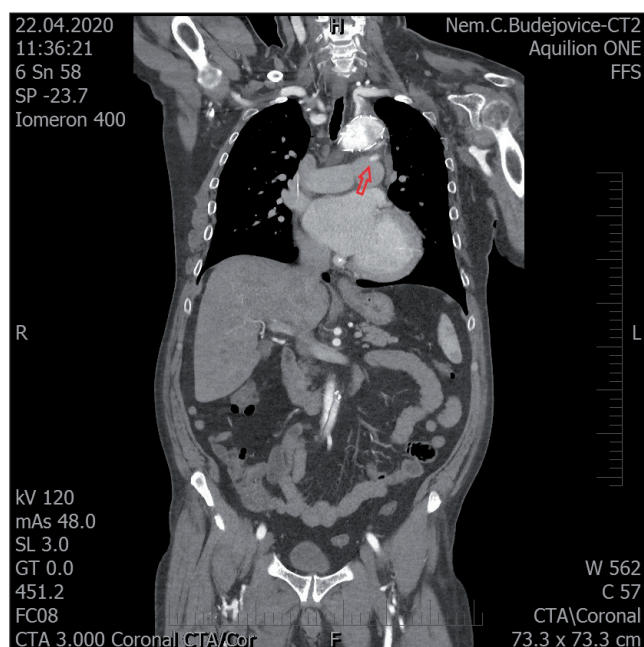
Obr. 5 – CTAG po debranchingu a implantaci stentgraftů



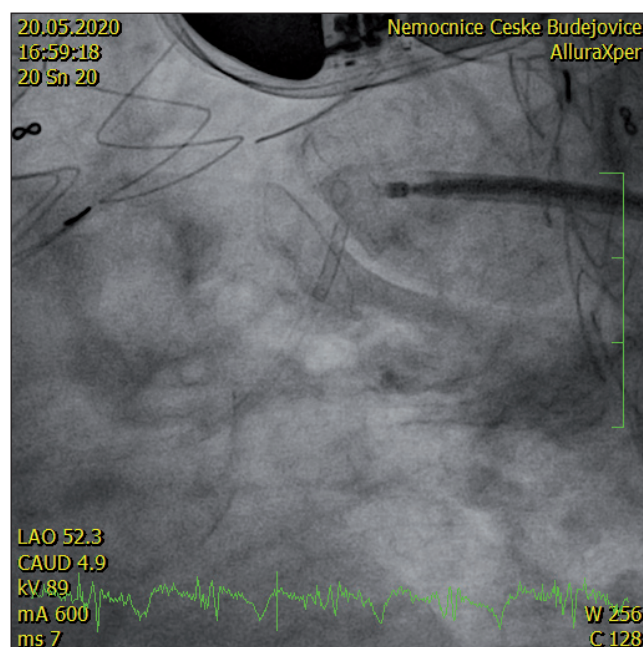
Obr. 7 – CTAG – stále průtočné falešné lumen aorty



Obr. 8 – 3D rekonstrukce průtočného falešného lumen



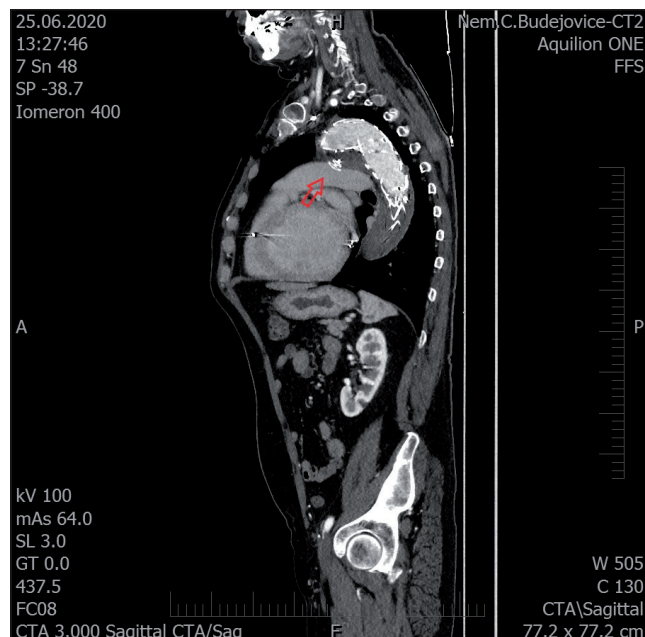
Obr. 9 – CTAG – perzistující Botallova dučeje (označeno červenou šipkou)



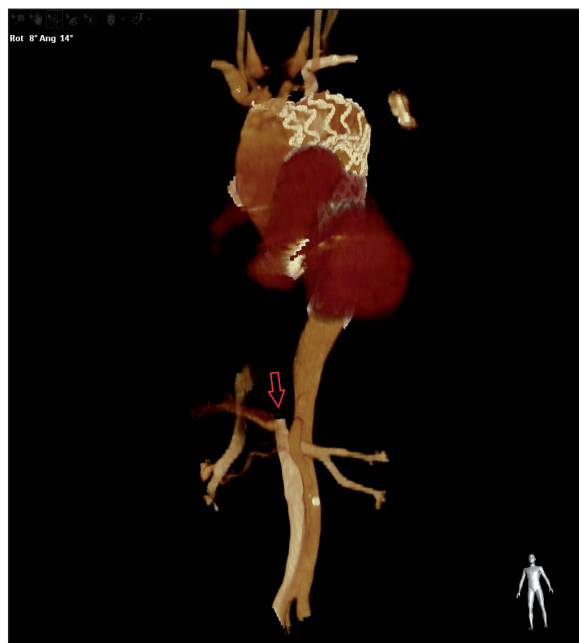
Obr. 10 – Angiografie po uzavření Botallovy dučeje okluderem

byla nově prokázána komunikace mezi hrudní aortou a plicnicí v místě původně popisované výchlipky (obr. 9, video 1). Díky stále průtočnému falešnému lumen nemohlo dojít k jeho trombotizaci, a tím i stabilizaci stěny hrudní aorty. Z obav z možné progresy velikosti a případné ruptury stěny aorty jsme se rozhodli k pokusu o uzavření komunikace Amplatzerovým okluderem. Výkon byl proveden femorálním přístupem cestou nepravého lumen se 7Fr (French) zaváděcím systémem. Komunikaci jsme proměřili 4mm koronárním balonkovým katétre, který při šetrné inflaci lu-

men zcela obturoval, a následně uzavřeli Amplatzerovým okluderem Figulla Flex ASD 7,5. Výkon proběhl bez komplikací, kontrolní nástřik falešného lumen potvrdil optimální pozici okluderu (obr. 10, video 2) a pacient byl propuštěn z nemocnice dva dny po zákroku. S odstupem jednoho měsíce bylo provedeno další kontrolní CTAG vyšetření aorty, kde již byla patrna kompletní trombotizace nepravého lumen hrudní části disekované aorty (obr. 11, 12). Pacient stále dochází na pravidelné kontroly cestou arytmiologické ambulance a je bez potíží.



Obr. 11 – CTAG – trombotizace falešného lumen aorty, Amplatzerův okluder v místě původní Botallovy dučej (označeno červenou šipkou)



Obr. 12 – 3D rekonstrukce aorty po výkonu – falešné lumen se již v proximální části neplní kontrastní látkou, dochází jen k plnění distální části falešného lumen disekce (červená šipka).

Diskuse

Jak již bylo zmíněno, preferovaným terapeutickým postupem u komplikované disekce aorty typu B je implantace stentgraftu (TEVAR). Smyslem implantace stentgraftu je překrytí proximálního entry disekce potahovanou částí stentgraftu. Tím dochází k zamezení průtoku krve falešným lumen, což umožňuje jeho kompletní trombotizaci, stabilizaci sestupné části hrudní aorty s eliminací rizika její

ruptury a nasměrování toku krve do pravého lumen disekované aorty.

Technickou úspěšnost implantace stentgraftu posuzujeme dle přítomnosti zatékání krve do falešného lumen (endoleak). V závislosti na velikosti endoleaku může docházet k nekompletní, nebo dokonce žádné trombotizaci falešného lumen a k následné progresi jeho velikosti. Podle mechanismu vzniku rozeznáváme několik typů endoleaků. V případě I. typu endoleaku (T1E) dochází k zatékání krve do falešného lumen kolem proximálního či distálního kotvení stentgraftu. Typ II (T2E) je stav, kdy do falešného lumen proudí krev retrográdně cestou volné větve. Endoleakem III. typu (T3E) se označuje situace, kdy je porušena integrita stentgraftu na podkladě trhliny, zalomení či jiného mechanického poškození struktury stentgraftu. Propustnost neporušené stěny stentgraftu při zvýšené porozitě materiálu je označována jako endoleak IV. typu (T4E). V případě, že není zobrazovacími metodami prokázán jasný zdroj toku krve do falešného lumen, hovoříme o V. typu endoleaku (T5E, endotension).

Existuje několik možností léčby endoleaku. U T1E a T3E je většinou indikována endovaskulární léčba. Ta spočívá v překrytí netěsnícího úseku dalším stentgraftem (stent-graft relining). U T2E je indikována léčba, pokud je hemodynamicky významný. Jeho léčba se provádí superselektivní embolizací příslušné volné větve (perigraft arterial sac embolization, PASE). Další možností léčby T2E je perkutánní aplikace trombinu přímo do vaku falešného lumen či chirurgický podvaz přívodné arterie. Endoleaky T4E a T5E je možno řešit konzervativně – sledováním. V případě nutnosti lze perkutánní punkcí falešného lumen (většinou pod CT navigací) odsát jeho obsah, a snížit tak endotenzi či postupovat obdobně jako u léčby T3E.

V našem případě jsme vzhledem k velikosti komunikace mezi nepravým lumen disekce a levou větví plicnice cestou perzistentně průtočné Botallovy dučej přistoupili k jejímu katetrizačnímu uzavření pomocí Amplatzerova síťového okluderu. Zároveň tento případ potvrzuje pravidlo, že léčba pacienta s akutním aortálním syndromem patří bezesporu do centra s komplexní kardiiovaskulární péčí. Důležitá je spolupráce mezi kardiologem, kardiochirurgem, anesteziologem a radiologem, která vede k celistvému pohledu na problematiku daného pacienta. Je nutné, aby ošetřující personál měl zkušenosti jak s řešením primárního problému, tak s případnými komplikacemi. To je zajištěno jen v případě, že je péče o takto komplikované pacienty centralizována. Námi zmíněný pacient je toho zářným příkladem. Nejprve byl na našem pracovišti vyšetřen pro epizodu synkopy, následně byl dispenzarizován pro chronické srdeční selhání, až vše vyústilo v nutnost řešit akutní aortální disekci typu B. Včasné odhalení suboptimálního výsledku endovaskulárního výkonu (TEVAR), důkladné prozkoumání předchozí dokumentace (především CT vyšetření) a pečlivé uvážení strategie řešení dané situace je nedílnou součástí celého procesu v péči o pacienta.

Závěr

Cílem kazuistiky je poukázat na celkem vzácnou příčinu suboptimálního výsledku endovaskulární léčby disekce

aorty typu B způsobenou perzistující Botallovou dučejí. Námi zvolený způsob jejího uzávěru je velice raritní a nesl s sebou jisté pochybnosti o technické proveditelnosti celého výkonu. Výsledek zákroku je však výborný a proběhl bez jakýchkoliv komplikací.

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Surgical management of ascending aorta pseudoaneurysm in a patient with COVID-19

Sandra Rečičárová^{a,b}, Peter Ivák^a, Jan Pirk^a

^a Department of Cardiovascular Surgery, Institute for Clinical and Experimental Medicine, Prague

^b First Faculty of Medicine, Charles University, Prague

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SOUHRN

Pseudoaneurysma hrudní aorty je raritní diagnóza asociovaná s vysokou mortalitou. Prezентujeme případ pacienta, u kterého vznikla velká falešná výduň deset let po provedení Bentallovy operace a jednonásobného aortokoronárního bypassu. Zároveň s daným nálezem se u něho prokázala covid-19 pozitivita. Po zálčení pneumonie byla úspěšně provedena operace, a to sešitím dvou defektů v aortálním konduitu. Jedná se o unikátní případ, kdy pacient přežil dva život ohrožující stavy.

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ABSTRACT

Pseudoaneurysm of the thoracic aorta is a rare condition associated with high mortality. We present a case of a patient who developed a huge pseudoaneurysm 10 years after the Bentall procedure and one aorto-coronary bypass while simultaneously being COVID-19 positive. After treating pneumonia, the surgery was successfully performed with suturing two defects in the aortic conduit. It is a unique case report where the patient survived two life-threatening conditions.

Introduction

Pseudoaneurysms of the thoracic aorta are contained ruptures in which the majority of the aortic wall has been disrupted and luminal blood is contained by surrounding mediastinal structures. They have a tendency to expand quickly and are associated with high mortality. Etiologically they occur after cardiac surgery, chest trauma, or infection. A golden standard for treatment is the surgical approach but since reoperative aortic surgery is a therapeutic challenge, transcatheter closure or conservative treatment is sometimes advised.¹

Case report

A 43-year-old man after the Bentall procedure and one aortocoronary bypass ad PDA (2010) was admitted to our Institution on 9th December 2020 with a diagnosis of an aortic pseudoaneurysm. He was previously hospitalized in another hospital for sharp chest pain and exertional dyspnea, where echocardiography revealed a pseudoaneurysm on the front side of the aortic conduit. His bio-

markers of inflammation were elevated, therefore he was treated with empirical broad-range antibiotics. Before he was transferred to our institution he tested PCR negative for COVID-19 on 9th December 2020.

On admission, the PCR test for COVID-19 was repeatedly negative and his biomarkers of inflammation were elevated as well as cardiac markers. Echocardiography was performed, and a leak in the area of reimplanted RCA to the pseudoaneurysm was described. Then a chest CT scan was completed, and a diagnosis of aortic pseudoaneurysm with dimensions 77 × 107 × 44 mm was confirmed. It also revealed no significant stenosis in LAD and RD, on the other hand, RCA and Cx weren't displayed which confirmed the suspicion of RCA detachment. The pseudoaneurysm caused compression of the conduit.

The operation performance was postponed, patient's inflammation biomarkers persisted high despite the administration of two empirical antibiotics. COVID-19 antigen rapid test was performed as a part of the regular screening process on the fifth day of hospitalization with a positive result as well as a later repeated PCR test. Chest X-ray confirmed right lobar pneumonia. The patient required high nasal flow oxygen and was treated con-

Address: Sandra Rečičárová, MD, MBA, Department of Cardiovascular Surgery, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, 140 00 Prague 4, e-mail: sandra.recicarova@ikem.cz
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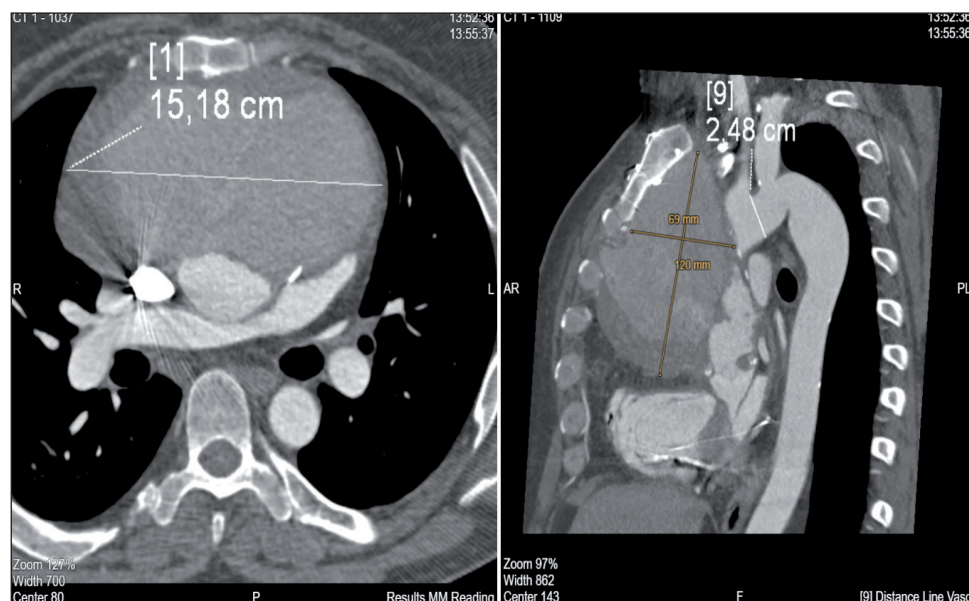


Fig. 1 – Chest CT scan before surgery.

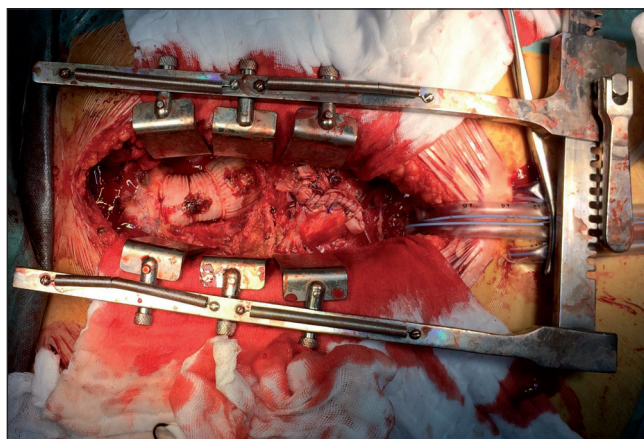


Fig. 2 – Sutured defects in conduit.

tinuously with antibiotics, steroids, and isoprinosine with good therapeutical and laboratory effects. Another chest CT scan completed before surgery on the 13th January 2021 manifested the presence of residual infiltrates on the lungs and a massive progression of the pseudoaneurysm to 150 mm with 2 possible entries (Fig. 1).

The patient subsequently underwent a cardiac operation on the 21st, January 2021 in deep hypothermia at 18 °C with cannulation of the subclavian artery and femoral vein. Two leaks were detected on the front side of the aortic conduit. The first defect was after central anastomosis of the bypass to the PDA into the conduit and the second was after reimplantation of RCA in the Bentall procedure. The first smaller defect was sutured, the second was bigger, and therefore circular suturing was performed with bovine pericardium (Fig. 2). A laceration of the right ventricle occurred during resternotomy and it was sutured continuously with bovine pericardium as well.

Recovery was uneventful. The patient was discharged on postoperative day 6 in stable condition. Another chest

CT scan was performed one month after surgery with a favorable outcome.

Discussion

The epidemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is causing the loss of thousands of lives because of its highly contagious nature and unprecedented global spread, its aggressive clinical presentation, and the lack of effective treatment. Active SARS-CoV-2 infection may precipitate an overproduction of early response proinflammatory cytokines, leading to five times higher mortality and longer post-operative stay. Moreover, studies have already proven that patients with cardiovascular diseases have a greater risk of increased SARS-CoV-2 infection prognosis.²

Several case reports have published their findings of artery pseudoaneurysm and SARS-CoV-2 concomitant presence but none of those included aortic pseudoaneurysm. Some of them speculate that pseudoaneurysm development was a consequence of advanced COVID-19 infection. In our case, the pseudoaneurysm likely developed before the COVID-19 infection nonetheless, the infection accelerated its rapid progression. Nonetheless, it is not possible to reliably claim whether this is a causality or a coincidence of the aortic pseudoaneurysm and COVID-19 infection. The vascular complications after COVID-19 infection and their possible association are still under debate.³⁻⁵

Another important factor is the timing of the operation since there are still no data on cardiac surgery optimal timing in a patient with COVID-19 infection. Our decision was established to operate on the patient only after successful treatment of pneumonia acknowledging the possibility of pseudoaneurysm rupture. In conclusion, decisions to operate should be based on the severity of the disease, patient factors, and institution capacity.

Conflict of interest

None declared.

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Post-infectious acute myocardial infarction following COVID-19 infection in a young patient

Rodolfo Caminiti^{a,b}, Giampaolo Vetta^{a,c}, Antonio Parlavecchio^{a,b},
Michele Magnocavallo^c, Stefano Postorino^b, Scipione Carerj^a,
Francesco Antonio Benedetto^b

^a Cardiology Unit, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

^b Interventional Cardiology Unit, Department of Cardiology, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

^c Department of Clinical, Internal, Anesthesiology and Cardiovascular Sciences, Policlinico Universitario Umberto I, Sapienza University of Rome, Rome, Italy

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SOUHRN

Dnes je již dobře známo, že onemocnění covid-19 může mít i různé extrapulmonální projevy. Mezi možné mechanismy postižení kardiovaskulárního systému patří přímé poškození myokardu v důsledku hyperkoagulability vyvolané systémovým zánětem, což může vyústit i v destabilizaci plátů v koronárních tepnách.

Popisujeme případ 30letého mladého muže po asymptomatickém onemocnění covid-19, který byl přijat na oddělení akutních příjmů nemocnice Grande Ospedale Metropolitano di Reggio Calabria (Itálie) s typickou bolestí na hrudi. U pacienta nebyla stanovena diagnóza kardiovaskulárního onemocnění, nebyly přítomny žádné rizikové faktory, ani kardiovaskulární onemocnění v rodinné anamnéze.

Urgentní koronarografie prokázala kritickou (80%) stenózu ve střední a proximální části r. interventricularis anterior tvořenou plátem vzhledu ateromového vředu.

Naše kazuistika upozorňuje na nutnost – bez ohledu na rizikové faktory kardiovaskulárního onemocnění – ověřit přítomnost či nepřítomnost onemocnění covid-19 u všech pacientů s akutním infarktem myokardu během této pandemie.

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ABSTRACT

It is now widely known that COVID-19 can also cause various extrapulmonary manifestations. Possible mechanisms of cardiovascular damage include direct myocardial damage due to hypercoagulability caused by systemic inflammation, which may also lead to destabilisation of coronary plaques.

We present a case of a 30-year-old young man following asymptomatic COVID-19 infection, who was admitted to the emergency room of the Grande Ospedale Metropolitano di Reggio Calabria, Italy, with typical chest pain. The patient had no cardiovascular disease, cardiovascular risk factors including no family history of cardiovascular disease.

Urgent coronary angiography showed critical stenosis of the middle-proximal portion of the left anterior descending artery (80%) with ulcerated plaque appearance.

Regardless of cardiovascular risk factors, our case report emphasises the need to determine COVID-19 status in all patients with acute myocardial infarction during this pandemic.

Keywords:

Acute myocardial infarction

Cardiovascular disease

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Young patients

Address: Rodolfo Caminiti, MD, Cardiology Unit, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy,

e-mail: rodolfocaminiti@msn.com

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Introduction

Severe acute respiratory syndrome coronavirus 2 virus and associated coronavirus disease 2019 (COVID-19) was officially detected for the first time in Wuhan and has spread throughout the world becoming a pandemic. Although COVID-19 causes respiratory symptoms in most patients, several studies showed extrapulmonary involvement, including the cardiovascular system. Possible mechanisms of cardiovascular damage include direct myocardial damage from hemodynamic derives or hypoxemia, myocarditis, microvascular dysfunction, or thrombosis due to hypercoagulability due to systemic inflammation, which can also lead to destabilization of coronary plaques.¹ In literature, there is evidence of the link between COVID-19 and coagulation abnormalities and the predisposition of patients to thrombotic disease, in both the venous and arterial circulation.² At coronary angiography, patients with COVID-19 and myocardial infarction may show both typical obstructive coronary arteries and normal angiographic epicardial coronary arteries.³ We present a case of a 30-year-old young man following asymptomatic COVID-19 infection, who was admitted to the emergency room of the Grande Ospedale Metropolitano di Reggio Calabria, Italy, with typical chest pain.

Case report

A 30-year-old young man was admitted to the emergency department of the Grande Ospedale Metropolitano of Reggio Calabria, Italy, for typical chest pain.

The patient had no cardiovascular disease, cardiovascular risk factors including no family history of cardiovascular disease. He was infected with asymptomatic COVID-19 about 20 days previously. An antihygienic nasopharyngeal swab resulted negative 10 days before admission to the emergency department.

On admission, electrocardiogram showed hyperacute T waves on precordial leads V_2 – V_4 (Fig. 1A). Admission blood tests demonstrated increased level of high sensitivity (HS) cardiac I-troponin 1260 ng/L (normal <12 ng/L) with increase of creatine phosphokinase (231 U/L; normal <170 U/L) and creatine kinase MB levels (17 U/L; normal <16 U/L). The C-reactive protein was just above the maximum limit (5.57 mg/L; normal <5 mg/L). The echocardiogram showed akinesia of the whole apex with a reduced ejection fraction (42%). Urgent coronary angiography within 1 h from hospital admission revealed critical stenosis of the middle-proximal portion of the left anterior descending artery (80%) with ulcerated plaque appearance (Fig. 1B). The coronary

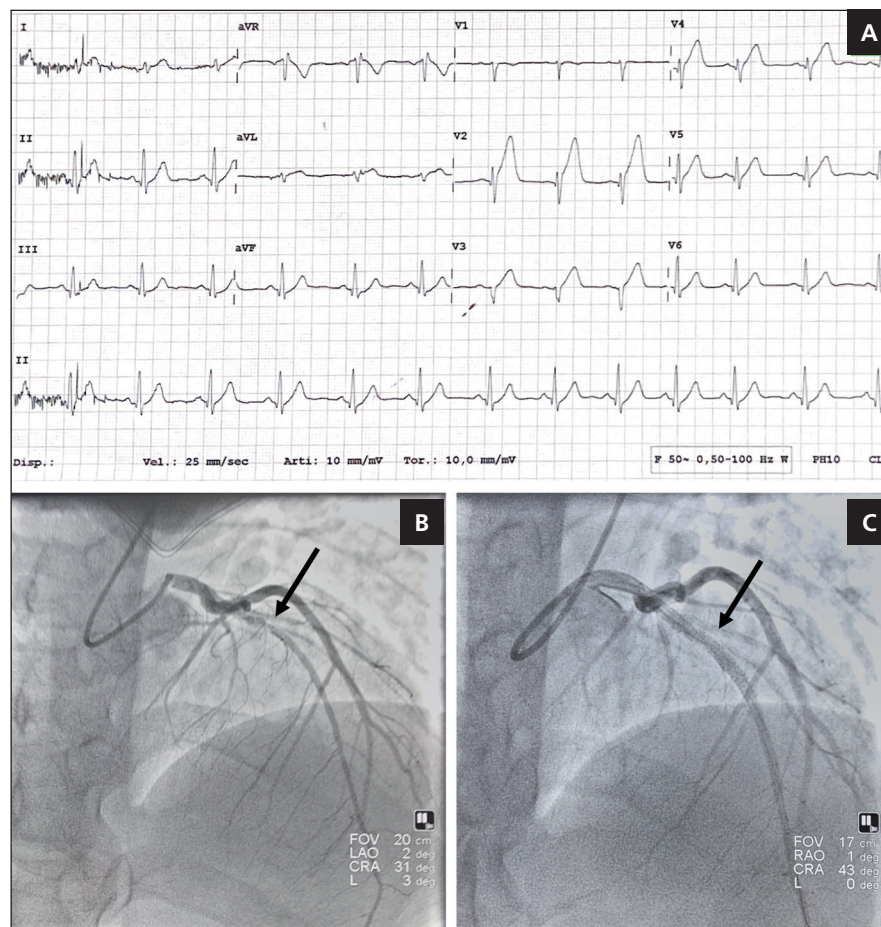


Fig. 1 – (A) Electrocardiogram at admission showing hyperacute T waves from V_2 – V_4 leads. (B) Baseline coronary angiogram showing severe stenosis of middle-proximal left descending coronary artery (black arrow). (C) Coronary angiogram after angioplasty (black arrow).

obstruction was successfully recanalized by the deployment of one Synergy everolimus-eluting stent 3.0 × 32 mm (Boston Scientific, Marlborough, MA, USA) (Fig. 1C). The patient was admitted to our Cardiology Intensive Care Unit.

The following day, laboratory tests showed HS I-troponin 25 260 ng/L, total cholesterol 190 mg/dL, HDL 29 mg/dL, LDL 85 mg/dL, Triglycerides 93 mg/dL. The patient was treated with acetylsalicylic acid, ticagrelor, high dose atorvastatin, sacubitril/valsartan and bisoprolol.

A new echocardiographic check before discharge showed a hypokinesia of the whole apex with an improvement of the ejection fraction (45%), normal right ventricular function, normal pulmonary systolic pressure and no valvular disease. The discharge electrocardiogram showed ST segment normalization.

Patient hospitalisation occurred without complications, with no evidence of arrhythmias on electrocardiographic monitoring.

The patient was discharged completely asymptomatic, after the markers of myocardial necrosis were negative.

Discussion

In our case report we describe a case of acute myocardial infarction in a young patient without cardiovascular risk factors following asymptomatic COVID-19 infection. To date, our case represents the youngest patient to suffer a type 1 acute myocardial infarction following an asymptomatic COVID-19 infection. In the case series by Sisakian and colleagues, STEMI patients with COVID-19 infection were young (33 and 35 years) without cardiovascular risk factors (one of the patients had a history of transient ischaemic attack) with onset of ventricular fibrillation.^{4,5} Instead, in the case-series by Bangalore and colleagues, patients with acute myocardial infarction and COVID-19 infection had different clinical as well as angiographic presentations.^{6,7} Indeed, the mean age of the patients was 63 years and most of them suffered from hypertension and diabetes mellitus. In addition, in 33% of patients at coronarography the coronary arteries were angiographically normal. In 37% of COVID-19 patients with acute myocardial infarction, there was no evidence of a culprit lesion on coronarography.^{3,8} These evidences suggest that several mechanisms are involved in the aetiology of acute myocardial infarction in COVID-19 patients, leading to an increased risk of myocardial infarction during COVID-19 infection, even in the absence of cardiovascular risk factors. Myocardial ischaemia in COVID-19 patients could be triggered by coronary dysfunction due to hyperinflammatory response.^{2,6} Cytokine release promotes T-cell and monocyte activation within an existing atherosclerotic plaque, destabilizing it through the release of histotoxic mediators leading to acute coronary syndrome. Moreover, the cytokines release, as interleukin-6, exerts proatherogenic effects, causing vascular smooth muscle proliferation, endothelial cell activation, and platelet activation.^{9,10}

Myocardial ischaemia can also be caused by microvascular dysfunction due to endothelial impairment.³

Endothelial dysfunction in COVID-19 patients is caused primarily by the downregulation of angiotensin-converting enzyme-2 (ACE-2) receptors, triggering the kallikrein-bradykinin system and resulting in increased vascular permeability. Virus-mediated vasculitis could be a further mechanism of microvascular dysfunction as the virus penetrates vascular endothelial cells via ACE-2 receptors, leading to inflammation and apoptosis. The multitude of pathways involved in the pathophysiology of myocardial infarction in COVID-19 infection results in a complex diagnostic and therapeutic management.^{7,10,11} Thus, the European Society of Cardiology developed Guidance for the Diagnosis and Management of Cardiovascular Disease during the COVID-19 Pandemic to guide the cardiologist's choices balancing the exposure of the health professional with the benefit to the patient.

Conclusion

COVID-19 infection by multiple pathophysiological mechanisms can lead to myocardial infarction even in young people without cardiovascular risk factors. Regardless of cardiovascular risk factors, our case report underlines the need to determine COVID-19 status in all patients with acute myocardial infarction during this pandemic. Further studies are needed to investigate the multiple mechanisms responsible for myocardial infarction in patients with COVID-19 infection and to assess optimal acute and long-term therapy.

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Conflict of interest

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Ethical approval

Ethical approval was waived by the local Ethics Committee of Grande Ospedale Metropolitano di Reggio Calabria in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

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Post-myocardial infarction left ventricular intramyocardial dissecting hematoma

Adam Vejmelek^a, Petr Němec^{a,b}, Petr Fila^{a,b}^a Centre of Cardiovascular Surgery and Transplantation, Brno^b Department of Cardiovascular and Transplant Surgery, Medical Faculty Masaryk University, Brno

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SOUHRN

Úvod: Intramyokardiální disekující hematom (IDH) je dutina ve stěně srdce vyplněná krví, která vzniká oslabením stěny nekrozou po infarktu myokardu. IDH se může vytvořit ve stěně levé komory, pravé komory nebo interventrikulárního septa.

Popis případu: Kazuistika popisuje pacienta s IDH jako vzácnou komplikaci po infarktu myokardu. Pacient byl hospitalizován pro trvající obtěžující kašel tři měsíce po prodělání infarktu myokardu řešeném implantací stentu. Dle echokardiografie bylo podezření na krytou rupturu volné laterální stěny s obrazem pseudoaneurysmatu, pro kterou bylo rozhodnuto o operačním řešení. Při operaci byl nalezen plošný dutiny ve stěně levé komory komunikující otvorem s levou komorou. Vnitřní i vnější stěna dutiny obsahovala srdeční svalovinu, a tak byla dutina diagnostikována jako IDH. Otvor i dutina byly uzavřeny stehy přes meshové podložky a suturou přes meshový proužek. Pooperační průběh se obešel bez komplikací a pacient byl propuštěn osmý den po operaci.

Diskuse: Diagnostika IDH se zakládá na anamnéze infarktu myokardu a na nálezech na echokardiografii. Mezi známky echokardiografického obrazu IDH patří vytvoření nové dutiny uvnitř srdeční stěny s echo-lucentním středem. Diferenciální diagnostika IDH zahrnuje aneurysma, pseudoaneurysma, trombus uvnitř dutiny LK nebo trabekuly komor.

Závěr: IDH je komplikace infarktu myokardu, na kterou je třeba pomyslet při diferenciální diagnostice nově vzniklé dutiny ve stěně levé komory na ultrazvukovém vyšetření. Konzervativní řešení je možné u IDH malých rozměrů, u kterých nedochází k progresi. U hemodynamické nestability pacienta nebo u velkých nebo progredujících IDH je namístě chirurgické řešení.

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ABSTRACT

Background: Intramyocardial dissecting hematoma (IDH) is blood-filled cavitation in the cardiac wall that can occur as a complication of myocardial infarction, chest trauma, or percutaneous intervention. It can develop in the left ventricular free wall, the right ventricle, or the interventricular septum.

Case report: The case report describes a patient with IDH as a rare complication of myocardial infarction. The patient was hospitalized for ongoing irritating cough three months after ST elevated myocardial infarction treated with percutaneous coronary intervention. The echocardiography showed the image of a pseudoaneurysm of the left ventricle. The patient underwent surgery where a cavitation inside the left ventricle myocardial wall communicating with the left ventricle was found. The inner and outer border of the cavitation included myocardium, therefore diagnosis of IDH was established. The communication and the cavitation were closed with pledgeted sutures and a direct suture with a mesh stripe. Postoperative hospitalization was without complications and the patient was dismissed the eighth day after the surgery.

Discussion: Diagnosis of IDH consists of anamnestic information of myocardial infarction and assessment on echocardiography. On echocardiography the IDH shows as a neocavitation within the heart wall with an echo-lucent center. The differential diagnosis of IDH includes aneurysm, pseudoaneurysm of the heart, thrombus of the ventricle and trabeculae.

Conclusion: The IDH is a post-infarction complication important to include in the differential diagnosis of newly formed cavitation inside the ventricle wall seen on echocardiography. Conservative management is suggested when the IDH is small and not growing. Surgery is indicated if the patient is unstable or the IDH is large or growing.

