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THE CZECH SOCIETY OF CARDIOLOGY

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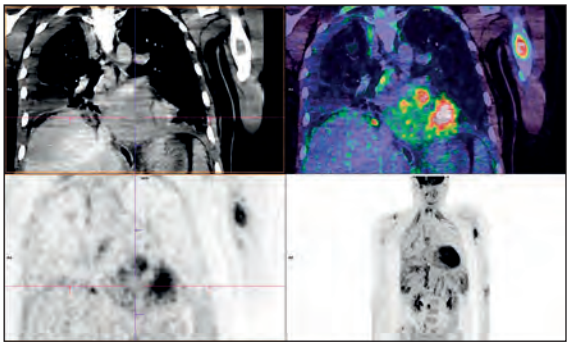
Cor et Vasa



^{18}F-FDG PET/CT – známky akumulace FDG v mediastinálním útvaru i uzlinách a drobné fokusy akumulace v pleurální dutině a kostech. *(Světlíková R, Opatrný J, Baxa J, Rokyta R. Diseminovaný epiteloidní hemangioendoteliom jako vzácná příčina nádorového postižení srdce. Kazuistika, str. 509–512.)*

Cor et Vasa

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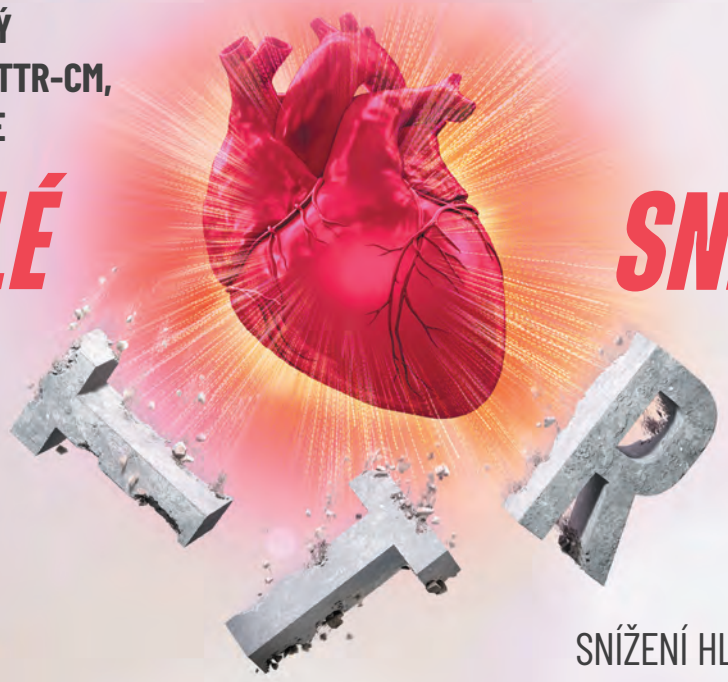
PRVNÍ SCHVÁLENÝ SILENCER* PRO ATTR-CM, KTERÝ ZAJIŠŤUJE

RYCHLÉ SNÍŽENÍ[1-3]



ZVOLTE PŘÍPRAVEK AMVUTTRA▼ JAKO 1. VOLBU PRO RYCHLÉ SNÍŽENÍ HLADIN TTR A ZLEPŠENÍ KARDIOVASKULÁRNÍCH VÝSLEDKŮ[1-3]

V randomizované studii u pacientů s ATTR-CM prokázala AMVUTTRA v porovnání s placebem významný přínos zahrnující:[1-3]

- **rychlé snížení hladiny TTR** již po 3 týdnech[1-3]
- **zlepšení neuropatického postižení** dle mNIS+7[1-3]
- **zlepšení kvality života** dle Norfolk QoL-DN[1-3]
- **zlepšení rychlosti chůze** (měřeno 6minutovým testem)[1-3]

ATTR-CM-transthyretinová amyloidní kardiomyopatie; mNIS+7-modifikované Neuropathy Impairment Score +7; Norfolk QoL-DN-Norfolk Quality of Life–Diabetic Neuropathy; TTR-transthyretin

Indikace

Přípravek Amvuttra je indikován k léčbě hereditární transthyretinové amyloidózy u dospělých pacientů s polyneuropatií v 1. či 2. stadiu (hATTR-PN).[1]

Přípravek Amvuttra je indikován k léčbě získané (wild-type, wtATTR) nebo hereditární transthyretinové amyloidózy u dospělých pacientů s kardiomyopatií (ATTR-CM).[1]

*Prostřednictvím přirozeného procesu zvaného RNA interference (RNAi) způsobuje vutrisiran v játrech katalytickou degradaci TTR mRNA, což vede ke snížení sérové hladiny variantního a získaného typu amyloidogenního proteinu TTR, čímž se snižuje ukládání amyloidu TTR ve tkáních.

▼Tento léčivý přípravek podléhá dalšímu sledování. To umožní rychlé získání nových informací o bezpečnosti. Žádáme zdravotnické pracovníky, aby hlásili jakákoli podezření na nežádoucí účinky na www.sukl.cz/nahlasit-nezadouci-ucinek.

Zkrácená informace o přípravku a reference jsou součástí tohoto materiálu a naleznete je na následující straně.

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Snížené hladiny vitaminu A v séru a doporučení k suplementaci

1. Podávání přípravku AMVUTTRA vede k poklesu sérových hladin vitaminu A na základě snížení sérového proteinu transthyretinu (TTR)[1]
2. U pacientů léčených přípravkem AMVUTTRA je doporučena suplementace vitamínu A v dávce přibližně 2 500 IU až 3 000 IU (ale ne vyšší) vitamínu A denně[1]
3. Pacienti by měli být odesláni k oftalmologovi, pokud se u nich rozvinou oční symptomy naznačující nedostatek vitaminu A (např. zhoršené noční vidění nebo noční slepota, přetrvávající suché oči, zánět oka, zánět nebo ulcerace rohovky, ztluštění rohovky nebo perforace rohovky,).[1]

Reference: 1. SPC Amvuttra EMA: https://www.ema.europa.eu/cs/documents/product-information/amvuttra-epar-product-information_cs.pdf **2.** Fontana M, et al. N Engl J Med 2025;392:33-44. **3.** Maurer MS, et al. Presented at the HFSA Annual Scientific Meeting, 27-30 Sept 2024.

Zkrácená informace o léčivém přípravku Amvuttra▼

Název přípravku: Amvuttra 25 mg injekční roztok v předplněné injekční stříkačce Účinná látka**:** vutrisiran sodný **Složení:** Jedna předplněná injekční stříkačka obsahuje vutrisiran sodný v množství odpovídajícím 25 mg vutrisiranu v 0,5 ml roztoku. **Léková forma:** Injekční roztok (injekce) **Terapeutická indikace:*** Získaná (*wild-type,* wtATTR) nebo hereditární transthyretinová amyloidóza u dospělých pacientů s kardiomyopatií (ATTR-CM), hereditární transthyretinová amyloidóza u dospělých pacientů s polyneuropatií v 1. či 2. stadiu (hATTR-PN). **Dávkování a způsob podání:*** Léčba má být zahájena pod dohledem lékaře se znalostmi léčby amyloidózy. Léčba má být zahájena co nejdříve po vzniku onemocnění, aby se předešlo nárůstu (kumulaci) postižení. Doporučená dávka přípravku Amvuttra je 25 mg, podávaná subkutánní injekcí jednou za 3 měsíce. U pacientů léčených přípravkem Amvuttra je doporučena suplementace vitamínu A v dávce přibližně 2500 IU až 3000 IU (ale ne vyšší) denně. U pacientů ve věku ≥ 65 let, u pacientů s lehkou nebo středně těžkou poruchou funkce ledvin, či lehkou nebo středně těžkou poruchou funkce jater není nutná úprava dávky. Přípravek nebyl studován u pacientů s těžkou poruchou funkce ledvin nebo s konečným stadiem onemocnění ledvin, nebo těžkou poruchou funkce jater. U těchto pacientů se má používat pouze tehdy, pokud očekávaný klinický přínos převáží nad potencionálními riziky. Přípravek Amvuttra může aplikovat zdravotnický pracovník, pacient nebo pečovatel. Pacienti nebo pečovatelé mohou injekčně aplikovat přípravek Amvuttra po proškolení zdravotnickým pracovníkem ve správné technice aplikace subkutánní injekce. **Kontraindikace:** Závažná hypersenzitivita (např. anafylaxe) na léčivou látku nebo na kteroukoli pomocnou látku. **Upozornění pro použití:** Deficit vitamínu A: Pacienti dostávající přípravek Amvuttra mají dostávat perorální suplementaci přibližně 2500 IU až 3000 IU (ale ne vyšší) vitamínu A denně, aby se snížilo možné riziko očních příznaků způsobených deficitem vitamínu A. **Lékové a jiné interakce:** Neočekává se, že by vutrisiran způsoboval interakce nebo že by byl ovlivňován inhibitory či induktory enzymů cytochromu P450, nebo že by moduloval aktivitu transportérů. Proto se neočekává, že by měl vutrisiran klinicky významné interakce s jinými léčivými přípravky. **Fertilita, těhotenství a kojení:** Léčba přípravkem Amvuttra snižuje sérové hladiny vitamínu A. Jak příliš vysoké, tak příliš nízké hladiny vitamínu A mohou být spojeny se zvýšeným rizikem malformace plodu. Je tedy nutné před zahájením léčby vyloučit těhotenství a ženy ve fertilním věku musí používat účinnou antikoncepci. Vzhledem k možnému teratogennímu riziku, vyplývajícímu z nevyrovnaných hladin vitamínu A, se přípravek Amvuttra nemá používat během těhotenství. Není známo, zda se vutrisiran vylučuje do lidského mateřského mléka. Na základě posouzení prospěšnosti kojení pro dítě a prospěšnosti léčby pro matku je nutno rozhodnout, zda přerušit kojení nebo ukončit/přerušit podávání přípravku Amvuttra. **Nežádoucí účinky:*** Časté nežádoucí účinky (≥ 1/100 až < 1/10): reakce v místě vpichu, zvýšená hladina alaninaminotransferázy a zvýšená hladina alkalické fosfatázy v krvi. **Inkompatibility:** Studie kompatibility nejsou k dispozici, a proto nesmí být tento léčivý přípravek mísen s jinými léčivými přípravky. **Uchovávání:** Neuchovávejte při teplotě nad 30 °C. Chraňte před mrazem. **Obsah balení:** Balení obsahuje jednu předplněnou injekční stříkačku určenou k jednorázovému použití. **Držitel rozhodnutí o registraci:** Alnylam Netherlands B.V., Antonio Vivaldistraat 150, 1083 HP Amsterdam, Nizozemsko. **Registrační číslo:** EU/1/22/1681/001 **Datum první registrace:** 15. září 2022 **Datum revize textu:** 06/2025.

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*Prosím, všimněte si změn v informacích o přípravku.

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Survival benefits of specialized heart failure clinics: Czech real-world evidence

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Klíčová slova:
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Farmakoterapie vedená doporučenými postupy
Specializované ambulance
Srdeční selhání

SOUHRN

Úvod: Srdeční selhání zůstává navzdory významnému pokroku ve farmakologické a přístrojové léčbě jednou z hlavních příčin morbidity a mortality celosvětově. Optimalizovaná farmakoterapie vedená doporučenými postupy (guideline-directed medical therapy, GDMT) a dostupnost specializované péče jsou zásadní pro zlepšení dlouhodobé prognózy pacientů. Vliv specializovaných ambulancí srdečního selhání na přežití pacientů v reálné klinické praxi však zůstává ve střední a východní Evropě nedostatečně zdokumentován.
Metody: Tato retrospektivní observační studie porovnávala dva vzájemně se doplňující soubory pacientů se srdečním selháním v České republice. Celostátní data byla získána z Národního registru hrazených zdravotních služeb (NRHZS) za období 2015–2023. Tato data byla porovnána se souborem 217 pacientů sledovaných ve specializované ambulanci srdečního selhání Ústřední vojenské nemocnice v Praze v letech 2017–2024. Pomocí deskriptivní statistiky a analýzy přežití byly hodnoceny farmakoterapie, dosažení cílových dávek doporučených guidelines, využití přístrojové léčby (ICD, CRT) a celková mortalita.
Výsledky: Pacienti sledovaní ve specializované ambulanci srdečního selhání byli častěji léčeni moderními prognosticky příznivými léčivy než pacienti v celostátním souboru. Výrazně častější bylo užívání inhibitorů angiotenzinového receptoru a neprilysinu (ARNI) a inhibitorů sodíko-glukózového kotransportéru 2 (SGLT2), stejně jako dodržování doporučených kombinací GDMT. Během dlouhodobého sledování činila celková mortalita v souboru specializované ambulance 10,6 %, přičemž odhadovaná míra přežití dosahovala 90,1 % ve 2 letech a 78,3 % v 7 letech. Léčba inhibitory SGLT2 a vyšší počet užívaných tříd prognosticky příznivé farmakoterapie byly spojeny s nižší mortalitou.
Závěr: Péče ve specializované ambulanci srdečního selhání byla spojena s vysokou mírou využití farmakoterapie vedené doporučenými postupy a numericky příznivějším přežitím ve srovnání s celostátními daty.

Keywords:
Guideline-directed medical therapy
Heart failure
Pharmacotherapy
Specialized clinics

ABSTRACT

Background: Heart failure (HF) remains a leading cause of morbidity and mortality worldwide despite major advances in pharmacological and device therapy. Optimized guideline-directed medical therapy (GDMT) and access to specialized care are crucial for improving long-term outcomes. The impact of specialized heart failure clinics on survival in real-world clinical practice remains insufficiently documented in Central and Eastern Europe.
Methods: This retrospective observational study compared two complementary datasets of HF patients in the Czech Republic. Nationwide data were obtained from the National Reimbursement of Healthcare Services Database (NRHZS) covering the period 2015–2023. These data were compared with a cohort of 217 patients followed at a specialized outpatient heart failure clinic at the Military University Hospital in Prague between 2017 and 2024. Pharmacotherapy patterns, achievement of guideline-recommended target doses, use of device therapy (ICD, CRT), and all-cause mortality were analyzed using descriptive statistics and survival analysis.
Results: Patients managed in the specialized heart failure clinic received modern disease-modifying therapies more frequently than patients in nationwide care. Use of angiotensin receptor–neprilysin inhibitors and SGLT2 inhibitors was markedly higher, as was adherence to recommended combinations of GDMT. During long-term follow-up, all-cause mortality in the specialized-clinic cohort was 10.6%, with estimated survival rates of 90.1% at 2 years and 78.3% at 7 years. Treatment with SGLT2 inhibitors and a higher number of prognostic drug classes were associated with lower mortality.
Conclusions: Management in a specialized outpatient clinic was associated with high uptake of guideline-directed medical therapy and numerically favorable survival compared with nationwide data.

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Introduction

Heart failure (HF) represents one of the most prevalent and challenging cardiovascular syndromes worldwide and remains a leading cause of morbidity, mortality, and healthcare expenditure. Despite substantial advances in pharmacological and device-based therapies over the past two decades, long-term prognosis of HF patients remains poor, particularly in elderly and multimorbid populations. The increasing prevalence of HF is largely driven by population ageing, improved survival after acute cardiovascular events, and broader recognition of the syndrome across healthcare systems.

Contemporary guideline-directed medical therapy (GDMT), including beta-blockers, renin–angiotensin system inhibitors, mineralocorticoid receptor antagonists, angiotensin receptor–neprilysin inhibitors (ARNI), and sodium–glucose cotransporter 2 (SGLT2) inhibitors, has been shown to significantly reduce mortality and hospitalization rates in randomized clinical trials. However, real-world implementation of these therapies remains suboptimal. Underutilization of novel agents, insufficient dose titration, and fragmented follow-up continue to limit the potential benefits of modern HF treatment, particularly outside specialized care settings.