Keywords:

Complication of myocardial
infarction

Echocardiography

Intramyocardial dissecting
hematoma

Myocardial infarction

Address: MUDr. Adam Vejmelek, Centre of Cardiovascular Surgery and Transplantation, Pekařská 53, 602 00 Brno, e-mail: adam.vejmelek@cktcz.cz

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Background

Intramyocardial dissecting hematoma (IDH) is a rare complication of acute myocardial infarction, chest trauma, or percutaneous intervention. It is a subtype of subacute myocardial rupture. IDH is blood-filled cavitation in the cardiac wall created by hemorrhagic infiltration into and through the myocardium of the ventricle or interventricular septum. The cavitation's borders are made of epicardium and myocardium externally, endocardium and myocardium internally. It can develop in the left ventricular free wall, the right ventricle, or the interventricular septum.^{1,2}

Formation of IDH may result from rupture of myocardial vessels in the weakened necrotic wall post-myocardial infarction, or from an acute increase of coronary capillary perfusion pressure.³ IDH can occur as a complication of myocardial infarction or after thoracic trauma.⁴ Mandke et al. described IDH as a rare complication after using a stabilizer in off-pump revascularization.⁵

The case report describes post-infarction IDH masquerading as a pseudoaneurysm.

Case report

A 75-year-old male patient with hypertension and diabetes had ST elevated myocardial infarction (STEMI) of the lateral wall. Cardiac catheterization after the STEMI showed total occlusion of an obtuse marginal artery (from left circumflex) treated with percutaneous coronary intervention (PCI) with a drug-eluting stent. After the STEMI the patient had Dressler pericarditis.

The patient was hospitalized in internal ward three months after the episode for an irritating cough. Echocardiography was performed and showed a pseudoaneurysm of the left ventricle. The pseudoaneurysm was localized between the basal and middle parts of the lateral wall. The patient was treated with antitussives, benzodiazepine, and nitrates for hypertension.

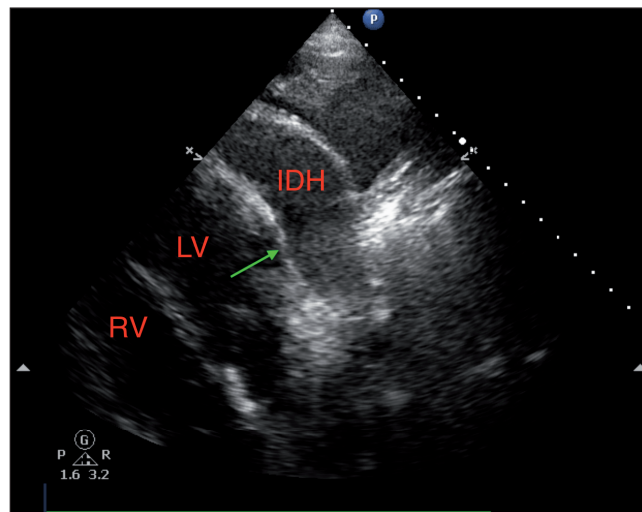


Fig. 1 – Echolucent cavitation in the LV wall (IDH) communicating with LV through a small hole (green arrow). IDH – intramyocardial dissecting hematoma; LV – left ventricle; RV – right ventricle.

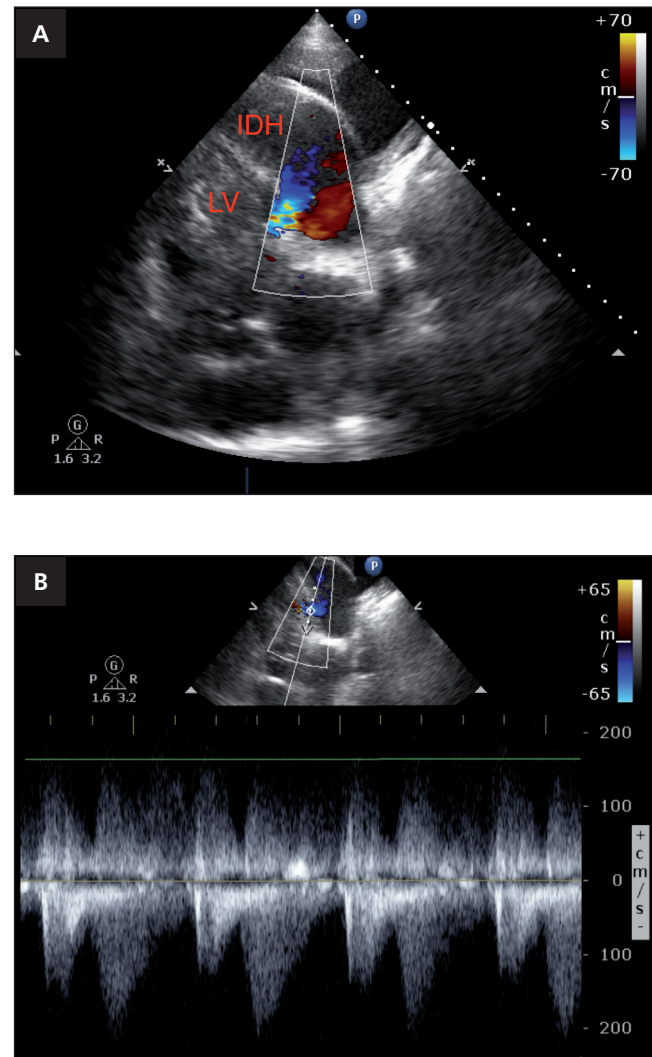


Fig. 2 (A) and (B) – To-and-fro flow inside the cavitation of the LV wall (IDH) confirmed by Doppler ultrasonography. IDH – intramyocardial dissecting hematoma; LV – left ventricle.

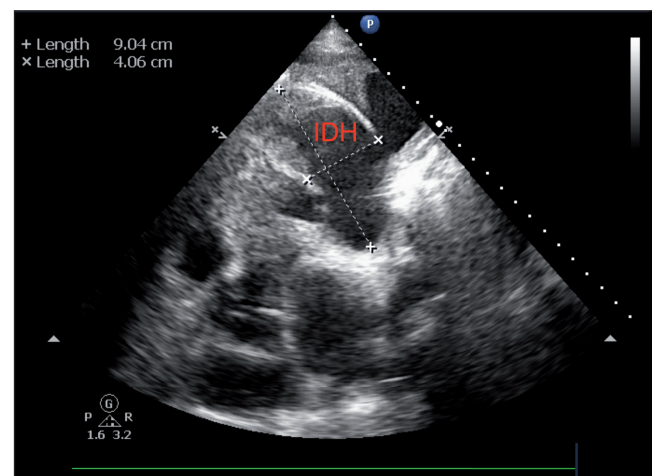


Fig. 3 – Size of the cavitation of the left ventricle. IDH – intramyocardial dissecting hematoma.

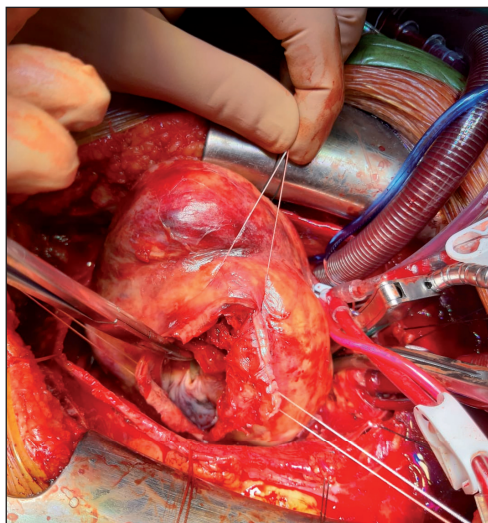


Fig. 4 – Cavitation 8 × 4 × 1 cm in the wall of the LV.

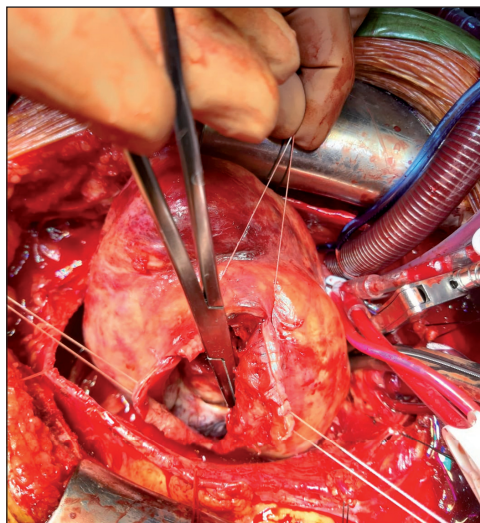


Fig. 5 – Cavitation communicating with the LV (forceps are going through the hole into the LV).

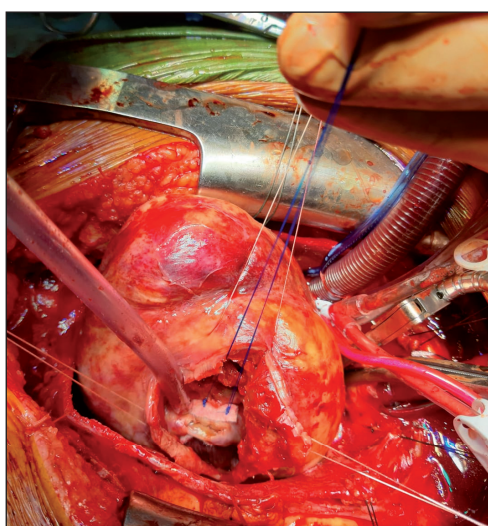


Fig. 6 – Closure of the hole communicating direct suture with meshed strips.

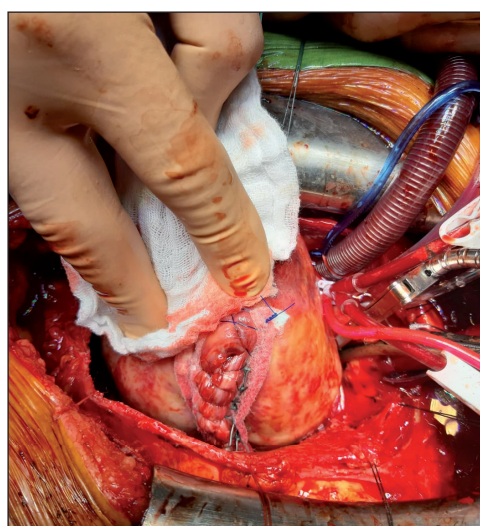


Fig. 7 – Closure of the cavitation with LV with pledget suture.

The patient was transferred to the Centre of Cardiovascular Surgery and Transplantation (CKTCH) for surgery. At admission he did not have any chest pain or shortness of breath. The only thing that bothered him was the coughing ongoing since the myocardial infarction.

Transthoracic echocardiography showed echolucent cavitation beside the posterior/lateral wall of the left ventricle (LV). The size of the cavitation was 4 × 9 cm and it communicated with LV through a small 1-cm hole in the lateral wall of the LV. Inside the cavitation there was a thrombus on the side nearer to the heart apex. The rest of the cavitation was free with blood flow going in-and-out of the cavitation confirmed by Doppler ultrasound (Fig. 1–3). The cavitation was diagnosed as pseudoaneurysm and cardiac surgery was indicated for the risk of complete rupture as a complication of post-myocardial infarction pseudoaneurysm.

The systolic function of LV was good with an ejection fraction of 65%, the heart did not have any other patho-

logies. There were bilateral pleural effusions – on the right side 400 ml, on the left 1000 ml.

At CKTCH new coronary angiography was performed with the finding: the left main coronary artery without stenosis, diffuse up to 50% stenosis of the proximal and middle part of the left anterior descending artery (LAD), the stent in the obtuse marginal artery (OM) had 90% restenosis and closure of peripheral part of OM. The right coronary artery was without stenosis.

The patient underwent an operation. Epicardium was heavily fibrotic and thick because of Dressler syndrome pericarditis. The patient was put on cardiopulmonary bypass (CPB) and the heart was arrested by cardioplegia.

There was a bulging of thinned wall on the lateral side of the LV. The wall was cut and opened at this site into flat cavitation. The cavitation was 8 × 4 × 1 cm in size (Fig. 4) and communicated with the LV through a 1.5 × 1 cm-big hole (Fig. 5). The inner and outer border of the

cavitation included myocardium, suggesting the diagnosis of IDH.

The hole communicating with the LV was closed with two pledged sutures (Fig. 6) and the cavitation was closed with a direct suture forced with a mesh stripe (Fig. 7). A sample of the outer layer of the cavitation wall was sent for histological examination. The patient's weaning from the CPB was without any complications. The CPB time was 87 minutes, and the heart arrest was 59 minutes long.

Postoperative hospitalization was without complications. On the seventh day after the surgery echocardiography was performed. There was hypertrophic LV with good systolic function and akinetic posterolateral wall of the LV. There was a pericardial effusion of 16 mm beside the lateral wall of the LV. The original cavitation of the IDH was filled with thrombus without any flow detection (Fig. 8). Histological examination confirmed the presence of dense fibrosis and atrophic cardiomyocytes.

The patient was dismissed on the eighth day after the surgery stable and in good condition.

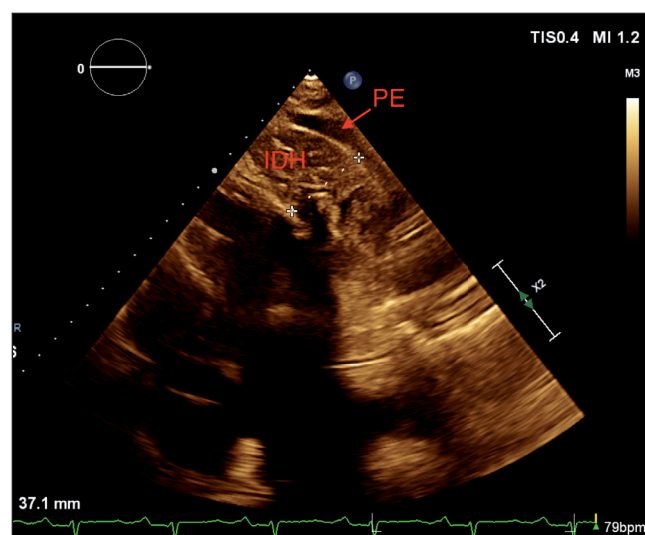


Fig. 8 – IDH filled with thrombus lateral to the LV. Pericardial effusion beside the IDH (PE – red arrow). IDH – intramyocardial dissecting hematoma; PE – pericardial effusion.

Discussion

Diagnosis of IDH can be challenging and is usually done perioperatively or at autopsy.⁶ The correct diagnosis consists of anamnestic information of recent myocardial infarction and assessment on transthoracic and/or transesophageal echocardiography, or in some cases on magnetic resonance.⁷ Differential diagnosis of IDH includes aneurysm, pseudoaneurysm (PSA) of the heart, both being more frequent complications of myocardial infarction, also thrombus of the LV and trabeculae.²

The signs of IDH on echocardiography to distinguish IDH from other possible diagnoses are:¹

1. The formation of neocavitation within the heart wall with an echolucent center.

2. Mobile thin layer surrounding the cavity made of intact endomyocardium.
3. The presence of myocardium on both the internal and external side of the cavity.
4. Changes in the echogenicity of the neocavitation suggesting blood content.
5. Continuity between the dissecting hematoma and the heart chamber.
6. Blood flow within the dissected hematoma confirmed by Doppler sonography.¹

The IDH is a dynamic entity and the sonography image changes with time. In the phase of formation of IDH and the phase of spontaneous reabsorption the sonography image is unrecognizable from the image of a thrombus inside the heart chamber. On the other hand, in the dissecting phase of IDH there is echolucent acoustic density similar to blood in the neocavitation.¹ Therefore, in stable patients, a series of ultrasonography examinations are necessary for the correct diagnosis of IDH.

Often the IDH cannot be distinguished from pseudoaneurysm until surgery or autopsy. The outer layer of the IDH consists of pericardium and myocardium in contrast to pseudoaneurysm, whose outer layer consists of the epicardium.²

In our patient the diagnosis of PSA was established based on large cavitation on echocardiography. Due to the high risk of PSA rupture the patient was indicated to prompt operation without any other supplemental examination like MRI or CT. The histological examination of perioperative outer layer biopsy showed the presence of cardiomyocytes and therefore confirmed the diagnosis of IDH.

The management of the IDH depends on various factors such as age, hemodynamic stability, the size of the IDH, LV function, and the presence of pericardial effusion. The conservative management is preferred when the patient is stable, the size of IDH is small and consistent and the echogenicity inside the IDH changes from blood to thrombus.

Surgery is suggested if the patient is hemodynamically unstable or there is the presence of pericardial effusion or the IDH is large or growing larger.⁷ One of the most severe complications of IDH is progression into complete myocardial rupture. Therefore, when the IDH is managed conservatively, observing the patient and performing a series of ultrasonographic examinations are necessary until spontaneous reabsorption of the IDH or formation of thrombus inside the IDH.⁸

Close monitoring or potential surgery is also suggested in patients older than 60 years, patients with low ejection fraction (EF <30%), patients with anterior MI, as these factors were the most serious independent mortality risk factors.⁹

Conclusion

The intramyocardial dissecting hematoma is a rare complication of myocardial infarction. It is important to include it in the differential diagnosis of post-myocardial infarction newly formed cavitation inside the left ventricle wall seen on ultrasonography. Conservative management

and further patient observation are suggested when the IDH is small and not growing. Surgery is indicated if the patient is unstable or the IDH is large or growing.

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Srdeční tamponáda jako závažný projev angiosarkomu

(Cardiac tamponade as a severe manifestation of angiosarcoma)

Daniel Baran, Tomáš Roubíček, Rostislav Polášek

Kardiocentrum, Krajská nemocnice Liberec, a.s., Liberec

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SOUHRN

Angiosarkom srdce je nejčastějším primárním maligním tumorem srdce. Je charakteristický rychlým a agresivním růstem. Nejčastěji postihuje pravostranné srdeční oddíly. V diagnostice jsou nejdůležitější zobrazovací metody a histologické vyšetření. Prognóza angiosarkomů je závažná. Jediným potenciálním kurativním základem je radikální chirurgická resekce. Popisujeme případ 20letého muže prezentujícího se srdeční tamponádou jako závažným projevem angiosarkomu.

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ABSTRACT

Angiosarcoma of the heart is the most common primary malignant tumour of the heart. It is characterized by rapid and aggressive growth. It most commonly affects the right side of the heart. Cardiac imaging and histology are the most important tests leading to right diagnosis. The prognosis of angiosarcomas is very poor. The only potential curative intervention is a radical surgical resection. We describe a case of a 20-year-old man presenting with cardiac tamponade as a severe manifestation of angiosarcoma.

Úvod

Nádory srdce se řadí mezi vzácná onemocnění.¹ Udávaná incidence je méně než dva případy na 100 000 pacientů.² Základní dělení je na primární, kdy nádor vychází ze samotné srdeční tkáně, a početně častější sekundární, kdy je srdce postiženo metastatickým rozsevem. Primární nádory se dále rozdělují na benigní, z nichž nejčastějším je myxom, a maligní.³ Incidence maligních variant se dle různých zdrojů pohybuje mezi 10–25 % primárních nádorů srdce.^{1,2} Nejčastějším typem primárního maligního tumoru srdce je angiosarkom.² Závažnost srdečních tumorů je obecně dána nespecifickými příznaky, které zahrnují dušnost nebo hemoptýzu. Dále se mohou objevit symptomy, jako je hubnutí, nechutenství, únava nebo horečka.⁴ Typickou lokalizací angiosarkomu jsou pravostranné srdeční oddíly.^{5,6} Často dochází k rozvoji perikardiálního výpotku, který může vést až k srdeční tamponádě.⁷ Základním pilířem v diagnostice je echokardiografické vyšetření, na které navazuje výpočetní tomografie (CT), magnetická rezonance, eventuálně pozitronová emisní tomografie/výpočetní tomografie (PET/CT). Již pomocí zobrazovacích metod lze odhadovat biologickou povahu srdečního tumoru.⁸ Pro

stanovení definitivní diagnózy je pak zejména v případě maligních tumorů nutné provedení histologického vyšetření ze vzorku nádorové tkáně včetně imunohistochemické analýzy.^{9,10} Vzhledem k rychlému a agresivnímu růstu je prognóza angiosarkomů velmi špatná. Udává se, že bez léčby přežívají pacienti v průměru několik měsíců.⁶ Jedinou potenciálně kurabilní metodou je radikální chirurgická resekce, na kterou v indikovaných případech navazuje systémová léčba.¹¹ Izolovaná systémová léčba a radioterapie jsou pouze paliativní zákroky určené pro inoperabilní pacienty.⁴ V posledních letech, patrně v důsledku rozšíření a lepší dostupnosti zobrazovacích metod, incidence srdečních tumorů stoupá.¹²

Kazuistika

Prezentujeme případ 20letého dosud zdravého aktivního pacienta s několikátýdenní anamnézou námahové dušnosti a intermitentní hemoptýzy. Při rozvoji prvních příznaků byl pacient krátce hospitalizován na interním oddělení, kde byla stanovena diagnóza exogenní alergické alveolitidy a zahájena léčba systémovými kortikoidy.

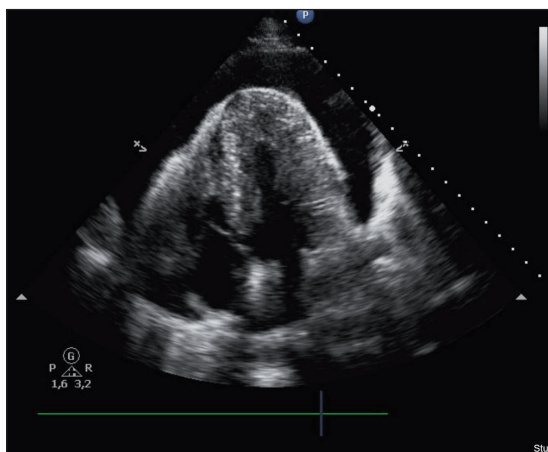
Adresa pro korespondenci: MUDr. Daniel Baran, Kardiocentrum, Krajská nemocnice Liberec, a.s., Husova 357/10, 460 63 Liberec, e-mail: daniel.baran@nemlib.cz
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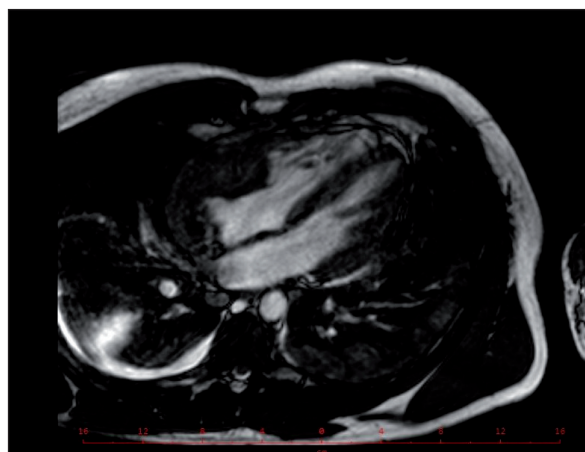
Ultrazvuk srdce nebyl během první hospitalizace proveden. Následně byl pacient vyšetřen na urgentním příjmu pro nově vzniklé pleurální bolesti. Na vstupním EKG byl přítomen sinusový rytmus 106/min. V krevním obraze dominovala výrazná leukocytóza 23 tisíc. Jinak byl krevní obraz a biochemie bez pozoruhodností. Za pobytu na urgentním příjmu došlo k synkopě s křečemi a stav se po jedné hodině ještě jednou opakoval. EKG během epizod nebylo monitorováno. Ihned po návratu vědomí byla zjištěna hypotenze a nižší saturace krve kyslíkem, obě patologie se spontánně upravily. Pro podezření na epileptogenní etiologii bezvědomí byl pacient vyšetřen neurologem, bylo provedeno nativní CT mozku s normálním nálezem a pacient byl přijat na neurologické oddělení k observaci. Krátce po příjmu na oddělení dochází u pacienta k poruše vědomí charakteru somnolence až soporu s vyjádřenými známkami šoku. Provedené akutní echo-



Obr. 2 – Nález angiosarkomu pravé síně, obrázek z CT vyšetření (zdroj Radiodiagnostické oddělení KNL)



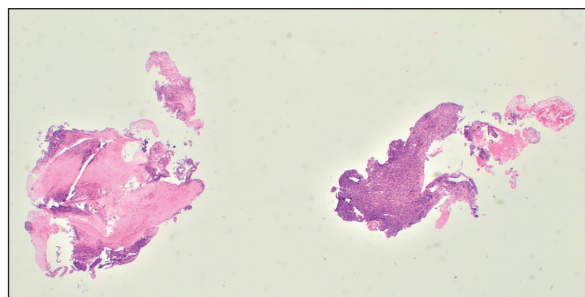
Obr. 1 – Echokardiografický nález objemného perikardiálního výpotku (zdroj Kardiologické oddělení KNL)



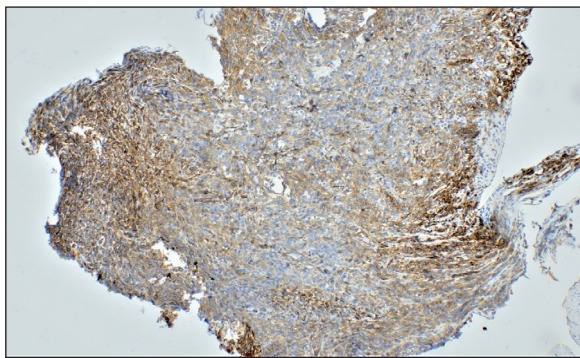
Obr. 3 – Nález angiosarkomu pravé síně, obrázek z magnetické rezonance (zdroj Radiodiagnostické oddělení VFN)

kardiografické vyšetření prokázalo objemný cirkulární perikardiální výpotek se známkami srdeční tamponády (obr. 1). Z apikálního přístupu byla provedena urgentní perikardiocentéza s odsátím celkem 550 ml hemoragické tekutiny (Hb ve výpotku 114 g/l). Po punkci došlo k okamžité stabilizaci pacienta. S ohledem na charakter výpotku bylo doplněno kontrastní CT hrudníku s nálezem kulovité hypodenzní struktury za hrudní kostí v oblasti mezi pravou síní a pravou komorou a mnohočetné plicní infiltráty obou plicních křídel jako suspektní metaprocess (obr. 2). Vzhledem k nálezu na CT a povaze výpotku byl pacient přeložen na kardiochirurgickou kliniku, kde bylo pokračováno v další diagnostice a léčbě. Diferenciálně diagnosticky byl zvažován lymfom, průtoková cytometrie z periferní krve a punktátu však tuto diagnózu nepotvrdila. Následně byla doplněna magnetická rezonance myokardu s nálezem angiomyosarkomu prorůstajícího do stěny pravé komory s propagací intrakavitálně, zasahující i pravou síň a částečně i dolní dutou žílu (obr. 3). Byla provedena endomyokardiální biopsie z tumorové masy v pravé síni. Histologické vyšetření prokazuje epitelioidně až vřetenobuněčně uspořádaný solidní tumor, imunohistochemická analýza prokázala přítomnost pozitivitu CD31, CD34 a ERG, nález, který je velmi senzitivní pro diagnózu

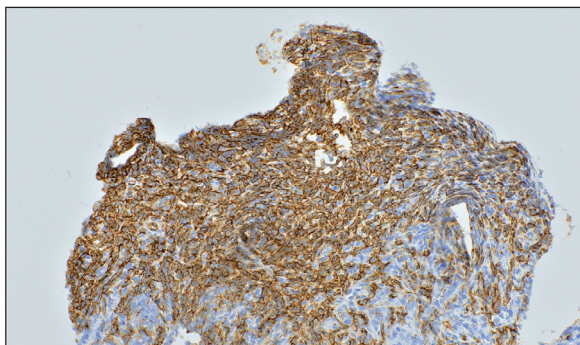
angiosarkomu¹⁰ (obr. 4–7). Během pobytu na kardiochirurgické klinice došlo u pacienta opakovaně k epizodám respirační insuficience s nutností použití neinvazivní ventilace. Jednorázově došlo při polohování k drenáži 600 ml sangvinolentní tekutiny z perikardu. Opakovanými echokardiografickými vyšetřeními však recidiva srdeční tamponády nebyla prokázána. Onkologickým týmem byl nález označen za inoperabilní a byla doporučena paliativní terapie epirubicinem. Vzhledem k nepříznivé prognóze



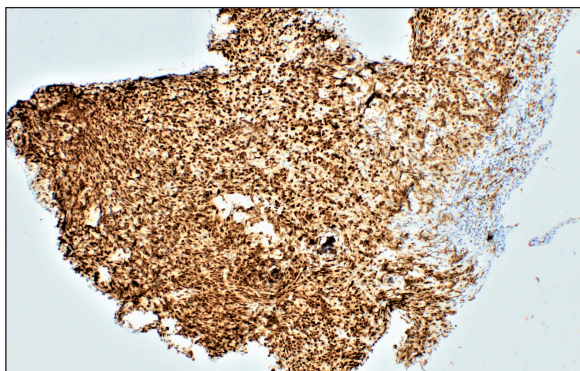
Obr. 4 – Biopstický vzorek angiosarkomu v barvení hematoxylin-eosinem – zvětšení 20× (publikováno se svolením prim. MUDr. Vítkové, MBA)



Obr. 5 – Imunohistochemické vyšetření – téměř difúzně pozitivní CD31, zvětšení 100× (publikováno se svolením prim. MUDr. Vítkové, MBA)



Obr. 6 – Imunohistochemické vyšetření – téměř difúzně pozitivní CD34, zvětšení 200× (publikováno se svolením prim. MUDr. Vítkové, MBA)



Obr. 7 – Imunohistochemické vyšetření vzorku – difúzní intraluminální pozitivita ERG, zvětšení 100× (publikováno se svolením prim. MUDr. Vítkové, MBA)

byl do péče o pacienta přizván paliativní tým, který spolupracoval při předávání informací o stanovené diagnóze a předpokládaném průběhu. Po prvním cyklu chemoterapie byl pacient přeložen na interní oddělení v místě bydliště. Pacient zemřel čtyři měsíce od rozvoje příznaků a dva měsíce od stanovení diagnózy.

Diskuse

Kazuistika popisuje typický průběh onemocnění angiosarkomem srdce. Ukazuje obtížnost stanovení správné diagnózy, kterou způsobují jeho nespecifické symptomy,

jež zahrnují typicky dušnost a které mohou vést iniciálně k jiné diagnóze. V našem případě to byla exogenní alergická alveolitida. Nádor je charakteristický rychlým růstem s časnou invazí srdečních struktur, která může mít za následek srdeční tamponádu. Po zjištění hemoragického charakteru perikardiálního výpotku bylo správně postupováno tím, že byla provedena CT angiografie hrudníku a bylo kontaktováno kardiocirurgické pracoviště, kam byl pacient následně přeložen. Malignita je po iatrogenní etiologii druhou nejčastější příčinou hemoragického perikardiálního výpotku.¹³ Kazuistika zároveň potvrzuje důraz kladený na časně a správně provedení zobrazovacích vyšetření, která mohou v řadě případů určit specifickou biologickou povahu srdečních tumorů. U maligních tumorů je pak nezbytné doplnění histologického vyšetření vzorku z biopsie. Velice přínosná zde byla především imunohistochemická analýza, která na základě pozitivit CD31, CD34 a ERG s vysokou senzitivitou potvrdila diagnózu angiosarkomu. Případ rovněž naznačuje velice špatnou prognózu pacientů s touto diagnózou. Často jde o jedince, kteří byli dosud bez kardiovaskulárního onemocnění a neměli ani typické rizikové faktory pro jeho rozvoj. I doba úmrtí od rozvoje symptomů v našem případě odpovídá statistikám inoperabilních pacientů.⁴ V současné době je jedinou kurativní léčebnou metodou radikální resekce,¹⁴ v některých případech doplněná o neoadjuvantní nebo adjuvantní chemoterapii. Primární systémová léčba nebo radioterapie jsou považovány za léčbu paliativní. Při chemoterapii angiosarkomů jsou využívány léky ze skupiny antracyklinů.^{6,15} Jako jeden z klíčových faktorů se ukázal i paliativní tým, který ošetřující lékaři zapojili do péče o pacienta, a pracovali i s jeho rodinou.

Závěr

Angiosarkom srdce je závažným maligním nádorem srdce s velmi špatnou prognózou.⁴ V naší kazuistice jsme prezentovali typický průběh tohoto onemocnění prezentujícího se zprvu s nespecifickými symptomy, které mohou vést k určené nesprávné diagnóze. Zároveň se ukázala důležitost včasného použití zobrazovacích metod. S ohledem na povahu onemocnění a krátkou dobu přežití se ukazuje i nezbytnost tvorby a správného fungování paliativních týmů v rámci poskytovatelů zdravotní péče.

Poděkování

Za spolupráci při tvorbě článku děkuji prim. MUDr. I. Vítkové, MBA (Ústav patologie VFN Praha), kolegovi MUDr. T. Roubíčkovi, Ph.D., (Kardiocentrum KN Liberec) a kolegovi MUDr. A. Latinákovi (Kardiocentrum KN Liberec).

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Beware of the Unexpected: Acute Coronary Thrombosis Following the Mildly Symptomatic COVID-19 Infection and Two Different Therapeutic Options

Murat Gul, Sinan Inci

Department of Cardiology, Medical Faculty, Aksaray University, Aksaray, Turkey

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SOUHRN

Onemocnění covid-19, které v březnu 2020 přerostlo v pandemii, se celosvětově vyznačovalo vysokou morbiditou a mortalitou. I když nejčastějším klinickým projevem jsou respirační symptomy, jsou časté i kardiální komplikace, které představují nové výzvy pro zdravotnický systém. Popisujeme případy dvou mírně symptomatických ambulantních pacientů s onemocněním covid-19, kteří se dostavili k lékaři s akutním infarktem myokardu s elevací úseku ST (STEMI) a vysokou zátěží tromby v koronárních tepnách bez aterosklerotických plátů. V kazuistice popisujeme dva odlišné postupy při léčbě, které dokonale ilustrují problémy, s nimiž se lze setkat při péči o pacienty s trombózou věnčitých tepen, u nichž byly diagnostikovány STEMI a onemocnění covid-19. Lékaři v klinické praxi musejí mít na paměti hyperkoagulační stav vyvolaný onemocněním COVID-19, a to i u mírně symptomatických ambulantních pacientů; účinnou alternativou perkutánní koronární intervence přitom může být agresivní farmakoterapie.

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ABSTRACT

COVID-19 infection was declared a pandemic in March 2020 and is responsible for high morbidity and mortality around the globe. Although the most common clinical presentation is respiratory, cardiac complications are common and create new challenges for healthcare. We discuss two mildly symptomatic outpatients with COVID-19 presenting with acute ST-elevation myocardial infarction (STEMI) and high coronary thrombus burden without atherosclerotic plaque. Our report describes two different therapeutic approaches that illustrate the challenges encountered in the management of disseminated coronary thrombosis in patients with STEMI and COVID-19. Clinicians should be aware of the high pro-coagulant state caused by COVID-19, even in mildly symptomatic outpatients, and aggressive pharmacological therapy may be an effective alternative treatment option to percutaneous coronary intervention.

Keywords:

Acute coronary thrombosis

COVID-19

Therapeutic options

Introduction

COVID-19 infection, which is caused by the novel coronavirus SARS-CoV-2, has rapidly emerged as a global public health problem. Although the most common clinical presentation is respiratory, cardiac complications are frequent and may be incidental even in the absence of underlying cardiovascular disease or comorbidities.¹ SARS-CoV-2 infection is closely associated with an increased thrombotic risk, mainly observed in the pulmonary or cerebral circulation.² However, these complications have been largely observed in hospitalized patients with extensive pulmonary involvement.³ Here, we report two patients with acute

coronary thrombosis following non-hospitalized mildly symptomatic COVID-19 infection. We also present two different therapeutic approaches that illustrate the challenges encountered in the management of severe coronary thrombosis in patients with ST-segment elevation myocardial infarction (STEMI) and COVID-19.

Case 1

A 47-year-old, healthy male patient was admitted to our emergency department with severe chest pain radiating to the jaw, which had started about 30 min before the

Address: Murat Gul, MD, Department of Cardiology, Medical Faculty, Aksaray University 68100 Aksaray, Turkey, e-mail: drmuratgul68@gmail.com

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presentation. He did not have a history of coronary artery disease (CAD), diabetes mellitus, or hyperlipidemia. He also denied smoking, alcohol intake, or substance abuse. He had a history of COVID-19 infection 12 days earlier, which was confirmed with reverse transcriptase-polymerase chain reaction testing (RT-PCR). However, he was treated as an outpatient and no specific therapy was instituted for COVID-19, as the patient remained without respiratory symptoms. Physical examination was unremarkable, with BP 135/82 mmHg and heart rate 75 beats per minute, regular. Also, body temperature was 37.1 °C, and peripheral O₂ saturation was 96%. Electrocardiography revealed sinus rhythm with STEMI in the anterior leads (V₁–V₅ leads) (Fig. 1A) but the chest radiogram was completely normal. The echocardiogram revealed hypokinesia of the anterior, anteroseptal, and lateral left ventricular walls with an ejection fraction of 40%. The echocardiogram also excluded the possibility of paradoxical embolism due to a foramen ovale or atrial septal defect as well as an intracardiac embolic source. Other laboratory tests showed changes in C-reactive protein at 7.6 mg/L (normal range: 0–5 mg/L), D-dimer 0.564 µg/mL (normal range: <0.52 µg/mL), LDH 5600 U/L (normal range: 120 to 246 U/L) and leukocytosis of 12.33 cell/µL. Troponin I value was 462 pg/mL (normal range <17.50 pg/mL).

Medical treatment was started with clopidogrel 600 mg and acetylsalicylic acid 300 mg and an emergent coronary angiogram was performed through right femoral access. Coronary angiography revealed a large burden of thrombotic stenosis of the proximal left anterior descending (LAD) artery, which extended to the distal left main coronary artery and an occlusive filling defect compatible with thrombus at the middle segment of the LAD (Figs 1B, 1C). Additionally, there were no atherosclerotic lesions in other coronaries. After heparinization with

10,000 units of unfractionated heparin, wiring was successfully performed; however, multiple balloon dilatation failed to restore blood flow. Afterwards repeated thrombus aspiration attempts (Hunter, IHT Cordynamic, Barcelona, Spain) also failed. Local low-dose fibrinolytic was administered then (10 mg Alteplase over 5–10 min) via a guiding catheter followed by 3 more rounds of aspiration, with a minimal recovery of distal flow. The decision was to manage LAD thrombus medically for 5 days with low-molecular-weight heparin and dual antiplatelet therapy, and a new procedure was performed. The final angiogram revealed no thrombus in the proximal LAD that did not cause luminal stenosis, and a patent distal bed without underlying atherosclerotic plaque (Fig. 1D). Finally, STEMI was assumed due to in situ thrombosis in the absence of atheroma in the LAD. The screening was negative for prothrombotic states (protein C, protein S, anticardiolipin antibody, and Factor V Leiden). In the hospital follow-up, adverse clinical, electrocardiographic, echocardiographic changes, and major or minor complications were not observed. The patient was discharged uneventfully with acetylsalicylic acid, clopidogrel, atorvastatin, ramipril, and metoprolol therapy 3 days later. Three months later, there were no notes at the follow-up visit.

Case 2

A 48-year-old male patient without cardiovascular risk factors presented to the emergency department with acute onset chest pain for 1 h. At presentation, the patient was afebrile with a blood pressure of 142/82 mmHg, respiratory rate of 18, and oxygen saturation of 94% on room air. Pulmonary and cardiovascular physical exams were

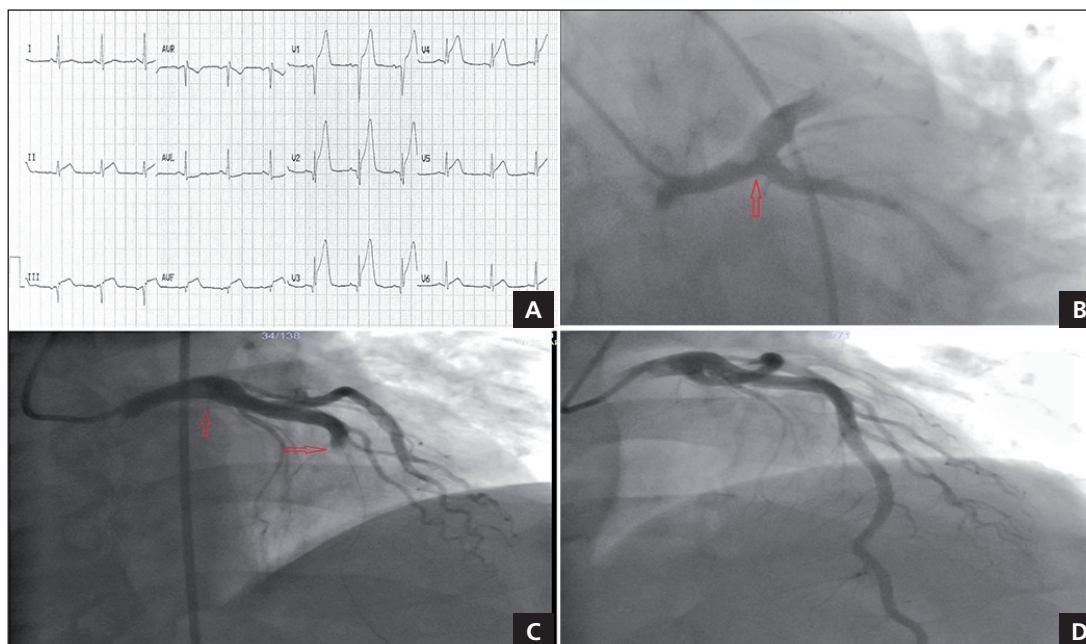


Fig. 1 – (A) Initial ECG revealed ST elevations in leads V₁–V₅. **(B, C)** Coronary angiography showed total occlusion of left anterior descending artery and left main thrombosis. **(D)** The final angiogram revealed resorbed thrombus in the left main and TIMI 3 flow is provided in left anterior descending artery.

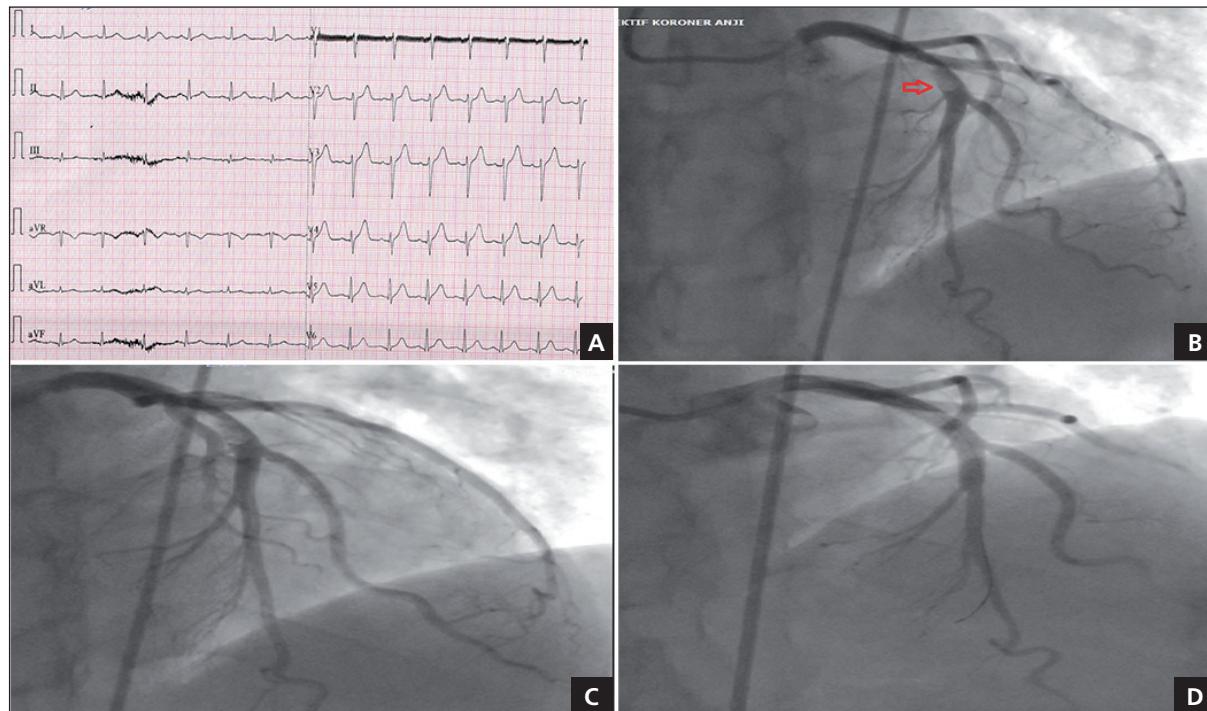


Fig. 2 – (A) The ECG showed new hyperacute T waves in leads V₁–V₆. **(B, C)** Coronary angiography demonstrated thrombus in the proximal left anterior descending artery. **(D)** The final angiogram showed excellent angiographic results and no complications after stenting.

also unremarkable. The ECG showed new hyperacute T waves in leads V₁–V₆ (Fig. 2A) and the patient immediately received loading doses of dual antiplatelet therapy (clopidogrel 600 mg and acetylsalicylic acid 300 mg). Emergent coronary angiography demonstrated a massive intraluminal thrombus leading to 80–90% stenosis in the proximal region of the LAD with distal TIMI 2 flow and no stenosis or atherosclerotic plaque in other coronary vessels (Figs 2B, 2C). Because of stuttering chest pain and high thrombotic load, an intra-arterial weight-adjusted dose of heparin was administered, after which the lesion was successfully treated with a drug-eluting stent with excellent angiographic results and no complications (Fig. 2D). The patient was transferred to the intensive care unit with complete resolution of symptoms and electrocardiographic improvement. The patient was treated with dual antiplatelet therapy and additional anticoagulation for 5 days.

C-reactive protein level was elevated at 9 mg/L (normal value <5), which normalized in subsequent days. The blood D-dimer level was 0.697 µg/mL (normal range: <0.52 µg/mL) and the fibrinogen level was 3.83 g/L, with only mild leucocyte elevation (14.3 cell/µL). An echocardiogram was performed to evaluate the possibility of intracardiac thrombus, vegetation, or paradoxical embolism. Normal biventricular size and function (left ventricular ejection fraction: 55%) were found without shunt or thrombus. There were no episodes of atrial fibrillation during the follow-up. A nasopharyngeal swab was performed using RT-PCR for SARS-CoV-2 due to suspicion of COVID-19 and it was positive. Computed tomography revealed no pulmonary involvement associated with COVID-19. Usual specific treatment was initiated for

COVID-19, as the patient remained without respiratory symptoms. The patient was discharged with acetylsalicylic acid, clopidogrel, statin, ramipril, and beta-blocker therapy. He was still asymptomatic under the same medical therapy at the 3th-month follow-up visit.

Discussion

COVID-19 infection was declared a pandemic in March 2020 and is responsible for high morbidity and mortality around the globe. With growing knowledge about COVID-19, acute cardiac events are also increasingly being reported. Cardiovascular manifestations are well-known complications of COVID-19 and range from myocardial injury to myocardial infarction, fulminant myocarditis, heart failure, malign arrhythmias, and cardiogenic shock.⁴

Numerous studies have demonstrated that patients with COVID-19 are prone to both venous and arterial thromboembolic complications, including venous thromboembolism, stroke, acute myocardial infarction, and acute lower extremity ischemia.^{5,6} Additionally, coronary thrombotic events have been reported even in patients receiving optimal antithrombotic therapy⁷ and effective anticoagulation therapy.⁸ Many different pathophysiological mechanisms have been proposed to explain the hypercoagulable state of COVID-19 infection. These include endothelial damage, elevated proinflammatory cytokines that activate the coagulation cascade and inhibit fibrinolysis, increased nonspecific inflammatory biomarkers, as well as several pro-coagulant factors such as the von Willebrand factor and factor VIII.⁸

We reported two different mildly symptomatic COVID-19 patients with no risk factors for CAD and had an episode of STEMI with a high thrombotic burden without evidence of atherosclerotic disease in other coronary arteries. Since patients do not have other known risk factors for coronary thrombosis, viral infection, and inflammatory response are likely to play an important role in the activation of the coagulation cascade as a cause of coronary thrombosis. Similar to previous reported cases, our patients had massive coronary thrombosis that was not associated with the severe acute respiratory syndrome, supporting the possibility of spontaneous thrombotic events even in COVID-19 patients without severe respiratory or systemic manifestations.^{7,9} Consequently, regarding the prevalence of COVID-19 and the fact that many patients may be asymptomatic, clinicians should be aware of the potential risk of outpatients combining STEMI and COVID-19.

COVID-19 has a negative impact on STEMI patients, either directly with an increased incidence of developing acute heart failure or indirectly through the increased delay between primary percutaneous coronary intervention and the first medical contact.⁷ Furthermore, PCI in the context of STEMI and heavy thrombus burden can be challenging as it is associated with complications such as distal embolization, no-reflow, slow flow, and stent thrombosis. The pathophysiology of STEMI in COVID-19 patients may not be associated with an unstable culprit lesion.^{10,11} Indeed, previous reports revealed that COVID-19 can induce spontaneous coronary thrombosis, even in the absence of atheroma.¹² Therefore, in the context of severe coronary thrombus without atherosclerosis, a delayed stent strategy may also be preferable, considering stent implant only in cases where an obvious stenosis/culprit lesion has been identified. Intracoronary low-dose thrombolysis, which is a safe and effective treatment,¹³ may be an alternative treatment option in patients with COVID-19, STEMI, and massive thrombotic burden, as in our first case. We believe that more aggressive pharmacological treatments, such as intracoronary fibrinolytic, glycoprotein IIb/IIIa inhibitor, and long-term use of anticoagulants, should be kept in mind along with the prothrombotic state associated with COVID-19 infection, especially in the case of failed PCI.

The main limitation of our report was the lack of advanced intracoronary imaging (IVUS, OCT) for diagnostic evaluation. The use of intracoronary imaging methods could provide reliable information for identifying possible etiological pathologies (plaque rupture, calcification, spontaneous coronary artery dissection, intramural hematoma, and intramural inflammation) and optimal therapeutic option.

Conclusion

Clinicians should be aware of the high pro-coagulant state caused by COVID-19, even in mildly symptomatic outpatients, and aggressive pharmacological therapy may be an effective alternative treatment option to PCI.

Conflict of interest

None.

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Anomalous origin of the left circumflex artery from right sinus of Valsalva: a rare case but with great clinical relevance

Cristina Poleggi^a, Davide Restelli^a, Alfredo Luongo^a, Federica Cocuzza^a,
Francesca Campanella^a, Mennili Sara^b, Alessio Currò^c, Antonino Recupero^a,
Michele Scarano^b

^a BIOMORF Department, Section of Cardiology, University of Messina, Messina, Italy

^b Cardiology Unit of Madonna del Soccorso Hospital, San Benedetto del Tronto, Italy

^c Cardiac Intensive Care, IRCCS-Piemonte Hospital, Messina, Italy

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SOUHRN

Anomální odstup z a. circumflexa se vyskytuje vzácně a běžně není příčinou infarktu myokardu. Popisujeme případ 61letého muže, který se dostavil na vyšetření s paroxysmální supraventrikulární tachykardií a atypickou bolestí na hrudi. Po odeznění arytmií prokázal EKG záznam abnormality vlny T, přičemž hodnoty srdečních enzymů byly přechodně zvýšené. Koronarografie sice prokázala anomální odstup LCx z pravého Valsalvova sinu, avšak žádné obturující aterosklerotické změny. Kazuistika se zabývá možnou souvislostí mezi vrozenou koronární anomálií a klinickými projevy pacienta.

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ABSTRACT

Anomalous origin of coronary artery (CA) is rare and does not generally lead to myocardial infarction. We report a case of a 61-year-old man presented with paroxysmal supraventricular tachycardia and atypical chest pain. After arrhythmia subsided, ECG showed T wave abnormalities and transient cardiac enzymes were found to be elevated. Coronary angiography demonstrated an anomalous origin of the left circumflex artery (LCx) from the right sinus of Valsalva but no obstructive atherosclerotic coronary lesions. The possible relation between the congenital coronary anomaly and the clinical manifestations of the patient is discussed.

Introduction

Most CA anomalies are incidentally detected during coronary angiography. The anomalous connection of the LCx to the right coronary artery (RCA) or sinus is considered the most frequent CA anomaly with an angiographic incidence of up to 0.67%. Among them, only those with an interarterial course are regarded as hidden conditions at risk of myocardial ischemia and sudden cardiac death (SCD).^{1–8}

We report an uncommon case of anomalous origin of LCx from the right sinus of Valsalva and a retroaortic path causing myocardial ischemia.

Clinical case

A 61-year-old Caucasian man presented to the emergency department complaining of palpitations and chest discomfort for an hour at rest. He had history of hypertension, diabetes and a single episode of atrial fibrillation. His medical treatment consisted of olmesartan 40 mg/die. On admission blood pressure was 140/70 mmHg, pulse rate 160 beats per minute (BPM), respiratory rate 20 per minute and body temperature 36 °C. The 12-lead ECG demonstrated atrial flutter with a 2:1 conduction ratio resulting in a ventricular rate of 157 BPM and ST segment depression in leads V₄–V₆ (Fig. 1). Transthoracic echocardiogra-

Address: Michele Scarano, MD, Cardiology Unit, Emergency Dept, Hospital "Madonna del Soccorso", Via Silvio Pellico n. 32, 63039 San Benedetto del Tronto, Ascoli Piceno, Italy, e-mail: m.braveheart1978@gmail.com

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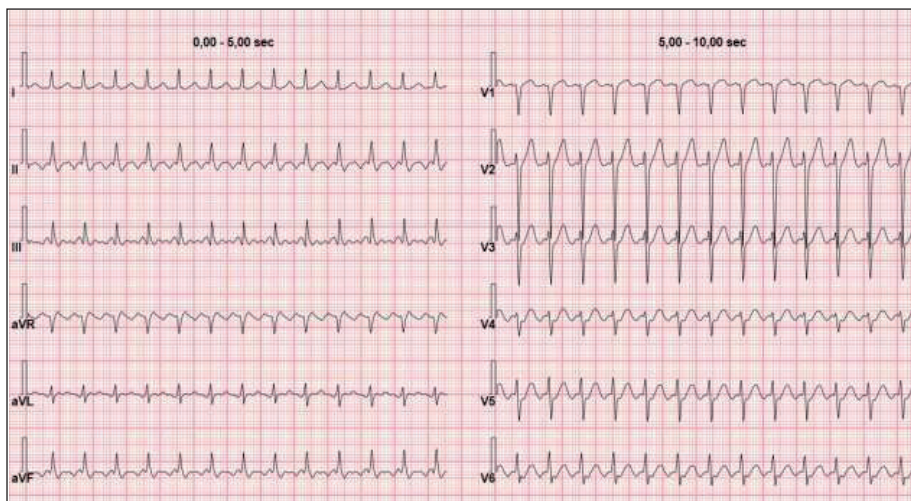


Fig. 1 – Initial 12-lead electrocardiogram (25 mm/s, 10.0 mm/mV).

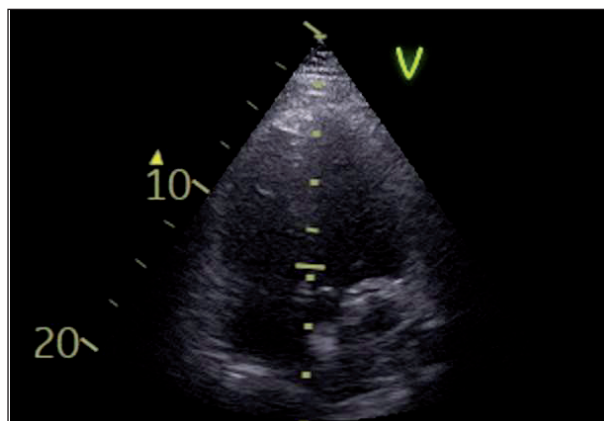


Fig. 2 – Transthoracic echocardiography in five-chamber apical view showing “RAC sign”, a binary structure above the mitral valve plane into the atrioventricular groove overlapping the aortic root.

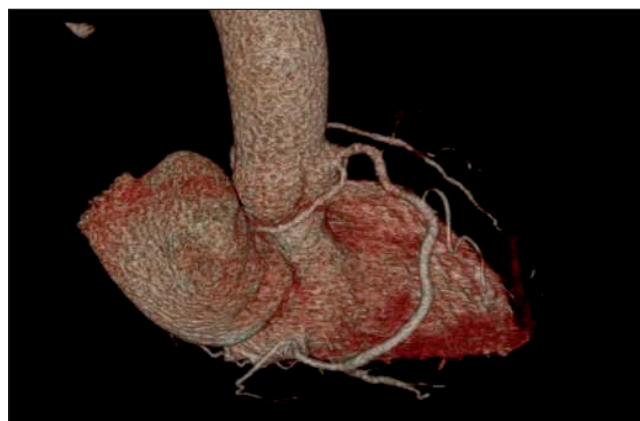


Fig. 4 – 3D volume rendered multi-detector CT image showing anomalous origin of LCx from right sinus of Valsalva with a retroaortic path.

phy revealed a preserved left ventricular ejection fraction and no segmental kinetic anomalies but a five-chamber apical view showed a “RAC sign”, related typically to anomalous retroaortic course of the left coronary artery (Fig.

2).^{9–28} Initial cardiac enzymes were in normal range. The patient was treated with intravenous infusion of amiodarone. He restored sinus rhythm in 2 hours and symptoms regressed completely, but the ECG taken after conversion

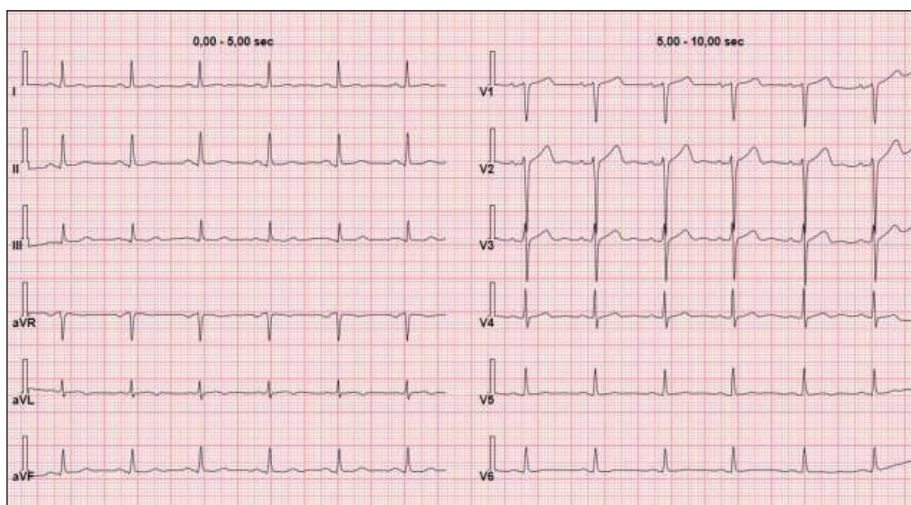


Fig. 3 – 12-lead electrocardiogram after sinus rhythm restoration showing negative T waves in I and aVL and flattened T waves in V₅ and V₆.

showed flattened T waves in leads V_5 and V_6 , negative T waves in leads I and aVL (Fig. 3) and cardiac enzymes had transient increase: troponin T hs 95 pg/mL (n.v. <14), creatine kinase-MB 40 U/L (n.v. >20), myoglobin 96 ng/mL (n.v. 23–72). After the acute episode ended the patient underwent cardiac computed tomography angiography (CTA) with evidence of anomalous origin of LCx from the right sinus of Valsalva with a retroaortic course and a normal peripheral distribution (Fig. 4). Due to uncertain significance of ECG findings and cardiac enzyme increase, a coronary angiography was ordered and excluded obstructive atherosclerotic coronary lesions. Nuclear myocardial perfusion imaging revealed reversible small subsegmental perfusion defects in mid inferolateral wall and apical lateral wall. We established a medical treatment with beta-blocker and avoidance of intense physical activity. At follow-up 3 months later the patient did not refer any symptoms.

Discussion

Anomalous origin of a CA from the opposite sinus of Valsalva has been associated with myocardial ischemia and SCD. Our patient had an anomalous connection of the LCx branch to the right sinus of Valsalva with a retroaortic course which is considered the most frequent CA anomaly. Although this anomaly is usually considered benign, cases of association with SCD, myocardial infarction and angina pectoris in the absence of atherosclerotic lesions have been reported.^{1,2} The factor responsible for this pathogenicity could be high orifice, ostial stenosis, slit-like/fish-mouth-shaped orifice, acute-angle take-off, intramural course and hypoplasia of the proximal coronary artery. Cardiac CTA did not reveal any of these characteristics in this patient. Thus, we hypothesized that the increased cardiac output and expansion of the great vessels during tachycardia or physical exertion could cause compression of the retroaortic segment or angling at its origin, narrowing the ostium to a slit and causing ischemia, a mechanism that has been reported in some studies.^{29,30}

ECG abnormalities, especially ST segment depression, are well documented in literature during supraventricular tachycardia as a response to pacing-induced stress. These changes are usually diffused and disappear after conversion to sinus rhythm.³¹ In this case, ST segment depression appeared in leads V_4 – V_6 during tachycardia while flattened and negative T waves in leads V_5 , V_6 , I and aVL were seen hours later, accompanied by cardiac enzyme buildup. Due to these findings we decided to exclude any coronary stenosis with a coronary angiography. As the epicardial coronary arteries did not show any pathology, we suggest that the patient had transient ischemia due to LCx anomaly. Last step to confirm myocardial ischemia in case of CA anomalies is non-pharmacological functional imaging (we used nuclear study), as recommended by guidelines.³²

As for the management of the anomalous aortic origin of a CA in adults, surgery is recommended as class IC in patients with typical angina symptoms who present with evidence of stress-induced myocardial ischemia in a matching territory or high-risk anatomy.^{32,33} Our patient

had evidence of stress-induced ischemia but he did not have clear manifestations of angina. He presented chest discomfort during supraventricular arrhythmia that remitted when sinus rhythm was restored. He did not refer any previous episode of angina. Among this type of CA anomalies it is known that interarterial path is most commonly related with fatal outcome while in retroaortic path SCD is rarely reported.³⁴ The age of our patient together with the retroaortic course of CA anomaly and the fact that his condition did not interfere with a normal life motivated us to use a conservative approach.

Conclusion

The fact that CA anomalies include many different entities and that any group has collected a large enough series to clarify the natural prognosis of each entity may contribute to our difficulty in the clinical identification and management of these conditions. We report a case of anomalous origin of LCx from right sinus of Valsalva causing transient myocardial ischemia in a patient that has always been asymptomatic. This anomaly has been and continues to be considered benign, nevertheless we suggest to judge the clinical significance of this kind of CA anomaly on a case-by-case integrated approach after exclusion of all other possible causes of signs or symptoms.

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Zprávy o knize

Abstrakta odborných akcí



Pan profesor MUDr. Jan Marek, Ph.D., FESC, slaví životní výročí



Profesor Jan Marek, v současné době vedoucí konzultant v dětském kardiocentru v Great Ormond Street Hospital for Children v Londýně, profesor na University College London a na Karlově univerzitě v Praze, dětský kardiolog, oslavil 16. 11. 2022 v plné síle šedesáté páté narozeniny.

V roce 1984 ukončil studium na 2. lékařské fakultě UK v Praze, postgraduální stáže absolvoval v Houstonu, Texas, USA (v rámci programu Texas-Czech Physician Exchange Program, založeného MUDr. Tomášem Klímou), dále pak v Torontu v Kanadě.

První část profesionální kariéry prožil v Dětském kardiocentru FN Motol, kde od roku 1991 vedl pracoviště echokardiografie a prenatální kardiologie a kde se podílel na vzniku a rozvoji prenatálního screeningu vrozených srdečních vad v Československu a České republice. V roce 2005 byl pozván a následně přijat na vedoucí místo neinvazivní diagnostiky a prenatální kardiologie v Great Ormond Street Hospital v Londýně, kde vede oddělení echokardiografie a prenatální kardiologie. V rámci Cardiovascular Institute při University College London se podílí na vývoji moderních diagnostických metod včetně 3D modelingu, virtuální reality a umělé inteligence, podílí se na vývoji diagnostických simulátorů a softwaru pro echokardiografické vyšetřování malých dětí.

Jan Marek úspěšně obhájil řadu vědeckých grantů, publikoval více než 300 článků a více než 130 v recenzovaných zahraničních časopisech, napsal učebnici echokardiografie a prenatální kardiologie a dalších 18 kapitol do převážně zahraničních monografií. Je čestným členem České kardiologické a Italské dětské kardiologické společnosti a řady dalších odborných společností ve světě, v některých působil ve vedoucích funkcích.

Je zakladatelem a spolumajitelem globální výukové společnosti Smart Heart Imaging & Teaching, jež se zabývá výukou echokardiografie a standardizací echokardiografických vyšetření v Evropě, Severní Americe a Asii.

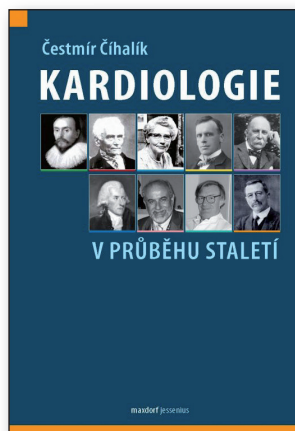
V pražském soukromém zdravotnickém zařízení Canadian Medical pracuje externě od roku 2015, kde se věnuje klinické dětské a prenatální kardiologii, je konzultantem pro pacienty s vrozenými srdečními vadami od prenatálního období do dospělosti. V rámci jeho návštěv České republiky zde pravidelně pro ČKS přednáší a úzce spolupracuje jak s jeho „domovským dětským centrem v pražském Motole“, tak s řadou dalších kardiologických pracovišť, přispívá také českým charitám.

Myslím, že je potřeba zdůraznit, že profesor Jan Marek odešel do Velké Británie na pozvání, ne proto, že by v zahraničí hledal práci, ale nikdy se (na rozdíl od mnoha ostatních) neodtrhl od české kardiologie a českých pacientů a naopak se celou dobu snaží pomáhat. Jeho pracovištěm GOSH prošlo dosud 15 českých lékařů na krátkodobých i dlouhodobých stážích, řada našich předních kardiologů u něj mohla přednášet. Právě pro všechny tyto aktivity dosáhl Honza ve Velké Británii nesmírného uznání, jeho „nadmárodní“ působení obsahuje prakticky celý svět, přitom zůstává skromným, sportovně naladěným přítelem, který kdykoliv poradí, pomůže, když je osloven. Jeho manželka MUDr. Daniela Marková je velmi úspěšná dětská lékařka, která pracuje na Klinice pediatrie a dědičných poruch metabolismu Všeobecné fakultní nemocnice v Praze, vybudovala specializované pracoviště pro dlouhodobé sledování předčasně narozených dětí – Centrum komplexní péče pro děti s perinatální zátěží. Spolu s manželkou se starají o umělecký odkaz manželčiny maminky, významné české sochařky Daniely Vinopalové. Recentně bylo její dílo vystaveno na prestižní výstavě v Londýně, the Frieze: Daniela Vinopalová at Frieze Masters Spotlight / Czech Centre London. Syn Lukáš odmítl následovat kariéru rodičů a po absolvování VŠE a Fakulty sociálních věd UK absolvoval master studium na London School of Economics a v současné době reprezentuje Českou republiku a Českou národní banku v Mezinárodním měnovém fondu ve Washingtonu, kde mu vloni manželka Hana porodila syna Tobiáše Iana. Čas volna a dobu k relaxaci tráví rodina nejraději v České Kanadě a v Mariánských Lázních, pobyt využívá ke kondiční cyklistice a s mnoha společnými kamarády k turistice a návštěvám kulturních akcí, výstav a koncertů.

Za výbor České kardiologické společnosti i osobně chci vyjádřit s obdivem upřímné díky za tu ohromnou spoustu práce, kterou Jan dosud vykonal pro českou, anglickou, evropskou a světovou kardiologii. Přejeme všichni Honzovi hlavně dobré zdraví, radost z hezké rodiny a také další úspěchy v nesmírně zajímavé práci, ve které dosáhl tak krásných úspěchů.

Jan Marek se podílí v rámci charitativní činnosti organizace Chain of Hope, vedené Sirem Maghdim Yacoubem, na řadě zahraničních misí ve světě a přispívá k charitativním akcím v ČR a Velké Británii. Profesor Jan Marek je nositelem Stříbrné medaile Jana Masaryka ministra zahraničních věcí ČR za přínos k rozvoji česko-britských vztahů a byl navržen na cenu ministra zahraničních věcí České republiky „Gratias Agit“ za šíření dobrého jména České republiky v zahraničí.

Srdečně, Michael Aschermann



Čestmír Číhalík: Kardiologie v průběhu staletí

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Doc. MUDr. Čestmír Číhalík, CSc., je docentem I. interní kliniky – kardiologické Lékařské fakulty Univerzity Palackého v Olomouci a Fakultní nemocnice Olomouc. Jako kardiolog se věnuje elektrofyziologii a interpretaci EKG.

Referovaná kniha je obsahově rozdělena na dvě části. V první části, po Úvodu (1. s.), následuje sedm kapitol, uvedených v tomto pořadí: 1. Historie fyzikálního vyšetření v kardiologii (9 s.), 2. Historie klinické elektrokardiografie (14 s.), 3. Historie elektrické impulzoterapie (8 s.), 4. Historie diagnostiky a nefarmakologické léčby ICHS a dalších intervenčních metod v kardiologii (9 s.), 5. Historie echokardiografie (2 s.), 6. Historie farmakoterapie ischemické choroby srdeční (10 s.) a 7. Historie vývoje antiarytmické léčby (9 s.). Kapitoly jsou různého rozsahu, od dvou do dvanácti tiskových stran, celkovým rozsahem 60 stran. Celý rozsah kardiologie ovšem nepokrývají, tematicky jsou výběrem.