Several observational studies and registries have demonstrated that structured management within specialized heart failure clinics is associated with improved adherence to guideline-recommended therapies, higher achievement of target drug doses, and better clinical outcomes. Multidisciplinary HF clinics typically provide protocol-driven pharmacotherapy titration, closer follow-up, patient education, and timely access to device therapy. Nevertheless, data directly comparing outcomes of patients treated in specialized HF clinics with nationwide real-world populations remain limited, particularly in the Central and Eastern Europe.

In the Czech Republic, previous nationwide analyses based on administrative healthcare databases have described trends in HF prevalence, incidence, and survival, revealing a persistently high disease burden and substantial gaps in GDMT implementation. At the same time, the role and impact of specialized HF outpatient clinics on patient outcomes at the population level have not been systematically evaluated.

Therefore, the aim of this study was to compare treatment patterns and survival outcomes between heart failure patients managed within a specialized outpatient HF clinic and patients captured in nationwide real-world data from the Czech Republic. By integrating data from the National Reimbursement of Healthcare Services Database with a well-characterized cohort from a specialized HF clinic, we sought to assess whether structured multidisciplinary care translates into measurable survival benefits in routine clinical practice.

Methods

Study design

This study was designed as a retrospective observational analysis comparing two complementary datasets of patients with heart failure (HF) in the Czech Republic. Nationwide administrative data were contrasted with a well-defined cohort of patients followed in a specialized outpatient heart failure clinic. The primary objective was to evaluate differences in treatment patterns, adherence to guideline-directed medical therapy (GDMT), and survival outcomes between routine nationwide care and structured specialized management.

Data sources

Nationwide data were obtained from the National Reimbursement of Healthcare Services Database (NRHZS), which captures comprehensive information on healthcare utilization reimbursed by the public health insurance system in the Czech Republic. The database includes diagnostic codes, hospitalizations, outpatient visits, prescribed pharmacotherapy, and device-based interventions. For the purpose of this study, data covering the period from January 1, 2015 to December 31, 2023 were analyzed.

The specialized cohort consisted of patients followed at the outpatient heart failure clinic within the Department of Internal Medicine of the Military University Hospital Prague. This clinic provides structured, guideline-based care with regular follow-up, protocol-driven pharmacotherapy titration, and access to advanced heart failure therapies. Patients were enrolled consecutively between January 2017 and December 2024.

Patient population and inclusion criteria

In the nationwide cohort, patients were identified based on the presence of a diagnosis of heart failure recorded as either a primary or secondary diagnosis using International Classification of Diseases, 10th Revision (ICD-10) codes I50.0, I50.1, or I50.9. Inclusion required at least one recorded hospitalization or outpatient encounter associated with HF during the study period.

In the specialized outpatient cohort, all consecutive adult patients with a confirmed clinical diagnosis of chronic heart failure managed in the specialized HF clinic were included. Diagnosis was established by the treating cardiologist or internist based on clinical presentation, imaging findings, and laboratory data in accordance with contemporary guideline recommendations.

Pharmacotherapy and device therapy assessment

Pharmacological treatment was assessed in both cohorts with a focus on guideline-directed medical therapy. The following drug classes were evaluated: beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), angiotensin receptor–neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), and sodium–glucose cotransporter 2 (SGLT2) inhibitors. In the specialized cohort, achievement of guideline-recommended target doses was systematically documented as part of routine clinical care.

Device therapy, including implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT), was recorded in both datasets where applicable. The presence of device therapy was identified using reimbursement and procedural codes in the nationwide database and clinical records in the specialized cohort.

Outcome measures

The primary outcome of interest was all-cause mortality. In the nationwide cohort, mortality was assessed using linked administrative records capturing death during hospitalization or documented termination of healthcare reimbursement. In the specialized cohort, survival status was obtained from clinical follow-up records and hospital information systems.

Secondary outcomes included patterns of pharmacotherapy use, adherence to GDMT, achievement of target doses, and utilization of device therapy. Comparisons between cohorts focused on differences in treatment intensity and their association with observed survival outcomes.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics, pharmacotherapy patterns, and device utilization in both cohorts. Continuous variables are presented as mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables are expressed as absolute numbers and percentages. Survival within the specialized outpatient cohort was assessed using Kaplan–Meier estimates. Comparisons between subgroups of patients within the cohort were performed using the log-rank test. Formal statistical comparison with nationwide registry data was not feasible due to the absence of patient-level data. Statistical analyses were performed using SPSS (version 25.0, IBM Corp., Armonk, NY, USA) and R statistical software. A two-sided *p*-value of less than 0.05 was considered statistically significant.

Ethical considerations

The study was conducted in accordance with Czech legislation governing the use of anonymized healthcare data and in compliance with the Declaration of Helsinki. Given the retrospective design and full anonymization of the data, individual informed consent was not required.

Results

Study population

The specialized outpatient cohort consisted of 217 patients followed at the heart failure clinic of the Department of Internal Medicine, Military University Hospital Prague. The clinic has provided continuous specialized care since 2017, with a primary focus on patients mainly with reduced left ventricular ejection fraction. Patients were followed between 2017 and early 2024, and data were obtained retrospectively from outpatient records and the electronic hospital information system.

Patient age ranged from 18 to 71 years. The mean age was 55.2 years, with a median of 58 years. Male patients predominated (165 patients, 76.0%), while 52 patients (24.0%) were female.

Baseline left ventricular ejection fraction (LVEF) ranged from 15% to 60%, with a mean value of 31.5% and a median of 30%. The majority of patients were classified as having heart failure with reduced ejection fraction (HFrEF, LVEF ≤40%), accounting for 192 patients (88.5%).

Table 1 – Baseline characteristics of the specialized heart failure clinic cohort

Characteristic	Value
Number of patients	217
Age, years (mean/median)	55.2/58
Male sex, n (%)	165 (76.0)
Female sex, n (%)	52 (24.0)
Left ventricular ejection fraction, % (mean/median)	31.5 / 30
HFrEF (LVEF ≤40%), n (%)	192 (88.5)
HFmrEF (LVEF 41–49%), n (%)	6 (2.8)
HFpEF (LVEF ≥50%), n (%)	19 (8.8)

HFmrEF – heart failure with mildly reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; LVEF – left ventricular ejection fraction.
Values are presented as absolute numbers and percentages unless otherwise stated.

Heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 41–49%) was present in 6 patients (2.8%), and heart failure with preserved ejection fraction (HFpEF, LVEF ≥ 50%) in 19 patients (8.8%) (**Table 1**).

Pharmacotherapy utilization

Pharmacological treatment at the time of the most recent outpatient visit reflected a high uptake of guideline-directed medical therapy. Beta-blockers were prescribed in

Table 2 – Distribution of heart failure-related pharmacotherapy in patients followed at the specialized outpatient heart failure clinic

Drug class	Number of patients	% of total
Beta-blockers	195	89.9
Angiotensin receptor–neprilysin inhibitors (ARNI)	175	80.6
Angiotensin-converting enzyme inhibitors (ACEi)	29	13.4
Angiotensin II receptor blockers (ARB)	9	4.1
Sodium–glucose cotransporter 2 inhibitors (SGLT2i)	171	78.8
Ivabradine	15	6.9
Furosemide	145	66.8
Mineralocorticoid receptor antagonists (MRA)	155	71.4
Indapamide	6	2.8
Hydrochlorothiazide	14	6.5
Vericiguat	16	7.4
Digoxin	3	1.4

Values are presented as absolute numbers and percentages of the total cohort.

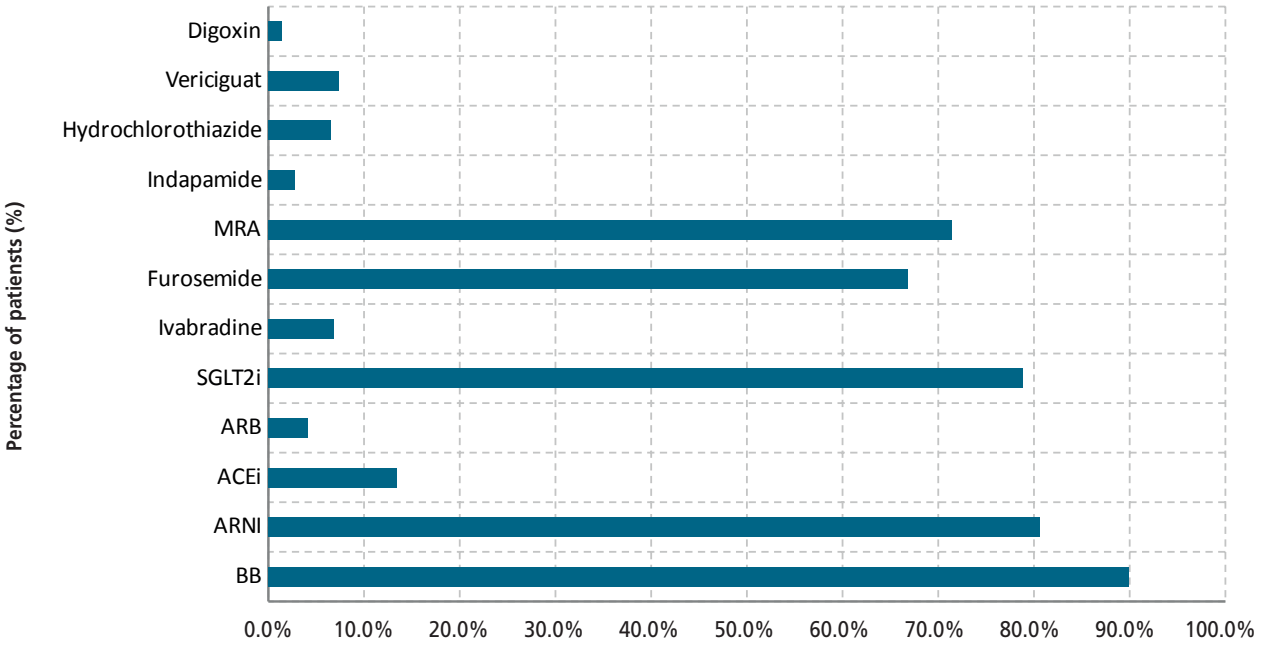

Fig. 1 Pharmacotherapy in the specialized heart failure clinic.

195 patients (89.9%), mineralocorticoid receptor antagonists in 155 patients (71.4%), and sodium–glucose cotransporter 2 inhibitors (SGLT2i) in 171 patients (78.8%). Loop diuretic therapy with furosemide was recorded in 145 patients (66.8%).

Angiotensin receptor–neprilysin inhibitors (ARNI) were used in 175 patients (80.6%). Angiotensin-converting enzyme inhibitors (ACEi) were prescribed in 29 patients (13.4%), and angiotensin receptor blockers (ARB) in 9 patients (4.1%), predominantly in patients not receiving ARNI therapy. Additional heart failure–related pharmacotherapy included ivabradine in 15 patients (6.9%), vericiguat in 16 patients (7.4%), digoxin in 3 patients (1.4%), hydrochlorothiazide in 14 patients (6.5%), and indapamide in 6 patients (2.8%) (**Table 2**, **Fig. 1**).

Among patients with heart failure with reduced ejection fraction (HFrEF; n = 192), ARNI therapy was prescribed in 175 patients (91.1%).

Compared with published nationwide Czech data, uptake of contemporary guideline-directed medical therapy was higher in the present cohort. In the nationwide analysis, ARNI and SGLT2 inhibitors were prescribed in 7.8% and 16.1% of patients, respectively, whereas in the present cohort these proportions reached 80.6% and 78.8% at the most recent outpatient visit. Similarly, beta-blockers were more frequently used (89.9% vs. 62.6%), while ACE inhibitors and ARBs were less common (13.4% and 4.1% vs. 42.1% and 16.5%, respectively).[1] Nationwide data did not allow stratification according to ejection fraction.

Target dose achievement

Achievement of guideline-recommended target doses was evaluated for key disease-modifying drug classes. Among patients treated with ARNI, target doses were achieved in 48 of 175 patients (27.4%). In patients receiving ACE inhibitors, target doses were achieved in 6 of 30 patients (20.0%). Due to the small number of patients treated with ARB (9 patients, 4.1%), further analysis of dose attainment in this subgroup was not performed. For beta-blockers, achievement of guideline-recommended target doses was observed in 20 of 195 treated patients (10.3%).

Device therapy utilization

Non-pharmacological treatment included device-based therapy in a substantial proportion of patients. Overall, implantable cardioverter-defibrillators were present in 69 patients (31.7%), and cardiac resynchronization therapy was utilized in 36 patients (16.5%). When restricted to patients with heart failure with reduced ejection fraction, device therapy utilization increased to 69 patients (35.9%) for implantable cardioverter-defibrillators and 36 patients (18.8%) for cardiac resynchronization therapy.

Survival and mortality outcomes

During the observation period from 2017 to 2024, a total of 23 deaths were recorded among 217 patients, corresponding to an all-cause mortality of 10.6%. Kaplan–Meier analysis demonstrated a gradual decline in cumulative survival over time; median survival was not reached. Estimated survival probability was 90.1% at 2 years, 84.7% at 4 years, and 78.3% at 7 years of follow-up.

Survival in the context of nationwide data

Survival outcomes of patients followed in the specialized heart failure outpatient clinic were interpreted in the context of previously published nationwide data. In a nationwide population-based study using the Czech National Healthcare Reimbursement Database, Táborský et al. reported an annual all-cause mortality rate of 15.9%

among heart failure patients in 2018, despite a gradual improvement over time. Mortality remained strongly age-dependent, reaching 17.7% in patients aged ≥65 years.[2] When contrasted with these population-level data, patients followed in the specialized heart failure outpatient clinic demonstrated favorable long-term cumulative survival within the observed follow-up period. Direct statistical comparison between cohorts was not performed due to the use of aggregated nationwide data and differences in age distribution and heart failure phenotype. It should be noted that nationwide mortality rates represent annual population-based estimates and are not directly comparable to cumulative Kaplan–Meier survival estimates.

Causes of death

Among the 23 deaths, 16 (69.6%) were classified as cardiac, 6 (26.1%) as non-cardiac, and 1 (4.3%) as unknown. Heart failure was the leading cardiac cause (12 cases, 52.2%), followed by ischemic heart disease including myocardial infarction (2 cases, 8.7%) and arrhythmogenic causes (2 cases, 8.7%). Non-cardiac causes included malignancy (2 cases, 8.7%), renal failure (2 cases, 8.7%), hemorrhagic shock (1 case, 4.3%), and infection (pneumonia; 1 case, 4.3%).

Treatment and age differences between survivors and non-survivors

Use of SGLT2 inhibitors differed between survivors and non-survivors (81.4% vs. 56.5%, respectively; p <0.05). The mean number of prognostic drug classes (ARNI or ACEi/ARB, beta-blocker, MRA, SGLT2 inhibitor) was 3.1 ± 0.8 among survivors and 2.5 ± 1.0 among non-survivors (p <0.05).

In unadjusted analysis, SGLT2 inhibitor therapy was associated with lower mortality (OR 0.41; 95% CI 0.18–0.93; p <0.05). No statistically significant associations with mortality were observed for ARNI (OR 0.71; 95% CI 0.29–1.72), MRA (OR 0.76; 95% CI 0.32–1.83), or beta-blockers (OR 0.81; 95% CI 0.29–2.25).

Non-survivors were older than survivors (77.4 ± 6.1 vs. 69.1 ± 9.7 years; p <0.001). Regarding device therapy, ICD was present in 6 non-survivors (26.1%) and CRT in 5 non-survivors (21.7%); differences in ICD and CRT prevalence between survivors and non-survivors were not statistically significant (ICD p = 0.489; CRT p = 0.618).