Na tyto kapitoly navazuje rozsáhlejší druhá část (210 s.) nazvaná Osobnosti kardiologie. Ta je souborem různých rozsáhlých medailonů známých i neznámých badatelů. Počet medailonů je úctyhodný, napočítal jsem jich celkem 524. Některé jsou o osobnostech slavných a známých, např. Karl Albert Ludwig Aschoff, Wilhelm His jr., Karel Frederik Wenckebach, Paul Dudley White, Sunao Tawara, Jan Evangelista Purkyně ad., některá jména (a nebylo jich málo) jsem neznal. Jednotlivé medailony mají rozsah od několika řádek do jedné tiskové strany. Liší se také množstvím i významností uvedených informací. U většiny (435) je ilustrační fotografie. (bez údaje, kdy byla pořízena). Mezi uvedenými jsou především lékaři (anatomové, fyziologové, patologové, kardiologové, kardiochirurgové, pediatři, neurofyziologové, intervenční radiologové a další), ale i botanici, bioinženýři, chemici a další profese. Ale ne všechny osobnosti uváděné v kapitolách první části mají zde svůj medailon a naopak.

Drtivý počet uvedených osobností jsou Američané, následují badatelé němečtí, angličtí, francouzští a italské. Je také uvedeno osm českých osobností: Samuel Sigmund Basch, Vojtěch Baruch Berkowitz, Johann Nepomuk Czermak, Jindřich Černohorský, William Ganz, Jan Evangelista Purkyně, Friedrich Richard Reinitzer a Jan Rosický. Mezi 524 osobnostmi je jen 5 žen (!), dvě Američanky, jedna Angličanka, jedna Argentinka a jedna Rakušanka.

Text uzavírá přehled použitých zkratk (0,3 s.), licence k fotografiím (10 s.), anglický souhrn (0,3 s.), český souhrn

jsem nenalezl, medailonek autora, až příliš stručný dvousloupcový věcný rejstřík (3,3 s.) a rovněž dvousloupcový jmenný rejstřík (6,5 s.).

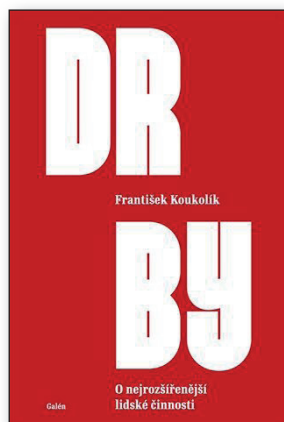
Koho jsem v rozsáhlém výčtu osobností nenalezl? Čtyři medailony by neměly chybět: Allana Cormacka a Godfreye Hounsfielda, s informací o výpočetní tomografii, za niž v roce 1979 dostali Nobelovu cenu. A také informace o strůjcích magnetické rezonance, dvojici inženýrů Paula C. Lauterbury a Petera Mansfielda, kteří byli Nobelovou cenou oceněni v roce 2003. V první části určitě neměly být opomenuty metody nukleární kardiologie a endomyokardiální biopsie, protože to jsou, podobně jako výpočetní tomografie a magnetická rezonance, významné diagnostické metody současné kardiologie. Také medailon Jana Evangelisty Purkyně (pouhých 15 řádek), vzhledem k jeho významu, (kdyby se v době, kdy žil, udělovaly Nobelovy ceny, určitě by byl laureátem), mohl být rozsáhlejší. V textu je několik drobných chyb, např. ze sovětského akademika Čazova, (společně s Bernardem Lownem nositele Nobelovy cenu míru za angažovanost v hnutí Lékaři proti nukleární válce) se stal Chazov (autor čerpal z anglického pramene a angličtina nezná dialektní znaménka). Údaj o prvním echokardiografickém vyšetření v tehdejší Československu bych upřesnil: to provedl s průmyslovým defektoskopem, zapůjčeným v závodě ŠKODA Plzeň v roce 1967 docent MUDr. Josef Hůla, CSc., z interní kliniky Lékařské fakulty Univerzity Karlovy v Plzni, jejímž přednostou byl profesor MUDr. Josef Sova, DrSc., který rozvoj této metody podporoval.

Knihu vydalo nakladatelství Maxdorf v edici Jessenius ve velmi dobré kvalitě. Určitě je obohacením informací o vývoji tak významného medicínského oboru, jímž kardiologie bezpochyby je.

Komu knihu doporučit?

Kniha potěší především milovníky medicínské historie a obohatí jejich knihovnu. A těm, kteří budou ve svých monografiích psát o historii jejich oboru, ušetří namáhavé hledání v literatuře.

Prof. MUDr. Jan Petrášek, DrSc.,
III. interní klinika, 1. lékařská fakulta Univerzity
Karlovy a Všeobecná fakultní nemocnice v Praze,
e-mail: petrjanv@email.cz



František Koukolík: Drby

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Prosím laskavé čtenáře, aby mi odpustili, že jsem si dovolil zařadit na toto místo nekardiologické téma. Číst ve výsostně kardiologickém časopise o drbech?

Knihu o této problematice by mohlo napsat jen několik lékařů. MUDr. František Koukolík, DrSc., mezi ně také patří. Je mj. autorem více než 30 knižních publikací a nositelem více než 10 prestižních ocenění jak za díla vědecká, tak za popularizaci vědy. Patří k ojedinělým autorům, kteří v seznamech literatury svých publikací mohou uvádět jako zdroj články z vysoce prestižních časopisů *Science* a *Nature*, které skutečně četl a rozuměl jejich obsahu.

Nevím, že by bylo toto téma v naší literatuře zpracováno. Autor rozdělil text do sedmi kapitol. 1. Definice (16 s.), 2. Emoce a poznávání (16 s.), 3. Děti a dospívající (10 s.), 4. Muži a ženy (8 s.), 5. Organizace (18 s.), 6. Sociální síť (12 s.) a 7. Celebrity (8 s.). Text uzavírá informace o autorovi a věčný dvousloupcový rejstřík (5 s.).

Co jsou drby, všichni vědí (nebo se to domnívají) a mají je spojeny s představou šíření nepravdivé negativní informace, ale ony drby mohou šířit i informaci pozitivní. Nejsou o to méně nebezpečné. Útlá brožurka, jen málo přes sto stran kapesního formátu, ale mnohokrát překvapí svým obsahem.

Důvodů je několik: nad problematikou drbů se zpravidla nezamýšlíme. Všichni je odsuzujeme, ačkoliv všichni

drbeme, skutečně všichni: ženy, muži, děti, bez rozdílu vzdělání, profese a stáří. Překvapí, že, co jsou drby, mají schopnost chápat už dvanáctileté děti, nás muže překvapí, že drbeme stejně často jako ženy (!), jen motivy našich drbů jsou jiné. Překvapí, že drbou i vědci (!). Překvapí, že i jak a jaké drby se zabydlují v organizacích. Překvapí, jak významnou roli hrají sociální sítě (Facebook, Instagram, YouTube, LinkedIn, TikTok aj.), které jsou jako stvořené pro šíření negativních drbů. Překvapí zjištění, že také na základě drbů vznikají současné tzv. celebrity; a některé často tam, kde vznikly, také zanikají. Překvapí zjištění, že někteří lidé při poslechu nebo sdělování drbu pociťují slast. A nejvíce jistě překvapí prokázané zjištění, že drbání je nejčastější lidskou činností.

Komu knihu doporučit?

Kniha je určena pro široký okruh čtenářů-laiků, nejen pro lékaře-kardiology (i když někdy drby mohou „vzít u srdce“), i když i ti (nejen ty) rádi (rády) drbou. Vždyť ruku na srdce, kardiologové! Vy jste nikdy nedrbali?

Prof. MUDr. Jan Petrášek, DrSc.,
III. interní klinika, 1. lékařská fakulta Univerzity
Karlovy a Všeobecná fakultní nemocnice v Praze,
e-mail: petrjanv@email.cz

Czech Cardiovascular Research and Innovation Day 2022

Hotel Hermitage, Praha, 28.–29. 11. 2022

ÚSTNÍ SDĚLENÍ – LÉKAŘI

■ ROLE OF ENDOMYOCARDIAL BIOPSY IN DIFFERENTIAL DIAGNOSIS OF NON-ISCHEMIC CARDIOMYOPATHY

Aiglová R¹, Táborický M¹, Flodrová P², Flodr P², Tüdös Z³, Kamínek M⁴, Zapletalová J⁵

¹ I. interní klinika – kardiologická, Fakultní nemocnice Olomouc, Olomouc; ² Ústav klinické a molekulární patologie, Lékařská fakulta Univerzity Palackého, Olomouc; ³ Radiologická klinika, Fakultní nemocnice Olomouc, Olomouc; ⁴ Klinika nukleární medicíny, Fakultní nemocnice Olomouc, Olomouc; ⁵ Ústav lékařské biofyziky, Lékařská fakulta Univerzity Palackého, Olomouc

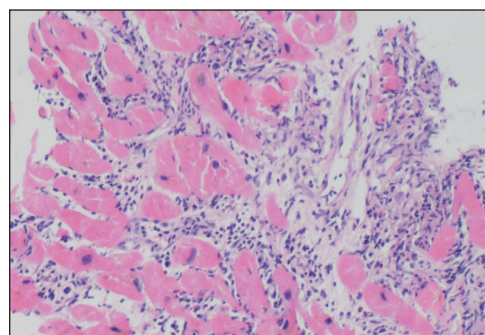
Introduction: Non-ischemic cardiomyopathies are a common cause of heart failure. This is a heterogeneous group that requires very detailed differential diagnosis, which results in targeted therapy of the underlying disease and an effort to improve the prognosis of these patients.

Aim: Assessment of the role of endomyocardial biopsy in the management of patients with non-ischemic cardiomyopathy.

File and methodology: Prospective evaluation of 151 patients who underwent endomyocardial biopsy (EMB), echocardiography, magnetic resonance imaging and basic laboratory tests. In our group of patients, the final diagnosis was determined on the basis of the overall clinical picture in 53% of patients, in 36.4% of patients it was confirmed histologically (predominantly myocarditis, TTR, and AL amyloidosis). The diagnosis of myocarditis was confirmed in 42 cases. The sensitivity and specificity of the EMB in myocarditis were 93.3% and 93.3%, respectively 100%. Amyloidosis was biopsied in 10 cases. In the case of amyloidosis, the sensitivity and specificity of the EMB were 100%. In the group of our patients, we compared the result of magnetic resonance imaging of the heart with a histological finding – a discrepancy was found in 45 cases (32.8%). In 25 cases, specific myocardial involvement was histologically demonstrated and the conclusion of magnetic resonance imaging was negative, on the contrary, in 20 cases without proven specific myocardial involvement, the result of magnetic resonance imaging was positive.

Conclusion: Non-ischemic cardiomyopathies are a very heterogeneous group. Due to this fact, a comprehensive approach to diagnosis is necessary, which combines both imaging and laboratory methods and in indicated cases endomyocardial biopsy. Early diagnosis is necessary to ini-

tiate specific therapy and thus influence the prognosis of patients.



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■ METFORMIN TREATMENT IS ASSOCIATED WITH IMPROVED QUALITY OF LIFE AND OUTCOME IN PATIENTS WITH DIABETES AND ADVANCED HEART FAILURE (HFREF)

Beneš J¹, Kotrč M¹, Kroupová K¹, Wohlfahrt P², Kovář J³, Franecková J⁴, Hošková L¹, Pelikánová T⁵, Kautzner J¹, Melenovský V¹

¹ Klinika kardiologie, IKEM, Praha; ² Centrum kardiovaskulární prevence, Thomayerova nemocnice, Praha; ³ Centrum experimentální medicíny, IKEM, Praha; ⁴ Pracoviště laboratorních metod, IKEM, Praha; ⁵ Klinika diabetologie, IKEM, Praha

Background: The role of metformin (MET) in the treatment of patients with advanced HFREF and type 2 diabetes mellitus (DM) is not firmly established. We studied the impact of MET on metabolic profile, quality of life (QoL) and survival in these patients.

Methods: A total of 847 stable patients with advanced HFREF (57.4±11.3 years, 67.7% NYHA III/IV, LVEF 23.6±5.8%) underwent clinical and laboratory evaluation and were prospectively followed for a median of 1126 (IQRs 410; 1781) days for occurrence of death, urgent heart transplantation or mechanical circulatory support implantation.

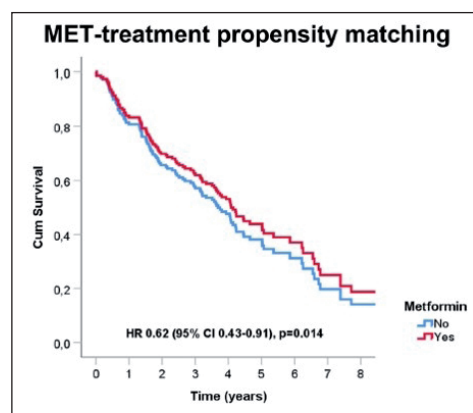
Results: A subgroup of 380 patients (44.9%) had DM, 87 of DM patients (22.9%) were treated with MET. Despite worse insulin sensitivity and more severe DM (higher BMI, HbA_{1c}, worse insulin resistance), MET-treated patients exhibited more stable HF marked by lower BNP level (400 vs. 642 ng/L), better LV and RV function, lower mitral and tricuspid regurgitation severity, were using smaller doses



of diuretics (all $p < 0.05$). Further, they had higher eGFR (69.23 vs. 63.34 ml/min/1.73 m²) and better QoL (MLHFQ: 36 vs. 48 points, $p = 0.002$).

Compared to diabetics treated with other glucose-lowering agents, MET-treated patients had better event-free survival even after adjustment for BNP, BMI, and eGFR ($p = 0.035$). Propensity score-matched analysis with 17 covariates yielded 81 pairs of patients and showed a significantly better survival for MET-treated subgroup ($p = 0.01$, Fig. 1).

Conclusion: MET treatment in patients with advanced HFrEF and DM is associated with improved outcome by mechanisms beyond the improvement of blood glucose control.



■ SAME DAY DISCHARGE VIA A DEDICATED RADIAL LOUNGE – RESULTS OF 1-YEAR EXPERIENCE DURING THE COVID-19 PANDEMIC

Bernat I, Horák D, Jirouš Š, Slezák D, Rokyta R

Kardiologická klinika, FN a LF UK v Plzni, Plzeň

Background: Same day discharge (SDD) is a validated option for selected patients (pts) undergoing coronary angiography (CAG) and percutaneous coronary interventions (PCI). We analyzed how the COVID-19 pandemic influenced patients' admissions to and discharges from our SDD radial lounge. We focused on safety and complications.

Methods: In 2021, 817 pts (age 65±11 years, 28% female) were admitted to the lounge. CAG was performed in 729 pts, and 176 (24%) underwent ad hoc PCI. Furthermore, 88 pts were admitted for implantable device replacement procedures.

Results: Out of 729 transradial CAGs 621 were performed by using the proximal radial approach (PRA) and 108 (15%) via the distal radial approach (DRA). Ninety % of all these procedures ($n = 655$) were performed from the nondominant left hand. PRA was associated with one radial artery occlusion (RAO) and longer compression time (92±24 min vs 75±26 min, $p < 0.05$). In the PRA group 23 postprocedural local hematomas <5 cm (3%) and 17 hematomas <10 cm (2%) were observed but did not require specific treatment. DRA was associated with only 4 super-

ficial hematomas <2 cm and no RAO. No other relevant complications occurred in the rest of pts. Ninety % of all pts ($n = 732$) were discharged home on the same day (≤6 hours after procedures) and none of them was readmitted within the next 24 hours. The remaining 10% of the patients ($n = 85$) were hospitalized after CAG and PCI, mostly because of severe coronary artery disease findings. **Conclusion:** During COVID-19 pandemic, CAG and PCI together with device replacement procedures in our SDD program were associated with a one-year saving of more than 700 overnight stays, minimal complications and 0,1% RAO rate.

Supported by the Charles University Research program "Cooperatio – Cardiovascular Science" and by MH CZ-DRO (Faculty Hospital in Pilsen – FNPI, 00669806).

■ TRANSLATIONAL RESEARCH IN THE FIELD OF INHERITED ARRHYTHMIAS

Bébarová M¹, Švecová O¹, Chmelíková L², Zelenák Š³, Radaszkiewicz K³, Hošek J⁴, Pásek M¹, Bárta T⁵, Synková I⁶, Novotný T⁷

¹ Department of Physiology, Masaryk University, Faculty of Medicine, Brno; ² Department of Biomedical Engineering, Brno University of Technology, Faculty of Electrical Engineering and Communication, Brno; ³ Department of Experimental Biology, Masaryk University, Faculty of Science, Brno; ⁴ Department of Molecular Pharmacology, Masaryk University, Faculty of Pharmacy, Brno; ⁵ Department of Histology and Embryology, Masaryk University, Faculty of Medicine, Brno; ⁶ Department of Internal Medicine, Hematology and Oncology, Masaryk University, University Hospital Brno and Faculty of Medicine, Center of Molecular Biology and Genetics, Brno; ⁷ Department of Internal Medicine and Cardiology, Masaryk University, University Hospital Brno and Faculty of Medicine, Brno

Inherited arrhythmias represent relatively rare, but life-threatening cardiac pathologies that are often associated with variants in cardiac ionic channel genes. A translational approach is essential to reveal the underlying arrhythmogenic mechanism and to find an improved treatment in the future.

Since 2016, we have performed functional analysis in selected arrhythmia-associated heterozygous genetic variants, including the patch clamp and microelectrode array techniques and confocal microscopy, either on human ionic channels transfected in a cell line or on hiPSC-derived cardiomyocytes. Detailed analysis was performed in two KCNQ1 variants associated with LQTS. T309I resulted in a complete loss of function in the homozygous setting (impaired channel trafficking) and a dominant-negative effect in the heterozygous setting. In contrast, R562S showed preserved channel trafficking and, in the heterozygous setting, haploin-



sufficiency. The physiologically important beta-adrenergic stimulation was missing in R562S channels. In silico simulations suggested delayed afterdepolarizations as a likely arrhythmogenic mechanism in both variants. Cardiac ionic channel gene variants can be also detected in some patients suffering from the “true” idiopathic VF. We have recently started functional analysis in two probands, the first one carrying two KCNH2 variants (A228V and S1021Qfs*98) and the second one a single RYR2 variant (Y4734C). In Y4734C-RYR2 variant, the pilot data detected an irregular electric activity of the patient-specific cardiomyocytes at specific conditions; a detailed analysis will follow.

Functional analysis is needed to reveal relationship between the identified genotype and phenotype. Identification of provoking circumstances that can result in unmasking of the phenotype in the “true” idiopathic VF could provide clinically-important data.

■ FUNCTIONAL ASSESSMENT OF MICROCIRCULATION IN TAKOTSUBO CARDIOMYOPATHY – A PILOT STUDY

Brázdil V¹, Hudec M¹, Boček O¹, Jeřábek P², Kaňovský J¹, Poloczek M², Štípal R², Kala P¹

¹ Interní kardiologická klinika, FN Brno a LF MU, Brno; ² Interní kardiologická klinika, FN Brno

Background: Takotsubo cardiomyopathy (TTC) is a severe disorder with an increasing incidence that often mimics acute coronary syndrome. Both of the entities are characterized by systolic dysfunction of the left ventricle myocardium. However, this dysfunction is reversible in most cases of TTC. The pathophysiology of TTC remains unclear. In this study, we aimed to assess the pathophysiology of TTC using the invasive functional testing of coronary microcirculation.

Methods: Ten female patients diagnosed with TTC were included in this pilot study. In all subjects we measured fractional and coronary flow reserve in the left anterior descending and left circumflex coronary arteries, and the index of microcirculatory resistance in the same arteries in addition to acute and late transthoracic echocardiography (TTE). The results of the microcirculatory assessment were statistically compared with normal population values.

Results: Whilst fractional flow reserve was normal in both assessed epicardial artery territories for all patients, both mean values of coronary flow reserve disclosed pathological microcirculatory findings and were pathological in nine out of ten subjects. Index of microcirculatory resistance revealed abnormal values in five out of ten patients for LAD and three out of ten for LCx.

Conclusions: Our pilot study confirmed non-obstructive findings in the epicardial coronary arteries assessed by FFR. On the other hand, the investigation of both CFR and iMR, microcirculatory functional testing, revealed pathological findings in a significant number of evaluated subjects. From this aspect, our study validates further research in the field of microcirculatory functions as

a possible mechanism in the origin of TTS. Our study will enroll 40 patients and is anticipated to complete enrollment by the end of 2022.

■ AN INTERPLAY OF GENETICS AND INFLAMMATION AFFECTING LEFT VENTRICULAR REVERSE REMODELLING IN DILATED CARDIOMYOPATHY

Chaloupka A¹, Krejčí J¹, Kubánek M², Piherová L³, Žampachová V⁴, Ozábalová E¹, Hude P¹, Poloczková H⁵, Špinarová L¹

¹ I. interní kardo-angiologická klinika, Fakultní nemocnice u sv. Anny v Brně a LF MU, Brno; ² Klinika kardiologie, Institut klinické a experimentální medicíny, Praha; ³ Klinika pediatrie a dědičných poruch metabolismu, 1. LF a VFN, Praha;

⁴ Patologický ústav, Fakultní nemocnice u sv. Anny v Brně a LF MU, Brno, ⁵ I. interní kardoangiologická klinika, Fakultní nemocnice u sv. Anny v Brně a LF MU, Brno

Recent-onset dilated cardiomyopathy (RODCM) is a disease of heterogeneous etiology including genetic, inflammatory, toxic and metabolic causes. The interplay between genetic background and myocarditis is still poorly understood and could improve risk stratification of patients with RODCM.

We aimed to determine the genetic background of RODCM by whole-exome sequencing (WES), evaluate the inflammation by endomyocardial biopsy (EMB) and correlate these findings with left ventricular reverse remodeling (LVRR) in the 12-month follow-up.

This single-centre prospective observational study enrolled 83 RODCM patients who underwent whole-exome sequencing; EMB and 12-month clinical and echocardiographic follow up. LVRR was defined as an absolute increase in LV ejection fraction and a relative decrease of LV end-diastolic diameter at 12 months. Inflammation was defined according to TIMIC immunohistochemical criteria.

WES identified disease-related gene variants (ACMG class 3–5) in 45 (54%) patients. Majority of the 28 detected genes were represented by variants of titin (TTN) in 9 (11%), other cardiomyopathic genes in 36 (43%) and none in 38 (46%) patients. EMB analysis uncovered inflammation in 28 (34%) cases. LVRR at 12 months occurred in 28 (34%) of all cases. Carriers of non-titin gene variants heralded a lower probability of 12-month LVRR (19%), followed by patients with a negative genetic result (42%). Interestingly, LVRR occurred most often in carriers of isolated TTN variants (56%) $p = 0.041$. In contrast, inflammation positively predicted LVRR ($p = 0.019$). Combination of genetic and EMB findings did not predict LVRR in 12 months.

In conclusion, carriers of non-titin disease-related variants are less likely to reach LVRR, while myocardial inflammation and isolated titin variants predict favorable remodeling in 12 months.



SILDENAFIL INHIBITS PULMONARY HYPERTENSION INDUCED BY LEFT HEART PRESSURE OVERLOAD IN RATS

Chovanec M¹, Ďurišová J², Kaftanová B³, Al-Hiti H⁴, Hampl V³, Herget J³

¹ Kardiologie, Nemocnice na Homolce, Prague;

² Department of Physiology, 2nd Medical School, Charles University, Prague; ³ Department of Physiology, 2nd Medical School, Charles University, Prague; ⁴ Cardiac Centre, IKEM, Prague

Pulmonary hypertension (PH) induced by pressure overload of the left heart has recently attracted attention in clinical practice. No specific treatment of PH is approved for this group of patients. We previously described a simple rodent model of this condition. We used this model to test a hypothesis that sildenafil can be beneficial in PH induced by experimental left ventricle pressure overload induced in adult male Wistar rats by partial intravascular obstruction of the ascending aorta. Three weeks after induction of PH, sildenafil was given (25 mg/kg), by esophageal gavage once a day for the next 2 weeks (group HFS, N = 7). The group HFS was compared to the group of rats with left heart pressure overload lasting for 3 weeks with no additional use of sildenafil (group HF, N = 9) and with the controls (group C, N = 6). Mean pulmonary arterial pressure was significantly lower in the group HFS compared to the group HF (12.9 ± 0.8 mmHg vs. 20.3 ± 1.0 mmHg, $p < 0.0001$, respectively) but was not different from the group C (10.7 ± 1.1 mmHg). Weight of the right ventricle relative to the body weight (RV/BW ratio) as well as right ventricle weight relative to the left ventricle plus septum (RV/LV+S ratio) were significantly lower in the group HFS compared to the group HF (RV/BW ratio: $4.1 \pm 0.3 \cdot 10^{-4}$ vs. $6.3 \pm 0.8 \cdot 10^{-4}$; $p < 0.01$, respectively and RV/LV+S ratio: 0.23 ± 0.02 vs. 0.41 ± 0.07 ; $p < 0.05$, respectively) but they were not different in the group HFS compared to the group C in both parameters. The amount of expired nitric oxide, measured by chemiluminescent method on day 10 of the left heart pressure overload, was significantly increased in the group HF compared to the group C (343.0 ± 30.5 pg/min/100 g vs. 239.8 ± 18.2 pg/min/100 g; $p < 0.05$, respectively).

Sildenafil attenuated the developed pulmonary hypertension caused by the left heart pressure overload in the rats.

PREDICTING LONG-TERM SURVIVAL AFTER AN ISCHEMIC STROKE

Cífková R¹, Wohlfahrt P¹, Krajčoviechová A¹, Mayer Jr O², Vaněk J³, Hlinovský D⁴, Kielbergerová L⁵, Lánská V⁶

¹ Center for Cardiovascular Prevention, 1st Faculty of Medicine Charles University and Thomayer University Hospital; ² 2nd Department of Internal Medicine, Charles University Medical Faculty and

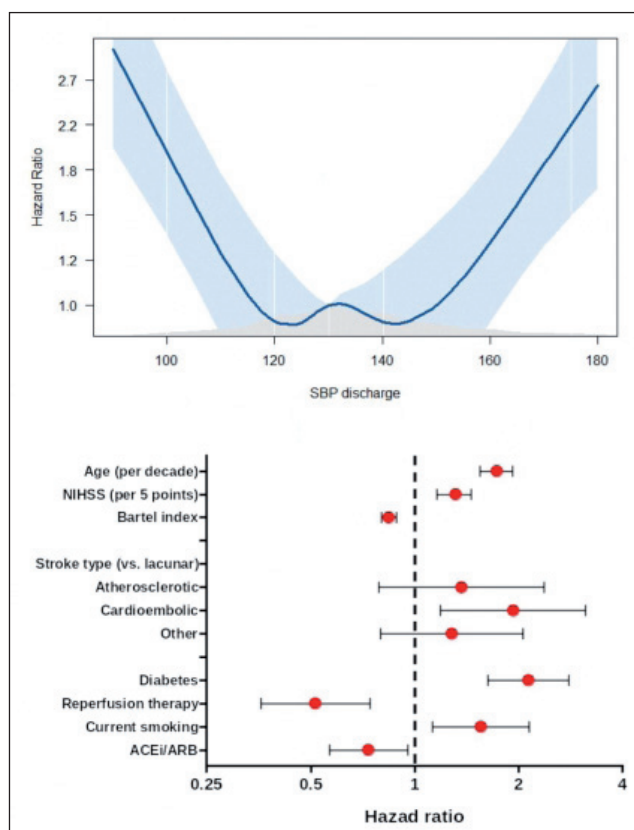
Teaching Hospital, Plzeň; ³ 2nd Department of Internal Medicine, Charles University Medical Faculty and Teaching Hospital, Prague; ⁴ Department of Neurology, Thomayer University Hospital, Prague; ⁵ Department of Neurosurgery and Department of Neurology, University Hospital, Plzeň; ⁶ Medical Statistics Unit, Institute for Clinical and Experimental Medicine, Prague

Background: To identify factors influencing long-term survival after ischemic stroke is of utmost importance. The aim of the present study was to analyze long-term survival and to assess factors associated with increased mortality following ischemic stroke.

Design and methods: Consecutive patients hospitalized between March 2009 and January 2012 for their first-ever ischemic stroke in 2 large tertiary hospitals in the Czech Republic were enrolled in this survey.

Results: In total, 736 patients (mean age 66 ± 11 years; 58% men) were included in this analysis. The cumulative risk of death at 1, 3, 5 and 10 years was 13.6%, 20.8%, 29.3% and 48.3%, respectively. After adjusting for age and gender, patients with discharge systolic blood pressure between 120 and 140 mmHg showed the lowest mortality risk (Fig. 1). Higher age, higher NIHSS and more severe functional impairment, diabetes and current smoking were associated with higher mortality risk, while the reperfusion therapy, and renin-angiotensin system blockers were associated with a lower mortality (Fig. 2).

Conclusions: Despite several advances in stroke management, the mortality remains high. Timely reperfusion therapy use together with renin-angiotensin system blockers may decrease the risk of mortality.





■ LONGITUDINAL TRENDS IN BLOOD PRESSURE, PREVALENCE, AWARENESS, TREATMENT, AND CONTROL OF HYPERTENSION IN THE CZECH POPULATION. ARE THERE ANY SEX DIFFERENCES?

Cífková R¹, Bruthans J², Wohlfahrt P³, Krajčoviechová A⁴, Jozífová M⁵, Linhart A⁶, Widimský J⁷, Filipovský J⁸, Mayer O⁹, Lánská V¹⁰

¹ Centrum KV prevence, 1. LF UK a FTN, Fakultní Thomayerova nemocnice, Praha;

² Centrum kardiovaskulární prevence, 1. lékařská fakulta UK a Fakultní Thomayerova nemocnice Praha, Praha; ³ Centrum kardiovaskulární prevence 1. LF UK a Fakultní Thomayerovy nemocnice, Fakultní Thomayerova nemocnice, Praha;

⁴ Centrum preventivní kardiologie, Fakultní Thomayerova nemocnice, Praha; ⁵ Centrum kardiovaskulární prevence, Fakultní Thomayerova nemocnice, Praha; ⁶ II. interní klinika, VFN Praha, Praha; ⁷ III. interní klinika, Všeobecná fakultní nemocnice, Praha; ⁸ II. interní klinika, FN Plzeň, Plzeň; ⁹ Centrum preventivní kardiologie, II. interní klinika, Plzeň; ¹⁰ Oddělení lékařské statistiky, IKEM, Praha

Background: Hypertension is the most common CVD increasing CV morbidity and mortality. Despite the broad availability of antihypertensive medication, control of hypertension is not satisfactory worldwide.

Objective: The study aim was to assess longitudinal trends in blood pressure, prevalence, awareness, treatment, and control of hypertension in a representative population sample of the Czech Republic from 1985 to 2016/2017, focusing on sex differences.

Methods: A total of randomly selected 7,606 men and 8,050 women aged 25–64 years were screened for major CV risk factors in seven independent cross-sectional surveys between 1985 and 2016/2017.

Results: Over a study period of 31/32 years, there was a significant decline in systolic and diastolic blood pressure in both sexes, whereas the prevalence of hypertension decreased only in women. There was an increase in hypertension awareness in both sexes over the entire study period with consistently higher rates in women. The proportion of individuals treated with antihypertensive drugs increased significantly in both sexes throughout the study, again with consistently higher rates in women. Control of hypertension increased significantly over the study period with consistently higher rates in women. The age-adjusted trends in blood pressure, prevalence, awareness, and treatment of hypertension were significantly different in men and women, always in favor of women. The age-adjusted trends in control

of hypertension in treated patients were equally poor in both sexes.

Conclusions: There are significant differences in longitudinal trends in blood pressure, prevalence, awareness, treatment, and control of hypertension between men and women, always in favor of women except for the control of hypertension in treated patients, where it is equally poor in both sexes.

■ CHARACTERISTICS AND OUTCOMES OF PATIENTS ADMITTED FOR ACUTE HEART FAILURE IN A SINGLE CENTRE STUDY

Dokoupil J¹, Hřečko J¹, Čermáková E², Adamcová M³, Pudil R¹

¹ I. interní kardioangiologická klinika, Fakultní nemocnice Hradec Králové, Hradec Králové; ² Ústav lékařské biofyziky, Lékařská fakulta v Hradci Králové, Hradec Králové; ³ Ústav fyziologie, Lékařská fakulta v Hradci Králové, Hradec Králové

Aims: Acute heart failure represents a medical condition with a very high mortality. The aim of our study was to characterize real-life patients admitted for acute heart failure in a region with one tertiary medical center and to describe risk factors of mortality.

Methods and results: We performed a retrospective analysis of patients admitted from January 2017 to December 2017 to Department of Cardiology of the University Hospital in Hradec Kralove. We identified 385 patients. The median of age was 74 years (IQR 67.5–80) and 34% of patients were females. The most common comorbidities were arterial hypertension (77.7%), dyslipidemia (67.3%), and coronary artery disease (63.1%). Coronary artery disease (52.7% of cases) and valve disease (28.1% of cases) were the most common etiologies of heart failure. The all-cause in-hospital mortality was 12.7%, 30-day mortality was 14.6% and 1-year mortality was 34%. Among risk factors of in-hospital mortality, the most significant factors were hemodialysis during the hospitalization (OR 15.82, 95% CI 2.96–84.57, $p = 0.0008$), chronic heart failure (OR 4.27, 95% CI 1.66–11.03, $p = 0.001$) and STEMI as a precipitating factor of heart failure (OR 4.19, 95% CI 1.23–14.25, $p = 0.023$). Hemodialysis during the hospitalization (OR 4.28, 95% CI 1.17–15.61, $p = 0.025$) and the comorbidity depression and anxiety (OR 3.49, 95% CI 1.45–8.39, $p = 0.005$) were the most significant risk factors of long-term mortality.

Conclusion: Our study confirms very high mortality rates among patients with acute heart failure underlying poor prognosis of these patients. Comorbidities, precipitating factors of heart failure, complications occurring during the hospitalization and the age of patients should be included in the risk stratification of in-hospital, 30-day and 1-year mortality.



■ EFFICACY AND SAFETY OF ENDOCARDIAL RADIOFREQUENCY CATHETER ABLATION OF INTERVENTRICULAR SEPTAL HYPERTROPHY IN THE TREATMENT OF HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY, PILOT EXPERIENCES

Doležalová K, Stárek Z, Jež J, Souček F, Lehar F, Špinarová L

I. interní kardioangiologická klinika, FN USA, Brno

Introduction: Endocardial radiofrequency ablation of septal hypertrophy (ERASH) is the new promising intervention method of treatment of patients with hypertrophic obstructive cardiomyopathy (HOCMP). The aim of our study is to prove safety and efficacy of ERASH in treatment of HOCMP.

Methods: Patients with maximal pharmacology treatment of HOCMP and lasting high gradient in left ventricle outflow tract (LVOTG) and limitation by symptoms are indicated to intervention treatment.

Results: From September 2018 up to September 2021 there were 6 patients who underwent ERASH with the average age 58 years. Average rest LVOTG was 99 mmHg and 115 mmHg after Valsava. Resulting average LVOTG after procedure was 21 mmHg in rest and 57,5 mmHg provoked. In 6 months follow up 63 mmHg resting and 72mmHg provoked. In two patients there was periprocedural pericardial effusion presented with pericardial drainage, one due to temporary pacemaker, and one permanent pacemaker implant due to AVB III. degree.

ERASH seems to be a promising new method in interventional treatment of HOCMP with similar efficacy and safety compared to ASA. Higher amount of complications was probably due to previous ASA procedure and learning curve.

■ LACTATE IN REFRACTORY OUT-OF-HOSPITAL CARDIAC ARREST. THE PRAGUE OHCA STUDY SUBANALYSIS

Dusík M¹, Šmalcová J¹, Rob D¹, Havránek Š¹, Šmíd O¹, Lahoda Brodská H², Huptych M³, Bělohávek J¹

¹ 2nd Department of Medicine – Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague; ² Institute of Medical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague; ³ Czech Institute of Informatics, Robotics and Cybernetics, Czech Technical University, Prague

Introduction: The prognosis of patients suffering refractory out-of-hospital cardiac arrest (OHCA) remains serious despite the implementation of extracorporeal cardiopulmonary resuscitation (ECPR). Serum lactate (s-Lac) level is

an easily measured parameter reflecting the severity of hypoperfusion and tissue hypoxia. We hypothesized, that early lactate levels might be useful in predicting the outcome after OHCA.

Methods: This is a post-hoc analysis of the biochemical data from the randomized clinical trial "Prague OHCA study" comparing invasive (ECPR) and standard approaches in refractory OHCA patients. Patients who have undergone ECPR ("ECPR group") treated with veno-arterial extracorporeal membrane oxygenation, and patients in whom the prehospital ROSC has been achieved ("ROSC group") were analyzed separately and irrespective of randomization schema. The s-Lac level was measured at admission to the hospital and then repeatedly every 4 hours during the first 24 hours. Based on the values, the total area under the curve (AUC) of s-Lac in the first 24 hours was calculated for every patient. The best Cerebral Performance Category (CPC) score reached during the 180 days long follow-up after the OHCA event was used to determine favorable (F; CPC 1, 2) and unfavorable outcome (UF; CPC 3, 4, 5).

Results: Out of 92 patients in the ECPR and 82 patients in the ROSC group, F outcome was reached in 24 (26%) and 48 (59%) subjects, respectively. The AUCs of s-Lac levels in the first 24 hours were significantly different between F and UF patients in both ECPR and ROSC groups. More details are in the Tables 1 and 2.

Conclusion: The AUCs of s-Lac levels measured during the first 24 hours after refractory OHCA are significantly different between patients with F and UF long-term neurological outcome regardless the use of ECPR methods.

Table 1 – ECPR group

Outcome	Favorable	Unfavorable	p
S-Lac at admission (mmol/L)	11.2 (9.2–13.8)	14.8 (12.1–17.5)	<0.001
S-Lac after 4 h (mmol/L)	4.9 (3.3–8.4)	8.3 (5.0–11.5)	<0.01
S-Lac after 8 h (mmol/L)	4.1 (2.8–5.4)	6.3 (3.5–9.2)	0.03
S-Lac after 12 h (mmol/L)	3.4 (2.1–5.2)	6.3 (3.4–8.5)	<0.001
S-Lac after 16 h (mmol/L)	3.3 (2.0–4.9)	5.7 (3.5–9.1)	<0.01
S-Lac after 20 h (mmol/L)	2.7 (1.8–3.4)	5.1 (3.0–8.7)	<0.01
S-Lac after 24 h (mmol/L)	2.4 (1.6–3.7)	4.8 (2.5–8.2)	<0.01
AUC of s-Lac in the first 24 h	108 (72.8–146)	154 (102.2–207.8)	<0.01

Table 2 – ROSC group

Outcome	Favorable	Unfavorable	p
S-Lac at admission (mmol/L)	7.8 (5.7–10.2)	9.7 (7.1–12.1)	0.055
S-Lac after 4 h (mmol/L)	2.5 (1.4–3.3)	3.2 (1.8–7.5)	0.017
S-Lac after 8 h (mmol/L)	1.8 (1.2–2.5)	3.9 (1.4–6.4)	0.02
S-Lac after 12 h (mmol/L)	1.5 (1.1–2.5)	2.4 (1.1–7.4)	0.04
S-Lac after 16 h (mmol/L)	1.5 (1.0–2.4)	2.7 (1.4–7.1)	0.03
S-Lac after 20 h (mmol/L)	1.6 (0.9–3.1)	2.5 (1.4–5.7)	0.07
S-Lac after 24 h (mmol/L)	1.4 (1.1–2.2)	1.9 (1.1–3.7)	0.14
AUC of s-Lac in the first 24 h	57 (46.7–74.7)	68 (50.4–143)	0.04

Data are expressed as median (IQR).

■ PARAMETERS OF ALLERGIC REACTION AFTER IMPLANTATION OF DIFFERENT PATENT FORAMEN OVALE OCCLUDERS – A PILOT PROSPECTIVE RANDOMIZED STUDY

Dvořáková A, Mates M, Kmoníček P, Kopřiva K, Neužil P

Komplexní kardiiovaskulární centrum, primariát kardiologie, Nemocnice Na Homolce, Praha

Primary endpoint: To compare parameters of the allergic response after transcatheter closure of the patent foramen ovale (PFO) using three different types of nitinol occluders in a pilot randomized trial.

Patient population and methods: 39 patients aged 29–72 (21 women and 18 men) who met institutional criteria for catheter based PFO closure were included in the study. Patients were divided into three groups according to the type of implanted occluder: 1. Amplatzer® (Abbott®) device made of nitinol with wire treatment to reduce nickel excretion and polyester fabric; 2. Figulla® device (Occlutech®) made of titanium oxide-coated nitinol and PET-patch; 3. the Ultrasept® (Cardia®) device which consists of nitinol coated with polyvinyl alcohol. Plasma CRP levels, full blood count including eosinophils, IgE, eosinophilic cationic protein (ECP), fibrinogen and a panel of cytokines were measured at baseline (24 hours before the procedure) and 6 hours, 24 hours, 7 days, 1 month and 6 months after occluder implantation.

Results: Only patients with normal baseline levels of IgE, eosinophils, ECP, and CRP were included for the final analysis (group 1 n = 7, group 2 n = 9, group 3 n = 6). Procedural success was 100% and there were no major complications. No significant changes in plasma levels of IgE and eosinophils were detected during the follow-up among the 3 groups of patients. The ECP values differed statistically among the individual groups 7 days after the procedure ($p = 0.025$), there were no significant deviations in the other observed times. No measurable increase in interleukins 1 and 6 was detected.

Conclusion: Despite the reported different manufacturing processes of the nitinol PFO occluders, there were no significant differences among the selected parameters of the allergic response immediately after implantation or during the six-month follow-up period.

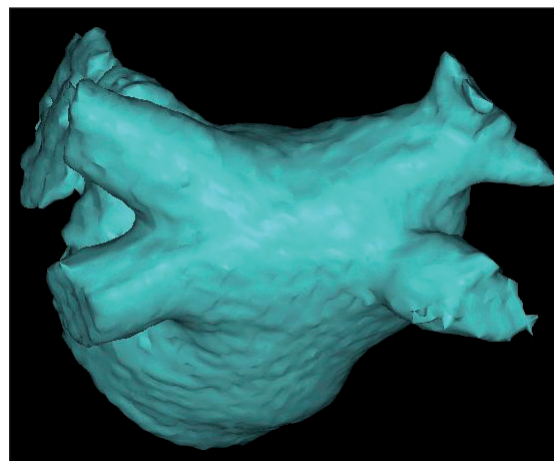
■ PULMONARY VEIN MORPHOLOGY IN PATIENTS UNDERGOING CATHETER ABLATION OF ATRIAL FIBRILLATION

Farkasová B¹, Pospíšil D¹, Míková M¹, Toman O², Fiala M³, Křikavová L⁴, Zouharová A⁵, Sepši M¹, Kala P¹, Novotný T¹

¹ Interní kardiologická klinika, FN Brno a LF MU, Brno; ² Interní kardiologická klinika, FN Brno, Brno; ³ Centrum kardiiovaskulární péče, Neuron

Medical s.r.o., Brno; ⁴ Klinika radiologie a nukleární medicíny, FN Brno, Brno; ⁵ Institut biostatistiky a analýz, LF MU, Brno

Variations in the anatomy of pulmonary veins (PVs) can influence selection of approaches of atrial fibrillation (AF) catheter ablation. Therefore, preprocedural evaluation and knowledge of PV anatomy is crucial for proper mapping and the successful ablation of AF. The aim of this observational study was to assess CT angiography scans and perform detailed analysis of PV morphology in patients scheduled for catheter ablation of AF. CT angiography was performed in 771 individuals (223 females, 548 males, mean age 58.4 ± 10.7 years). PV anatomy was evaluated using 3D models. The patterns used for evaluation included typical anatomy with four separate PVs, a common left ostium, and various types of accessory veins either alone or in combination with common left ostia. An anatomical variant with common left ostium was observed as the most prevalent anatomy (44%). The typical variant was observed in 34.8% of patients. Accessory PVs were observed predominantly on the right side. The prevalence of anatomical variants did not differ between sexes with the exception of the unclassifiable category U (4.4% vs 9%, $p < 0.05$). Information about a considerable number of atypical anatomies is as important as knowledge and understanding of the anatomical variations of PVs. This may influence the choice of instrumentation.



■ USAGE OF ULTRA-SHORT-TERM HEART RATE VARIABILITY ANALYSIS DURING HEAD-UP TILT TESTING IN DIAGNOSTICS OF CARDIOINHIBITORY REFLEX SYNCOPE

Galuszka J¹, Vykoupil K¹, Zapletalová J², Táborský M³

¹ I. interní klinika – kardiologická, FN Olomouc, LF UP, Olomouc; ² Ústav biofyziky, Univerzita Palackého, Olomouc; ³ I. interní klinika – kardiologická, Fakultní nemocnice Olomouc a LF UP, Olomouc



Background: Participation of autonomic nervous system activity in origin of neurally mediated reflex syncope is research topic for decades but so far without consensus how to realize autonomic function evaluation during head-up tilt testing.

Purpose: Heart rate variability analysis during head-up tilt testing in ultra-short time period closely surrounding syncope or end of testing.

Methods: Head-up tilt testing (45 min protocol at 60 degrees in standard conditions) in 48 patients with history of syncope divided in group A (REFERENCE) without syncope during testing (24 patients, 14 men, age median 33.7 years) and group B (BRADYCARDIAC) (24 patients, 13 men, median age 40.5 years) with cardioinhibitory reactions during testing, defined according to guidelines. There were no significant differences in age or sex between both study groups.

Heart rate variability parameters: LF (low frequency) in n.u., HF (high frequency) in n.u., LF/HF ratio were evaluated in the last 1 minute time segment with sinus rhythm in tilting position before end of tilting or syncope and in the first minute in recovery supine position. Mann-Whitney U test, Chi-square test p -value and Shapiro-Wilk test were used for statistical data processing with p -value significance level 0.05.

Results: The last minute of tilting: Groups A : B median values: LF 84.7 : 74.9 (p 0.018), HF 15.3 : 25.2 (p 0.018), LF/HF 6.25 : 3.4 (p 0.025).

The first minute of recovery in supine position: Groups A : B median values: LF 76.9 : 64.9 (p 0.001), HF 23.1 : 35.1 (p 0.001), LF/HF 4.4 : 1.85 (p 0.0002).

Conclusion: Presented results revealed statistically significant changes indicating vagal predominance before cardioinhibitory syncope in comparison with reference group.

■ SGC STIMULATOR (BAY 41-8543) FOR THE TREATMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION (HFrEF) AND CARDIO-RENAL SYNDROME

Gawrys O¹, Husková Z¹, Škaroupková P¹, Honetschlägerová Z¹, Vaňourková Z¹, Kikerlová S¹, Melenovský V², Červenka L¹

¹ Experimental Medicine Centre, IKEM, Praha;

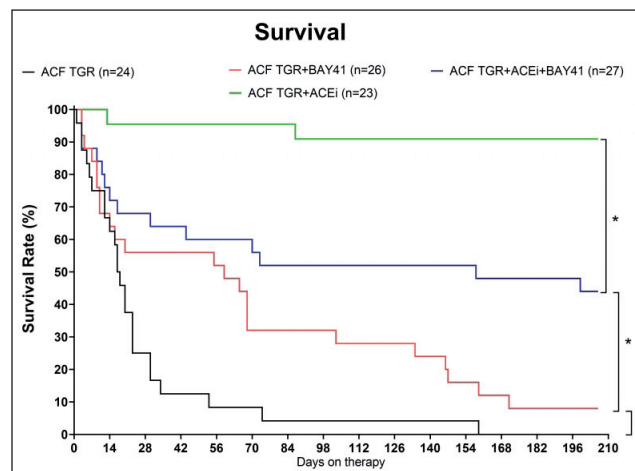
² Department of Cardiology, IKEM, Praha

Heart failure with reduced ejection fraction (HFrEF) is considered to be one of the major epidemics of the 21st century. The prognosis and life expectancy is dreadful for patients that develop concurrent impairment of kidney function, so called "cardio-renal syndrome".

In the present study we investigated the activity of NO-independent sGC stimulator, called BAY 41-8543 (BAY41), in ren-2 transgenic hypertensive rats (TGR) with aorto-caval fistula (ACF)-induced HFrEF. The effectiveness of the BAY41 administered alone (3 mg/kg/day) or combined with an ACE inhibitor (ACEi, Trandolapril, 0.25 mg/kg/day) on the survival rate was investigated for 30 weeks.

Blood pressure was measured in separate experiments for 2 weeks.

BAY41 significantly improved the survival in comparison to untreated animals with HFrEF. After 60 days the survival rate of ACF TGR treated with BAY41 was still 50%, while in untreated group it was already below 10%. However, after some time the beneficial activity of BAY41 started to decline. Additionally, BAY41 administered together with ACEi decreased the beneficial activity of the ACEi. The telemetry data revealed a transient decrease in blood pressure (-10 mmHg) two days after BAY41 administration, but early on SBP started to rise and by the end of the 2-week observation it was on the same level as in untreated rats (124 ± 2 vs 134 ± 3 mmHg, respectively; NS). It seems that the sGC stimulation is a promising strategy to treat HFrEF based on improved survival. However, the results in the combination group call for special attention. One hypothesis is that the dose regimen of BAY41 could be improved, e.g. higher dosage of sGC stimulator combined with titration protocol should be tested, i.e. to avoid the initial hypotension, but to prevent the "escape" from the treatment after long-term administration.



■ ROSS PROCEDURE PROVIDES SURVIVAL BENEFIT OVER MECHANICAL VALVE IN ADULTS: A PROPENSITY-MATCHED NATIONWIDE ANALYSIS

Gofus J¹, Fila P², Drábková S³, Žáček P¹, Ondrášek J², Němec P², Tuna M¹, Jarkovský J³, Vojáček J¹

¹ Kardiochirurgická klinika, Fakultní nemocnice Hradec Králové, Hradec Králové; ² Department of Cardiovascular Surgery and Transplantation, Centre of Cardiovascular Surgery and Transplantation, Brno; ³ Institute of Health Information and Statistics of the Czech Republic, Prague

Objectives: The choice of optimal surgical treatment for young and middle-aged adults with aortic valve disease remains a challenge. Mechanical aortic valve replace-



ment (mAVR) is generally preferred despite promising recent outcomes of the Ross procedure. We aimed to compare both strategies at a nationwide level.

Methods: This was a retrospective analysis of prospectively recorded data from the National Registry of Cardiac Surgery. Using propensity-score matching, we compared the outcomes of patients undergoing the Ross procedure in two dedicated centers with all mAVRs performed in the Czech Republic between 2009 and 2020.

Results: Throughout the study period, 296 adults underwent the Ross procedure and 5120 had a mAVR. We found and compared 291 matched pairs. There was no in-hospital mortality and the risk of perioperative complications was similar in both groups. Over the average follow-up of 4.1 vs 6.1 years, the Ross group had a lower all-cause mortality (0.7 vs 6.5 %; $p = 0.015$). Unlike the Ross group, the mAVR group had significantly lower relative survival when compared with the age- and sex-matched general population at 10 years postoperatively (97.1%, CI 86.8–108.7 vs 93.5%, CI 88.1–99.2). There was no difference in the risk of reoperation (4.5 vs 5.5%; $p = 0.66$).

Conclusions: The Ross procedure offers a significant mid-term survival benefit over mAVR. Both procedures have a comparable risk of perioperative complications. For young and middle-aged adults with aortic valve disease, Ross procedure should be considered a procedure of choice in dedicated centers.

■ CATHETER ABLATION OF PATIENTS WITH NON-PAROXYSMAL ATRIAL FIBRILLATION BY FOCAL AND ROTATIONAL ACTIVITY MAPPING USING CARTO FINDER SOFTWARE

Hassouna S, Heřman D, Osmančík P

Kardiologie, FNKV, Praha

Introduction: Catheter ablation in patients with non-paroxysmal atrial fibrillation (AF) still doesn't give satisfactory results. One of the last developed methods in AF ablation is the ablation of regions with focal and rotational activities that contribute in maintaining of AF. CARTO Finder module was developed just to highlight the regions of repetitive focal and rotational activities during AF using endocardial high-density mapping. Our aim is to present initial results with the CARTO Finder module in non-paroxysmal AF.

Methods: Patients with symptomatic non-paroxysmal AF who were referred for catheter ablation were included in the study. The regions of focal and rotational activities in the left and right atrium were mapped using Pentarey multipolar catheter and CARTO Finder module. The ablation consisted of pulmonary vein isolation, followed by ablation of highlighted regions of focal and rotational activities. If AF persisted after the ablation, electrical cardioversion was done. Holter recordings were done at 3, 6, 9 and 12 months during follow-up.

Results: A total of 13 patients (5 women), mean age 63.8±8.7 years, weight 93.2±17.6 kg, were included. Mean duration of the procedure was 217.2±39 min, no complication occurred during the procedure. AF was present in all patients at the beginning of the procedure. The left atrial volume was 186.2±22.7 mL. Using the CARTO Finder module, 2.3±1.0 regions of focal, and 0.6±0.7 regions of rotational activity were found. Typical regions of findings were the base of the left atrial appendage and the endocardial side of the CS. Termination to SR or organization to regular atrial tachycardia occurred in only 2 patients, all other patients underwent electrical cardioversion. The mean follow-up time was 205.4±53.1 days, with 7 of 10 patients followed for longer than 6 months (70%) maintained SR.

Conclusion: The acute termination of AF to SR or organization into a regular atrial tachycardia using CARTO Finder module was not frequent. On the other hand, clinical results in terms of SR maintenance were promising in the pilot cohort of patients.

■ CATHETER ABLATION OF ATRIAL FIBRILLATION/TACHYCARDIA IN PATIENTS WITH PULMONARY HYPERTENSION: A MULTICENTRE RANDOMIZED TRIAL

Havránek Š¹, Fingrová Z¹, Skála T², Reichenbach A³, Dusík M¹, Ambrož D¹, Dytrych V¹, Jansa P¹, Hutýra M², Wichterle D⁴

¹ II. interní klinika, VFN Praha, Praha; ² I. interní klinika, FN Olomouc, Olomouc; ³ Klinika kardiologie, IKEM, Praha; ⁴ Klinika kardiologie, Institut klinické a experimentální medicíny, Praha

Background: Atrial fibrillation (AF) and related atrial tachycardias (ATs) are common arrhythmias in patients with pulmonary hypertension (PH). The long-term efficacy and safety of radiofrequency catheter ablation (RFCA) for AF/AT in the PH population have not yet been prospectively studied. We investigated the hypothesis of whether extensive RFCA of the arrhythmogenic substrate on top of selective ablation of clinical arrhythmia alone results in superior clinical outcomes in patients with PH and AF/AT.

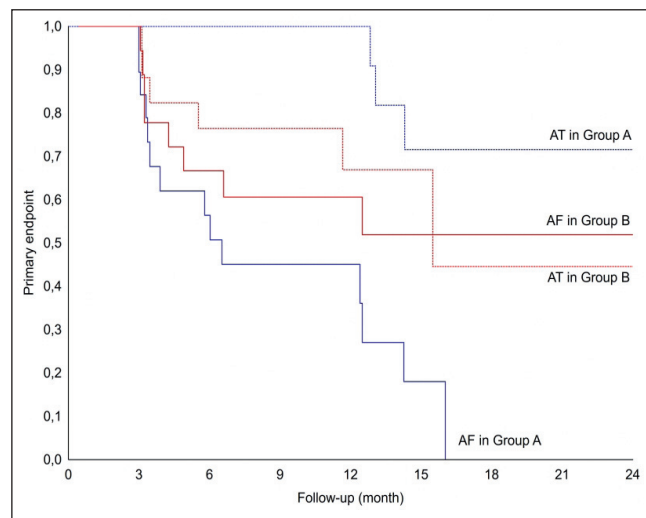
Methods: Patients with combined post- and pre-capillary or isolated pre-capillary PH and AF/AT indicated to RFCA were enrolled in 3 centers and randomized 1 : 1 into two parallel treatments arms: (A) "Clinical" ablation and (B) "Clinical" plus substrate-based ablation. The primary endpoint of the study was documented arrhythmia recurrence >30 s without antiarrhythmic drugs during the post-blanking period after the index ablation.

Results: A total of 77 patients (71 [61; 75] years; 41 males) were enrolled in the study. 43 (56%) patients had AF and 34 (44%) had AT. The median duration of the follow-up period was 14 (12; 21) months. The primary endpoint occurred in a comparable number of patients in group A and B (17 patients [45 %] vs. 15 patients [42 %]; HR: 1.03; 95% CI 0.51 to 2.06; $p = NS$). When compared to AF



patients (irrespective to randomization schema), the primary endpoint occurred significantly less frequently in AT group (9 [25%] vs. 23 [61%]; HR 0.3 (95% CI 0.14 to 0.66); $p = 0.003$). The occurrence of the primary endpoint in AF and AT patients according to the randomization group is visualized in Figure.

Conclusion: The trial in patients with PH and AF/AT prospectively demonstrated that more extensive ablation is not associated with improved clinical outcomes. However, better results were achieved in patients with AT. NCT04053361.



■ NITRIC OXIDE RELEASING PACING LEAD TO PREVENT INFECTION IN CARDIAC PACING

Hála P¹, Lautner-Csorba O², Gorur R², Popková M³, Somay V³, Janák D³, Mlček M³, Neužil P⁴, Kittnar O³, Major T⁵

¹ Kardiologie, Nemocnice Na Homolce, Praha; ² Department of Chemistry, University of Michigan, Ann Arbor, United States; ³ Institute of Physiology, Charles University, Prague; ⁴ Cardiology, Na Homolce Hospital, Praha; ⁵ Department of Chemistry, University of Michigan, Ann Arbor, USA

Background: Effective prevention of pacing lead infection could reduce morbidity and save lives. It has been demonstrated that nitric oxide (NO) can inhibit bacterial adhesion and reduce biofilm formation. We tested a di-azaniumdiolated dibutylhexanediamine (DBHD/N₂O₂, a potent NO donor) coated pacing lead to prevent its bacterial infection.

Methods: Silicone pacing lead was coated with two layers of 25 weight% DBHD/N₂O₂ in Carbosil and topped with one layer of plain Carbosil. The NO release profile of the coated lead is measured with an ozone chemiluminescent method at 37 °C in phosphate buffered saline (PBS, pH = 7.4). In a bioreactor the lead is then exposed

to bacterial cultures of *S. aureus* and *P. aeruginosa* and its antibacterial capacity evaluated by biofilm homogenization and plating on agar for CFU counting of viable bacteria per surface area. Complete pacing system with the DBHD/N₂O₂ coated pacing lead is then implanted in small animal model (rabbit) and tested for function and durability.

Results: Initial NO flux of DBHD/N₂O₂ coating was 0.8 ± 0.1 [$\times 10^{10}$ mol/min/cm²] and stayed between the effective range >0.5 flux unit for seven days. Preliminary results on coated catheter surfaces demonstrated almost 95% decrease of biofilm formation: 89 ± 9.7 vs. $5.2 \pm 1.1 \times 10^3$ CFU ($p < 0.001$). In-vivo, cardiac pacing was properly functional in all subjects for over 6 months with mean impedance of 750 Ohm, average bipolar ventricular sensing of 9.2 mV (min 7.4, max 12) and pacing threshold of 1.7 V@0.4 ms (min 0.2, max 2.7).

Conclusion: Presented pacing lead with DBHD/N₂O₂ coating demonstrated a potent antibacterial effect while retaining optimal pacing parameters. This effective elimination of biofilm formation can likely prevent potential clinical infection especially in complex pacing procedures or immunocompromised patients.

■ POSTPROCEDURAL ULTRASOUND EVALUATION OF PROXIMAL AND DISTAL RADIAL ARTERY AFTER CATHETERIZATION USING DISTAL RADIAL ACCESS

Horák D, Bernat I, Jirouš Š, Slezák D, Rokyta R

Kardiologická klinika, FN Plzeň, Plzeň

Distal radial access (DRA) becomes now more and more popular among interventional cardiologists. It is well known that utilization of DRA effectively spares proximal radial artery in terms of minimizing the rate of the radial artery occlusion (RAO). The aim of our study was to evaluate patency not only of proximal radial artery, but also of distal radial artery using ultrasound (US) as the most reliable method. We evaluated 115 patients who underwent catheterization via distal radial access (dTRA). Following the procedure and after successful hemostasis, arterial patency and diameter at conventional transradial access (cTRA) and distal puncture sites (either in the anatomical snuffbox or the dorsal distal RA) were assessed. No RAO were found in the proximal or distal RA and there were no significant other complications including hematomas >2 cm. The mean diameter of the radial artery at conventional puncture site was 2.86 ± 0.49 mm and at distal puncture site 2.31 ± 0.47 mm ($p < 0.001$). Postprocedural compression time of dTRA was very short (80 ± 36 min). In conclusion distal radial access was associated with the absence of early arterial occlusion, and other relevant complications.

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■ COMPARISON OF SIX DECISION AID RULES FOR DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION IN ELDERLY PATIENTS PRESENTING TO THE EMERGENCY DEPARTMENT WITH ACUTE CHEST PAIN

Hřečko J, Pudil R, Dokoupil J, Pařízek P

I. interní kardiologická klinika, Fakultní nemocnice Hradec Králové, Hradec Králové

Objective: This study aimed to evaluate the accuracy and effectiveness of different strategies for the diagnosis of acute myocardial infarction (AMI) in the elderly in real-life clinical practice.

Methods: Patients older than 70 years presenting to the emergency department with chest pain were included. The performance of six decision aid rules (T-MACS, HEART, EDACS, TIMI, GRACE, and ADAPT) and solo troponin T strategy for diagnosing AMI was evaluated by calculating sensitivity, specificity, odds ratios, negative and positive predictive values.

Results: A total of 250 patients, with a mean age of 78.5 years, were enrolled. Forty-eight patients (19.2%) had an acute myocardial infarction in a 30-day follow-up period. The sensitivity for ruling-out AMI was 100% for T-MACS, HEART, and ADAPT; 97.9% for EDACS, 93.8% for TIMI, and 81.3% for GRACE and solo TnT strategy. For ruling-in AMI, the specificity was 97.5% for T-MACS, 95% for TIMI, 83.2% for HEART, 81.7% for GRACE, and 46% for ADAPT.

Conclusion: T-MACS decision aid had the best performance for rule-out and rule-in diagnostics of AMI. Risk stratification of patients with suspected acute coronary syndrome based on decision aid rules can be used in real-life practice, even in the population of the elderly.

■ MYOCARDIAL INVOLVEMENT DETECTED USING CARDIAC MAGNETIC RESONANCE IMAGING IN PATIENTS WITH SYSTEMIC SCLEROSIS – A PROSPECTIVE OBSERVATIONAL STUDY

Hromádka M¹, Baxa J², Rajdl D³, Rokyta R¹

¹ Kardiologická klinika, FN a LF UK Plzeň, Plzeň; ² KZM, FN Plzeň, Plzeň; ³ Ústav klinické biochemie a hematologie FN Plzeň, LF v Plzni, UK v Praze, FN Plzeň, Plzeň

Introduction and objectives: Cardiac involvement in systemic sclerosis (SSc) patients affects mortality. Cardiac magnetic resonance (CMR) is capable of detecting structural changes, including diffuse myocardial fibrosis that may develop over time. Our aim was to evaluate myocardial structure and function changes using CMR in patients with SSc without known cardiac disease during a 5-year follow-up and find possible correlations with selected biomarkers.

Methods: A total of 25 patients underwent baseline and follow-up CMR examinations according to a pre-specified protocol. Standard biochemistry, five biomarkers (hsTnI,

NT-proBNP, Galectin-3, sST2, and GDF-15), and disease-specific functional parameters enabling classification of disease severity were also measured.

Results: After five years, no patient suffered from manifest heart disease. Mean extracellular volume (ECV) and T1 mapping values did not change significantly ($p \geq 0.073$). However, individual increases in native T1 time and ECV correlated with increased Galectin-3 serum levels ($r = 0.56$; $p = 0.0050$, and $r = 0.71$; $p = 0.0001$, respectively). Progression of skin involvement assessed using Rodnan skin score and a decrease in diffusing capacity of the lungs were associated with increased GDF-15 values ($r = 0.63$; $p = 0.0009$, and $r = -0.51$; $p = 0.011$, respectively).

Conclusions: During the 5-year follow-up, there was no new onset of heart disease observed in patients with SSc. However, in some patients, CMR detected progression of sub-clinical cardiac fibrosis that significantly correlated with elevated Galectin-3 levels. GDF-15 values were found to be associated with disease severity progression.

■ FAMILIAL HYPERCHOLESTEROLEMIA MUTATIONS IN CZECH POPULATION AND IN CZECH PATIENTS WITH ACUTE CORONARY SYNDROME

Hubáček J¹, Piňha J², Adámková V³

¹ PEM, Laboratoř molekulární genetiky, IKEM, Praha;

² IKEM, Praha; ³ PPK, IKEM, Praha

Introduction: Familial hypercholesterolemia (FH) is the most common monogenic disease associated with increased risk of atherosclerotic cardiovascular disease (ACVD). FH is caused by mutations in the LDL-receptor or in the Apolipoprotein B (ApoB); changes in other genes occur rarely. Carriers of these mutations usually have high cholesterol levels, but the quantification of the relationship between these mutations and cholesterol levels in FH patients with ASCVD and in the general population has not yet been analyzed in detail. We investigated the presence of these mutations in the Czech population and in patients with ASCVD and analyzed the relationship of these mutations with cholesterol levels.

Methods: We analyzed the presence of the three most common Czech mutations in the genes for the LDL receptor (*Asp266Glu* and *Gly592Glu*) and for apoB (*Arg3527Gln/Trp*) in 6 012 individuals from the post-MONICA study (age 49.7 ± 11.2 years; 53% women) and in 3 097 patients with acute coronary syndrome (ACS) (age 57.6 ± 8.7 years; 100% men).

Results: A total of 38 FH mutation carriers were detected. The prevalence of LDL-R mutations did not differ between patients with ACS and controls (3.0% vs. 2.5%). APOB mutations were significantly more frequent in patients than in the population (3.5% vs. 0.5%; $p < 0.0005$; OR [95% CI] = 7.1 [2.0–25.5]). Only 1/3 of carriers of the screened mutations had significantly elevated total cholesterol (values in the upper decile of the population distribution – above 7.5 mmol/L).

Conclusion: We described the prevalence of carriers of the most common mutations in LDL receptor and APOB



in the Czech population and in Czech patients with ACS. It is not unconditionally true that the presence of the mutation is associated with above-average total or LDL cholesterol values.

■ DRUG-ELUTING BALLOON COMPARED TO DRUG-ELUTING STENT TREATMENT IN DES RESTENOSIS

Hudec M¹, Brázdil V¹, Kaňovský J¹, Štípal R², Poloczek M¹, Boček O¹, Jeřábek P¹, Kameník M³, Kala P¹

¹ IKK, FN Brno a LF MU, Brno; ² IKK, FN Brno, Brno; ³ IKK, FN Brno and 3. LF UK, Praha

Introduction: One of the possible complications after drug eluting stent (DES) implantation is in-stent restenosis (ISR). There are two main recommended treatment methods – using a drug-eluting balloon (DEB) or implantation of another DES. Our aim was to compare long-term outcome of the patients with ISR according to the method used.

Sample and methodology: Monocentric retrospective data analysis. Between 2013 and 2018, there were 116 consecutive patients with ISR in previously implanted DES. One of two recommended treatment methods was used – either another DES implantation or a drug-eluting balloon dilatation (DEB). The first group of 71 patients was treated with an implantation of another DES (DES+) and the second group of 45 patients was treated with DEB (DEB+). The primary endpoint was composite of cardiovascular (CV) mortality, rehospitalization for CV related diagnosis, and target lesion revascularization (TLR) in more than 3 years follow-up period.

Results: In a follow-up period, no significant difference was found between DES+ a DEB+ group in composite endpoint (27 [38% of DES+ group] vs. 18 [40% of DEB+ group]; p -value = 0,885), nor in a relative frequency of and individual events.

Conclusion: Only few randomized trials have focused on DES-ISR. We present real-life data with a long follow-up of events. Despite the follow-up period length, statistical significance of events difference wasn't found. Hypothetically, using intravascular imaging (IVI) to get more information about ISR (its nature, plaque burden, tissue characteristics, possible mechanical problem in original stent) might be helpful for treatment and decision making. However, routine use of IVI in ISR therapy needs to be verified by larger randomized trial.

■ TRANSOESOPHAGEAL ECHOCARDIOGRAPHY FINDINGS IN YOUNG PATIENTS WITH CRYPTOGENIC ISCHEMIC STROKE

Hutrya M¹, Šaňák D², Král M², Přeček J³, Čecháková E⁴, Köcher M⁴, Veverka T², Tüdös Z⁵, Táborský M³

¹ I. interní klinika – kardiologická, Fakultní nemocnice Olomouc, Olomouc; ² Neurologická klinika, Fakultní nemocnice Olomouc, Olomouc;

³ I. interní klinika – klinika kardiologie; ⁴ Radiologická klinika, Fakultní nemocnice Olomouc, Olomouc; ⁵ Radiologická klinika, Fakultní nemocnice Olomouc

Background and purpose: The cause of ischemic stroke (IS) remains often unclear in young patients. Relevant structural heart abnormalities with known embolic potential may represent cause of IS also in young population. The use of transesophageal echocardiography (TEE) allows reliable detection of most relevant structural pathologies. The aim was to assess frequency and spectrum of relevant cardiac abnormalities in young IS patients.

Subjects and methods: The study set consisted of young acute IS patients <50 years enrolled in the prospective HISTORY (Heart and Ischemic STroke Relationship study) study, registered on ClinicalTrials.gov NCT01541163. In all patients, the brain ischemia was confirmed on CT or MRI. Admission ECG, serum specific cardiocarkers, TEE, 24-hour and 3-week ECG-Holter were performed in all patients.

Results: Out of 1284 patients enrolled in the HISTORY study, 135 (73 males, mean age 40.2±8.1 years) were <40 years. The relevant TEE abnormalities were present in 47 (35%) of these patients. Patent foramen ovale (PFO) with evident left to right shunt was detected in 38 (28%) patients, with significant right to left shunt in 25 (19%) patients, and other atrial septal defect with clinically significant bidirectional flow in 4 (3%) patients. Significant valvular heart disease was present in 2 (1%) patients (1 bicuspid aortic valve with moderate aortic regurgitation, 1 chronic severe mitral regurgitation), and 4 (3%) patients severe left ventricular (LV) systolic dysfunction (LVEF ≤35%) due to idiopathic dilated cardiomyopathy. Left atrial myxoma was detected in 1 patient.