Discussion

Principal findings

To our knowledge, this study represents the first direct real-world comparison between a structured specialized heart failure outpatient clinic and nationwide administrative data in the Czech Republic. It provides real-world evidence demonstrating that management of heart failure patients within a specialized outpatient clinic is associated with a high level of adherence to guideline-directed medical therapy and favorable survival outcomes. Patients followed in the specialized heart failure clinic were predominantly characterized by a reduced ejection fraction phenotype, received modern disease-modifying pharmacotherapy at high rates, and exhibited lower all-cause mortality compared with nationwide data.[2]

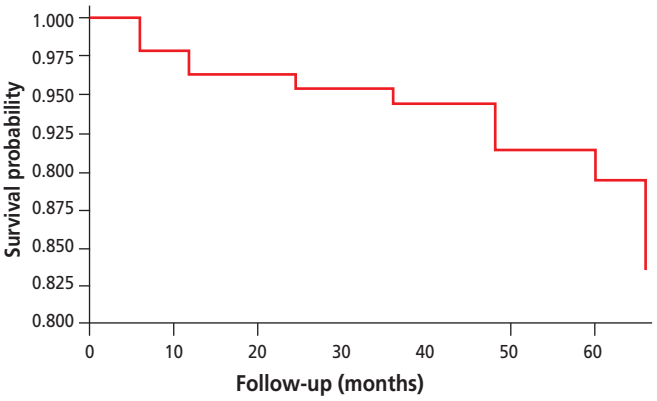

Fig. 2 – Kaplan–Meier overall survival curve.

The specialized outpatient cohort was highly enriched with patients with heart failure with reduced ejection fraction, accounting for nearly 90% of the population. This reflects targeted referral and selection of patients most likely to benefit from evidence-based pharmacological and device-based therapies, for which the strongest prognostic benefit has been demonstrated in randomized trials and contemporary guidelines.[3] Utilization of modern pharmacotherapy, particularly angiotensin receptor–neprilysin inhibitors and sodium–glucose cotransporter 2 inhibitors, was markedly higher than reported in nationwide Czech data.[1,2]

Despite high prescription rates, achievement of guideline-recommended target doses remained limited, particularly for beta-blockers. Even in a specialized setting, achievement of full target doses remains challenging in routine practice, reflecting patient tolerance and clinical complexity rather than insufficient therapeutic intent. This finding is consistent with previous real-world studies showing that dose optimization represents a major unmet need in heart failure management, even in specialized care settings.[4] Nevertheless, the observed association between more comprehensive pharmacotherapy and improved survival supports the concept of cumulative benefit from combination therapy.

Lower all-cause mortality was observed when survival outcomes were interpreted in the context of previously published nationwide data.[2] Kaplan–Meier analysis demonstrated high cumulative survival over long-term follow-up. Although differences in patient selection must be considered, these findings support the concept that specialized outpatient care may contribute to improved outcomes in patients with chronic heart failure. Overall survival of patients followed at the specialized heart failure clinic is shown in **Figure 2**. These observations should be viewed in light of substantial differences in patient selection and age distribution between specialized outpatient cohorts and unselected nationwide populations.

Patient selection and phenotype

Interpretation of the present findings must take into account the specific patient selection and phenotype of the specialized outpatient cohort. Patients followed in

the specialized heart failure clinic were younger than those typically reported in nationwide registries, where the mean age of heart failure patients commonly exceeds 70–75 years.[1,5] Age is a major determinant of prognosis in heart failure and represents an important confounder when comparing outcomes between specialized and unselected populations.

Nearly 90% of patients in the specialized cohort had heart failure with reduced ejection fraction, whereas population-based datasets report a substantially higher proportion of patients with preserved or mildly reduced ejection fraction.[2,6] This predominance of HFrEF reflects both the clinical focus of the specialized clinic and the fact that patients with reduced ejection fraction derive the greatest benefit from contemporary disease-modifying therapy.[1]

The predominance of male patients is consistent with registry data demonstrating higher prevalence of HFrEF among men, while women are more frequently represented in HFpEF populations.[6] Taken together, these characteristics indicate that patients followed in the specialized clinic constitute a prognostically more favorable subgroup. However, this selection reflects the real-world role of specialized heart failure clinics as referral centers for patients most likely to benefit from intensive, guideline-directed management.

Impact of optimized pharmacotherapy

Optimized pharmacotherapy represents the cornerstone of contemporary heart failure management and a central component of care delivered in specialized heart failure clinics. In the present study, uptake of angiotensin receptor–neprilysin inhibitors and sodium–glucose cotransporter 2 inhibitors substantially exceeded rates reported in nationwide Czech analyses as well as in other contemporary European and international real-world registries, where implementation gaps in guideline-directed medical therapy remain evident.[1,2,7]

Despite high prescription rates, achievement of guideline-recommended target doses remained limited across all major drug classes. This observation is consistent with prior real-world studies demonstrating that dose escalation is frequently constrained by hypotension, renal dysfunction, bradycardia, and drug intolerance.[4] Importantly, evidence suggests that even submaximal doses confer prognostic benefit compared with non-use, supporting early initiation and gradual titration whenever feasible.[8]

A key finding of the present analysis is the association between overall pharmacotherapy intensity and survival. Survivors received a significantly higher number of prognostically relevant drug classes compared with non-survivors, supporting the concept of comprehensive guideline-directed medical therapy.

Treatment with SGLT2 inhibitors was associated with a statistically significant reduction in mortality, consistent with findings from randomized trials and meta-analyses demonstrating early and robust benefits of this drug class across a broad spectrum of heart failure patients.[8] However, this observation should not be interpreted as evidence of superiority of SGLT2 inhibitors over other foundational therapies. In our cohort, angiotensin receptor–neprilysin inhibitors, beta-blockers, and mineralocorticoid receptor antagonists were prescribed in a very high proportion of patients, resulting in limited exposure variability and reduced statistical power to detect between-group differences.

By contrast, SGLT2 inhibitors were introduced later during the study period and showed greater prescription heterogeneity, which may have facilitated detection of their protective association in a simple univariable model. Given the limited number of events and the absence of multivariable adjustment, these findings should be interpreted as supportive of the four-pillar therapeutic strategy as a whole rather than as evidence favoring any single drug class.

Role of device therapy

Device-based therapy represents an important component of comprehensive heart failure management, particularly in patients with reduced ejection fraction at increased risk of sudden cardiac death or ventricular dyssynchrony. In the present study, the prevalence of implantable cardioverter-defibrillators and cardiac resynchronization therapy was comparable to that reported in the Czech and international registries focusing on advanced heart failure populations.[6,9,10]

No statistically significant association between device therapy and mortality was observed. This finding should be interpreted in the context of indication bias, as device therapy is typically indicated in patients with more advanced disease and higher baseline risk. Similar observations have been reported in other observational studies, where the survival benefit demonstrated in randomized trials is attenuated in real-world analyses due to confounding by indication and limited statistical power.[6] Importantly, the clinical benefits of implantable cardioverter-defibrillators extend beyond all-cause mortality and primarily involve prevention of sudden cardiac death, as demonstrated in landmark randomized trials.[11,12] Cardiac resynchronization therapy has been shown to improve symptoms, reduce heart failure hospitalizations, and induce reverse ventricular remodeling.[13–15] Therefore, assessment based solely on all-cause mortality may underestimate the overall clinical impact of device therapy in specialized outpatient settings.[3]

Survival benefit of specialized heart failure clinics

The favorable survival observed in the present specialized outpatient cohort may reflect both patient characteristics and organizational aspects of care delivery. Although differences in age distribution and heart failure phenotype must be acknowledged, structured management within a dedicated heart failure clinic likely contributes to optimized implementation of guideline-directed medical therapy.

Specialized clinics enable rapid initiation of novel pharmacological agents, structured up-titration protocols, close monitoring of treatment tolerance, and timely referral for device therapy when indicated. Continuity of care, regular follow-up, and management by experienced clinicians may facilitate early recognition of clinical deterioration and prevention of adverse outcomes.

Observational studies from Western and Northern Europe have reported improved outcomes in patients managed

within structured heart failure programs or multidisciplinary disease management systems.[16–18] Similarly, registry-based analyses suggest that earlier initiation and sustained implementation of comprehensive pharmacotherapy are associated with more favorable survival trajectories.[5,8]

Recent prospective evidence further highlights the importance of intensive outpatient management. The STRONG-HF trial demonstrated that rapid initiation and up-titration of guideline-directed medical therapy combined with close post-discharge follow-up significantly reduced 180-day heart failure readmission and all-cause mortality.[19] These findings emphasize the clinical relevance of early treatment optimization and structured patient contact during follow-up.

Data from the ESC Heart Failure Long-Term Registry provide additional context. In that large contemporary European cohort, patients were generally older, more heterogeneous with respect to ejection fraction, and characterized by substantial comorbidity burden. Despite widespread use of evidence-based therapies, 1-year mortality remained considerable.[5] In comparison, patients followed in our specialized outpatient clinic were younger, predominantly had heart failure with reduced ejection fraction, and demonstrated higher uptake of contemporary disease-modifying therapies, which may partly explain the more favorable survival observed in our cohort.

Clinical implications

The present results have several important implications for clinical practice and healthcare organization. They support early referral of eligible patients to specialized heart failure services, particularly those with reduced ejection fraction who stand to benefit most from optimized therapy. Dedicated heart failure clinics are uniquely positioned to initiate combination therapy early, manage side effects, and pursue dose optimization through structured follow-up.

At the healthcare system level, expansion of specialized heart failure clinics and regional care networks may represent an effective strategy to improve outcomes and reduce the burden of heart failure. Although such models require investment, their potential to improve survival and reduce hospitalizations suggests favorable cost-effectiveness in the long term.

Our findings from routine clinical practice are consistent with these results and suggest that specialized heart failure outpatient clinics may provide an effective framework for treatment optimization, monitoring, and patient education in routine clinical practice. In contrast to randomized clinical trials, our study reflects everyday care in a specialized setting and demonstrates that high uptake of modern disease-modifying therapies and favorable long-term survival can be achieved in a real-world population. This supports the role of structured multidisciplinary care as an important component of contemporary heart failure management.

Study limitations

Several limitations should be acknowledged. The retrospective observational design precludes causal inference, and residual confounding cannot be excluded. The specialized cohort represents a selected population that was younger and predominantly affected by heart failure with reduced ejection fraction, limiting direct comparability with nationwide populations. In addition, the relatively small sample size and limited number of deaths restrict statistical power, particularly for subgroup analyses.

Pharmacotherapy data reflect treatment at the most recent outpatient visit and do not fully capture longitudinal treatment changes, adherence, or reasons for dose reduction. Furthermore, nationwide data used for contextual comparison rely on administrative coding and lack detailed clinical parameters.

Although the majority of patients had heart failure with reduced ejection fraction, a smaller proportion of patients with heart failure with mildly reduced or preserved ejection fraction was also included. As several disease-modifying pharmacological therapies and device-based interventions are primarily indicated for patients with heart failure with reduced ejection fraction, their overall utilization rates may appear lower when calculated for the entire cohort. This should be taken into account when interpreting the presented treatment data.

Finally, data on heart failure-related rehospitalizations were not available in the analyzed dataset and therefore could not be evaluated. Rehospitalization rates nevertheless represent an important clinical outcome and should be addressed in future studies assessing the impact of specialized heart failure outpatient care.

Nationwide data used for contextual comparison were available only in aggregated form and did not allow patient-level matching with respect to age, comorbidities, or heart failure phenotype. Therefore, formal statistical comparison of survival between the cohorts was not performed.

Despite these limitations, the study provides valuable real-world insight into the impact of specialized outpatient care on heart failure management and outcomes.

Conflict of interest

The authors declare that they have no conflicts of interest related to this manuscript.

Funding

This research received no external funding.

Ethical statement

The study was conducted in accordance with Czech legislation governing the use of anonymized healthcare data and in compliance with the principles of the Declaration of Helsinki.

Informed consent

Given the retrospective design of the study and the use of fully anonymized data, individual informed consent was not required.

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Původní sdělení | Original research article

Endothelial Dysfunction in Non-Diabetic Patients and Coronary Calcification: A Different Pathway to Coronary Artery Disease?

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Endoteliální dysfunkce

SOUHRN

Cíl: Cílem studie bylo posoudit, zda je endoteliální dysfunkce (ED) u pacientů s ischemickou chorobou srdeční (ICHS) spojena s nižší prevalencí koronárních makrokalcifikací (CMC), jež představují marker pokročilejší a obvykle stabilnější remodelace aterosklerotického plátu.
Metody: Tato sekundární analýza zahrnovala 77 konsekutivních pacientů zařazených do studie FiGARO. Endoteliální funkce byla hodnocena pomocí přístroje EndoPAT 2000, přičemž ED byla definována jako index reaktivní hyperemie (RHI) < 1,67. Koronární angiogramy byly retrospektivně přehodnoceny zaslepenými hodnotiteli s cílem stanovit přítomnost angiograficky patrných makrokalcifikací. Pacienti byli rozděleni do tří, předem definovaných skupin: diabetici, nediabetici se zachovanou endoteliální funkcí (RHI ≥ 1,67) a nediabetici s ED. Mezi skupinami byly porovnány klinické charakteristiky, tradiční rizikové faktory a angiografické nálezy. Nezávislé prediktory CMC byly identifikovány pomocí logistické regrese.
Výsledky: Endoteliální dysfunkce byla přítomna u 21 pacientů (27,3 %) a diabetes mellitus u 24 pacientů (31,2 %). Celková prevalence CMC činila 22,1 %. U nediabetických pacientů se prevalence CMC významně lišila mezi endoteliálními fenotypy: 31,6 % u osob se zachovanou endoteliální funkcí oproti 8,8 % u osob s ED (p = 0,04). Nediabetičtí pacienti s ED vykazovali nejnižší prevalenci CMC, a to navzdory obdobnému věku i zátěži rizikovými faktory. Zachovaná endoteliální funkce byla u nediabetiků nezávislým prediktorem přítomnosti CMC (poměr šancí [OR] 4,77; 95% poměr spolehlivosti [CI] 1,03–22,0; p = 0,045), přičemž tento vztah přetrval i po adjustaci na věk, dyslipidemii, arteriální hypertenzi, chronické onemocnění ledvin a aktivní kouření (OR 6,96; 95% CI 1,27–38,19; p = 0,026).
Závěry: U nediabetiků s ICHS je endoteliální dysfunkce spojena s výrazně nižší prevalencí koronárních makrokalcifikací, což naznačuje převahu nekalcifikovaného aterosklerotického fenotypu. Tato zjištění podporují koncept odlišných mechanismů aterogeneze, v jejichž rámci ED bez současných metabolických abnormalit odráží časnější, zánětlivě podmíněnou vaskulární patologii, nikoli pokročilou remodelaci spojenou s makrokalcifikacemi. Neinvazivní hodnocení endoteliální funkce tak může přispět k přesnějšímu odhadu rizika identifikací pacientů, kteří s vyšší pravděpodobností nesou nekalcifikované a potenciálně vulnerabilní pláty, a poskytovat tak doplňkovou informaci nad rámec tradičních kardiovaskulárních rizikových faktorů.

ABSTRACT

Objective: To evaluate whether endothelial dysfunction (ED) in patients with coronary artery disease (CAD) is associated with a lower prevalence of coronary macrocalcifications (CMC), a marker of more advanced and typically more stable plaque remodelling.
Methods: This secondary analysis included 77 consecutive patients enrolled in the FIGARO trial. Endothelial function was evaluated using the EndoPAT 2000 device, with ED defined as RHI <1.67. Coronary angiograms were re-assessed by blinded reviewers for the presence of angiographically visible macrocalcification. Patients were categorised into three predefined groups: diabetics, non-diabetics with preserved endothelial function (RHI ≥1.67), and non-diabetics with ED. Clinical characteristics, risk factors, and angiographic fin-

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dings were compared across groups. Logistic regression was used to identify independent predictors of CMC.
Results: ED was present in 21 patients (27.3%), and diabetes mellitus in 24 (31.2%). Overall, CMC was identified in 22.1% of the cohort. Among non-diabetic patients, the prevalence of CMC differed markedly across endothelial phenotypes: 31.6% in non-diabetics with preserved endothelial function versus only 8.8% in non-diabetics with ED (p = 0.04). Despite similar age and risk-factor burden, non-diabetic patients with ED had the lowest prevalence of CMC. In non-diabetics, preserved endothelial function independently predicted the presence of CMC (OR 4.77, 95% CI 1.03–22.0; p = 0.045). This association remained significant in multivariable analysis adjusting for age, dyslipidaemia, arterial hypertension, CKD, and active smoking (OR 6.96, 95% CI 1.27–38.19; p = 0.026).
Conclusions: Among non-diabetic patients with CAD, endothelial dysfunction is associated with a markedly lower prevalence of coronary macrocalcification, indicating a non-calcified atherosclerotic phenotype. These findings support the concept of divergent atherosclerotic pathways, in which ED without metabolic abnormalities reflects earlier, inflammation-driven vascular pathology rather than calcific remodelling. Non-invasive endothelial function testing may help refine risk stratification by identifying patients more likely to harbour non-calcified and potentially vulnerable plaques, thereby providing complementary information beyond traditional cardiovascular risk factors.