Conclusion: The relevant structural abnormalities with embolic potential were detected using TEE in 35% of young IS patients. Routine use of TEE to elucidate the causes of IS, has a role especially in young patients who present with IS and no cardiovascular risk factors.

■ A SINGLE CENTRE PROSPECTIVE STUDY COMPARING THE 0/1H AND 0/3H RULE OUT/RULE IN ALGORITHMS FOR MYOCARDIAL INFARCTION IN REAL CLINICAL PRACTICE OF UNIVERSITY HOSPITAL EMERGENCY DEPARTMENT

Jakubo V¹, Lokaj P¹, Šimáčková H², Křivanová A³, Doleček M⁴, Beňovská M⁵, Kala P¹, Pařenica J¹

¹ Interní kardiologická klinika, Fakultní nemocnice Brno a Lékařská fakulta Masarykovy univerzity, Brno; ² Klinika interní, geriatry a praktického lékařství, Fakultní nemocnice Brno a Lékařská fakulta Masarykovy univerzity, Brno; ³ Interní hematologická klinika, Fakultní nemocnice Brno a Lékařská fakulta Masarykovy univerzity, Brno; ⁴ Klinika anesteziologie, resuscitace a intenzivní

medicíny, Fakultní nemocnice Brno
a Lékařská fakulta Masarykovy univerzity,
Brno; ⁵ Ústav laboratorní medicíny – Oddělení
klinické biochemie, Fakultní nemocnice Brno, Brno

Background: High-sensitivity cardiac troponin (hs-cTn) is a key biomarker used in the assessment of patients presenting with chest pain. The European Society of Cardiology (ESC) recently changed recommendations in favor of using the ESC 0/1 h instead of the ESC 0/3 h algorithm if a hs-cTn assay with a validated algorithm is available.

Aim: To evaluate the diagnostic performance of both ESC rapid rule out/rule in algorithms in real clinical practice.

Methods and results: We prospectively enrolled 672 patients presenting with symptoms of acute coronary syndrome without ST elevation to the emergency room of the university hospital. Safety was compared using the negative predictive value (NPV) for the rule-out group, and accuracy using the positive predictive value (PPV) for the rule-in group. The final diagnosis was decided by 2 independent cardiologists using all available information, including cardiac catheterization and non-invasive imaging. Patients were contacted 3 months after discharge by telephone calls. Among 672 patients AMI was the final diagnosis in 152 (21%). NPV for rule-out was higher in 0/1h algorithm (99.5%) than in 0/3h algorithm (98.9%). PPV was comparable between both algorithms (60.4% versus 60.3%). No death occurred in the rule-out group during three months of follow-up.

Conclusion: Both 0/1h and 0/3h algorithms were comparable in diagnostic accuracy for rule-in. The 0/1h algorithm in our study was revealed to be safer than the 0/3h algorithm.

21 YEARS FOLLOW-UP OF LIVER FUNCTION IN PATIENTS AFTER FONTAN OPERATION

Jičínská D¹, Materna O¹, Antonová P², Koubský K¹,
Jičínský M¹, Štefánek M³, Janoušek J¹,
Chaloupecký V¹

¹ Dětské kardiocentrum, Fakultní nemocnice v Motole, Praha; ² Klinika kardiovaskulární chirurgie, Fakultní nemocnice v Motole, Praha; ³ Klinika zobrazovacích metod, Fakultní nemocnice v Motole, Praha

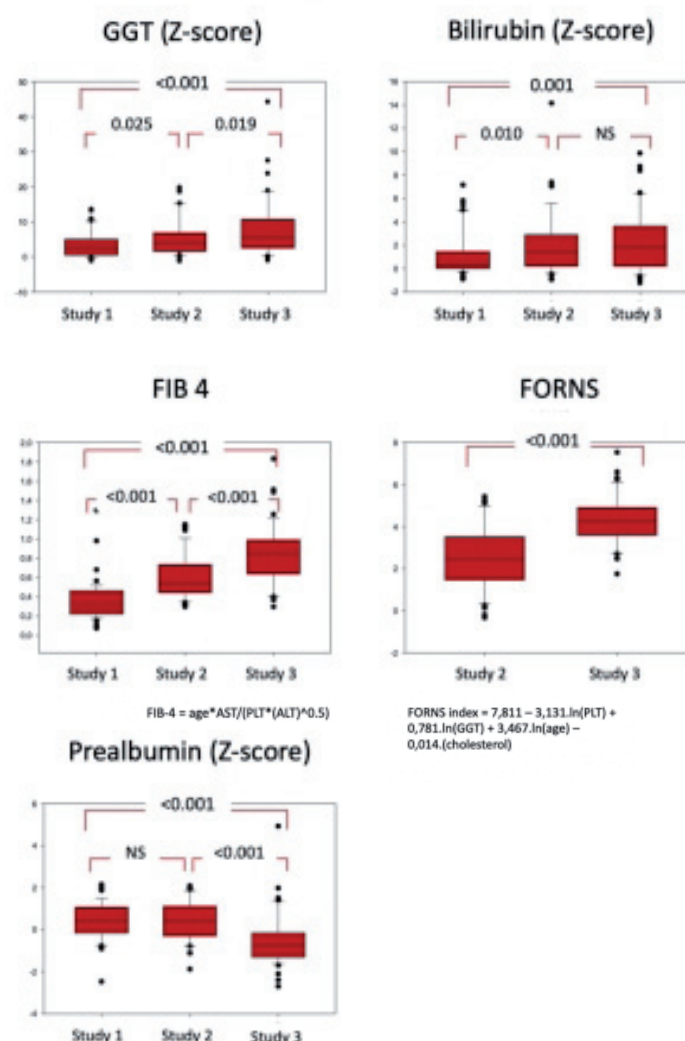
Introduction: Fontan circulation is associated with suboptimal outcome due to chronic venous congestion. The aim of this longitudinal study was to analyze the influence of long-term venous congestion on liver function in patients with univentricular circulation after total cavopulmonary connection (TCPC).

Methods: 47 patients (22 women) who underwent TCPC at median (IQR) age of 4 (3–6) years were repeatedly examined during subsequent follow-up Studies

1–3 at 5 (3–6), 13 (11–14) and 21 (20–22) years after TCPC, respectively. Cardiac function was semiquantitatively evaluated by echocardiography, liver function was examined by a panel of biochemical and hematological tests. Moreover, liver elastography, enhanced liver fibrosis test (ELF) and quality of life were evaluated in Study 3.

Results: Progressive impairment of liver function was found between the Studies. There was a significant increase in levels of gamma glutamyl transferase ($p < 0.001$), bilirubin ($p = 0.001$), the FIB-4 ($p < 0.001$) and Forns index ($p < 0.001$); and decrease in levels of prealbumin ($p < 0.001$). In Study 3 abnormal ELF score (> 7.7) was found in 95% of patients and abnormal elastography (> 7.2 kPa) in all subjects. Good systolic ventricular function was present in 83% subjects. 17% of patients rated their health as excellent, 51% as very good, 23% as good, 9% as fair and none as poor. There was no correlation between the liver tests and ventricular function nor the subjective quality of life.

Conclusion: Progressive impairment of liver function occurs during long-term follow-up majority of patients after TCPC despite preserved single ventricle function and good quality of life.





■ LONG-TERM CARDIOVASCULAR OUTCOME IN PATIENTS AFTER PPCI FOR STEMI. WHAT IS THE RISK PROFILE FOR CARDIOVASCULAR MORTALITY?

Klančík V¹, Pešl L², Neuberg M³, Toušek P⁴, Kočka V⁴

¹ Third Faculty of Medicine, Charles University, Prague, Hospital České Budějovice, a.s., Department of Cardiology, České Budějovice; ² Department of Cardiology, Hospital České Budějovice, a.s., České Budějovice; ³ Partner of INTERCARDIS Project, Medtronic Czechia, Praha; ⁴ Department of Cardiology, University Hospital Královské Vinohrady, Praha

Background: Long-term cardiovascular mortality (CM) after primary percutaneous coronary intervention (pPCI) for ST-elevation myocardial infarction (STEMI) is poorly evaluated.

Methods: Retrospective, academic, two-centre analysis of all consecutive patients presenting with acute STEMI from March 2008 to December 2019. 5263 patients were evaluated. Cardiovascular risk factors and comorbidities were evaluated using medical histories obtained at the initial presentation. Patients were followed-up up for 12 years after STEMI. Mortality data was acquired from the State Institute of Health Information and Statistics of the Czech Republic.

Results: The mean follow-up duration was 5.1 years and the mean age at presentation was 63.9 years. Men were presented in 70.7%. The mortality associated with cardiovascular diseases was approx. 65%. Myocardial infarction (MI) was the cause of death in 27.2% of cases. Patients with CM were significantly older (73.7 years) opposite to remaining patients (61.9 years). CM was significantly higher in women opposite to men (24.3% to 14.3%) and women were significantly older (77.2 to 71.2 years). The most often cause of death was coronary heart disease and heart failure, strokes and pulmonary embolism were in the minority. According to the univariate analysis of CM, risk factors for adverse cardiovascular outcome were identified as age, sex, arterial hypertension, stroke, renal insufficiency, diabetes mellitus, MI, heart failure, active smoking, Killip class, STEMI localization, single- or multi-vessel disease, pPCI success and left ventricle ejection fraction. The strongest predictors were renal insufficiency and stroke.

Conclusion: CM was the leading cause of death in the 5-year outcome after pPCI. Focus on the compensation of identified risk factors could be a suitable way to reduce cardiovascular morbidity and mortality.

■ RETROSPECTIVE COMPARISON OF AORTIC VALVE ANNULUS EVALUATION IN PATIENTS WITH SEVERE AORTIC STENOSIS IN PATIENTS PLANNED FOR TAVI PROCEDURE

Kmoníček P, Mates M, Kopřiva K, Mráz T, Holý F

Kardiologické oddělení, Nemocnice Na Homolce, Praha

Aim of study: To compare aortic annulus evaluation using echocardiography 2D or 3D reconstruction versus MDCT examination using dedicated 3 mensio software.

Cohort and methods: We examined 55 patients (28 female, 27 male) aged 53–95 years who were scheduled for TAVI procedure on behalf of severe aortic stenosis diagnosed before. All patients were interrogated by TEE and most of them with TOE using i33 Philips echocardiographic equipment and with Siemens Somatom Definition Flash MDCT hardware. We compared results of aortic annulus diameter calculated from aortic annuli perimeter measurement and determination of aortic annular eccentricity index defined as 1-Dmin/Dmax. Values >0.25 were considered significant as a risk factor for residual postprocedural aortic regurgitation after TAVI.

Results: Aortic annulus diameter obtained from 2D echocardiography were on average 1.6±1.98 mm smaller in comparison to MDCT measurement using 3 mensio dedicated software. Values of aortic annulus eccentricity index were significantly underestimated when we compared 3D echocardiography reconstruction on average by 0.13±0.068. Using 3D reconstruction no severe eccentricity index was reached – MDCT results were from this point of view different

Conclusion: 2D echocardiography underestimated results of aortic annulus size in comparison with MDCT examination with dedicated, when software 3 mensio was used. 3D TOE significantly underestimates annular eccentricity index calculation in patients with severe aortic stenosis.

■ FFR VERSUS IFR IN ASSESSMENT OF LESION HEMODYNAMIC SIGNIFICANCE AND EXPLANATION OF THEIR DISCREPANCIES. INTERNATIONAL, MULTICENTER AND PROSPECTIVE TRIAL – THE FIGARO STUDY.

Kovárník T, Matsuo H, Jeřábek Š, Král A, Zemánek D, Branny M, Kala P, Mates M, Mrozek J, Linhart A

II. interní klinika, VFN Praha, Praha

Background: Prospective registry of FFR/iFR discrepancy.

Methods: FR/iFR were analyzed using a Verrata wire, and coronary flow reserve (CFR) was analyzed using a Comomap machine (both Philips-Volcano). The risk polymorphisms for endothelial nitric oxide synthase (ENOS), and for hemoxygenase-1 (HO-1) were analyzed.

Results: In total, 1884 FFR/iFR measurements from 1564 patients were included. The FFR/iFR discrepancy occurred in 393 measurements (20.9%): FFRp (positive) / iFRn (negative) type (264 lesions, 14.0%), and FFRn/iFRp (129 lesions, 6.8%) type. CFR was measured in 343 lesions, correlating better with iFR ($R = 0.56$, $p < 0.0001$) than FFR ($R = 0.36$, $p < 0.0001$). The CFR value in FFRp/iFRn lesions (2.24 ± 0.7) was significantly higher compared to both FFRp/iFRp (1.39 ± 0.36), and FFRn/iFRn lesions (1.8 ± 0.64 , $p < 0.0001$).

Multivariable logistic regression analysis confirmed: 1. sex, age, and lesion location in the right coronary artery as predictors for FFRp/iFRn discrepancy; 2. hemoglobin level, smoking, and renal insufficiency as predictors for FFRn/iFRp discrepancy.

The FFRn/iFRp type of discrepancy was significantly more frequent in patients with both risk type of polymorphisms (ENOSr+HO-1r): 8 patients (24.2%) compared to FFRp/iFRn type of discrepancy: 2 patients (5.9%), $p = 0.03$.

Conclusions: Predictors for FFRp/iFRn discrepancy were sex, age, and location in the right coronary artery. Predictors for FFRn/iFRp were hemoglobin level, smoking, and renal insufficiency. The risk type of polymorphism in *ENOS* and *HO-1* genes was more frequently found in patients with FFRn/iFRp type of discrepancy.

LV SIZE NEEDS TO BE INCORPORATED IN LV FUNCTION ASSESSMENT IN HFrEF PATIENTS

Kroupová K¹, Wohlfahrt P², Kotrč M¹, Melenovský V¹, Kautzner J¹, Beneš J¹

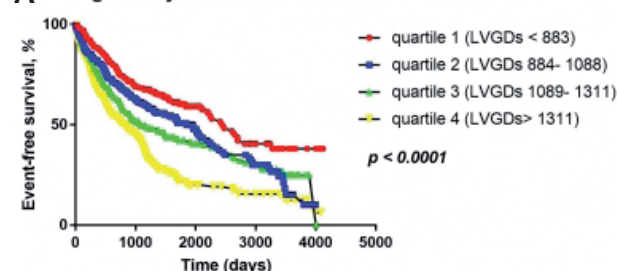
¹ Klinika kardiologie, IKEM, Praha; ² Centrum kardiovaskulární prevence, Fakultní Thomayerova nemocnice, Praha

Background: Left ventricular (LV) size is associated with outcome in HFrEF patients, but neglected in the assessment of LV performance. We have aimed to develop and test the new parameter integrating the information about both LV function and size.

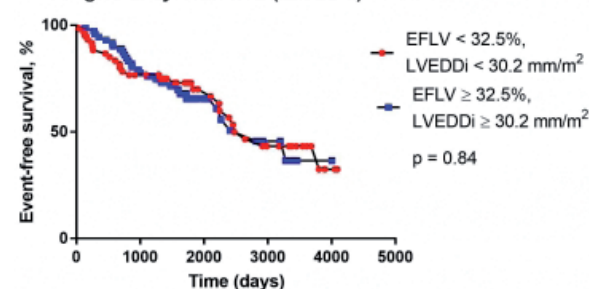
Methods and results: A group of 844 stable patients with advanced HFrEF (57.9±11.3 years, 67.9% NYHA III/IV, LVEF 23.6±5.8) underwent an echocardiographic evaluation and were prospectively followed for a median of 1110 days (IQRs 407, 1780 days) for the occurrence of an adverse outcome (death, urgent heart transplantation or mechanical circulatory support implantation) that was observed in 512 patients (60.7%). LV size (LV-end-diastolic diameter indexed for body size, LVEDDi) was associated with adverse outcome even when adjusted for LV ejection fraction (HR 1.04, 95% CI 1.02–1.06, $p = 0.0001$). In order to integrate LV size and function into one score parameter, we have developed a parameter called missing LV-ejection fraction (calculated as 55% LVEF) and LV-global dysfunction score (LVGDs), defined as missing EF times LVEDDi. LVGDs showed a superior prognostic role compared to LVEF ($\Delta AUC \geq 2.2$ in four defined time points, $p < 0.05$). When subdivided into quartiles according to LVGDs, in each quartile patients with better LVEF but more dilated LV had similar outcome as those with worse LVEF but smaller LV size ($p > 0.23$).

Conclusion: LV dilatation is a manifestation of LV dysfunction in HFrEF patients. Integrating both LV size and LVEF into one parameter provides more accurate information about the degree of LV disease and prognosis.

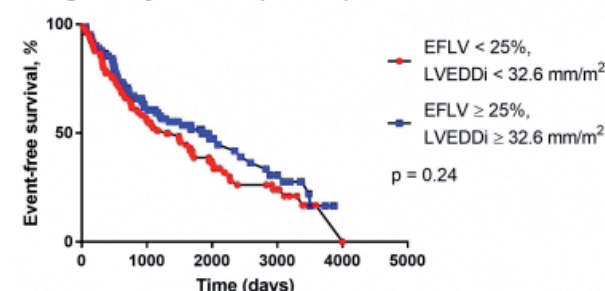
A LV global dysfunction and outcome



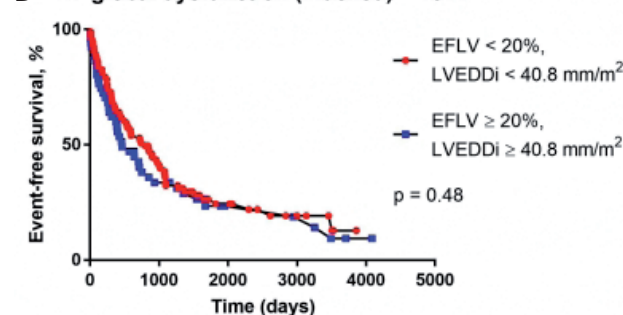
B LV global dysfunction (indexed) < 883



C LV global dysfunction (indexed) 883-1088



D LV global dysfunction (indexed) > 1311



CATHETER THROMBECTOMY FOR ACUTE ISCHEMIC STROKE IN CARDIOLOGY CATH LAB: 10-YEAR RESULTS

Křeček J¹, Kučera D¹, Kožnar B¹, Sulženko J¹, Widimský P¹, Štětkářová I², Peisker T², Vaško P²

¹ Kardiologická klinika, Fakultní nemocnice Královské Vinohrady, Praha; ² Neurologická klinika, Fakultní nemocnice Královské Vinohrady, Praha



Background and aim: Acute ischemic stroke is a devastating disease with high mortality and frequent permanent severe functional disability. Catheter thrombectomy is traditionally performed in neuroradiology centers; however, they are not widely available and thus unable to meet the population needs. This study investigated whether this gap can be filled by involving interventional cardiologists.

Methods: Study was initiated in 2012 as a prospective single arm study testing these questions: Whether catheter thrombectomy can be performed safely and effectively in cardiology Cath Lab and achieve results comparable to neuroradiology centers, whether direct thrombectomy can be an alternative to bridging thrombolysis followed by thrombectomy. Additional question was added to the protocol in 2018: What are the outcomes of patients in whom thrombectomy is done between 6–24 hours after stroke onset.

Inclusion criteria: NIHSS ≥ 6 , < 6 (24) h from symptoms onset.

Exclusion criteria: Inability to start intervention within 60 minutes after hospital arrival, intracranial bleeding, any chronic severe disease limiting prognosis.

Results: Between October 2012 and May 2022, a total of 507 patients with moderate-to-severe acute ischemic stroke were enrolled. Table contains main results. Other observations included: short learning curve for experienced interventional cardiologists, worse outcomes of posterior circulation strokes, high number of rehospitalizations (most related to concomitant diseases, not to the treated stroke).

Conclusion: Catheter thrombectomy in cardiology Cath Lab is feasible and safe and may achieve results similar to those of neuroradiology centers. Direct thrombectomy offers results comparable to bridging thrombolysis followed by thrombectomy. Cardiologists should be involved in stroke teams to provide treatment to broad patient populations.

Endpoint	Rate	Comparable data from HERMES metaanalysis
Primary endpoint (mRs 0–2 at 90 days, i.e. functional neurologic independence after stroke) in the entire cohort	47%	N.A.
Primary endpoint among patients with anterior stroke (n = 421)	48.9%	46%
Complete neurologic recovery (mRs = 0)	20%	10
7-day all-cause mortality	16.6%	N.A.
3-month all-cause mortality	31.2%	15.3%
Symptomatic intracranial hemorrhage	6.5%	4.4%
Distal embolization to another territory with clinical impairment	3.7%	N.A.
Arterial dissection or perforation	3.7%	N.A.
Long-term follow-up	997 $\pm$ 571 days	N.A.
Mean number of rehospitalizations per patient during follow-up	3 $\pm$ 3.3	N.A.

■ BIOMECHANICAL RUPTURE RISK ASSESSMENT IN MANAGEMENT OF PATIENTS WITH ABDOMINAL AORTIC ANEURYSM IN COVID-19 PANDEMIC

Kubiček L¹, Vitásek R², Schwarz D², Staffa R¹, Polzer S²

¹ II. chirurgická klinika, Centrum cévních onemocnění, FN u sv. Anny v Brně, Brno; ² Katedra aplikované mechaniky, VŠB – Technická univerzita Ostrava, Ostrava

Background: The acute phase of the COVID-19 pandemic requires a redefinition of healthcare system to increase the number of available intensive care units for COVID-19 patients. This leads to the postponing of elective surgeries including the treatment of abdominal aortic aneurysm (AAA). The probabilistic rupture risk index (PRRI) recently showed in another experimental project its advantage over the diameter criterion in AAA rupture risk assessment. Its major improvement is in increased specificity and yet has the same sensitivity as the maximal diameter criterion. The objective of this study was to test the clinical applicability of the PRRI method in a quasi-prospective patient cohort study.

Methods: Nineteen patients (14 males, 5 females) with intact AAA who were postponed due to COVID-19 pandemic were included in this study. The PRRI was calculated at the baseline via Finite Element Method models. If a case was diagnosed as high risk (PRRI $> 3\%$), patient was offered priority in AAA intervention. Cases were followed until September 10th 2021 and a number of false positive and false negative cases were recorded.

Results: Each case was assessed within 3 days. Priority in intervention was offered to two patients with high PRRI. There were 4 false positive (higher PRRI value without consequent AAA rupture) cases and no false negative (low PRRI value with consequent AAA rupture) cases classified by PRRI. In three cases, the follow up was too short to make any conclusion.

Conclusion: Integrating PRRI into clinical workflow is technically and logistically possible. Longitudinal validation of PRRI showed auspicious results and it may lead to more precise diagnostic evaluation in comparison to maximal diameter criterion and subsequent personalization of therapeutic approach to patients with AAA.

■ LONG-TERM CLINICAL OUTCOMES AND LEFT VENTRICULAR REVERSE REMODELING IN PATIENTS WITH RECENTLY DIAGNOSED UNEXPLAINED DILATED CARDIOMYOPATHY

Kuchynka P¹, Podzimeková J¹, Marek J¹, Daněk B², Vítková I³, Kreidlová M⁴, Roblová L¹, Kovárník T¹, Linhart A¹, Paleček T¹

¹ First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague,



2nd Department of Medicine – Department of Cardiovascular Medicine, Praha; ² University of Washington Medical Center, Division of Cardiology, Seattle, United States; ³ First Faculty of Medicine, Charles University and General University Hospital in Prague, Institute of Pathology, Praha; ⁴ First Faculty of Medicine, Charles University and General University Hospital in Prague, Institute of Medical Biochemistry and Laboratory Diagnostics, Praha

Background: Left ventricular reverse remodeling (LVRR) and favorable prognosis of patients with recently diagnosed dilated cardiomyopathy (DCM) have been documented in studies with short-term follow-up. The aim of our study was to assess the long-term clinical course and stability of LVRR in these patients.

Methods: We prospectively studied 133 patients with recently diagnosed unexplained DCM, with heart failure symptoms lasting < 6 months and LV ejection fraction <40% persisting after at least one week of therapy. All had endomyocardial biopsy (EMB) at the time of diagnosis and serial echocardiographic and clinical follow-up over five years.

Results: LVRR was observed in 46% patients at one year, in 60% at two years and 50% at five years. Additionally, 2% of patients underwent heart transplantation and 12% experienced heart failure hospitalization. In multivariate analysis, baseline right atrial size, BNP level, and PR interval were independently associated with mortality ($p < 0.05$ for all). The number of macrophages in EMB was associated with overall survival in univariate analysis only. LVRR at one year of follow-up was associated with lower rate of mortality and heart failure hospitalization ($p = 0.025$).

Conclusions: LVRR occurs in over half of patients with recent onset unexplained DCM during first two years of optimally guided heart failure therapy and then remains relatively stable during five-year follow-up. The reversion of the process of adverse LV remodeling corresponds to a low rate of mortality and heart failure hospitalizations during long-term follow-up.

■ THE SECURE STUDY, A TRIAL WITH SIGNIFICANT CONTRIBUTION FROM THE CZECH REPUBLIC

Lubanda J, Linhart A

II. interní klinika kardiologie a angiologie,
Všeobecná fakultní nemocnice a 1. LF UK, Praha

Backgrounds: A polypill with key medications associated with improved outcomes (aspirin, ACE inhibitor, and statin) has been proposed as a simple approach to the secondary prevention of cardiovascular (CV) death and complications after myocardial infarction (MI). This strategy was tested in the SECURE trial which results were recently presented. The Czech Republic was a part of the consortium of 11 European research institutions conducting the trial.

Methods: Patients with MI within the previous 6 months were assigned to a polypill-based strategy or usual care. The polypill arm consisted of aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg). The primary composite outcome was CV death, nonfatal type 1 MI, nonfatal ischemic stroke, or urgent revascularization. The secondary endpoint was a composite of previous except urgent revascularization.

Results: 2499 patients were followed for a median of 36 months. The Czech Republic enrolled 174 subjects in the trial from 9 participating centers. A primary-outcome event occurred in 118 of 1237 patients (9.5%) in the polypill group and in 156 of 1229 patients (12.7%) in the usual-care group (HR, 0.76; 95% CI; $p = 0.02$). The secondary-outcome occurred in 8.2% in the polypill group and 11.7% in the usual-care group (HR, 0.70; 95% CI, $p = 0.005$). Medication adherence was higher in the polypill group. Comparison of the Czech cohort to other countries did not show significant difference in all prespecified outcomes.

Conclusions: Treatment with a polypill after MI resulted in a significantly lower risk of major adverse CV events. We are happy that the Czech Republic was an active part of this trial and was able to significantly contribute to its positive results.

Ref.: Castellano JM et al. Polypill Strategy in Secondary Cardiovascular Prevention. *N Engl J Med* 2022;387:967–977.

■ IN VITRO ASSESSMENT OF ANTI-INFLAMMATORY AND CYTOTOXICITY PROPERTIES OF COLCHICINE

Malý M¹, Viktorová J², Strnad O², Ruml T²,
Stránská M³

¹ Interní klinika – Kardiologické oddělení,
Ústřední vojenská nemocnice – Vojenská
fakultní nemocnice, Praha; ² Ústav biochemie
a mikrobiologie, Vysoká škola chemicko-
technologická Praha; ³ Ústav analýzy potravin
a výživy, Vysoká škola chemicko-technologická,
Praha

Inflammation plays a substantial role in the process of atherosclerosis. The key players are monocytes transformed to macrophages and coronary artery endothelial cells. Limited anti-inflammatory drugs are currently available – antibodies for IL-1 (CANTOS) and colchicine (COLCOT, LoDoCo-2 trial). Here, we describe the molecular mechanism of colchicine downregulation of inflammation processes in connection to its cytotoxic effects on treated cells.

Human coronary artery endothelial cells (HCAEC) were polarized toward M1 pro-inflammatory phenotype responsible for production of IL-6. The production of IL-6 was negated by addition of colchicine in dose-dependent manner. 13.4 ± 0.8 mg/L of colchicine decreased the production of IL-6 by 50% in HCAEC cells.

Similarly, human monocytic cell line THP-1 was differentiated into macrophages by incubation in the pres-



ence of phorbol-12-myristate-13-acetate, which leads to a macrophage-like phenotype characterized by changes in morphology and adhesion. In concentrations higher than 7.5 mg/L, colchicine significantly increased the production of TNF α and IL-6 indicating induction of stress conditions and production of inflammatory markers by macrophages.

Colchicine did not show direct cytotoxicity against HCAEC or THP-1 (24h treatment) even at the highest tested concentration of 100 mg/L, but induced the expression of nephrotoxic markers in human renal tubular epithelial kidney cells.

In summary, our in vitro results show the potential of colchicine to reduce inflammation in coronary artery endothelial cells, but at the same dose, colchicine induces stress conditions and an inflammatory environment in monocytes. At the same time, it is necessary to draw attention to the nephrotoxic effects of colchicine.

■ ROLE OF MYOCARDIAL DEFORMATION ANALYZED BY 3D ECHOCARDIOGRAPHY IN FABRY DISEASE

Marek J, Rob D, Dostálová G, Kuchynka P, Hlubocká Z, Chocholová B, Linhart A

II. interní klinika – klinika kardiologie a angiologie, Všeobecná fakultní nemocnice Praha, Praha

Introduction: Fabry disease is a multisystemic lysosomal storage disorder caused by a defect in the gene coding the alpha-galactosidase A enzyme. Cardiac involvement typically manifests as a phenocopy of hypertrophic cardiomyopathy. Three-dimensional echocardiography can analyze myocardial deformation of the LV in both circumferential and longitudinal dimensions. Our goal was to assess the role of 3D deformation in relation to heart failure severity and long-term prognosis.

Methods: We analyzed data from 75 patients. 3D echocardiography was acquired using GE Vivid 9 and E95 machines. Death and all-cause cardiovascular hospitalizations over a median follow-up of 3.1 years were assessed.

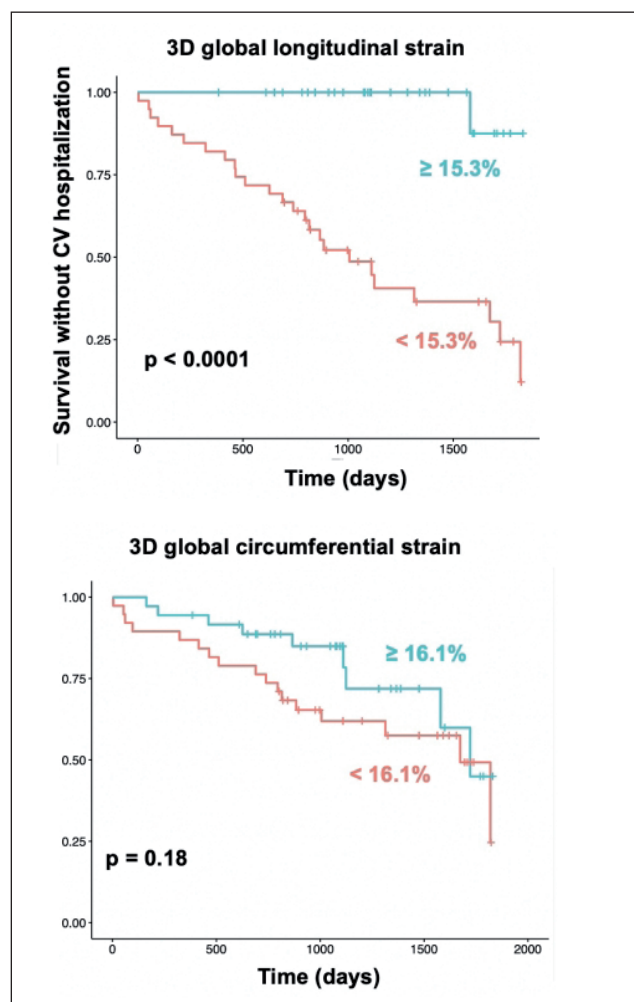
Results: Average age was 47 $\pm$ 14 years and 44% of patients were male. Overall, 51% of patients had hypertrophy or concentric remodeling of the LV. Average EF was 65 $\pm$ 6% and two patients had EF <50%. Average value of 3D GLS and GCS was 15 $\pm$ 5 % and 16 $\pm$ 4%, respectively.

A stronger correlation was observed for NT-proBNP with 3D GLS ($r = 0.49$, $p < 0.0001$) while correlation with 3D GCS was also significant, but weaker ($r = 0.38$, $p < 0.001$). Ejection fraction by 3D was weakly correlated with NT-proBNP ($r = 0.25$, $p = 0.036$).

In the long-term follow-up, 3D GLS was significantly associated with long-term outcome (HR 0.79, CI 0.72–0.87, $p < 0.0001$, log rank $p < 0.0001$) while 3D GCS was borderline associated and only as a continuous variable (HR 0.87, CI 0.77–0.98, $p = 0.0183$, log rank $p = 0.18$). 3D EF was not associated with long-term outcome ($p = 0.42$ and 0.92).

Conclusion: 3D GLS was strongly associated with HF severity measured by natriuretic peptides and long-term prog-

nosis. Only borderline association of 3D GCS and no association of EF with prognosis was observed. Longitudinal deformation analysis remains important for assessment of LV function in Fabry disease.



■ ABSENCE OF HEART RATE VARIABILITY CHANGE DURING FOLLOW-UP AFTER COVID-19 DOESN'T SUGGEST DIRECT CARDIOVASCULAR IMPACT

Matejová G¹, Radvan M², Kala P², Kameník M¹, Koc L¹

¹ Interní kardiologická klinika, Fakultní nemocnice Brno, Brno; ² Fakultní nemocnice Brno

Objective: To evaluate the need for cardiac monitoring of unselected patients recovered from COVID-19 and to estimate the risk of development of arrhythmias after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Results: Presence of significant pathology detected was rare (one paroxysmal atrial fibrillation in 73-year-old woman with dilated left atrium; 71-year-old man

with atrioventricular blockade with indication for implantation of the pacemaker, when cardiac MRI didn't find any signs of myocardial inflammation. After evaluation both were not related to previous SARS-CoV-2 infection.

During one-year follow-up after COVID-19 infection there was no change in heart rate variability evaluated by SDNN (V_1 vs V_3 156.6±40.6 vs 156.0±38.0; $p = 0.855$), rMSSD (V_1 : 33±13.95 to 30.6±12.89; $p = 0.175$) and triangle (V_1 : 28.5±7.8 to 29.5±8.8; $p = 0.488$). Dividing heart rate oscillations into low-frequency (LF), and high-frequency (HF) bands, we have found statistically significant changes between V_1 a V_3 for LF (718±433.7 to 646±361; $p = 0.024$) and HF (341.5±335 to 268.0±266; $p = 0.032$). These parameters are mostly affected by breathing rate and are representing possible autonomic dysregulation (HF/LF ratio).

Conclusion: Despite many information regarding cardiac impairment of SARS-CoV2 our study does not suggest an increased risk of development of arrhythmias after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) even in a population with high proportion of ongoing symptomatology. Some findings may suggest autonomic dysfunction after COVID-19. Based on our results the routine ECG monitoring is currently not recommended after COVID-19 recovery.