Keywords:
Coronary artery disease
Coronary calcification
Coronary pathophysiology
Endothelial dysfunction

Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide and arises through multiple pathogenetic pathways that share common risk factors but produce distinct morphological and clinical phenotypes of atherosclerosis. The classical model describes a chronic process driven by lipid infiltration, inflammation, oxidative stress, and endothelial dysfunction (ED), yet emerging evidence demonstrates that atherosclerosis is a heterogeneous disease whose dominant biological drivers vary considerably among individuals.[1]

Coronary calcification comprises a spectrum of mineralization patterns ranging from early microcalcifications to extensive macrocalcified deposits. Microcalcifications, detected as part of coronary artery calcium scoring during computed tomography, are thought to reflect active inflammatory processes and have been associated with plaque vulnerability and higher acute event risk.[2,3] In contrast, dense macrocalcifications, detectable on invasive coronarography – large, radiopaque calcific deposits corresponding to advanced fibrocalcific plaque – represent later, consolidated stages of atherosclerosis and are generally associated with greater plaque stability and lower propensity to rupture compared with non-calcified or microcalcified plaques.[4,5]

ED is widely recognized as an early and pivotal event in atherogenesis. It results from reduced nitric oxide bioavailability, increased oxidative stress, inflammatory activation, and impaired vascular homeostasis, and can be assessed through invasive or non-invasive techniques such as peripheral arterial tonometry (PAT).[6] Although ED is universally accepted as a risk factor for atherosclerosis,[7] its downstream consequences appear to differ depending on the aetiology of endothelial injury. In diabetes mellitus (DM) and metabolic syndrome, ED is driven predominantly by metabolic disturbances – including hyperglycaemia, insulin resistance, dyslipidaemia, and accumulation of advanced glycation end products – which promote endothelial activation, inflammation, and pro-calcific vascular remodelling.[8,9] Experimental and clinical studies have shown that in these condition, the ED accompanies accelerated osteogenic transformation of vascular smooth muscle cells, endothelial-to-mesenchymal transition, and ultimately vascular and coronary calcification.[10,11] In contrast, ED arising in the absence of metabolic dysregulation – such as that associated with hypertension, smoking, inflammatory stress, or impaired shear-stress signalling – may represent a biologically distinct phenotype and appears to reflect primarily inflammatory and functional endothelial impairment without the metabolic triggers known to drive calcific remodelling and as a consequence, it may be associated with earlier or predominantly non-calcified forms of atherosclerosis.[12] Non-invasive ED assessment using flow-mediated dilation or peripheral arterial tonometry has shown consistent associations with cardiovascular events; however, the evidence for its incremental predictive value beyond traditional risk factors remains limited to high risk population undergoing invasive coronarography.[13]

Based on this conceptual framework, we hypothesized that ED in non-diabetic patients with CAD could be associated with a distinct, predominantly non-macro calcified atherosclerotic phenotype with higher risk of plaque instability, whereas preserved endothelial function in non-diabetic patients is associated with macrocalcification burden similar to atherosclerosis phenotype in patients with diabetes.

Methods

We performed a secondary analysis of consecutive patients with known CAD enrolled in the FiGARO trial (NCT03033810), an international, multicentre prospective study comparing discrepancies between fractional-flow reserve (FFR) and instantaneous wave-free ratio (iFR) in the evaluation of coronary lesions.[14] The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee of the General University Hospital in Prague. All participants provided written informed consent prior to enrolment.

Endothelial function was evaluated by reactive-hyperaemia peripheral artery tonometry (RH-PAT) technique using the EndoPAT 2000 device (Itamar Medical, Caesarea, Israel), a validated peripheral arterial tonometry sys-

tem.[15] All examinations were performed according to the standard protocol in a quiet, temperature-controlled environment after an overnight fast and withholding vasoactive medications. Patients rested supine for at least 15 minutes before testing. Fingertip probes recorded pulse amplitude at baseline and during reactive hyperaemia induced by 5-minute brachial artery occlusion.[16] The device automatically calculated the reactive hyperaemia index (RHI); RHI values <1.67 were considered indicative of ED in accordance with published studies.[15,17]

Coronary angiograms of all included patients were re-evaluated for the presence of coronary macrocalcification (CMC) by two independent reviewers blinded to the ED results. Angiographically visible calcification was defined according to established interventional criteria as radiopaque, intraluminal or vessel-wall calcific deposits identifiable on fluoroscopy.[18] Calcification visible before contrast injection and in more than one projection were classified as CMC.

Baseline characteristics, including cardiovascular risk factors – body mass index (BMI), diabetes mellitus, arterial hypertension, dyslipidaemia, smoking status, chronic kidney disease (CKD), were obtained from clinical records and physical examinations.

Table 1 – Baseline characteristics of study population

Variable	N (%); median (IQR) / mean (SD)
Age	67.00 (13.00)
Female	16 (20.78%)
Height (cm)	175.00 (10.00)
Weight (kg)	90.00 (20.00)
BMI (kg/m^2)	28.95 (6.29)
Diabetes mellitus	24 (31.17%)
Arterial hypertension	59 (76.62%)
Dyslipidaemia	52 (67.53%)
CKD	9 (11.69%)
COPD	13 (16.88%)
Smoking history	58 (75.32%)
Current smoker	32 (41.56%)
PAD	17 (22.08%)
Coronary macrocalcification	17 (22.08%)
RHI	1.47 (0.42)
LVEF (%)	60.00 (18.00)
Hb (g/l)	138.50 (22.25)
WBC	8.23 (3.55)
Creatinine	84.00 (26.50)
LM stenosis	13 (17.57%)
LAD stenosis	31 (40.26%)

BMI – body mass index; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; IQR – interquartile range; Hb – hemoglobin; LAD – left anterior descending artery; LM – left main artery; LVEF – left ventricle ejection fraction; N – number of participants; PAD – peripheral artery disease; RHI – reactive hyperemia index; SD – standard deviation; WBC – white blood cell count.

For purposes of analysis, first the patients with/without ED were compared, second the population was divided into three subgroups – diabetics, non-diabetics without ED; non-diabetics with ED. Continuous variables are reported as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for skewed data. Categorical variables are presented as counts and percentages. Group differences were assessed using the Student's t-test for continuous variables and the χ^2 test for categorical variables. Logistic regression was used for uni- and multivariate testing. All tests were two-sided, and *p*-values <0.05 were considered statistically significant. Statistical analyses were performed using R version 4.4.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 77 patients were included (median age 67 years; 20.8% females). Baseline characteristics are summarized in **Table 1**.

Diabetes mellitus was present in 24 patients (31.2%), while endothelial dysfunction (RHI < 1.67) was observed in 21 patients (27.3%).

Compared with patients without ED, those with ED had significantly higher prevalence of diabetes (9.5% vs. 39.3%, $p = 0.03$) as depicted in **Table 2.**

No significant differences were found in age, smoking status, dyslipidaemia, presence of CKD, or prevalence of prior acute myocardial infarction. However, the trend towards higher prevalence of peripheral artery disease in patients with endothelial dysfunction was observed

Table 2 – Differences between patients with and without endothelial dysfunction

Comorbidity	RHI >1.67	RHI <1.67	*p*-value
Total	21 (27.3%)	56 (72.7%)	
Male	15 (71.4%)	46 (82.1%)	0.47
Discrepancy	11 (52.4%)	20 (35.7%)	0.29
AMI history	9 (42.9%)	24 (42.9%)	1.00
Diabetes mellitus	2 (9.5%)	22 (39.3%)	**0.03**
Arterial hypertension	14 (66.7%)	45 (80.4%)	0.34
Dyslipidaemia	11 (52.4%)	41 (73.2%)	0.14
CKD	2 (9.5%)	7 (12.5%)	1.00
Stroke history	2 (9.5%)	4 (7.1%)	1.00
COPD	4 (19.0%)	9 (16.1%)	1.00
Smoking history	15 (71.4%)	43 (76.8%)	0.85
Current smoker	8 (38.1%)	24 (42.9%)	0.91
PAD	1 (4.8%)	16 (28.6%)	0.05
Coronary macrocalcification	7 (33.3%)	10 (17.9%)	0.25

AMI – acute myocardial infarction; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; PAD – peripheral artery disease; RHI – reactive hyperemia index.

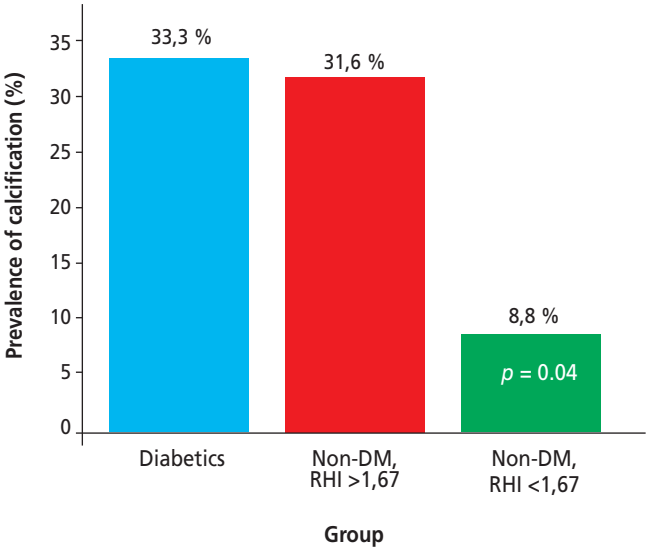

Fig. 1 – Differences in prevalence of coronary calcification according to diabetes or ED status.

Coronary macrocalcification was present in 22.1% of the entire cohort. When patients were stratified into three predefined phenotypic groups — diabetics, non-diabetics without ED, and non-diabetics with ED — a significant difference in CMC prevalence emerged as shown in **Figure 1**.

Non-diabetic patients with ED also exhibited the lowest prevalence of CMC despite comparable age and risk-factor burden (**Table 3**).

Among non-diabetic patients, presence of normal endothelial function (RHI >1.67) independently predicted the presence of CAC (OR 4.77, 95% CI 1.03–22.0; p = 0.045).

In a multivariable logistic regression model restricted to non-diabetic patients and including age, dyslipidaemia, arterial hypertension, CKD, and active smoking as covariates, RHI >1.67 remained a strong and independent predictor of CMC (OR 6.96, 95% CI 1.27–38.19; p = 0.026). None of the traditional risk factors reached statistical significance in this model (**Supplementary material 1**).

Discussion

In this study, we demonstrate that among non-diabetic patients with established CAD, the presence of endothelial dysfunction (ED) as assessed by the RHI-PAT method is associated with a markedly lower prevalence of coronary macrocalcification. This observation suggests that, in the absence of diabetes, ED may signal a distinct atherosclerotic phenotype characterized predominantly by non-calcified plaque components.

Previous work has shown that diverse pathogenic pathways shape the morphology of atherosclerotic plaques. Metabolic dysregulation – as seen in diabetes mellitus or chronic kidney disease – has consistently been linked to an increased burden of coronary artery calcium and more advanced mineralized atherosclerosis.[19,20] Our findings extend these observations by demonstrating that non-diabetic CAD patients with ED exhibit significantly fewer coronary macrocalcifications compared with both non-diabetic individuals without ED and with diabetic patients. Although ED is commonly observed in diabetes,[21] its presence in non-diabetic individuals likely reflects alternative mechanisms—such as inflammation, impaired nitric oxide bioavailability, endothelial activation, or prothrombotic imbalance—that promote the formation of non-calcified or minimally calcified plaques rather than mineralized lesions.

The inverse association between ED and coronary macrocalcification in non-diabetic patients may therefore reflect different stages of plaque evolution. Macrocalcification represents a late and largely reparative phase of atherosclerosis,[4] whereas ED in the absence of metabolic disease corresponds to an earlier, inflammation-driven phenotype characterized by diminished nitric oxide signalling, endothelial activation, and increased vascular permeability.[12] These processes favour the formation of non-calcified plaques but do not provide the osteogenic stimulus required for advanced mineralization.[11] By excluding patients with diabetes – where ED develops within a pro-calcific metabolic milieu – our data isolate a non-metabolic ED phenotype linked to less mature, less mineralized plaque architecture, providing a coherent mechanistic basis for the markedly lower prevalence of macrocalcification observed in this subgroup.

Table 3 – Differences between patients divided by presence of diabetes mellitus and endothelial dysfunction

Parameter	Diabetics	Non-diabetics preserved RHI	Non-diabetics, reduced RHI	*p*-value
Age (median, IQR)	69.0 (IQR 9.75)	65.0 (IQR 14.50)	65.5 (IQR 11.25)	0.47
Smoking history (%)	75.0%	68.4%	79.4%	0.67
Current smoker (%)	20.8%	42.1%	55.9%	0.03
Arterial hypertension (%)	91.7%	63.2%	73.5%	0.08
Dyslipidaemia (%)	87.5%	47.4%	64.7%	0.02
CKD (%)	16.7%	10.5%	8.8%	0.65
Triple-vessel disease (%)	70.8%	52.6%	55.9%	0.40
Coronary calcification (%)	33.3%	31.6%	8.8%	0.04

CKD – chornic kidney disease; RHI – reactive hyperaemia index.

Importantly, accumulating evidence indicates that the degree of coronary calcification is not only a marker of plaque burden but also of plaque stability. Dense macrocalcifications are repeatedly associated with a lower risk of major adverse cardiovascular events (MACE), whereas non-calcified and low-attenuation plaques confer a higher risk of instability and rupture.[22,23] Against this background, the relative absence of macrocalcification in non-diabetic patients with ED may identify a subgroup with more active, inflammation-driven, and potentially higher-risk plaque biology despite comparable angiographic disease severity.

These findings may have practical clinical implications. Contemporary trials support conservative management strategies in stable CAD,[24,25] yet the ability to identify patients who harbour predominantly non-calcified and potentially vulnerable plaques remains limited in routine practice. Endothelial function testing – simple, non-invasive, and easily repeatable – may offer a complementary tool for refining risk stratification in non-diabetic patients with CAD. Such individuals with ED could represent candidates for intensified diagnostic assessment, including coronary computed tomography angiography, which is particularly sensitive for detecting non-macro calcified plaque features. Furthermore, this phenotype may benefit from more aggressive preventive measures, including tighter LDL-C lowering or anti-inflammatory strategies, given the biologically active nature of non-calcified atherosclerosis.

In summary, our data support the concept of two divergent atherosclerotic phenotypes in non-diabetic CAD: (1) a calcific–metabolic phenotype characterized by preserved endothelial function, and (2) a non-calcified, ED-driven phenotype potentially reflecting heightened inflammatory activity. Future imaging and mechanistic studies are warranted to clarify the determinants of these patterns and to determine whether integrating endothelial function into clinical decision-making can improve patient outcomes.

Limitations

This study has several limitations. It was a single-center analysis with a relatively small sample size, which may limit generalizability. Endothelial function was measured peripherally using EndoPAT, which may not fully reflect coronary endothelial physiology. Finally, the cross-sectional design precludes causal inference despite multivariable adjustment.

Conclusion

In non-diabetic patients with coronary artery disease, endothelial dysfunction was associated with a significantly lower prevalence of coronary macrocalcification. This finding supports the existence of distinct atherosclerotic phenotypes and suggests that endothelial function assessment may aid in refining cardiovascular risk stratification beyond traditional factors in the era of data supporting conservative treatment of stable CAD.

Conflict of interest
The authors have no relevant financial or non-financial interests to disclose.