■ TUMOR NECROSIS FACTOR-RELATED APOPTOSIS-INDUCING LIGAND (TRAIL) IS ASSOCIATED WITH CARDIAC INJURY AND STROKE SEVERITY IN PATIENTS AFTER ACUTE ISCHEMIC STROKE

Mihalovič M¹, Mikulenka P², Línková H¹, Lauer D², Štětkářová I², Toušek P¹

¹ Kardiocentrum, 3. LF UK, FNKV, Praha;

² Neurologická klinika, 3. LF UK, FNKV, Praha

Stroke is accompanied by pathological disturbances leading to autonomic dysfunction and systemic inflammation. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a protein involved in several pathological conditions including cardiovascular diseases. We aimed to assess TRAIL level dynamic changes and its relation to stroke severity, impact on short-term outcome and association with markers of cardiac injury in patients after acute ischemic stroke (AIS).

In our study 104 patients after AIS were enrolled. Blood samples were obtained from patients at the time of admission, 24 and 48 hours later to determine level of TRAIL, NT-proBNP, and hs-TnI. Twelve lead ECG at admission, 24, 48 hours later were obtained. Neurological examination including NIHSS at admission and modified Rankin Scale (mRS) at 90 days following the patient's discharge from the hospital were performed.

In the results we observed association between lower TRAIL and NT-proBNP elevation at admission, after 24 and 48 hours of hospitalization and there was negative

association between TRAIL and hs-cTnI at admission. Moreover, we observed a connection between lower TRAIL and stroke severity evaluated by NIHSS on first day. Lower TRAIL showed significant association with severe disability and death evaluated by mRS at 90 days both after 24 and 48 hours of hospitalization. Lower TRAIL was associated with the occurrence of PVCs and prolonged QTc interval.

Our study showed that lower TRAIL is associated with stroke severity, unfavorable functional outcome and short term mortality in patients after acute ischemic stroke. Moreover, we described association with markers of cardiac injury and ECG changes. It is necessary to distinguish whether these abnormalities presenting in stroke patients are caused by coexisting ischemic heart disease or by brain injury directly.

■ ACUTE SEVERE HEART FAILURE IMMEDIATELY REDUCES HEART RATE VARIABILITY: AN EXPERIMENTAL STUDY IN PORCINE MODEL

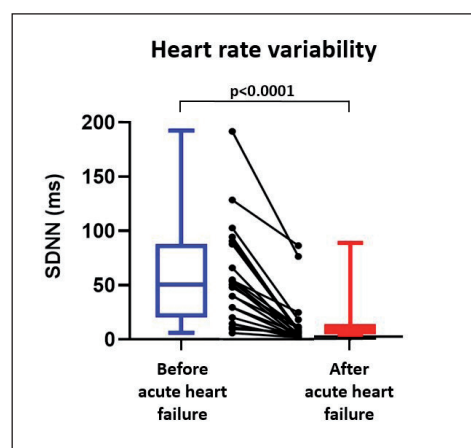
Naar J¹, Mlček M², Krüger A¹, Vondráková D¹, Janotka M¹, Popková M², Kittnar O², Neužil P¹, Ošťádal P¹

¹ Kardiologické oddělení, Nemocnice Na Homolce, Praha; ² Department of Physiology, First Faculty of Medicine, Charles University, Praha

Background: There are substantial differences in autonomic nervous system activation among heart failure (HF) patients and immediate effect of acute HF on autonomic function is not fully understood.

Objective: The aim our study was to assess the effect of experimental acute HF on heart rate variability (HRV).

Materials and methods: Twenty-four female swine of mean body weight 45 kg were used. Acute severe HF was induced by global myocardial hypoxia. In each subject,





two 5-minute electrocardiogram segments were analyzed and compared: before the induction of myocardial hypoxia and >60 min after the development of severe HF. HRV was assessed by time-domain, frequency-domain and nonlinear analytic methods.

Results: Induction of acute HF led to significant decrease in cardiac output, left ventricular ejection fraction and rise in heart rate. Development of acute HF was associated with a significant reduction of standard deviation of intervals between normal beats (50.8 [20.5–88.1] ms vs. 5.9 [2.4–11.7] ms, $p < 0.0001$) – Figure 1. Highly significant a uniform reduction of HRV was observed also in other time-domain and main nonlinear analytic methods. Similarly, frequency-domain HRV parameters were significantly changed.

Conclusion: Acute severe HF induces an immediate reduction in HRV.

■ EXCESS ISCHEMIC TACHYARRHYTHMIAS TRIGGER PROTECTION AGAINST MYOCARDIAL INFARCTION IN HYPERTENSIVE RATS

Neckář J¹, Alánová P¹, Olejníčková V¹, Papoušek F¹, Hrdlička J¹, Hejnová L², Behuliak M³, Šilhavý J⁴, Štengl M⁵, Kolář F¹

¹ Developmental Cardiology, Institute of Physiology, Czech Academy of Sciences, Prague; ² Physiology, Faculty of Science, Charles University, Prague; ³ Experimental Hypertension, Institute of Physiology, Czech Academy of Sciences, Prague; ⁴ Genetics of Model Diseases, Institute of Physiology, Czech Academy of Sciences, Prague; ⁵ Physiology, Faculty of Medicine in Pilsen, Charles University, Pilsen

Increased level of C-reactive protein (CRP) is a risk factor for cardiovascular diseases, including myocardial infarction and hypertension. Here, we analyze the effects of CRP overexpression on cardiac susceptibility to ischemia/reperfusion (I/R) injury in adult spontaneously hypertensive rats (SHR) expressing human CRP transgene (SHR-CRP). Using an in vivo model of coronary artery occlusion, we found that transgenic expression of CRP predisposed SHR-CRP to repeated and prolonged ventricular tachyarrhythmias. Excessive ischemic arrhythmias in SHR-CRP led to a significant reduction of infarct size (IS) compared with SHR. The proarrhythmic phenotype in SHR-CRP was associated with altered heart and plasma eicosanoids, myocardial composition of fatty acids in phospholipids, and autonomic nervous system imbalance before ischemia. To explain unexpected IS-limiting effect in SHR-CRP, we performed metabolomic analysis of plasma before and after ischemia. We also determined cardiac ischemic tolerance in hearts subjected to remote ischemic preconditioning (RIPer) and

in hearts ex vivo. Acute ischemia in SHR-CRP markedly increased plasma levels of multiple potent cardioprotective molecules that could reduce IS at reperfusion. RIPer provided IS-limiting effect in SHR that was comparable with myocardial infarction observed in naïve SHR-CRP. In hearts ex vivo, IS did not differ between the strains, suggesting that extra-cardiac factors play a crucial role in protection. Our study shows that transgenic expression of human CRP predisposes SHR-CRP to excess ischemic ventricular tachyarrhythmias associated with a drop of pump function that triggers myocardial salvage against lethal I/R injury likely mediated by protective substances released to blood from hypoxic organs and tissue at reperfusion.

■ IDENTIFICATION OF PLASMATIC MICRORNAS ASSOCIATED WITH PULMONARY EMBOLISM IN PATIENTS WITH ACUTE-ONSET DYSPNEA – PILOT RESULTS

Novák J¹, Macháček T², Ulrichová L¹, Trachtová K², Souček M¹, Kianička B¹

¹ II. interní klinika, Fakultní nemocnice u svaté Anny v Brně a Lékařská fakulta Masarykovy univerzity, Brno; ² Ondrej Slaby Research Group, Central European Institute of Technology, Masaryk University, Brno

Introduction: Acute-onset dyspnea represents one of the most common reasons for evaluation of the patient at the emergency departments. Differential diagnostics of acute-onset dyspnea requires thorough physical and paraclinical examination. To establish the diagnosis of pulmonary embolism (PE), there is currently no enough sensitive and specific biomarker and diagnosis needs to be confirmed by CT pulmonary angiography (CTPA). Circulating microRNAs (miRNAs, miRs) represents an intriguing group of biomarkers that were shown to be altered between healthy individuals and PE patients. Aim of the current study was to identify miRNAs distinguishing dyspneic patients with and without PE.

Methods: 28 consecutive patients with acute onset dyspnea suspected of having PE based on clinical exam and lab testing were enrolled. Patients underwent CTPA to confirm (n = 17) or exclude (n = 11) PE. Prior CTPA, all patients signed informed consent and then underwent blood sampling into EDTA tubes. Plasma was separated and total RNA was isolated using miRNeasy Serum/Plasma Kit®. Seven samples were used for next-generation sequencing on Illumina NextSeq 550 (n = 4 CTPA-confirmed PE and n = 3 CTPA-excluded PE). Sequencing data were analyzed in R with DESeq2 and EdgeR packages.

Results: 975 miRNAs were identified in the plasmatic samples. Levels of 50 miRNAs were shown to be altered between patients w/o PE (unadjusted p -value < 0.05). Out of



these, five miRNAs presented total number of reads >200 and the fold change >0.5, which makes them potential PE biomarkers: miR-155-5p, -625-3p, -7-5p, -29a-3p, and -361-3p.

Conclusion: We have identified a group of 5 plasmatic miRNAs whose levels differ between patients with acute onset dyspnea with CTPA confirmed or excluded PE. Validation on independent large set of patients is now pending to confirm their potential diagnostic utility.

■ L-LACTATE AND ISCHEMIA-MODIFIED ALBUMIN AS MARKERS OF INTESTINAL ISCHEMIA AFTER ABDOMINAL AORTIC SURGERY

Novotný T¹, Staffa R¹, Tomandl J², Křivka T³, Kříž Z¹, Šponiar J¹

¹ II. chirurgická klinika, Centrum cévních onemocnění, FN u sv. Anny v Brně a LF MU, Brno;

² Biochemický ústav, Lékařská fakulta Masarykovy univerzity, Brno; ³ Klinika zobrazovacích metod, FN u sv. Anny v Brně a LF MU, Brno

Introduction: Postoperative intestinal ischemia (PII) is a severe complication in abdominal aortic surgery. Early diagnosis is needed to commence the treatment while the ischemia is reversible. The aim of the study was to evaluate the diagnostic accuracy of L-lactate and ischemia-modified albumin (IMA) for PII detection.

Methods: We have conducted a prospective non-randomized observational cohort study in eighty patients (62 men and 18 women) with a mean age of 68.0±8.4 years undergoing elective aortic surgery. We took blood samples at precisely defined time points in relation to the surgical procedure. The primary method for intestinal ischemia detection was contrast-enhanced magnetic resonance enterocography.

Results: We recorded six cases of PII (7.5%). Both markers had different postoperative kinetics. L-lactate was the more accurate marker in all clinically relevant postoperative time points. Postoperative kinetics showed that we must always consider the blood sampling time in relation to the procedure for proper interpretation. L-lactate proved the highest accuracy, sensitivity, and negative predictive value 24 hours after the declamping of the reconstruction. However, specificity and positive predictive value were lower. The combination of the most accurate timepoints of both markers led to an increase in specificity and positive predictive value.

Conclusion: Based on our results, the postoperative levels of L-lactate might help to detect PII if proper time points are used. IMA is a worse marker compared to L-lactate. Its value might be in the combination with other markers to improve the accuracy of prediction. Our data must be confirmed in larger studies.

This study was supported by the Ministry of Health of the Czech Republic, grant no. 17-29701A. All rights reserved.

■ STRESS PULMONARY CIRCULATION PARAMETERS IN PATIENTS AFTER A HEART TRANSPLANT AND CANCER SURVIVORS: A CARDIOVASCULAR MAGNETIC RESONANCE STUDY

Opatřil L¹, Panovský R¹, Mojica-Pisciotti M², Máchal J³, Krejčí J⁴, Holeček T⁵, Feitová V⁵, Kincl V¹, Kepák T⁶, Špinarová L⁷

¹ I. interní kardioangiologická klinika, Mezinárodní centrum klinického výzkumu, FN u sv. Anny, Lékařská fakulta Masarykovy univerzity, Brno; ² FN u sv. Anny, Mezinárodní centrum klinického výzkumu, Brno; ³ Ústav patologické fyziologie, Lékařská fakulta Masarykovy univerzity, Brno; ⁴ I. interní kardioangiologická klinika, Lékařská fakulta Masarykovy univerzity, FN u sv. Anny, Brno;

⁵ Klinika zobrazovacích metod, Mezinárodní centrum klinického výzkumu, FN u sv. Anny, Brno;

⁶ FNB, FN u sv. Anny, Masarykova Univerzita, Klinika dětské onkologie, Lékařská fakulta Masarykovy univerzity, Mezinárodní centrum klinického výzkumu, Brno; ⁷ I. interní kardioangiologická klinika FN u sv. Anny, Lékařská fakulta Masarykovy univerzity, Brno

Background: Pulmonary circulation parameters such as pulmonary transit time (PTT), heart rate corrected PTT (PTTc) and pulmonary transit beats (PTB) can be evaluated using several methods, including the first-pass perfusion from cardiovascular magnetic resonance. Up to 58% of patients after HTx have diastolic dysfunction detectable only in stress conditions. By using adenosine stress perfusion images, stress analogues of the mentioned parameters can be assessed. By dividing stress to rest biomarkers, potential new ratio parameters (PTT ratio and PTTc ratio) can be obtained.

The objectives were to provide more evidence about stress pulmonary circulation biomarkers, present stress to rest ratio parameters, and assess these biomarkers in patients with presumed diastolic dysfunction after heart transplant (HTx) and in childhood cancer survivors (CCS) without any signs of diastolic dysfunction.

Methods: In this retrospective study, 48 patients after HTx, divided into subgroups based on echocardiographic signs of diastolic dysfunction (41 without, 7 with) and 39 CCS were enrolled.

Results: PTT in rest conditions were without significant differences when comparing the CCS and HTx subgroup without diastolic dysfunction (4.96±0.93 s vs. 5.51±1.14 s, $p = 0.063$) or with diastolic dysfunction (4.96±0.93 s vs. 6.04±1.13 s, $p = 0.13$). However, in stress conditions, both PTT and PTTc were significantly lower in the CCS group than in the HTx subgroups, (PTT: 3.76±0.78 s vs. 4.82±1.03 s, $p < 0.001$; 5.52±1.56 s, $p = 0.002$). PTT ratio and PTTc ratio were below 1 in all groups.



Conclusions: Stress pulmonary circulation parameters obtained from CMR showed prolonged PTT and PTTc in HTx groups compared to CCS, which corresponds with the presumption of underlying diastolic dysfunction. The ratio parameters were less than 1.

■ EFFECT OF VENOARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION ON LEFT VENTRICULAR FUNCTION IN CARDIOGENIC SHOCK WITH AORTIC STENOSIS OR MITRAL REGURGITATION: AN EXPERIMENTAL STUDY IN PORCINE MODEL

Ošťádal P¹, Vondráková D¹, Popková M², Hrachovina M², Krüger A¹, Janotka M¹, Naar J¹, Kittnar O³, Neužil P¹, Mlček M³

¹ Kardiocentrum, Kardiologické oddělení, Nemocnice Na Homolce, Praha; ² Fyziologický ústav, 1. LF UK;

³ Fyziologický ústav, 1. LF UK, Praha

Background: Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is widely used in the treatment of cardiogenic shock (CS). However, increased VA-ECMO blood flow (EBF) may significantly impair left ventricular (LV) performance. The objective of the present study was to assess the effect of VA-ECMO on LV function in acute CS with concomitant severe aortic stenosis (AS) or mitral regurgitation (MR) in a porcine model.

Methods: Eight female swine underwent VA-ECMO implantation and acute CS was induced by global myocardial hypoxia. Subsequently, severe AS was simulated by obstruction of the aortic valve, while severe MR was induced by mechanical destruction of the mitral valve. LV performance variables were measured at different rates of EBF rates (ranging from 1 to 4 L/min), using LV pressure-volume catheter. Data are expressed as median (interquartile range).

Results: In severe AS, increasing EBF from 1 to 4 L/min was associated with a significant elevation in mean arterial pressure (MAP), from 33.5 (24.2–34.9) to 56.0 (51.9–73.3) mmHg ($p < 0.01$). However, LV volumes (end-diastolic, end-systolic, stroke) remained unchanged, and LV end-diastolic pressure (LVEDP) significantly decreased from 24.9 (21.2–40.0) to 19.1 (15.2–29.0) mmHg ($p < 0.01$). In severe MR, increasing EBF resulted in a significant elevation in MAP from 49.0 (28.0–53.4) to 72.5 (51.4–77.1) mmHg ($p < 0.01$); LV volumes remained stable and LVEDP increased from 17.1 (13.7–19.1) to 20.8 (16.3–25.6) mmHg ($p < 0.01$).

Conclusion: Results of this study indicate that the presence of valvular heart disease may alleviate negative effect of VA-ECMO on LV performance in CS. Severe AS fully protected against LV overload, and partial protection was also detected with severe MR, although at the cost of increased LVEDP and, thus, higher risk for pulmonary edema.

■ CARDIAC TOLERANCE TO ISCHEMIA: DEVELOPMENTAL AND SEX DIFFERENCES

Ošťádal B¹

¹ Oddělení vývojové kardiologie, Fyziologický ústav AVČR, Praha

Keywords: Neonatal heart, female heart, ischemia/reperfusion injury, cardiac ischemic tolerance, mitochondrial permeability transition pore

Age and sex play essential role in the cardiac tolerance to ischemia/reperfusion (I/R) injury: cardiac resistance significantly decreases during postnatal maturation and female heart is more tolerant as compared with the male myocardium.¹ The mechanisms of the high tolerance of the neonatal and female hearts have not yet been satisfactorily clarified. Some recent data indicate that mitochondria could play an important role in this effect. It is widely accepted that mitochondrial dysfunction and particularly mitochondrial permeability transition pore (MPTP) opening plays a major role in determining the extent of cardiac I/R injury. We have observed that the MPTP sensitivity to the calcium load differs in mitochondria isolated from neonatal and adult myocardium as well as from adult male and female hearts. Neonatal and female mitochondria are more resistant both in the extent and in the rate of mitochondrial swelling induced by high calcium concentration. Our data further suggest that age- and sex-dependent specificity of the MPTP is not the result of different amounts of ATP synthase and cyclophilin D (CypD): neonatal and adult hearts, similarly as the male and female hearts contain comparable amount of MPTP and its regulatory protein CypD.^{2,3} We can speculate that the lower sensitivity of MPTP to the calcium induced swelling may be related to the higher ischemic tolerance of both neonatal and female myocardium.⁴

■ HOME BLOOD PRESSURE TELEMONITORING (HBPTM) WITH CONCURRENT MEASUREMENT OF PHYSICAL ACTIVITY COMPARED TO DAYTIME AMBULATORY BLOOD PRESSURE MONITORING (ABPMD) – HOW ARE THE RESULTS OF APPLIED RESEARCH USED?

Peleška J¹, Mužík J¹, Čamek R², Fiala D¹, Doksanský M¹, Hána K³, Vranka J⁴, Doležil D⁴, Jozífová M⁵, Reissigová J⁶

¹ Faculty of Biomedical Engineering, Czech Technical University, Prague; ² Cardiology Clinic, Institute of Preventive and Sports Medicine, Prague, Prague;

³ First Faculty of Medicine, Charles University, Prague; ⁴ Prague Municipal Medical Center, Prague;

⁵ First Faculty of Medicine, Centre of Cardiovascular Prevention, Charles University and Teaching Thomayer Hospital, Prague; ⁶ Institute of Computer Science, Czech Academy of Sciences, Prague



Objective: Despite the comparability of both methods in majority of cases (ESH 2021), physicians do not trust their patients to measure their BP correctly. The aim of this study was to ascertain that the BP measurements (BPM) are consistent and reliable.

Design and method: We enrolled 144 treated patients with essential hypertension aged 24–85 years (60% males) – all considered by their physicians as well controlled. The therapy was not changed during this study.

Mean week cycle systolic BP (SBP) of HBPTM (BP monitor Fora P30+, mobile phone for data transfer) at the beginning and end of 3 months study (triplets of BPM in morning and evening) and mean SBP of ABPMD (SEIVA Tono-Track) were compared. The required 5 minutes of physical inactivity before BPM were checked in by Xiaomi MiBand 2 smart wristbands. BP and HR values were accessible to patients and their physicians on a secure server. The data were evaluated using a linear mixed model.

Results: The values of SBP in both HBPTM and ABPMD remained steady during the trial. The mean SBP of ABPMD was consistently higher by approximately 3 mmHg compared to the mean SBP of HBPTM both at the beginning (134.5 ± 10.6 vs. 130.7 ± 9.4 mmHg) and the end (133.0 ± 11.0 vs. 129.7 ± 10.6 mmHg), $p < 0.001$.

Diani telemedicine system enables recording of all BPM with the marked insufficient rest before BPM, a calculation of week total, morning and evening mean BP with export of logbook in pdf, a day profile with BPM each hour to detect hypotension. It is easy to browse through week cycles of HBPTM, to record patient troubles and therapy changes. The system reports occurrence of arrhythmia by e-mail and voice evaluation of actual BPM.

Conclusions: Our results suggest that HBPTM is comparable to ABPMD. HBPTM is suitable for long-term BP follow-up and is technically sound. Questions around regulations and financing remain to be resolved.

■ DUAL CARDIOMYOCYTE CLUSTER ARRHYTHMIAS DETECTED BY ATOMIC FORCE MICROSCOPY

Rotrekl V¹, Pešl M², Pivato R², Svěrák F³, Kabanov D⁴, Klimovič Š⁴, Stárek Z⁵, Příbyl J⁶

¹ Department of Biology, and SCDM, Faculty of Medicine, Masaryk University, and ICRC, St. Anne's University Hospital, Brno; ² I. interní kardioangiologická klinika a Biologie LF MU a ICE, ICRC, Fakultní nemocnice u sv. Anny, Brno; ³ Biologie, Masarykova univerzita, Brno; ⁴ Nanobiotechnologie, CEITEC MU, Brno; ⁵ I. interní kardioangiologická klinika a ICE, ICRC, Lékařská fakulta, Masarykova univerzita a Fakultní nemocnice u sv. Anny, Brno; ⁶ CEITEC MU, Masarykova univerzita, Brno

Single cardiomyocytes (CMs) present unstable beating patterns, partially compensated in a clustered syncytium. We have proposed and tested a novel biosensor utilizing two clusters of cardiomyocytes for advanced

detection of cardiac arrhythmias and subsequent drug testing.

Methods: hESC's clusters were differentiated into spherical CMs syncytium. Two such spheres were seeded on adherent plates in the vicinity and within four days spontaneously formed electrically connected syncytium resembling the human myocardium and its conductive system. Contraction of twin clustered spontaneously synchronized by day 4. The Atomic Force Microscope (AFM) vertical deflection enabled measurement and calculation of absolute cardiomyocyte contraction force,¹ while lateral force measurement was tracking synchronized or independent contraction behavior of twin clusters.² Caffeine induced arrhythmia as a model drug.³ After its administration subsequent beating patterns were monitored by AFM lateral force recording and calcium fluorescence imaging as a reference method for describing non-synchronized contractions of cardiomyocytes. Caffeine increased the beat rate of the syncytium. This was reflected by both the change in vertical and lateral deflection. A significant increase in standard deviation was observed immediately after caffeine injection for both the lateral and the vertical deflection.

Results: Caffeine affected the synchronization of vertical and lateral displacement of the AFM cantilever, characteristic of independent lateral and vertical deflections, interpreted as defects in signal spreading through the bridge resulting in the irregular beat of the two clusters.

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■ DUCHENNE MUSCULAR DYSTROPHY: CARDIAC PHENOTYPE AS A RESULT OF DNA DAMAGE-INDUCED CHANGE OF STEM CELL FATE

Rotrekl V¹, Pešl M², Beckerová D², Jelínková Š³, Lacampagne A⁴, Meli A⁴

¹ Department of Biology, and SCDM, Faculty of Medicine, Masaryk University, and ICRC, St. Anne's University Hospital, Brno; ² I. interní kardioangiologická klinika a Biologie LF MU a ICE,



ICRC, Fakultní nemocnice u sv. Anny, Brno;

³ Department of Biology, Masaryk University, Faculty of Medicine, Brno; ⁴ INSERM U1046, University of Montpellier I+II, Montpellier, France

Duchenne muscular dystrophy (DMD) is caused by impaired dystrophin. Majority of the DMD patients suffer from cardiomyopathy, arrhythmias, and heart failure is the predominant cause of death. However, many works showed the molecular mechanisms leading to the DMD cardiomyocyte death during recent decades, and the delayed onset of progressive cardiomyopathy is still unclear. Recently the involvement of progenitor population failure destabilizing muscle homeostasis was implicated and inducing progressive muscle wasting. DMD patient-specific induced pluripotent stem cell model and human embryonic stem cells with dystrophin mutation introduced by CRISPR/Cas technology (DMD hPSC for both models) were used to uncover the involvement of cardiac progenitor cells (CPCs) depletion and its mechanism in humans to cardiac failure. The absence of dystrophin in DMD hPSC resulted in dysregulation of nitric oxide synthase (NOS), which in turn spiked the excessive release of reactive oxygen species (ROS). We show that ROS are associated with increased DNA damage and elevated mutant frequency in DMD hPSCs. Scavenging the ROS and/or inhibition of NOS resulted in DNA damage reduction. Contrary to WT mouse hearts was observed a dramatic increase in CPCs population in young adult (2–3 months) MDX mice hearts is followed by a steep decrease in mature animals. CPCs depletion in MDX animal hearts is associated with elevated nuclear DNA damage.

The elevated proliferation of CPCs together with NOS induced-ROS mediated-genomic instability leads to CPCs depletion, and subsequently to limited ability to maintain homeostasis of the heart muscle.

The work was supported by the Eu Regional Development Fund-Project ENOCH CZ.02.1.01/0.0/0.0/16_019/000 0868; by National Institute for Research of Metabolic and Cardiovascular Diseases EXCELES, ID LX22NPO5104 funded by "Next Generation EU".

■ THE USE OF TELEMEDICINE IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION – A PILOT STUDY

Přeček J, Štýbnar M, Hetclová D, Kubová K, Rada M, Hutýra M

I. interní klinika – kardiologická, FN Olomouc, Olomouc

Background: Pulmonary arterial hypertension (PAH) is a rare disease whose treatment is concentrated in specialized treatment centers. The severity of the disease and the specific pharmacotherapy used require the need for intensive monitoring of health status and ongoing treatment. Telemedicine solutions open the way to new possibilities for monitoring patients and optimizing treatment to improve quality of life and prognosis. The available

evidence for the application of telemedicine in PAH is still limited.

Study design and methods: A total of 24 patients with pulmonary arterial hypertension were enrolled in a prospective, non-randomized study. Patients were divided 1:1 to standard care and use of telemedicine intervention. The telemedicine intervention included regular use of a dedicated mobile phone/tablet app with measurement of vital signs by an external device (blood pressure, heart rate, oxygen saturation, body weight), as well as the possibility of use video consultation, messaging, sending photos and other files. After 6 months of intervention, the incidence of rehospitalization for worsening PAH, natriuretic peptides (NT-proBNP) levels and quality of life measured by questionnaires (LPH, GSE, Beck scale) were compared.

Results: In the telemedicine group, there was a trend towards a nonsignificant decrease in natriuretic peptide levels (NT-proBNP: –135.7 ng/l in telemedicine group vs. +100.87 ng/l in control group; $p = 0.25$) and a significant improvement in quality of life parameters assessed by the questionnaire (LPH: –18 vs. +2; $p < 0.05$; GSE +8 vs. 0; $p < 0.05$). No difference in rehospitalizations was observed between the two groups.

Conclusions: This study demonstrated the feasibility of telemedicine intervention in patients with pulmonary arterial hypertension and the improvement of quality of life parameters using this intervention.

■ GENDER DIFFERENCES AND SURVIVAL AFTER OUT OF HOSPITAL CARDIAC ARREST

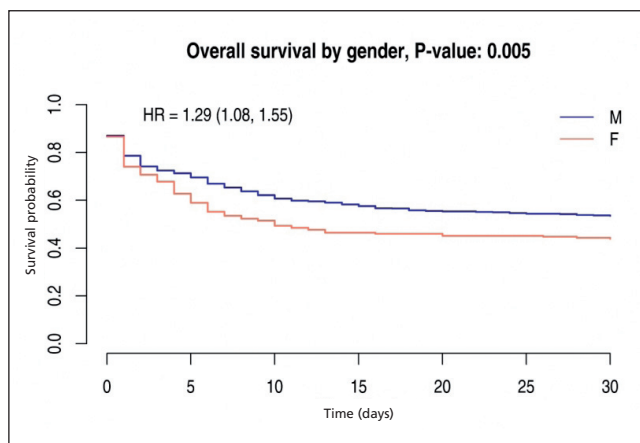
Rob D¹, Kaválková P², Šmalcová J¹, Franěk O³, Komárek A⁴, Pisinger M⁵, Bělohávek J¹

¹ II. interní klinika kardiologie a angiologie, VFN, Praha; ² II. interní klinika VFN kardiologie a angiologie, VFN; ³ Zdravotnická záchranná služba hl. m. Prahy, Praha; ⁴ Department of Probability and Mathematical Statistics, Univerzita Karlova, Faculty of Mathematics and Physics; ⁵ Cardiology, Hospital Ceske Budejovice, Ceske Budejovice

Background: Published evidence regarding the effect of gender on outcome after out of hospital cardiac arrest (OHCA) is inconsistent. We aimed to investigate the association of gender to outcome and resuscitation characteristics in OHCA patients admitted to the cardiac arrest center.

Methods: In this analysis of registry data, all patients admitted for OHCA were included. The influence of gender on 30-day survival and good neurological outcome (cerebral performance category of 1 or 2) were examined using Kaplan–Meier estimates and multivariable logistic regression.

Results: In total, 932 patients were analyzed (239 women, 26%). Women were older (64 vs 60 years, $p < 0.001$) and less commonly had a shockable rhythm (47% vs 65%,



$p < 0.001$) compared to men. Women were less likely to have a cardiac cause of arrest (54% vs 75%, $p < 0.001$), received less therapeutic hypothermia (74% vs 86%, $p < 0.001$) and coronary angiography (63% vs 79%, $p < 0.001$). The overall 30-day survival was lower for women (45% vs 53%, log-rank $p = 0.005$) as well as good neurological outcome (37% vs 46%, $p = 0.008$). However, according to the multivariate logistic regression, gender was not associated with survival (OR 0.98, 95% CI 0.65–1.50, $p = 0.94$) nor with good neurological outcome (OR 0.91, 95% CI 0.59–1.40, $p = 0.67$).

Conclusions: Women admitted for OHCA to a cardiac center had a different cause of arrest that had a different treatment and outcome compared to men. Survival and good neurological outcome were lower in women; however, after adjusting for baseline characteristics, gender was not associated with survival nor neurological outcome.

■ HEART FAILURE IN FABRY DISEASE REVISITED: APPLICATION OF CURRENT HEART FAILURE GUIDELINES AND RECOMMENDATIONS

Rob D, Marek J, Dostálová G, Linhart A

II. interní klinika kardiologie a angiologie, VFN, Praha

Aims: Fabry disease (FD) is often associated with heart failure (HF). However, data on HF prevalence, prognosis, and applicability of echocardiographic criteria for HF diagnosis in FD remain uncertain.

Methods: We evaluated patients with FD for symptoms and natriuretic peptides indicating HF. Then we analyzed the diagnostic utility of the currently recommended echocardiographic criteria for HF diagnosis and their relationship to natriuretic peptides. Finally, we examined the association between HF and echocardiographic criteria with clinical events during follow-up.

Results: Of 116 patients with FD, 47 (41%) had symptomatic HF (58±11 years, 62% male). HF with preserved

ejection fraction (HF-pEF) was diagnosed in 43 (91%) patients. Left ventricular mass index (LVMI) had the highest diagnostic utility (sensitivity 71% and specificity 83%) for HF diagnosis, followed by $E/e' > 9$ (sensitivity 76% and specificity 78%) and global longitudinal strain (GLS) $< 16\%$ (sensitivity 54% and specificity 88%). Natriuretic peptides correlated significantly with LVMI ($r = 0.60$), E/e' ($r = 0.54$), and GLS ($r = 0.52$) (all P s < 0.001). During follow-up (mean 1208 ± 444 days), patients diagnosed with HF had a higher rate of mortality and worsening HF (33% vs. 1.5%, $p < 0.001$). Abnormal LVMI, $E/e' > 9$, and GLS $< 16\%$ were all associated with higher all-cause mortality and worsening HF.

Conclusions: This study found a high prevalence of HF in FD. HF-pEF was the dominant phenotype. LVMI, E/e' , and GLS yielded the highest diagnostic utility for HF diagnosis and were correlated with natriuretic peptides levels. Echocardiographic criteria proposed by current guidelines apply to Fabry patients and predict future events. Fabry patients with HF had high event rates and significantly worse prognosis than patients without HF.

■ FEASIBILITY OF EVALUATION OF POLAR H10 CHEST-BELT ECG IN PATIENTS WITH A BROAD RANGE OF HEART CONDITIONS

Skála T, Vícha M, Vácha J, Rada M, Flašík J, Táborský M

I. interní klinika, FN Olomouc, Olomouc

Background: The chest-belt can be used to obtain a 1-lead ECG. It was validated for the determination of heart rate and for the possibility to detect atrial fibrillation (AF) compared to ECG-Holter on a short ECG recording in selected patients. Validation of the possibility to evaluate long ECG recordings in patients with heart diseases has not been done.

Methodology and results: 54 hospitalized patients, 53 outpatients and 54 healthy controls were enrolled in the study ($n = 161$ in total). Using a Polar H10 chest-belt, 1–2 hours of ECG were recorded in all patients (1 153 229 heartbeats, average heart rate 76.6/min, 86.3% in sinus rhythm, 13.7% with atrial fibrillation, 0.46% atrial premature beats, 0.49% ventricular premature beats). The presence of noise was 2.16% (A: 2.31%; B: 1.95%; C: 2.20%). 1 128 319/1 153 229 were evaluated as easy to interpret. Using ECG from the belt, the basic rhythm was reliably determined by the physician in majority of patients (51/54, 94.4% in hospitalized patients; in 100% of outpatients and healthy controls) when compared to 12-lead ECG. 3 cases were evaluated as unclear; in all of these cases, all QRS complexes were stimulated by a pacemaker. In hospitalized patients, real-time ECG from the belt was comparable to telemetric ECG monitoring (match in 53/54, 98.1%).

Conclusion: The ECG obtained from the chest-belt in hospitalized patients, outpatients and healthy con-



trols is usable for evaluation of baseline rhythm, atrial fibrillation and premature contractions with a minimal proportion of difficulties to interpret recordings due to artefacts. Caution should be exercised in interpretation of the ECG in patients with stimulated rhythm and in patients with atrial flutter. The chest belt can be used as a means for continuous monitoring of ECG, evaluation of rhythm and screening for atrial fibrillation.

COMBINED STRATEGY FOR LARGE-BORE ARTERIOTOMY CLOSURE AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION

Sluka M¹, Nykl R¹, Ostránský J²

¹ I. interní klinika kardiologická, Fakultní nemocnice Olomouc, Olomouc; ² I. interní klinika kardiologická, Fakultní nemocnice Olomouc, Olomouc

Background: The vascular complications remain relevant following transcatheter aortic valve implantation (TAVI). They are frequently associated with vascular closure device failure (VCD). Their incidence depends on different factors with reported rate between 4–19%. Vascular complications affect morbidity and mortality. The most commonly used VCDs include the suture-based ProGlide and the plug-based MANTA. The MANTA device was not superior to the use of 2 ProGlides in their direct comparison in terms of access site-related vascular complications. The alternative but less frequently used strategy is intentional combination of one suture-based VCD – ProGlide with small-bore plug-based VCD AngioSeal. The data supporting this approach are very limited, but showing lower rate of additional endovascular interventions when compared with vascular closure using two suture-based VCDs.