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Ethical statement
The study was conducted in accordance with the Declaration of Helsinki.

Informed consent
Written informed consent was obtained from all individual participants included in the study.

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Původní sdělení | Original research article

Účinnost psychologických intervencí v léčbě arteriální hypertenze: přehledová studie

(The efficacy of psychological interventions in the treatment of arterial hypertension: a narrative review)

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Hypertenze
Kvalita života
Nefarmakologická léčba
Psychologické intervence

SOUHRN

Cíl: Cílem této přehledové studie bylo zhodnotit účinnost psychologických intervencí v léčbě arteriální hypertenze se zaměřením na jejich vliv na krevní tlak, psychologické ukazatele (stres, úzkost, deprese) a kvalitu života pacientů.
Metodika: Byly analyzovány randomizované kontrolované studie publikované v letech 2015–2025, vyhledané v databázích PubMed, ScienceDirect a Cochrane Library. Zařazeny byly studie hodnotící kognitivně-behaviorální terapii (KBT), intervence založené na všímavosti (mindfulness) a zvládání stresu a relaxační techniky. Metodologická kvalita studií byla hodnocena pomocí škály PEDro.
Výsledky: Do přehledu bylo zařazeno 17 randomizovaných kontrolovaných studií (RCT). Většina studií prokázala statisticky významné snížení systolického krevního tlaku, zejména u intervencí založených na KBT a mindfulness. Kognitivně-behaviorální terapie vykazovala nejrobustnější dlouhodobý efekt na krevní tlak, adherenci k léčbě a kvalitu života. Mindfulness intervence byly spojeny s redukcí stresu, úzkosti, deprese a s příznivými změnami biologických markerů zánětu. Relaxační techniky měly rychlý fyziologický efekt, který byl nejsilnější při kombinaci s kognitivně-behaviorálními přístupy.
Závěr: Psychologické intervence představují účinný a klinicky relevantní doplněk standardní léčby arteriální hypertenze. Jejich integrace do komplexní péče může přispět ke zlepšení kontroly krevního tlaku, psychické pohody i kvality života pacientů.

Keywords:
Hypertension
Non-pharmacological therapy
Psychological intervention
Quality of life

ABSTRACT

Aim: The aim of this narrative review was to evaluate the effectiveness of psychological interventions in the treatment of arterial hypertension, with a particular focus on their impact on blood pressure, psychological outcomes (stress, anxiety, depression), and quality of life.
Methods: Randomized controlled trials published between 2015 and 2025 were identified through searches of PubMed, ScienceDirect, and the Cochrane Library. Studies evaluating cognitive behavioral therapy (CBT), mindfulness-based interventions, relaxation techniques, and stress management programs were included. Methodological quality was assessed using the PEDro scale.
Results: A total of 17 RCTs were included in the review. Most studies reported a statistically significant reduction in systolic blood pressure, particularly in interventions based on CBT and mindfulness. CBT demonstrated the most robust long-term effects on blood pressure reduction, treatment adherence, and quality of life. Mindfulness-based interventions were consistently associated with reductions in perceived stress, anxiety, and depressive symptoms, as well as favorable changes in biological markers of inflammation. Relaxation techniques produced rapid physiological effects, which were most pronounced when combined with cognitive-behavioral approaches.
Conclusion: Psychological interventions represent an effective and clinically relevant adjunct to standard hypertension management. Their integration into comprehensive care may improve blood pressure control, psychological well-being, and overall quality of life in patients with arterial hypertension.

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Úvod

Kardiovaskulární onemocnění (KVO) patří mezi hlavní příčiny morbidity a mortality na celosvětové úrovni a zároveň představují významnou zátěž pro zdravotnické systémy i společnost jako celek.[1,2] Jedním z nejvýznamnějších a zároveň dobře ovlivnitelných rizikových faktorů KVO je arteriální hypertenze, která představuje zásadní globální zdravotní problém současnosti. Podle údajů Světové zdravotnické organizace (WHO) trpělo v roce 2024 hypertenzí přibližně 1,4 miliardy osob ve věku 30–79 let, přičemž adekvátní kontrola krevního tlaku byla dosažena pouze u 23 % nemocných. Onemocnění často probíhá asymptomaticky, a proto zůstává téměř u poloviny postižených nediagnostikováno. Hypertenze je přitom hlavní příčinou předčasné mortality a významně se podílí na rozvoji infarktu myokardu, cévní mozkové příhody, srdečního selhání a chronického onemocnění ledvin.[3]

Vedle závažných somatických důsledků má hypertenze rovněž výrazný dopad na psychickou oblast. Pacienti s hypertenzí a dalšími kardiovaskulárními onemocněními často vykazují zvýšenou míru stresu, úzkosti a celkově sníženou kvalitu života.[4] Psychický stres, ať již souvisí s chronickým onemocněním, nebo vyplývá z externích životních zátěží, může dále přispívat ke zvyšování krevního tlaku a udržování bludného kruhu mezi psychickou zátěží a somatickými projevy onemocnění.[5] Chronická aktivace stresové odpovědi je spojena se zvýšenou aktivitou sympatického nervového systému a elevací koncentrací stresových hormonů, což vede k vazokonstrikci, tachykardii a dlouhodobému zvyšování krevního tlaku.[6] WHO[3] proto zdůrazňuje potřebu komplexního přístupu k léčbě hypertenze, který vedle farmakoterapie a úpravy životního stylu zahrnuje také nefarmakologické intervence zaměřené na modifikovatelné rizikové faktory, zejména na zvládání stresu a podporu dlouhodobé adherence k léčbě.

V posledních desetiletích se tak vedle farmakologické léčby stále více uplatňují psychologické intervence zaměřené na behaviorální, emoční a kognitivní mechanismy regulace krevního tlaku. Na základě přehledu intervencí uvedených v práci autorů Zou et al.[7] lze u pacientů s hypertenzí rozlišit několik hlavních terapeutických přístupů využívaných v klinické praxi, mezi něž patří integrovaná a koordinovaná péče, behaviorální a psychologické intervence a dále intervence zaměřené na fyzické zdraví a životní styl. Předkládaná přehledová studie se zaměřuje výhradně na behaviorální a psychologické způsoby ovlivnění hypertenze, které tvoří důležitou součást nefarmakologické léčby a představují doplněk standardní farmakoterapie.

Behaviorální a psychologické intervence jsou primárně zaměřeny na ovlivnění zdravotního chování, redukci stresu a podporu psychické pohody pacientů. Mezi klíčové přístupy patří behaviorální aktivace,[8,9] která podporuje systematické zapojování pacientů do smysluplných a příjemných činností. U osob s hypertenzí může tento přístup vést ke snížení psychické zátěže, omezení pasivního a sedavého životního stylu a ke zvýšení celkové úrovně aktivity, což může mít nepřímý, avšak klinicky relevantní dopad na regulaci krevního tlaku. Součástí behaviorální aktivace bývá strukturované plánování aktivit, stanovování realistických cílů a průběžná podpora adherence ke změnám životního stylu.

Další významnou oblast představuje psychoterapie, zejména kognitivně-behaviorální terapie (KBT).[10] Kognitivně-behaviorální terapie se zaměřuje na identifikaci a modifikaci maladaptivních myšlenkových schémat, nácvik dovedností zvládání stresu a rozvoj efektivních copingových strategií. Copingové strategie jsou vysvětleny jako specifické vědomé postupy (kognitivní či behaviorální), které jedinec využívá ke zvládnutí vnitřních nebo vnějších stresových situací. U pacientů s hypertenzí může tento terapeutický přístup přispívat ke snížení stresové reaktivity, lepšímu zvládání emočně náročných situací a ke zvýšení adherence k léčebným doporučením, což je klíčové pro dlouhodobou kontrolu krevního tlaku.

Zvláštní pozornost si zasluhují intervence založené na všímavosti (mindfulness-based interventions, MBIs), zejména programy snižování stresu založené na všímavosti (mindfulness-based stress reduction, MBSR) a kognitivní terapie založené na všímavosti (mindfulness-based cognitive therapy, MBCT). Mindfulness je definována jako záměrné a nehodnotící zaměření pozornosti na prožitky v přítomném okamžiku (tělesné vjemy, emoce, myšlenky), které vede k deaktivační odpovědi organismu a snížení stresové reaktivity. Tyto přístupy využívají techniky meditace, všímavého uvědomování a strukturované programy redukce stresu, které podporují vnímání tělesných a emočních procesů v přítomném okamžiku. Pravidelná praxe mindfulness může vést ke snížení psychofyziologického napětí, ovlivnění regulace autonomního nervového systému a ke zlepšení subjektivní pohody, což je zvláště významné u pacientů, u nichž se hypertenze rozvíjí v souvislosti s chronickým stresem.[11]

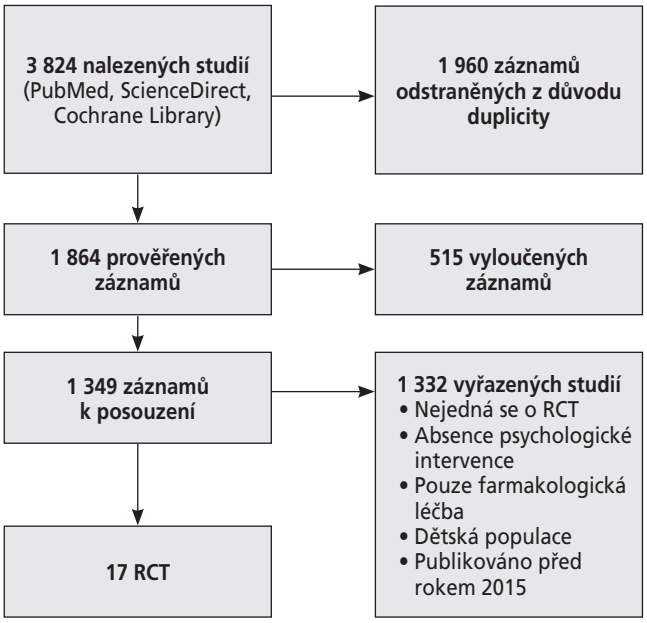
Další často využívanou metodou je progresivní svalová relaxace, založená na střídavém napínání a uvolňování jednotlivých svalových skupin. Tato technika přispívá ke snížení svalového i psychického napětí, redukci úzkosti a celkové aktivace sympatického nervového systému. V kontextu hypertenze může pravidelné zařazování relaxačních technik podpůrně působit na snížení krevního tlaku a zlepšení schopnosti pacientů regulovat stresové reakce.[12]

Celkově lze shrnout, že behaviorální a psychologické intervence tvoří důležitou a klinicky relevantní součást komplexní péče o pacienty s hypertenzí. Zaměřují se na oblasti, které farmakologická léčba sama o sobě nepostihuje, a mohou významně přispět ke zlepšení dlouhodobé kontroly krevního tlaku, adherence k léčbě i celkové kvality života pacientů.

Cílem tohoto přehledového článku bylo systematicky zhodnotit účinnost psychologických intervencí na hodnoty krevního tlaku u dospělých pacientů s arteriální hypertenzí.

Materiál a metodika

Za účelem nalezení studií nejvyšší úrovně důkazů hodnotících účinnost psychologických intervencí u pacientů s hypertenzí byly prohledávány elektronické databáze PubMed, ScienceDirect, Cochrane Library. Při vyhledávání byly použity klíčová slova: *hypertension, high blood pre-*



Obr. 1 – Schéma vyhledávání záznamů. RCT – randomizované kontrolované studie.

ssure, psychological intervention, non-pharmacological therapy (MeSH).

Vyhledávání bylo zaměřeno na randomizované kontrolované studie, publikované v posledních deseti letech, tj. od roku 2015 do roku 2025. Byla stanovena následující zařazující kritéria: typ studie: dále RCT, stáří studie: deset let, jazyk publikace: anglický. Vylučující kritéria: studie zaměřené výhradně na farmakoterapii, práce bez jasně definované psychologické intervence, studie u pediatrické populace, studie starší 10 let.

Prohledávání a hodnocení studií bylo provedeno dvěma nezávislými hodnotiteli. Celkem bylo identifikováno 3 824 záznamů, z nichž bylo 1 960 odstraněno z důvodu duplicity. Zbývajících 1 864 záznamů bylo prověřeno na základě názvu a abstraktu, přičemž 515 záznamů bylo vyloučeno. Do posouzení plného textu postoupilo 1 349 studií, z nichž 1 332 nesplnilo zařazující kritéria. Do konečného přehledu bylo zahrnuto 17 randomizovaných kontrolovaných studií (**obr. 1**).

Pro posouzení metodologické kvality a rizika zkreslení zahrnutých RCT byla použita škála PEDro.[13,14] Tento nástroj je vysoce validní pro hodnocení studií zabývajících se nefarmakologickými a behaviorálními intervencemi. Škála hodnotí 11 kritérií, přičemž výsledné skóre (0–10 bodů) je odvozeno z položek 2 až 11. Kvalita zařazených studií v tomto přehledu se pohybovala v rozmezí 4 až 8 bodů. Hodnocení kvality probíhalo nezávisle u dvou hodnotitelů a výsledné skóre bylo stanoveno na základě vzájemného konsenzu.

Výsledky

Tabulka 1 shrnuje vybrané behaviorální a psychologické intervence u pacientů s hypertenzí, které byly zařazeny do přehledové analýzy. Studie jsou seřazeny abecedně podle prvního autora a zahrnují výhradně RCTs. Přehled uvádí autora, rok publikace, zemi původu, velikost vzorku, typ intervence, charakter kontrolní skupiny, délku intervence a hlavní zjištění vztahující se ke změnám krevního tlaku a psychologických či biologických ukazatelů.

Do přehledu bylo zahrnuto celkem 17 studií. Nejstarší zařazená studie pochází z roku 2015,[15] zatímco nejnovější data reprezentuje studie z roku 2025.[16] Délka trvání intervencí se pohybovala od jednorázové intervence[16] až po [24] měsíců[17], přičemž většina výzkumných programů byla realizována v rozmezí 8 až 12 týdnů.[11,15,18–24] Kontrolní podmínky nejčastěji zahrnovaly běžnou péči, edukaci, farmakoterapii nebo aktivní kontrolní skupiny.

Z hlediska geografického původu byly studie realizovány v širokém spektru zemí, přičemž největší zastoupení měly práce z Íránu,[11,15,18,19,22] USA,[21,26,27] Číny[16,17,24] a Kanady,[27,28] následované výzkumy ze Španělska,[23,29] Indie[20] a Saúdské Arábie.[30]

Formát realizace intervencí byl rozdělen na skupinovou a individuální formu. Skupinový formát byl typický pro programy založené na mindfulness a klasické KBT.[11,15,18–25] Naproti tomu individuální přístup byl volen v případech digitálních intervencí, jako je využití aplikací v chytrých telefonech,[26] online e-poradenství[27,29] nebo u technik, jako jsou progresivní svalová relaxace a dechová cvičení.[30] V jednom případě se jednalo o kombinovaný formát.[16]

Základní zjištění ukazují, že psychologické a behaviorální intervence mají významný vliv na somatické i psychické parametry pacientů. Většina studií reportovala statisticky významné snížení systolického krevního tlaku.[10,11,15,17,18,20–23,26–28,30]

Významným aspektem sledovaných intervencí byl jejich vliv na psychické zdraví a celkovou pohodu pacientů. Intervence zaměřené na mindfulness a KBT vedly ke konzistentnímu snížení symptomů úzkosti a deprese. Tento efekt byl jasně prokázán u skupinových programů.[11,23,24] Dále bylo zaznamenáno výrazné snížení vnímaného stresu a hněvu, což jsou klíčové faktory ovlivňující kardiovaskulární zdraví. Pozitivní změny v těchto oblastech uváděli například Babak et al.[18] a Momeni et al.,[22] kteří u kardiaků a hypertoniků potvrdili efektivitu MBSR v redukci stresové zátěže. V USA bylo navíc u individuálních digitálních intervencí prokázáno snížení reaktivity kortizolu na stres.[26]

Zlepšení kvality života bylo dalším dominantním zjištěním napříč studiemi. Dlouhodobé intervence trvající dva roky vedly k trvalému zvýšení skóre kvality života související se zdravím.[17] K tomuto zlepšení přispěl nejen pokles krevního tlaku, ale také osvojení lepších copingových strategií pro zvládání zátěžových situací[15] a zvýšení sebeúčinnosti (self-efficacy) u pacientů,[24] která je definována jako subjektivní přesvědčení pacienta o vlastní schopnosti úspěšně realizovat činnosti nezbytné k dosažení kontroly nad onemocněním, např. dodržování dietního režimu nebo adherence k léčbě. Specifické biologické přínosy zahrnovaly snížení oxidačního stresu a hodnoty zánětlivého markeru interleukin 6 (IL-6).[19]

Dlouhodobé programy (1–2 roky) navíc prokázaly potenciál ke zlepšení adherence k léčbě[27] a snížení incidence cévních mozkových příhod.[17] Někteří autoři rovněž zdůrazňují potřebu individualizace intervencí na základě

Tabulka 1 – Přehled behaviorálních a psychologických intervencí u pacientů s hypertenzí (seřazeno abecedně podle autora)

Autor (rok)	Počet participantů	Intervence	Kontrolní skupina	Délka intervence, formát	Hlavní zjištění
Ahmadpanah et al. (2016),[11] Irán	60	Metakognitivní mindfulness + farmakoterapie	Pouze farmakoterapie	8 týdnů, skupinový	Psychoterapeutická léčba hypertenze snížila TK a symptomy deprese a úzkosti. Pozitivní účinky byly pozorovatelné při následném sledování o 8 týdnů později.
Babak et al. (2022),[18] Irán	80	Mindfulness	Běžná péče	12 týdnů, skupinový	Signifikantní pokles STK a DTK, zlepšení kvality života, snížení stresu
Birashk et al. (2018),[19] Irán	60	KBT + léky, mindfulness + léky	Léky	8 sezení, skupinový	KBT vedla ke snížení oxidačního stresu a hodnoty IL-6, ale **účinek nebyl statisticky významný ve srovnání s kontrolní skupinou**. Její efekt byl slabší než u mindfulness intervence. **Mindfulness** prokázala **významné snížení oxidačního stresu i koncentrace IL-6** oproti kontrolní skupině a byla **účinnější než KBT**, zejména v redukci zánětlivého markeru IL-6.
Clemow et al. (2018),[25] USA	92	KBT	Běžná péče	6 měsíců, skupinový	KBT intervence pro zvládání stresu a hněvu vedla ke statisticky významnému a klinicky významnému snížení STK. DTK nebyl významně snížen. Skóre měření emočního vyčerpání a depresivní ruminace ukázalo významné zlepšení a korelovalo se se snížením STK.
Dou et al. (2025),[16] Čína	240	Relaxace, relaxace + KBT	Běžná péče	Jednorázová intervence, individuální i skupinový	Nejsilnější účinek na snížení systolického i diastolického krevního tlaku měla kombinace relaxačního tréninku a kognitivní intervence. Samostatná relaxační terapie měla na STK omezený vliv.
Kumar et al. (2017),[20] Indie	40	Mindfulness	Běžná péče	8 týdnů, skupinový	Intervence vedla ke statisticky významnému snížení STK ve srovnání s kontrolní skupinou. U DTK nebyl rozdíl statisticky významný.
Lindsay et al. (2018),[26] USA	153	Mindfulness – smartphone	Edukace	15 lekcí, individuální	Intervence pomocí telefonu je účinná při snižování reaktivity kortizolu a STK na stres a pro dosažení těchto účinků je klíčové naučit se přijímat vlastní zkušenosti.
Liu et al. (2017),[17] Čína	409	KBT	Standardní péče	2 roky, individuální	Pokles STK a DTK, zlepšení kvality života a snížení prevalence cévní mozkové příhody
Loucks et al. (2023),[21] USA	201	Mindfulness	Běžná péče	9 týdnů, skupinový	Snížení STK o 4,9 mm Hg a zvýšení všímavosti ke stravě
Mensorio et al. (2019),[29] Španělsko	106	online KBT + psychoedukace	Běžná péče	13 týdnů, individuální	Významné rozdíly v antropometrických proměnných po intervenci (tj. BMI a obvod pasu), externím stravovacím stylu a skóre úzkosti a stresu
Momeni et al. (2016),[22] Irán	60	Mindfulness	Aktivní kontrola	8 týdnů, skupinový	Významný rozdíl mezi skupinami, pokud jde o hodnoty STK, vnímaného stresu a hněvu po testu. Skupiny se významně nelišily, pokud jde o DTK.
Nejati et al. (2015),[15] Irán	30	Mindfulness	Jóga	8 týdnů, skupinový	Pokles STK i DTK, zlepšení copingových strategií
Nolan et al. (2018),[27] Kanada	264	Online KBT	Standardní péče	12 měsíců, individuální	Zlepšení adherence, mírné snížení TK. Po 12 měsících vyvolalo online poradenství oproti kontrole větší snížení STK. U mužů v online skupině byly oproti kontrolní skupině zaznamenány také nižší hodnoty DTK, non-HDL cholesterolu, celkového cholesterolu a poměru celkového a HDL cholesterolu.
Pathan et al. (2023),[30] Saúdská Arábie	64	PMR, SBE, PMR+SBE	Běžná léčba	4 týdny, individuální	Kombinované intervence SBE a technik PMR mohou účinně snížit srdeční frekvenci, dechovou frekvenci, krevní tlak a úzkost u pacientů s hypertenzí ve srovnání s oběma technikami podávanými samostatně.
Ponte Márquez et al. (2019),[23] Španělsko	70	Mindfulness + meditace	Edukační kontrola	8 týdnů, skupinový	Významné snížení STK. Účinek se projevil zejména na klinicky měřeném STK a na 24hodinovém a nočním systolickém tlaku. U intervenční skupiny došlo také ke zlepšení psychologických charakteristik – byli méně hodnotící, více přijímající a méně depresivní.

Pokračování na další straně

Tabulka 1 – Přehled behaviorálních a psychologických intervencí u pacientů s hypertenzí (seřazeno abecedně podle autora)

Autor (rok)	Počet participantů	Intervence	Kontrolní skupina	Délka intervence, formát	Hlavní zjištění
Tanaka & Nolan (2018),[28] Kanada	263	E-poradenství (KBT + motivační rozhovory)	Standardní edukační materiály	12 měsíců, individuální	Byly identifikovány dva psychobehaviorální profily: **adaptivně přizpůsobení pacienti** s nízkou psychickou tísní a vysokou motivací ke změně chování a **afektivně distresovaní pacienti** s klinicky významnými symptomy deprese, vyšším stresem a vyšším BMI. Po 12 měsících byly u adaptivně přizpůsobených pacientů zaznamenány významné poklesy STK, zatímco u DTK se změny neprokázaly. Tito pacienti také výrazně častěji dokončili studii. U afektivně distresované skupiny nebylo možné výsledky statisticky hodnotit, avšak data naznačovala potenciální přínos intervence.
Zhang et al. (2024),[24] Čína	60	Mindfulness + edukace	Edukace	10 týdnů, skupinový	Výrazné snížení STK, pokles úzkosti a deprese a zlepšování skóre sebeúčinnosti

BMI – index tělesné hmotnosti; DTK – diastolický tlak; IL-6 – interleukin 6; KBT – kognitivně-behaviorální terapie; PMR – progresivní svalová relaxace; SBE – pomalé dýchání; STK – systolický tlak; TK – tlak krevní.

psychobehaviorálního profilu pacienta pro dosažení maximální efektivity léčby [28] (viz **tabulku 1**).

Diskuse

Výsledky této přehledové studie potvrzují, že arteriální hypertenze představuje komplexní biopsychosociální onemocnění, jehož průběh a léčebné výsledky jsou významně ovlivňovány psychickými a behaviorálními faktory. Chronický stres, úzkost a depresivní symptomatika přispívají ke vzniku i udržování zvýšeného krevního tlaku prostřednictvím dlouhodobé aktivace osy hypotalamus–hypofýza–nadledviny, zvýšené sympatické aktivity a následných neuroendokrinních a vaskulárních změn, včetně vazokonstrikce, endoteliální dysfunkce a systémového zánětu.[31–33] Tyto poznatky podporují současná mezinárodní doporučení, která zdůrazňují význam nefarmakologických intervencí jako doplňku farmakoterapie u pacientů s hypertenzí.[34,35]

Z analyzovaných psychologických intervencí se jako nejrobustnější z hlediska účinku na krevní tlak, adherenci k léčbě a kvalitu života jeví kognitivně-behaviorální terapie. Zahrnuté studie konzistentně prokazují snížení systolického krevního tlaku jak u krátkodobých skupinových programů, tak zejména u dlouhodobých individuálních intervencí.[16,17,25] Zvláštní význam má prospektivní studie Liu et al.,[17] která jako jediná hodnotila efekt psychologické intervence v horizontu dvou let a prokázala nejen trvalé snížení krevního tlaku a zlepšení kvality života, ale také nižší incidenci cévních mozkových příhod. Tento nález naznačuje, že dlouhodobá psychologická intervence může mít i preventivní kardiovaskulární efekt.

Mechanismus účinku KBT je pravděpodobně multifaktoriální. Terapie přispívá ke snížení stresové reaktivity, korekci maladaptivních kognitivních schémat a podpoře změn zdravotního chování, zejména v oblasti fyzické aktivity, stravovacích návyků a adherence k farmakoterapii.[36,39–42] Přímý biologický efekt KBT na zánětlivé procesy se však jeví jako méně výrazný než u intervencí založených na všímavosti, což naznačují srovnávací studie sledující oxidační stres a hodnoty IL-6.[19]

Relaxační techniky představují další důležitý pilíř nefarmakologické léčby hypertenze. Zahrnuté studie potvrzují jejich schopnost rychle snižovat krevní tlak, srdeční frekvenci a subjektivně vnímaný stres prostřednictvím modulace autonomního nervového systému.[44–46] Jejich efekt je však často krátkodobý a nejvýraznější přínos byl zaznamenán při kombinaci s kognitivně-behaviorálními přístupy.[16,30] To podporuje koncept, že relaxace účinně tlumí akutní fyziologickou aktivaci, zatímco dlouhodobá kontrola hypertenze vyžaduje současnou změnu kognitivních a behaviorálních vzorců.

Intervence založené na všímavosti (mindfulness-based interventions, MBI) se v posledních letech profilují jako perspektivní doplněk léčby hypertenze. Řada studií prokázala statisticky významné snížení systolického krevního tlaku, redukci stresu a zlepšení kvality života.[18,20–23] Mechanismus jejich účinku je komplexní a zahrnuje nejen snížení stresové reaktivity, ale také podporu seberegulace, akceptace onemocnění a dlouhodobé adherence k léčbě.[50,51] Zajímavým zjištěním je, že mindfulness intervence mohou mít silnější biologický efekt na zánětlivé markery než KBT,[19] avšak jejich účinnost na krevní tlak se zdá být výraznější u pacientů současně léčených farmakoterapií.[49]

Z hlediska formy realizace intervencí je nutné rozlišovat mezi klasickými psychologickými postupy a širšími behaviorálními či edukativními programy realizovanými digitální cestou. Studie využívající e-counseling[27] byly primárně zaměřeny na podporu režimových opatření a adherence k léčbě, přičemž psychologické techniky sloužily spíše jako podpůrný nástroj změny chování. Digitální forma proto nemusí být vhodná pro všechny pacienty a její indikace by měla zohledňovat individuální preference, životní styl a míru již existující zátěže spojené s prací u počítače. Přesto může e-Health představovat přínosnou alter-

nativu pro pacienty s omezenou dostupností péče nebo sníženou mobilitou.

Výsledky přehledu dále podtrhují význam individualizace psychologických intervencí. Analýza psychobehaviorálních profilů naznačuje, že odpověď na intervenci se může lišit podle psychologického a behaviorálního profilu pacienta. U adaptivně přizpůsobených pacientů byl po 12 měsících prokázán významný pokles STK, zatímco u afektivně distresované skupiny nebylo možné efekt vzhledem k dostupným datům statisticky spolehlivě vyhodnotit.

Metodologická omezení

Navzdory slibným výsledkům je nutné zohlednit metodologická omezení zahrnutých studií, zejména jejich krátkodobý charakter, heterogenitu intervencí a relativně malé velikosti vzorků. Tyto faktory limitují zobecnitelnost závěrů a zdůrazňují potřebu dalších dlouhodobých, metodologicky kvalitních studií zaměřených nejen na změny krevního tlaku, ale i na klinicky významné výstupy, jako je výskyt kardiovaskulárních komplikací.

Závěr

Psychologické intervence mohou představovat účinný a klinicky relevantní doplněk standardní léčby arteriální hypertenze a odpovídají současnému biopsychosociálnímu pojetí tohoto onemocnění. Výsledky zahrnutých studií ukazují, že zejména kognitivně-behaviorální terapie, intervence založené na všímavosti a strukturované relaxační techniky mohou přispívat ke zlepšení kontroly krevního tlaku, psychické pohody, adherence k léčbě a kvality života pacientů.

Dostupné výsledky rovněž naznačují, že příznivý efekt psychologických intervencí může přetrvávat i při dlouhodobém sledování. Ve dvouleté studii bylo vedle snížení krevního tlaku a zlepšení kvality života zaznamenáno také snížení výskytu cévních mozkových příhod. Vzhledem k omezenému počtu dlouhodobých studií je však třeba tyto výsledky interpretovat obezřetně.

Psychologická intervence není univerzálním řešením pro všechny pacienty s hypertenzí. Její využití by mělo vycházet z individuálních potřeb pacienta a z přítomnosti psychických či behaviorálních faktorů, které mohou ovlivňovat kontrolu krevního tlaku, zvládání onemocnění nebo adherenci k léčbě.

Pro klinickou praxi lze zvážit psychologickou intervenci zejména u následujících skupin pacientů:

1. **Pacienti s afektivním distresem** – osoby s přítomnými symptomy deprese, úzkosti nebo vysokou mírou subjektivně vnímaného stresu. K jejich identifikaci lze využít krátké screeningové nástroje (např. PHQ-9, GAD-7) nebo cílený klinický rozhovor. U těchto pacientů lze zvážit zejména kognitivně-behaviorální přístupy nebo intervence založené na všímavosti.
2. **Pacienti s nízkou adherencí k léčbě** – zejména pokud se na nedostatečném dodržování léčebného režimu podílí nízká motivace, obtíže se změnou zdravotního chování nebo maladaptivní přesvědčení o nemoci a léčbě. Psychologická intervence může být zaměřena na podporu změny zdravotního chování, posílení sebeúčinnosti a dlouhodobé adherence.
3. **Pacienti s vysokou stresovou reaktivitou** – jedinci, u nichž je patrná souvislost mezi emoční zátěží, pracovním stresem či konfliktními situacemi a opakovanou elevací krevního tlaku. Vhodné mohou být programy zvládání stresu, mindfulness a relaxační techniky, případně jejich kombinace s kognitivně-behaviorálními přístupy.
4. **Pacienti s opakovaně neuspokojivou kontrolou krevního tlaku, u nichž mohou hrát významnou roli psychické a behaviorální faktory** – u těchto pacientů lze psychologické vyšetření nebo konzultaci zvážit jako součást komplexního managementu onemocnění.

Budoucí výzkum by se měl zaměřit na standardizaci psychologických intervencí, identifikaci faktorů, které mohou předpovídat jejich účinnost, a především na dlouhodobé studie sledující nejen změny krevního tlaku a psychologických ukazatelů, ale také klinicky významné kardiovaskulární výstupy. Perspektivní oblast představují rovněž digitální formy intervencí, jejichž využití by mělo reflektovat individuální potřeby, preference a možnosti jednotlivých pacientů.

Cílené začlenění psychologických postupů do komplexní péče o pacienty s arteriální hypertenzí tak může přispět ke zlepšení kontroly onemocnění, psychické pohody a kvality života pacientů.