Methods: Retrospectively analyzed comparison of two strategies: use of two suture-based ProGlides (SB group) vs intentional combination of one ProGlide with plug-based AngioSeal 8F (CB group). The primary endpoint was occurrence of access site-related vascular complications at 30-days.

Results: We compared 71 consecutive patients treated between Aug/2020 and May/2021 with 95 consecutive patients treated between May/2021 and Apr/2022. There wasn't significant difference in patient's characteristics (SB vs. CB group): mean age 81 vs 79 years, females 54.9% vs 52%, STS score 3.47% vs 3.46%, oral anticoagulation 38.6% vs 40.1%. Lower rate of vascular complication was observed in CB group 3.1% vs 7.1%.

Conclusion: The combination of one suture-based VCD with one plug-based VCD is effective and safe. This strategy was associated with lower rate of vascular complication compare the use of 2 suture-based VCDs in our patient's cohort following TAVI.

GDF-15 LEVEL CHANGES IN EARLY AND LATE PERIOD AFTER CATHETER ABLATION OF ATRIAL FIBRILLATION

Steklá B, Marek J, Šimek J, Dusík M, Fingrová Z, Linhart A, Havránek Š

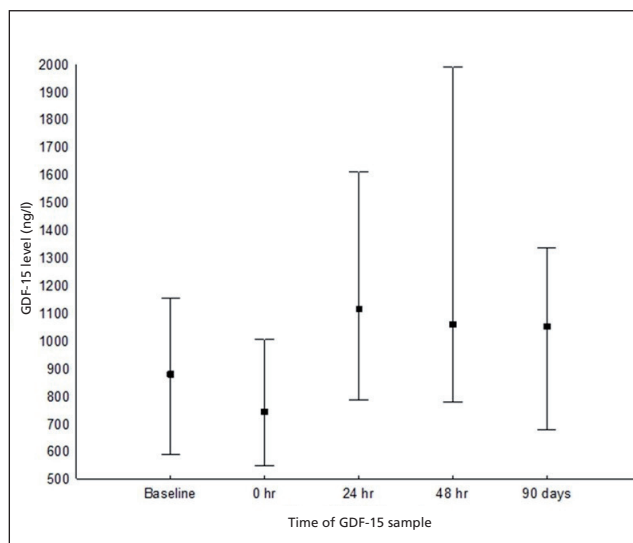
II. interní klinika, VFN, Praha

Introduction: GDF-15 (growth differentiation factor 15) is protein from transforming growth factor β (TGF- β) cytokine family. In patients with atrial fibrillation (AF) GDF-15 is a potent marker of bleeding adverse events in anti-coagulated patients and a predictor of overall mortality. Aim of the study was to describe how catheter ablation of atrial fibrillation affects GDF-15 levels in early and late period.

Methods: We enrolled 18 patients (median 58 [50; 67] years, 56 % males) undergoing radiofrequency catheter ablation (RFCA) of AF who underwent 5 sequential blood takes (before RFCA – baseline, right after RFCA [0 hr], 24 and 48 hours after RFCA and 90 days after RFCA) to analyze GDF-15 level.

Results: Out of all patients, 9 patients (50%) had paroxysmal and 9 (5 %) persistent AF. Mean (IQR) radiofrequency time was 48 (36; 60) minutes. The dynamics of GDF-15 levels is visualised in Figure. GDF-15 level peak was registered 24 hours after ablation with median (IQR) 1115 (794; 1549) ng/l. After 90 days from ablation there still persisted higher GDF-15 levels in relation to input levels ($p < 0.05$ in all comparisons). Weak correlation ($r = 0.6$; $p < 0.05$) between peak GDF-15 values and peak NT-proBNP was found.

Conclusion: Even though GDF-15 is considered as a nonspecific biomarker reflecting general condition of patient, the levels are significantly affected by RFCA of AF.



Dynamics of GDF-15 values (median; IQR).

THE HEMODYNAMIC EFFECT OF SIMULATED ATRIAL FIBRILLATION ON LEFT VENTRICULAR FUNCTION

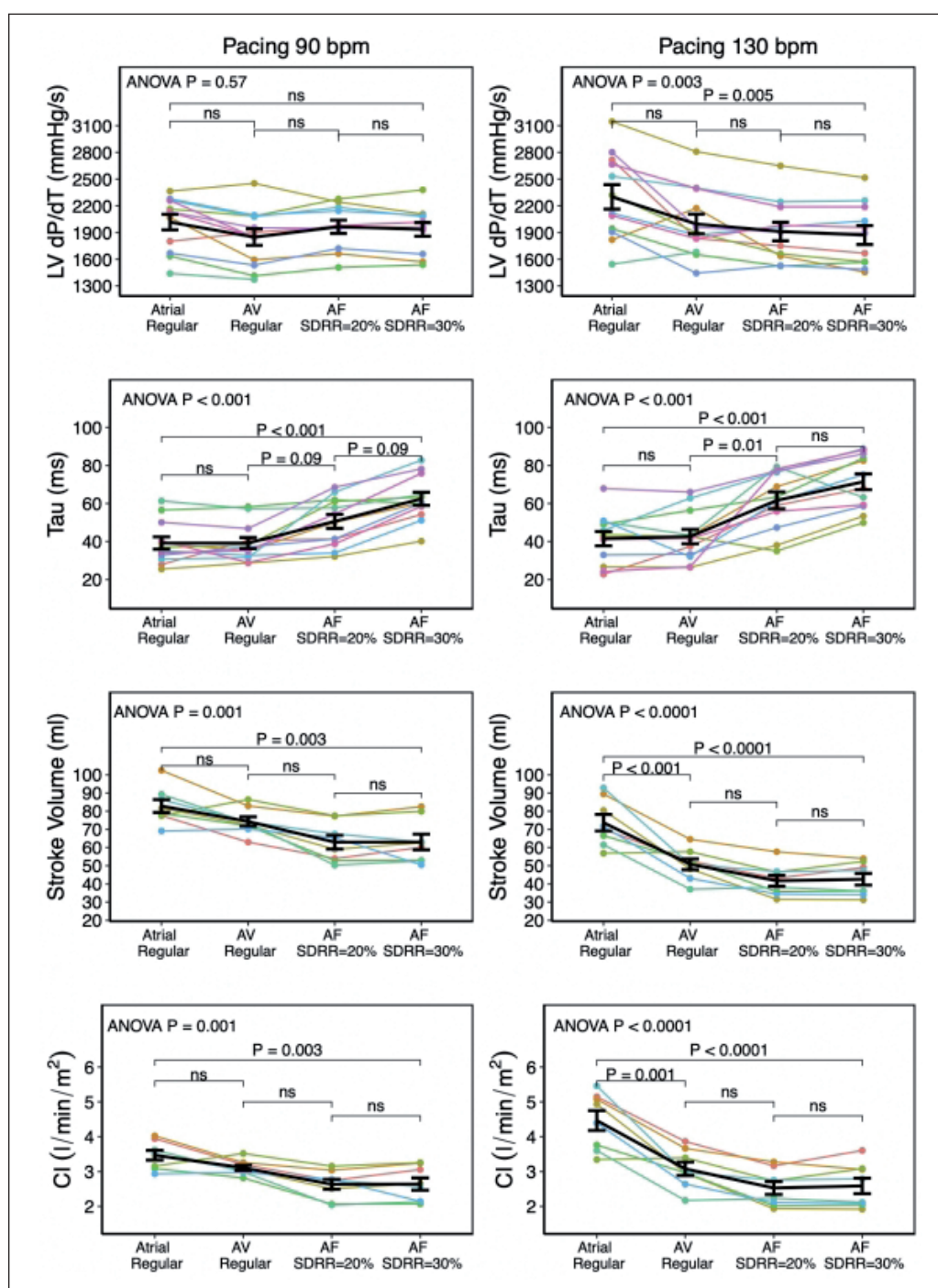
Stojadinović P¹, Deshraj A², Wichterle D³, Fukunaga M¹, Peichl P¹, Kautzner J¹, Šramko M⁴

¹ Klinika kardiologie, IKEM, Praha; ² Institute of Physiology, First Faculty of Medicine, Charles University, Praha; ³ Praha; ⁴ IKEM

Background: Atrial fibrillation (AF) is the most common sustained arrhythmia in humans. The onset of the ar-

rhythmia can significantly impair cardiac function. This hemodynamic deterioration has been explained by several mechanisms such as the loss of atrial contraction, shortening of ventricular filling, or heart rhythm irregularity. This study sought to evaluate the relative hemodynamic contribution of each of these components during in-vivo simulated human AF.

Methods: Twelve patients undergoing catheter ablation for paroxysmal AF were paced simultaneously from the proximal coronary sinus and the His bundle region according to prescribed sequences of irregular R-R intervals with the average rate of 90 bpm and 130 bpm, which were extracted from the database of digital ECG recordings of





AF from other patients. The simulated AF was compared to regular atrial pacing with spontaneous atrioventricular conduction and regular simultaneous atrioventricular pacing at the same heart rate. Beat-by-beat left atrial and left ventricular pressures including LV dP/dT and Tau index were assessed by direct invasive measurement; beat-by-beat stroke volume and cardiac output (index) were assessed by simultaneous pulse-wave doppler intracardiac echocardiography.

Results: Simulated AF led to significant impairment of left ventricular systolic and diastolic function. Both loss of atrial contraction and heart rate irregularity significantly contributed to hemodynamic impairment. This effect was pronounced with increasing heart rate.

Conclusion: Our findings strengthen the rationale for therapeutic strategies aiming at rhythm control and heart rate regularization in patients with AF.

■ LEFT BUNDLE BRANCH PACING OF PROXIMAL LEFT BUNDLE BRANCH AND SEPTAL FASCICLE PRODUCES MORE PHYSIOLOGICAL ACTIVATION COMPARED TO PACING OF THE ANTERIOR FASCICLE

Süssenbek O¹, Jurák P², Jastrzebski M³, Štros P¹, Waldauf P⁴, Smíšek R², Halánek J⁵, Znojilová L⁶, Osmančík P¹, Čurila K⁶

¹ III. interní klinika, FNKV, Praha 10; ² ÚPT, AVČR, Brno; ³ Oddział Kliniczny Kardiologii, Szpital Uniwersytecki w Krakowie, Krakow, Poland; ⁴ Klinika anesteziologie a resuscitace, Fakultní nemocnice Královské Vinohrady, Praha; ⁵ ÚPT AVČR, Brno; ⁶ Kardiologická klinika, Fakultní nemocnice Královské Vinohrady, Praha

Background: Left bundle branch pacing is defined as the pacing of the trunk or its proximal fascicles. It is unknown, whether a difference between captures with normal or deviated axes and proximal vs distal locations exists.

Objective: To study ventricular activation during nonselective LBB pacing (NSLBBp) in different QRS axes and proximal vs. distal pacing positions using ultra-high-frequency ECG (UHF-ECG).

Methods: NSLBBp captures were classified as superior (−30°; −90°), normal (−29°; 60°), or inferior (61°; 120°) QRS axis and proximal LBBp (LBBpo to ventricular EGM ≥25 ms) vs fascicular LBBp (LBBpo-V <25 ms and corresponding axes for anterior, septal and posterior fascicle). UHF-ECG electrical dyssynchrony parameters: e-DYS (difference between the first and last ventricular activation), local depolarization durations in precordial leads (V₁–V₈d), and their mean value (Vd_{mean}) were calculated.

Results: No difference in any parameters was found in the axes comparison. NSLBBp of anterior fascicle had longer Vd_{mean} (50±2ms) compared to septal and posterior fascicle (45±2ms and 46±1ms with $p < 0.05$ and $p = NS$, respectively) and proximal LBBp (44±1ms; $p < 0.015$).

Conclusion: Although NSLBBp of proximal left bundle branch or septal fascicle produces slightly more physiological activation compared to pacing of the posterior and anterior fascicle, the clinical relevance of this finding is yet unclear.

This work was supported by the Charles University Research program 260530/SVV/2020.

■ HYPERTRIGLYCERIDEMIC GENE SCORE IN PATIENTS WITH APOE2/E2 GENOTYPE AS A POSSIBLE PREDICTOR OF FAMILIAL DYSBETALIPOPROTEINEMIA

Šatný M¹, Altschmiedová T¹, Todorovová V¹, Vrablík M¹, Kyselák O², Soška V², Hubáček J³

¹ III. interní klinika VFN, VFN v Praze, Praha; ² II. interní klinika, FNUSA, Brno; ³ CEM, IKEM, Praha

Introduction: Familial dysbetalipoproteinemia (FD) is an autosomal recessive (rarely dominant) inherited disorder that is almost exclusively associated with the apolipoprotein E gene (APOE). However, only a small proportion of patients with the typical APOE2/E2 genotype develop phenotype – the mixed dyslipidemia (DLP) – in the context of other metabolic or as yet undescribed genetic factors.

Methods: We screened 71 FD patients and 90 controls (all APOE2/E2 homozygotes, according the rs429358) for 18 single nucleotide polymorphisms (SNPs) in genes involved in triglyceride metabolism.

Results: Two SNPs were significantly associated with the FD phenotype (rs439401 within APOE and rs964184 within APOA5). An unweighted gene risk score (GRS; sum of risk alleles) was analyzed as a genetic predictor of FD development in patients with the APOE2/E2 baseline genotype. The unweighted GRS constructed from the 5 strongest SNPs (within the APOE, APOA5, CFT1, LPL, and TYW1B genes) reliably discriminated between FD and controls (OR 4.97; CI [2.24–11.06], $p < 0.00003$).

Conclusions: Several SNPs, i.e., individual additive genetic factors, were found to influence the development of FD. Thus, unweighted GRS clearly improves the prediction of FD development in APOE2/E2 homozygotes.

■ VENTRICULAR ARRHYTHMIAS IN PATIENTS WITH IMPLANTED ICD: A POST HOC ANALYSIS OF PRAGUE OHCA TRIAL

Šotolová I, Válek M, Šmalcová J, Rob D, Havránek Š, Bělohávek J

II. interní klinika, VFN, Praha

Background: Implantable cardioverter defibrillators (ICD) or cardiac resynchronization therapy (CRT-D) devices are



routinely implanted as a secondary prevention of sudden cardiac death, however, the number and characteristics of ventricular arrhythmias after the secondary prevention implantation has been analyzed rarely. No data are available in patients after refractory out-of-hospital cardiac arrest (OHCA) treated with extracorporeal cardiopulmonary resuscitation (ECPR) methods.

Purpose: The aim is to specify cumulative incidence of malignant arrhythmias during follow-up in survivors of refractory OHCA partially treated with ECPR with later ICD/CRT-D implantation.

Patients and methods: We performed a post-hoc analysis of the ICD interrogation records of patients after refractory OHCA who were originally randomized to either standard care of invasive care (intra-arrest transport, ECPR and invasive assessment) within Prague OHCA trial, and were referred to ICD or CRT/CRT-D implantation.

Results: A total of 31 patients were included in post-hoc analysis. Of these, 17 were randomized to invasive group and 14 to standard resuscitation care. The mean age of the patients in the invasive and standard groups was 55 and 53 years, respectively. 93% and 81% were males with follow-up for 43 and 49 months. 7 and 11 patients had non-sustainable ventricular tachycardia in invasive and standard group ($p = 0.09$). ICD or CRT-D shocks were observed in 3 patients in the invasive group and in 6 patients in the standard care group ($p = 0.12$).

Conclusion: Among patients who were randomized to Prague OHCA trial and later underwent ICD or CRT-D implantation, ventricular arrhythmias seemed to be more frequently detect

■ COMPARISON OF ANGIOGRAPHIC EVALUATION AND HEMODYNAMIC MEASUREMENT OF THE SIGNIFICANCE OF NON INFARCT-RELATED RESIDUAL STENOSIS IN STEMI PATIENTS – SINGLE CENTER EXPERIENCE

Špaček M, Vácha J, Nykl R, Přechek J, Hutýra M, Sluka M, Táborský M

I. interní klinika – kardiologická, Fakultní nemocnice Olomouc, Olomouc

Introduction: Up to 50% of patients with STEMI have >50% stenosis in a major non-infarct related artery. Several studies have evaluated the prognostic value of completion of revascularization using selection based on angiographic evaluation, invasive hemodynamic measurement with fractional flow reserve (FFR) or combined approach.¹⁻⁵ In our single center study, we compared subjective angiographic evaluation with invasive hemodynamic measurement.

Methods: We examined 51 patients (62.7 ± 10.2 years) with acute STEMI who had at least one residual (50–

90%) stenosis in non infarct-related major coronary artery (excluding left main coronary artery). Overall 65 stenoses ($67.9 \pm 10.7\%$) were evaluated angiographically during primary PCI and were recommended for either completion of revascularization or conservative approach taking into consideration stenosis severity, localization of stenosis (proximity) as well as the supplied vascular territory. During subsequent rehospitalization, invasive measurement of hemodynamic significance using FFR was performed and guided the final revascularization strategy (FFR value of ≤ 0.80 considered significant).

Results: Based on angiographic evaluation, a total of 44 stenoses were recommended for treatment, whereas only 31 stenoses were revascularized based on FFR measurement. Moreover, subjective evaluation and hemodynamic measurement were discrepant in 27 out of 65 (41.5%) stenoses.

Conclusion: We observed weak correlation between subjective angiographic evaluation and invasive hemodynamic measurement. More stents would be used based on angiographic evaluation compared to FFR measurement.

Supported by MH CZ – DRO (FNOI, 00098892).

■ RADIOFREQUENCY CATHETER DENERVATION OF SINUS NODE BY TARGETTING THE RIGHT ANTERIOR GANGLIONATED PLEXUS: TOWARDS MINIMIZING THE LESIONS SET

Štiavnický P, Wichterle D, Jansová H, Stojadinović P, Peichl P, Hašková J, Čihák R, Kautzner J

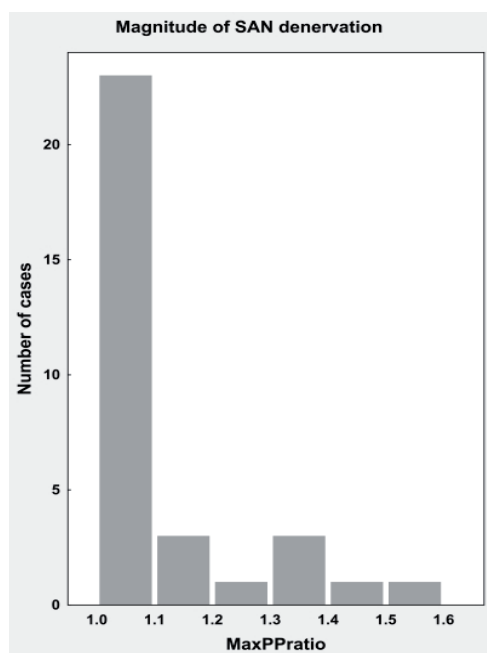
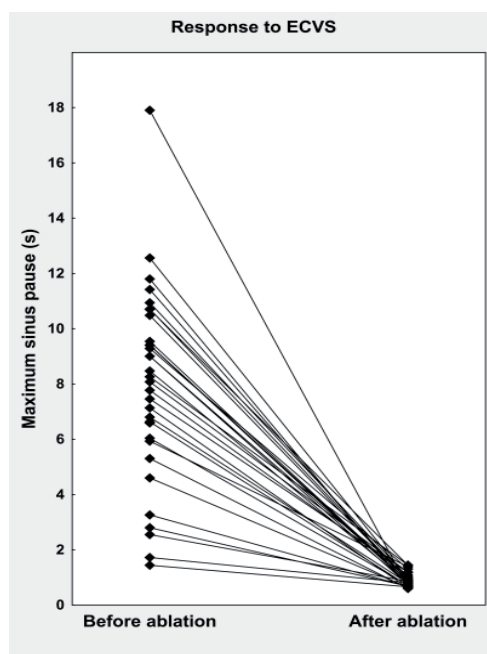
Klinika kardiologie, IKEM, Praha

Background: Radiofrequency catheter (RF) ablation of the superior ganglionated plexus (RAGP) that modifies parasympathetic innervation of the sinus node (SAN) is used for the treatment of functional bradyarrhythmias. The RAGP is usually targeted from the endocardial aspect of both the right and left atria.

Objective: To investigate the acute effect of a minimized biatrial set of ablation lesions aimed at denervating the SAN.

Methods: In patients with cardioinhibitory reflex syncope ($n = 25$) or symptomatic functional sinus bradycardia ($n = 7$), a minimum of 2 – 2 and a maximum of 2 × 3 RF lesions (at the discretion of the operator) were created from both sides of the superior interatrial septum with a setting of 30 W/30 s and strictly contralateral configuration. The response to extracardiac vagus nerve stimulation (ECVS) was assessed before and after ablation. This response was quantified by the ratio of the maximum induced P-P interval and the cycle length of the current sinus rhythm (MaxPPratio).

Results: In 32 patients (41 ± 13 years, 56% men), ablation of RAGP (2×3 and 2×2 lesions in 23 and 9 patients, respec-



tively) resulted in attenuation of the response to ECVS from 7.9 ± 3.5 s to 0.9 ± 0.2 s (Fig., left panel). After ablation, only 9 patients had MaxPPratio >1.1 and none of the patients had MaxPPratio >1.6 (Fig., right panel). In 6 patients with MaxPPratio >1.3 , the extension of original lesions easily suppressed the residual responsiveness of SAN to ECVS.

Conclusion: Batrial RAGP ablation with a total RF time of 2–3 minutes resulted acutely in virtually complete SAN denervation in 72% of patients. Highly significant, but incomplete SAN denervation in remaining patients was successfully treated by extension of original ablation clusters. The long-term durability of SAN denervation associated with this ablation strategy remains to be investigated.

■ DETECTION OF ARRHYTHMIAS IN PATIENTS WITH CARDIAC AMYLOIDOSIS USING IMPLANTABLE ECG RECORDERS

Táborský M

I. interní klinika, FN Olomouc, Olomouc

Introduction: Cardiac amyloidosis frequently results in congestive cardiac failure and arrhythmias,

Methods: 112 transthyretin amyloidosis (TTR) patients with completed underlying diagnosis including 99mTc-DPD scan, genetic testing and endomyocardial biopsy (27%) without documented arrhythmias were randomized to standard clinical follow-up including arrhythmias or implantation of an ECG loop recorder (ILR). The classic FU took place in a heart failure clinic, and the group of patients with ILR was monitored by remote control with automatic daily report of the occurrence of arrhythmias by an independent organization. If an arrhythmia was detected, the patient was contacted immediately. The mean follow-up time for both groups was 17 ± 7 months.

Results: The results are summarized in Table 1.

Standard FU (n = 56)	Intensive FU (ILR) (n = 55)	p
AF 11 (19.6%)	AF 19 (49%)	<0.05
AV block 6 (10.7%)	AV block 11 (20%)	<0.05
Non sust. VT 8 (14.2%) non. sus.	VT 27 (49%)	<0.05
Sust. VT 0	Sust. VT 6 (10.9%)	<0.05
VF 0	VF 1 (1.81%)	<0.05
AT 1 (1.8%)	AT 4 (7.3%)	<0.05

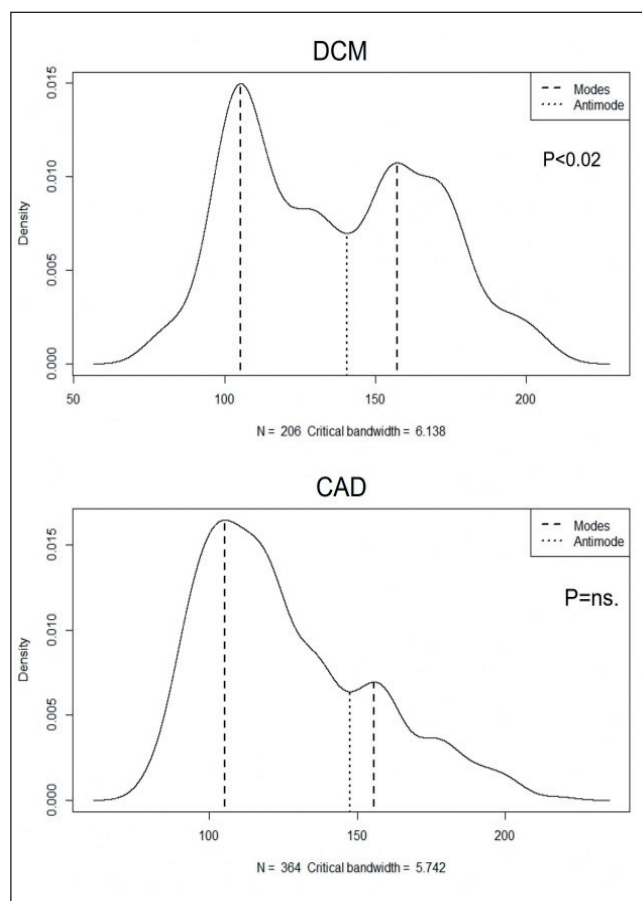
Conclusions: Currently, there is no consensus on the absolute benefit that ICDs in patients with cardiac amyloidosis. When non-sustained VT and syncope are captured and documented, ICD implantation for prevention of SCD in CA is most likely a reasonable approach. However, intensive monitoring of arrhythmias in patients with CA using ILR can lead to accurate and early detection of ventricular arrhythmias in particular and early initiation of ICD treatment as a prevention of SCD. Documentation of ventricular arrhythmias in CA patients was significantly higher by ILR ($p < 0.005$) and was a clear predictor of patient survival (HR 2.51).

■ BIMODAL DISTRIBUTION OF QRS COMPLEX DURATION IN PATIENTS WITH DILATED CARDIOMYOPATHY UNDERGOING AN ICD IMPLANT PROCEDURE

Vančura V, Vejvoda V, Jandík T, Šmíd J, Ulrychová M, Rokyta R

Kardiologická klinika, Komplexní kardiiovaskulární centrum FN, Lékařská fakulta UK v Plzni, Plzeň

Background: In patients with heart failure with reduced ejection fraction (HFrEF), QRS duration is of the utter-



most importance. Substantial proportion of patients with HFrEF and sufficiently prolonged QRS complex, especially those with left bundle branch block may significantly benefit from cardiac resynchronization therapy. The aim of the study was to analyse the distribution of the QRS durations in patients with HFrEF undergoing ICD implant procedure to better understand the phenomenon of QRS prolongation.

Methods: All patients with HFrEF caused by coronary artery disease (CAD) or dilated cardiomyopathy (DCM) undergoing the implant procedure in our center between January 2013 and December 2021 were analyzed for the inclusion into the study. The exclusion criteria were (1) coincidence of CAD with DCM, (2) upgrade from any other cardiac rhythm management device, (3) unavailability of the ECG recording on ECG recording on Mortara ELI350 or ELI380 (4) more than one ventricular premature beat in the recording. The study used automatically measured QRS duration using the EKG machine.

Results: The study included 570 patients, 206 with DCM and 364 with CAD. All patients taken together had tendency to bimodal distribution of QRS duration ($p = 0.052$). In CAD patients, the distribution was unimodal ($p = ns.$), whereas the DCM group had bimodal distribution ($p < 0.02$). The border zone between both distributions was at 134–137 ms (no patient with QRS 135–136 ms). The bimodality was even more pronounced in women with DCM ($p < 0.002$).

Conclusions: Bimodal distribution of QRS duration values in patients with DCM supports the idea of sudden change of bundle conduction rather than slow progression of local changes. In CAD, scars and other local impairments in conduction may hide these changes and no clear border zone can be set.

■ COMPARISON OF NEURON-SPECIFIC ENOLASE, TAU-PROTEIN, AND NEUROFILAMENT LIGHT CHAIN VALUES FOR EARLY PROGNOSTICATION IN CARDIAC ARREST SURVIVORS

Vondráková D¹, Krüger A¹, Janotka M¹, Naar J², Neužil P¹, Sobek O³, Ošťádal P¹

¹ Kardiologie, Nemocnice na Homolce, Praha; ² Kardiologie, Nemocnice Na Homolce, Praha; ³ Topelex, s.r.o.

Introduction: Early prognostication in cardiac arrest survivors remains challenging despite multimodal approach. Currently, the only guidelines recommended biomarker for early prognostication is neuron-specific enolase (NSE).

Objectives: The aim of our study was to compare prognostic values of NSE with novel biomarkers serum tau protein (Tau) and neuro-filament light chain (Nfl) at different timepoints after cardiac arrest.

Methods: Eligible patients were out-of-hospital cardiac arrest survivors. Blood samples for the measurements of NSE, Tau and Nfl levels were drawn at 24 hrs (D1), 48 hrs (D2), 72 hrs (D3), and 96 hrs (D4) after hospital admission. Thirty-day neurological outcomes according to the Modified Rankin Scale (mRS) were evaluated as clinical endpoints, poor outcome was defined as mRS 4–6.

Results: We enrolled 43 patients in our study. The area under the ROC curve (AUC) for NSE was 0.776, $p < 0.001$ at D1, 0.911, $p < 0.001$ at D2, 0.982, $p < 0.001$ at D3, and 1.0, $p < 0.001$ at D4. The AUC for Tau was 0.823, $p < 0.001$ at D1, 0.893, $p < 0.001$ at D2, 0.938, $p < 0.001$ at D3, and 0.980, $p < 0.001$ at D4. The AUC for Nfl was 0.614, $p = 0.232$ at D1, 0.782, $p = 0.001$ at D2, 0.969, $p < 0.001$ at D3, and 0.990, $p < 0.001$ at D4. The comparison of ROC curves revealed trend to lower AUC for Nfl at D1 in comparison to NSE ($p = 0.151$) and Tau ($p = 0.077$) with comparable values at D2, D3 and D4. The highest sensitivity for the prediction of poor prognosis with 100% specificity was detected for Tau values at D1 (33.3%) or D2 (70.0%) and for NSE values at D3 (92.9%) or D4 (100%).

Conclusions: Our results indicate that the novel biomarkers Tau and Nfl have comparable predictive value for clinical outcomes as NSE at 48 to 96 hrs after cardiac arrest. At the first day after admission the highest predictive value has Tau followed by NSE.



■ NATION-WIDE SCREENING OF FABRY DISEASE IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY IN THE CZECH REPUBLIC (BY DRY BLOOD SPOT METHOD)

Zemánek D¹, Januška J², Honěk T³, Čurila K⁴, Kubánek M⁵, Šindelářová Š⁶, Zahálková L⁷, Klofáč P⁸, Dostálová G⁹, Linhart A⁹

¹ II. interní klinika 1. LF UK, VFN, Praha;

² Department of Cardiology, Cardiocentre Podlesí, Trinec; ³ 1st Department of Internal Medicine – Cardioangiopathy, St Anne's University Hospital and Masaryk University, Brno; ⁴ Department of Cardiology, 3rd Faculty of Medicine, Charles University and University Hospital Královské Vinohrady, Praha; ⁵ Department of Cardiology, Institute for Clinical and Experimental Medicine, Praha; ⁶ Department of Cardiology, Hospital České Budějovice, České Budějovice; ⁷ 1st Department of Medicine – Cardioangiopathy, Charles University Faculty of Medicine and University Hospital, Hradec Králové; ⁸ Department of Cardiology, Regional Hospital Liberec, Liberec; ⁹ 2nd Department of Internal Medicine Cardiology and Angiology, General University Hospital and 1st Medical School of Charles University, Praha

Aims: Fabry disease (FD) is a rare X-linked genetic disorder caused by a-galactosidase A (AGALA) deficiency. While "classic" variant has multisystemic manifestation, the more recently described "later-onset" variant is characterized by predominant cardiac involvement that often mimics hypertrophic cardiomyopathy (HCM).

Methods and results: Consecutive unrelated patients with HCM were screened for FD in 16 (out of 17) cardiac centers in the Czech Republic covering specialized cardiology care from June 2017 to December 2018. AGALA activity and globotriaosylsphingosine (lyso-Gb3) levels were measured in all subjects using the dry blood spot method. FD was suspected in male patients with AGALA activity <1.2 μmol/h/L and in females with either low AGALA activity or lyso-Gb3 >3.5 ng/mL. Positive screening results were confirmed by genetic testing. We evaluated 589 patients (390 males, 66%) with HCM (mean maximal myocardial thickness 19.1±4.3 mm). The average age was 58.4±14.7 years. In total, 17 patients (11 males, 6 females) had positive screening results and subsequently six of them (4 males and 2 females) had a genetically confirmed pathogenic variant (total prevalence of 1.02 %). Five of these patients were carrying the p.N215S mutation known to cause a typical later-onset cardiac FD.

Conclusion: We confirmed the prevalence of FD repeatedly reported in previous screening programs (approximately 1 % irrespective of gender) in a non-selected HCM population in Central Europe. Our findings advocate a routine screening for FD in all adult patients with HCM phenotype including both genders. The dry blood spot method used led to identification of clearly pathogenic variants.

■ ALVEOLAR MACROPHAGES DO NOT CONTRIBUTE TO THE DEVELOPMENT OF HYPOXIC PULMONARY HYPERTENSION BY CONTRIBUTING TO RADICAL TISSUE INJURY

Žaloudíková M¹, Minaříková M¹, Hampl V¹, Srbová M²

¹ Department of Physiology, Second Faculty of Medicine Charles University, Praha; ² Department of Medical Chemistry and Clinical Biochemistry, Second Faculty of Medicine Charles University, Praha

We have shown previously that alveolar macrophages (AM) are involved in the development of hypoxic pulmonary hypertension (HPH). Since it was demonstrated that one aspect of HPH development is an increase in radical tissue damage, and AM represent an important source of reactive oxygen species, we hypothesized that AM contribute to the development of HPH in this way. We used liposome-encapsulated clodronate (CL) to eliminate AM in male Wistar rats (200–250 g). Control groups received either pure liposome (without clodronate; L) (both Encapsula, à 300 μl, 1st, 5th, 10th days intratracheally) or no medication (C). Animals were kept in normoxia (N, n = 18) or exposed to 15-day isobaric hypoxia (FiO₂ 0.1) (H, n = 19). After the end of the exposure, bronchoalveolar lavage and lung tissue were collected. Oxidative damage was tested by determining the concentration of nitrotyrosine and malondialdehyde in lung tissue extracts. Furthermore, superoxide production was measured using vanadate-dependent chemiluminescence. In all groups, exposure to hypoxia resulted in an increase in concentrations of nitrotyrosine (N: CL 20.2±1.2, L 19.8±3.0, C 18.2±1.7, H: CL 28.8±2.6, L 27.2±0.9, C 29.9±2.0 ng/mg of protein) and malondialdehyde (N: CL 5.5±0.9, L 6.2±0.6, C 5.6±1.6, H: CL 16.7±3.8, L 15.4±0.7, C 9.4±2.3 mmol/mg of protein). However, administration of pure liposomes or liposomes containing clodronate had no effect on nitrotyrosine and malondialdehyde concentrations compared to the control group. Moreover, exposure to hypoxia attenuated superoxide production in AM (H 3.7±0.6, N 13.5±1.4 relative units per cell). We conclude that AMs are not involved in the development of HPH directly through their contribution to radical tissue damage.





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