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Původní sdělení | Original research article

Effect of Prosthesis Orifice Area on Left Ventricular Reverse Remodeling After Surgical Aortic Valve Replacement

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SÚHRN

Cieľ: Cieľom štúdie bolo zhodnotiť, či veľkosť chlopňovej protézy po chirurgickej náhrade aortálnej chlopne (SAVR) ovplyvňuje rozsah reverznej remodelácie ľavej komory, a to aj pri neprítomnosti nezhody medzi pacientom a protézou.
Materiál a metódy: Do štúdie bolo zaradených 216 pacientov, ktorí v období od januára 2021 do decembra 2024 podstúpili izolovanú primárnu SAVR pre aortálnu stenózu s použitím jedného modelu chlopňovej protézy a ktorí nemali predoperačne ani pooperačne prítomnú fibriláciu predsiení. Echokardiografické parametre boli hodnotené predoperačne a jeden rok po operácii. Zmeny remodelácie ľavej komory boli analyzované vo vzťahu k indexovanej geometrickej ploche ústia protézy (iGOA).
Výsledky: Pri jednoročnej kontrole bolo zaznamenané významné zlepšenie takmer všetkých echokardiografických parametrov. Väčšia iGOA bola významne spojená s echokardiograficky zaznamenaným väčším nárastom indexovanej plochy aortálnej protézy (iAVA) (B = 0,321; 95% CI 0,134–0,509; p = 0,004) a s výraznejším zmenšením indexovaného end-systolického a end-diastolického rozmeru ľavej komory (iLVeSD a iLVeDD) (B = –6,578; 95% CI –13,071 až –0,086; p = 0,047 a B = –2,48; 95% CI –4,815 až –0,144; p = 0,038). Pri väčšej chlopňovej protéze sa pozoroval aj štatisticky nevýznamný trend k výraznejšiemu zlepšeniu ejekčnej frakcie ľavej komory (LVEF), k väčšiemu poklesu indexovanej hmotnosti ľavej komory (LVMi) a indexovanému objemu ľavej predsiene (LAVi).
Záver: Použitie väčšej chlopňovej protézy pri SAVR je spojené s výraznejšou reverznou remodeláciou ľavej komory, a to aj pri neprítomnosti nezhody medzi pacientom a protézou. Štatisticky významný vplyv na krátkodobé prežívanie sa nepreukázal.

Keywords:
Aortic stenosis
Indexed geometric orifice area
Reverse left ventricle remodeling
Surgical aortic valve replacement

ABSTRACT

Aim: This study aimed to evaluate whether valve prosthesis size after surgical aortic valve replacement (SAVR), even in the absence of patient–prosthesis mismatch, influences the magnitude of reverse left ventricular remodeling.
Material and methods: A total of 216 patients undergoing isolated SAVR for native AS with a single prosthetic valve model and without preoperative or postoperative atrial fibrillation between January 2021 and December 2024 were included. Echocardiographic parameters were assessed preoperatively and at 1-year follow-up. Changes in left ventricular remodeling were analyzed in relation to indexed geometric orifice area (iGOA).
Results: At 1-year follow-up, significant improvement was observed in nearly all echocardiographic parameters. Larger iGOA was significantly associated with an increase in indexed aortic valve area difference (B = 0.321, 95% CI 0.134–0.509; p = 0.004) and greater reductions in indexed left ventricular end-systolic and end-diastolic diameters (iLVeSD and iLVeDD) (B = –6.578, 95% CI –13.071 to –0.086, p = 0.047; B = –2.48, 95% CI –4.815 to –0.144, p = 0.038; respectively). A nonsignificant trend toward greater improvement in left ventricle ejection fraction (LVEF) and greater reductions in left ventricle mass index (LVMi) and left atrium volume index (LAVi) was also observed with larger valve prosthesis.
Conclusion: Larger prosthetic valve size during SAVR is associated with more pronounced reverse left ventricular remodeling, even in the absence of patient–prosthesis mismatch. No statistically significant effect on short-term survival was observed.

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Introduction

Aortic stenosis (AS) represents the most prevalent valvular heart disease in Western countries.[1] The incidence of this valvular disease increases with age, affecting approximately 2% of individuals older than 65 years and up to 12% of the population older than 75 years.[2,3] According to current European Association for Cardio-Thoracic Surgery (EACTS) guidelines, valve intervention (either surgical or transcatheter) is primarily indicated at an advanced stage of the disease.[4] However, increasing evidence suggests that significant myocardial alterations occur already in the preclinical stages of AS, with increased afterload triggering left ventricular remodeling before the onset of clinical symptoms.[5,6] Sustained pressure overload and altered hemodynamics lead to the classical development of left ventricular (LV) hypertrophy.[5,7,8] Impaired myocardial perfusion due to supply–demand mismatch promotes myocyte loss and fibrosis, with irreversible replacement fibrosis and partially reversible diffuse fibrosis.[3] LV remodeling leads to deterioration of both systolic and diastolic LV function.[5]

Aortic valve (AV) replacement (AVR) remains the gold standard of treatment for symptomatic severe AS. It is the most frequently performed valvular intervention, with approximately 280,000 procedures performed worldwide each year.[1] AVR effectively eliminates left ventricular outflow obstruction. This results in a significant reduction of the transvalvular pressure gradient. The decrease in afterload is expected to initiate reverse left ventricular remodeling (RLVR).[5,6,8,9] The extent of this reverse remodeling appears to depend on the degree of afterload reduction and on the presence of potentially reversible myocardial changes prior to the intervention. However, echocardiographic follow-up at 1 year after surgical or transcatheter AV replacement in the PARTNER 2 trial demonstrated improvement in the stage of cardiac damage in 16% of patients, no change in 58%, and worsening in 27%.[3] This suggests that reverse remodeling is a complex process dependent on multiple factors, including changes at the subcellular level.[7]

An important determinant of outcomes after AVR is the size of the implanted prosthetic valve, as reflected by the postoperative indexed aortic valve area (iAVA). Numerous studies have reported worse outcomes when the iAVA after AVR is <0.65 cm²/m², a condition defined as severe patient–prosthesis mismatch (PPM).[10–14] However, the PARTNER studies did not demonstrate impaired survival in patients with measured moderate PPM, defined by an measured iAVA between 0.65 and 0.85 cm²/m².[13] Moreover, some studies have reported a lower incidence of reoperation in patients with moderate PPM compared not only with those with severe PPM but also with patients without PPM (iAVA >0.85 cm²/m²).[12] In contrast, our previous study demonstrated preferentially better survival in patients with larger iAVA of a bioprosthetic valve compared with those with iAVA values at the borderline between moderate PPM and no PPM.[15] It is therefore notable that further increases in iAVA beyond the thresholds defining PPM are associated with more favorable myocardial adaptation and more pronounced RLVR. Therefore, this study aimed to determine whether prosthetic valve size after surgical AVR, even in the absence of standard PPM criteria, influences the magnitude of RLVR.

Material and methods

This retrospective observational study included all patients who underwent surgical aortic valve replacement at our department between January 2021 and December 2024. Patients who underwent concomitant cardiac surgical procedures were excluded. Patients undergoing redo aortic valve surgery and those in whom surgery was not indicated for native aortic valve stenosis were excluded subsequently. Data regarding the type of implanted prosthetic valve and the presence of preoperative and postoperative atrial fibrillation were obtained through a review of medical records. To ensure homogeneity of the hemodynamic properties of the implanted valve, the most frequently used prosthetic valve model was identified. All patients who received a prosthetic valve other than this most commonly implanted model were subsequently excluded. Furthermore, to achieve homogeneity in left ventricular response to post-operative hemodynamics following aortic valve replacement, patients with preoperative or postoperative permanent or persistent atrial fibrillation were excluded. Ultimately, only patients who underwent isolated surgical aortic valve replacement with a single prosthetic valve model for native aortic valve stenosis and without preoperative or postoperative permanent or persistent atrial fibrillation were included in the final analysis.

The following preoperative and operative data were obtained for all patients through a review of medical records: age at the time of surgery, use of a minimally invasive approach via partial upper ministernotomy (PUMS), cardiopulmonary bypass (CPB) time, aortic cross-clamp time, need for postoperative surgical re-exploration, size of the implanted prosthetic valve (mm), length of hospital stay, body mass index (BMI), and the presence of diabetes mellitus, hepatopathy, chronic obstructive pulmonary disease (COPD), and a history of stroke. Based on the size of the implanted prosthetic valve and the patient's body surface area (BSA) at the time of the surgery, the indexed geometric orifice area (iGOA) was calculated for each patient. Echocardiographic (ECHO) parameters were obtained at two time points: preoperatively and at 1-year follow-up. The following ECHO variables were analyzed: left atrial (LA) diameter, left ventricular ejection fraction (LVEF), mean transaortic gradient, peak transaortic gradient, peak aortic jet velocity, interventricular septal diameter (IVSD), indexed left atrial volume (LAVi), the E/e′ ratio (the e′ value was calculated as the average of medial and lateral e′ velocities), ECHO derived indexed aortic valve area (iAVA), indexed left ventricular end-systolic diameter (iLVeSD), and indexed left ventricular end-diastolic diameter (iLVeDD). Finally, left ventricular mass index (LVMi) was calculated both preoperatively and at follow-up. Changes in ECHO parameters were expressed as the difference (Δ) between values obtained at 1-year follow-up and those measured preoperatively. Patient survival was determined using publicly available data based on the patients' health insurance records.

Results are presented as the number of positive cases/total number of patients (percentage) for qualitative variables and as mean ± standard deviation for quantitative variables. Differences between preoperative and postoperative ECHO parameters were assessed using a paired Student's t-test. The association between iGOA and changes in ECHO parameters was evaluated using linear regression analysis. The impact of iGOA on patient survival was assessed using Cox proportional hazards regression analysis. Statistical analyses were performed using Microsoft Excel and IBM SPSS Statistics, version 20, with a significance level set at p <0.05.

Results

A total of 910 patients who underwent AVR between January 2021 and December 2024 were initially identified. After exclusion of patients who underwent concomitant cardiac surgery, those undergoing redo aortic valve surgery, and those operated on for indications other than aortic stenosis, 327 patients remained. The most frequently implanted prosthetic valve model was used in 238 patients from this cohort. Among these, permanent or persistent atrial fibrillation (AF) was identified preoperatively or postoperatively in 22 patients (**Fig. 1**). Consequently, the final statistical analysis included 216 patients in whom preoperative and operative characteristics, as well as ECHO parameters obtained preoperatively and at 1-year follow-up, were evaluated. In this cohort, changes in ECHO parameters and patient survival were further analyzed in relation to the iGOA.

Preoperative and operative characteristics of the study population are summarized in **Table 1**. When changes in ECHO parameters were evaluated (1 year after surgery versus preoperatively), statistically significant differences were observed in 10 of the 11 assessed variables. A significant reduction in left atrial diameter of 1.44 mm was noted, along with an increase in LVEF of 2.44%. Mean and peak transaortic pressure gradients decreased significantly by 37 mmHg and 61 mmHg, respectively, accompanied by a reduction in peak aortic jet velocity of 2.11 m/s. Interven-

Table 1 – Preoperative parameters and comparison of echocardiographic measurements obtained preoperatively and 1 year after aortic valve replacement

Clinical parameter	Preoperatively		
Age	66.54 ± 7.36		
PUMS	76/216 (35%)		
CPB time (min)	85.18 ± 22.27		
Clamp time (min)	69.39 ± 16.25		
Surg. revision	13/216 (6%)		
Prothesis size (mm)	22.29 ± 1.67		
Hospitalization (days)	10.56 ± 4.8		
BMI (m^2/kg)	31.58 ± 17.88		
Diabetes mellitus	62/216 (29%)		
Hepatopathy	30/216 (14%)		
Stroke history	13/216 (6%)		
COPD	28/216 (13%)		
	Preoperatively	**1 year after surgery**	***p***
LA diameter (mm)	**42.44 ± 6.32**	**41.00 ± 6.02**	**<0.0001**
LVEF (%)	**55.02 ± 9.4**	**57.46 ± 6.24**	**<0.0001**
Mean grad. AV (mmHg)	**52.26 ± 19.25**	**14.80±5.19**	**<0.0001**
Peak grad. AV (mmHg)	**87.46 ± 28.59**	**26.39 ± 9.58**	**<0.0001**
V_{max} AV (m/s)	**4.61 ± 0.73**	**2.5 ± 0.46**	**<0.0001**
IVSD (mm)	**13.95 ± 2.35**	**12.35 ± 2.01**	**<0.0001**
LAVi (mL/m^2)	39.91 ± 13.45	38.17 ± 10.69	0.4519
E/avrg e'	**10.15 ± 3.78**	**9.21 ± 3.26**	**0.0064**
iAVA (cm^2/m^2)	**0.37 ± 0.1**	**0.78 ± 0.19**	**<0.0001**
iLVeSD ($mm/m^{2)}$	**17.96 ± 4.93**	**15.91 ± 3.19**	**0.0035**
iLVeDD (mm/m^2)	**25.23 ± 3.63**	**24.78 ± 2.77**	**<0.0001**
LVMi (g/m^2)	130.27 ± 41.06	99.06 ± 22.66	<0.0001

AV – aortic valve; BMI – body mass index; CPB – cardiopulmonary bypass; iAVA – indexed aortic valve area; iLVeDD – indexed left ventricular end-diastolic diameter; iLVeSD – indexed left ventricular end-systolic diameter; IVSD – interventricular septal diameter; LA – left atrium; LAVi – indexed left atrial volume; LVEF – left ventricular ejection fraction; PUMS – partial upper ministernotomy; V_{max} AV – peak aortic jet velocity.

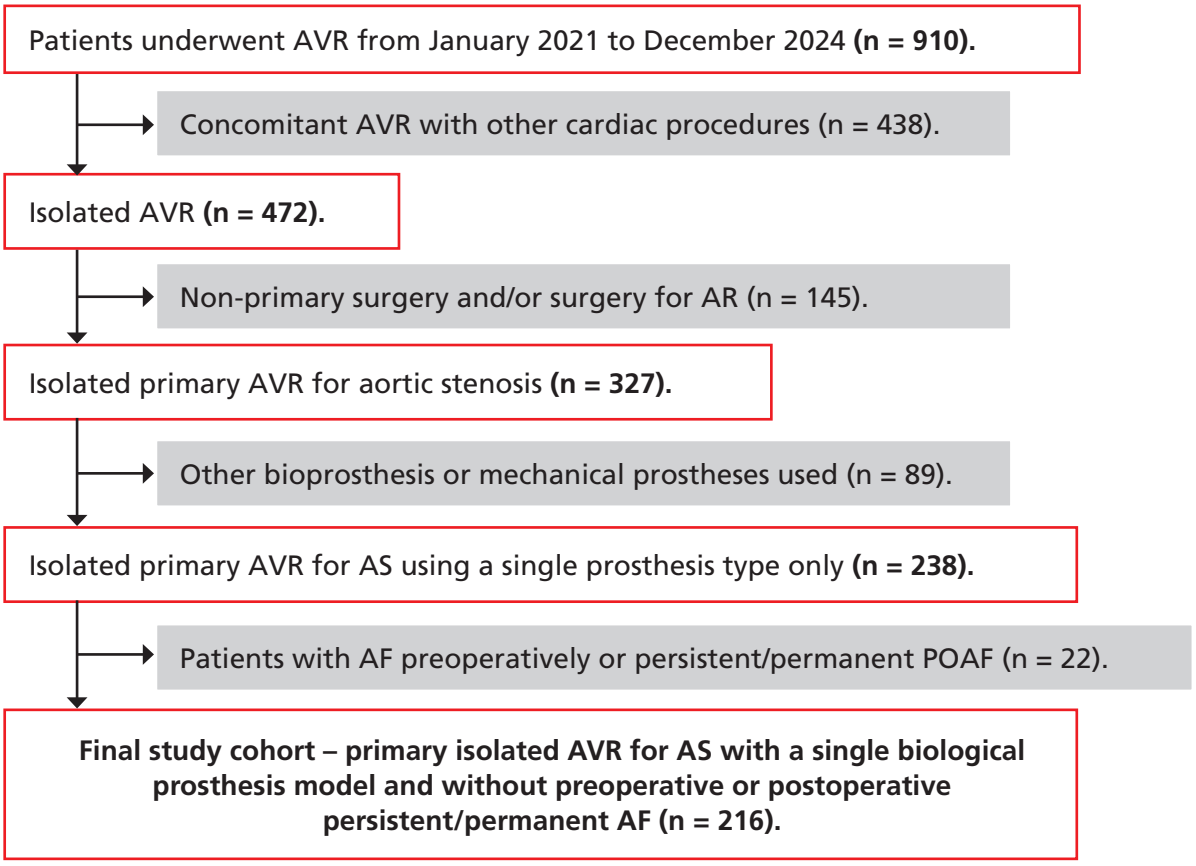

Fig. 1 – Patient flow diagram showing cohort selection with inclusion and exclusion criteria. AF – atrial fibrillation; AR – aortic regurgitation; AS – aortic stenosis; AVR – aortic valve replacement; POAF – postoperative atrial fibrillation.

tricular septal thickness decreased by 1.6 mm, and the E/e' ratio declined by 0.89, calculated as the average of medial and lateral e' velocities. The iAVA more than doubled compared with preoperative values, increasing by 0.41 cm²/m². Indexed left ventricular end-systolic and end-diastolic diameters decreased by 2.02 and 0.45 mm/m², respectively. A significant reduction in LVMi was observed, decreasing from 130.27 ± 41.06 g/m² preoperatively to 99.06 ± 22.66 g/m² at 1-year follow-up, corresponding to a mean reduction of 29.33 g/m² (p <0.0001). No statistically significant change was observed in LAVi, which showed a nonsignificant reduction of 1.74 mL/m² (**Table 1**).

Assessment of the impact of iGOA on changes in ECHO parameters identified three variables whose changes were significantly associated with prosthetic valve size, as reflected by iGOA. Larger iGOA was associated with

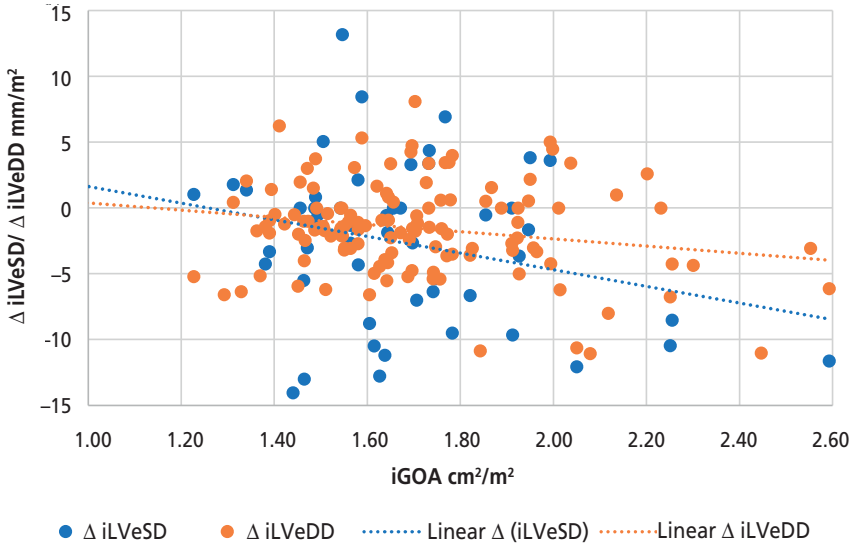

Fig. 2 – Scatter plot with a linear regression line showing the association between valve prosthesis iGOA and the 1-year change in ΔiLVeSD, and ΔiLVeDD. iGOA – indexed geometric orifice area; Δ iLVeDD – 1-year change in indexed left ventricular end-diastolic diameter; Δ iLVeSD – 1-year change in indexed left ventricular end-systolic diameter.

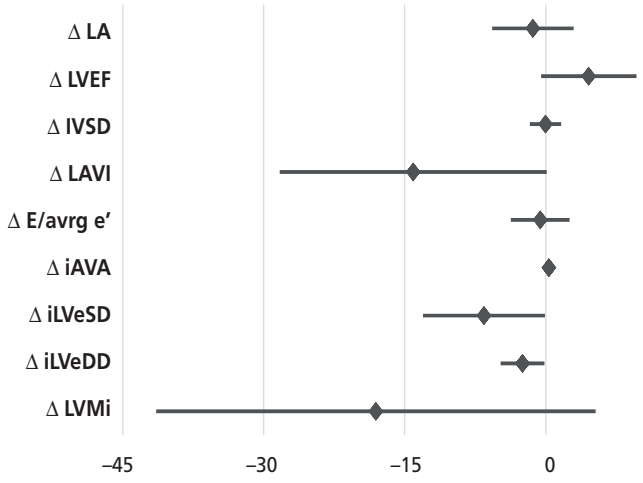

Fig. 3 – Graphical representation of the linear regression between prosthesis iGOA and 1-year changes in left atrial and left ventricular echocardiographic parameters.

a significantly greater increase in iAVA (B = 0.321, 95% CI 0.134–0.509; p = 0.004) and with significantly greater reductions in iLVeSD and iLVeDD (B = –6.578, 95% CI –13.071 to –0.086, p = 0.047; B = –2.48, 95% CI –4.815 to –0.144, p = 0.038; respectively) (**Table 2**, **Figs 2, 3**). Borderline associations were observed between iGOA and increase in LVEF (B = 4.566, 95% CI –0.513 to 9.645, p = 0.078), as well as reduction in LAVi (B = –14.114, 95% CI –28.317 to –0.089, p = 0.051). A numerically greater, but not statistically significant, reduction in LVMi was also observed in patients receiving a valve prosthesis with larger iGOA (B = –18.083; 95% CI –41.461 to 5.296; p = 0.128) (**Table 2**, **Figs 3, 4**). No significant association was found between iGOA and changes in LA diameter, IVSD or the E/e' ratio (**Table 2**, **Figs 3, 4**). Cox regression analysis did not demonstrate a statistically significant effect of prosthetic valve size, as defined by iGOA, on short-term patient survival (HT = 1.138, 95% CI 0.012–1.649, p = 0.118) (**Fig. 5**).

Discussion

Imaging modalities for the assessment of reverse left ventricular remodeling

Transthoracic ECHO represents the gold standard for the diagnosis of aortic stenosis as well as for the assessment of the compensatory left ventricular response to this condition. Moreover, it is a well-established modality for evaluating the extent of RLVR following AVR.[5] In addition to standard parameters, which were also included in the present study, left ventricle global longitudinal strain has recently been incorporated among parameters used to identify and quantity RLVR.[6,16] Another modality for the assessment of reverse remodeling is cardiac magnetic resonance imaging (MRI).[8,17] The presence of reverse remodeling is defined by a >15% reduction in end-diastolic volume, a >15% decrease in indexed left ventricular mass, a >10% reduction in geometric remodeling (LV mass / end-diastolic volume ratio), or a >10% increase in left ventricular ejection fraction (LVMi).[18] LVMi has also been evaluated in studies using ECHO, where it is mathematically derived from IVSD, LVeDD, and posterior wall thickness.[6] The same calculation method was applied in the present study. The literature reports a reduction in LVMi from 123.6 ± 32.1 to 109.7 ± 28.9 g/m² three months after TAVI.[6] Notably, our results demonstrate a slightly more pronounced reduction (mean decrease of 29.33 g/m²) one year after surgical AVR. Cardiac magnetic resonance imaging allows differentiation of left ventricular mass regression into cellular and extracellular components. Using this approach, a predominantly cellular regression of 18.7% and a smaller contribution from extracellular mass regression of 7.2% have been documented two months after aortic valve replacement.[17]

Echocardiographic markers of reverse remodeling

The first group of parameters that directly quantify improvement in hemodynamic conditions after aortic valve replacement includes aortic valve area (AVA), transaortic pressure gradients, and blood flow velocity across the prosthesis. An increase in AVA has been documented following both

Table 2 – Linear regression analysis of the association between iGOA of implanted valve prosthesis and changes in left atrial and left ventricular ECHO parameters (1-year postoperative minus preoperative)

	Coef.	95% CI		*p*
		Lower	Upper	
Δ LA diameter (mM)	–1.376	–5.703	2.951	0.53
Δ LVEF (%)	4.566	–0.513	9.645	0.078
Δ IVSD (mM)	–0.033	–1.694	1.629	0.969
Δ LAVi (mL/m^2)	–14.114	–28.317	0.089	0.051
Δ E/avrg e´	–0.592	–3.721	2.537	0.708
Δ iAVA (cm^2/m^2)	**0.321**	**0.134**	**0.509**	**0.001**
Δ iLVeSD (mm/m^2)	**–6.578**	**–13.071**	**–0.086**	**0.047**
Δ iLVeDD (mm/m^2)	**–2.48**	**–4.815**	**–0.144**	**0.038**
Δ LVMi (g/m2)	–18.083	–41.461	–5.296	0.128

iAVA – indexed aortic valve area; iLVeDD – indexed left ventricular end-diastolic diameter; iLVeSD – indexed left ventricular end-systolic diameter; IVSD – interventricular septal diameter; LA – left atrium; LAVi – indexed left atrial volume; LVEF – left ventricular ejection fraction.

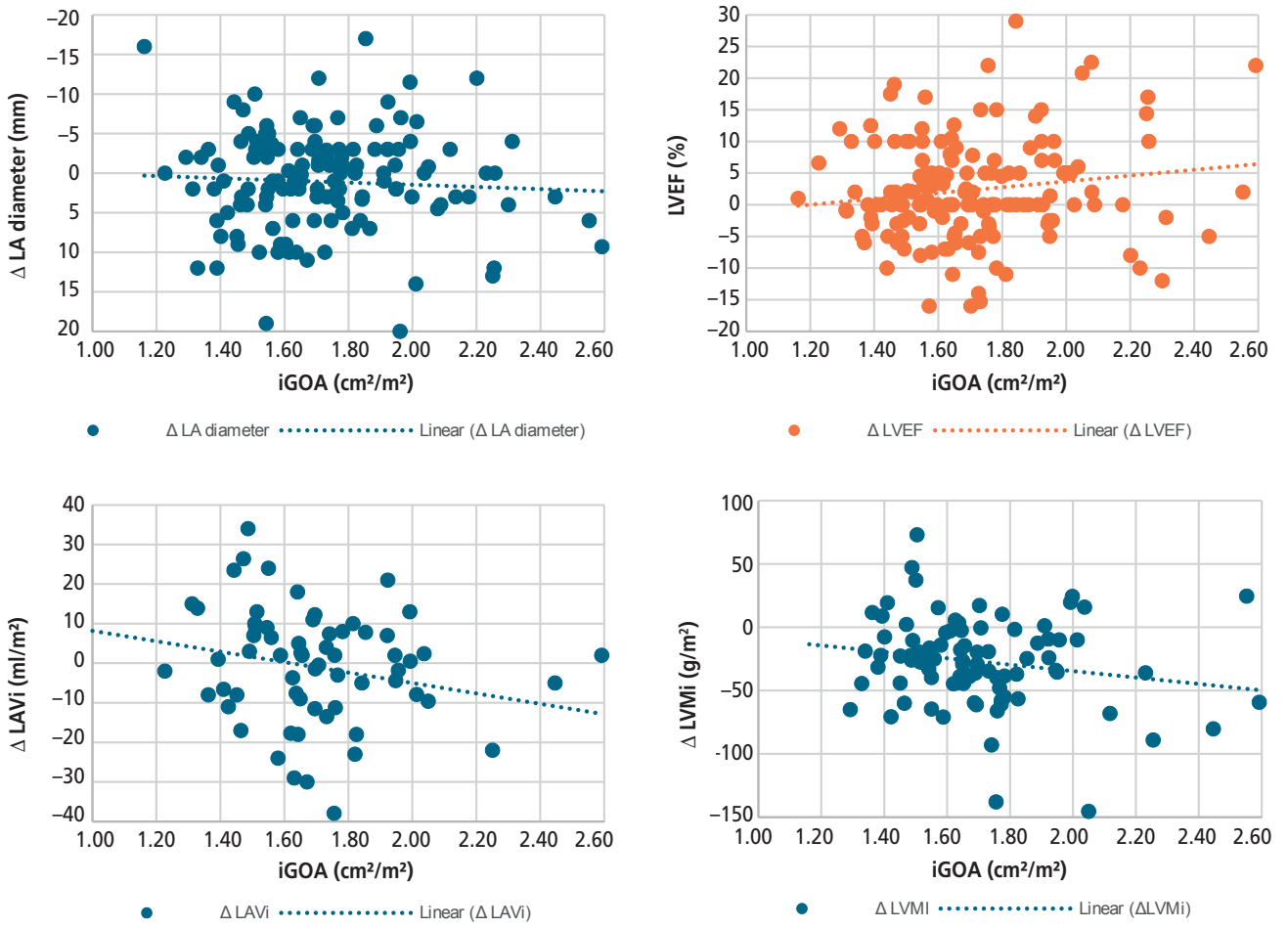

Fig. 4 – Scatter plots with linear regression lines showing the associations between prosthesis iGOA and 1-year changes in ΔLA diameter, ΔLVEF, ΔLAVI, and ΔLVMi. iGOA – indexed geometric orifice area; ΔLVMi – 1-year change in left ventricular mass index; ΔLA – 1-year change in left atrium; ΔLAVi – 1-year change in indexed left atrial volume; ΔLVEF – 1-year change in left ventricular ejection fraction.

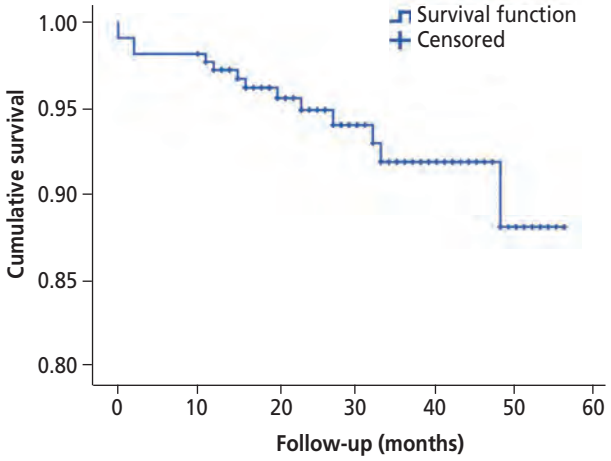

Fig. 5 – Kaplan–Meier analysis of survival with Cox regression analysis of the effect of iGOA on survival (HR = 1.138, 95% CI 0.012–1.649, *p* = 0.118).

surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI). A meta-analysis including data from 27 studies reported a mean AVA increase of 0.99 cm² after TAVI and 1.19 cm² after SAVR, which is consistent with our findings of an increase in iAVA of 0.41 cm²/m² at a mean body surface area (BSA) of 1.98 ± 0.21 m² (unpublished data).[5] The above-mentioned meta-analysis further reported a mean reduction in the transaortic mean pressure gradient of 38.23 mmHg, which closely corresponds to the reduction of 37 mmHg observed in our study.[5] Even smaller studies focusing on reverse remodeling after transcatheter or surgical AVR have documented an increase in aortic valve area of 0.9–1.11 cm² and reductions in mean and peak transaortic gradients of 35–46 and 33–69 mmHg, respectively.[6,19,20] These findings are consistent with the results observed in our study.

Secondary parameters reflecting reverse left ventricular remodeling most commonly include LVEF and LVeDD. This pattern of remodeling is specifically associated with changes related to aortic stenosis and differs from the remodeling observed in other aortic valve pathologies.[21] A meta-analysis including 37 studies reported a mean increase in LVEF of 2.35% after AVR, independent of the time interval from surgery within a range of one month to one year, as well as a mean reduction in LVeDD of 1.78 mm, with the most pronounced decrease documented at six months after the procedure.[5] In the present study, a significant increase in LVEF of 2.44% and a reduction in indexed left ventricu-

lar end-diastolic diameter of 0.45 mm/m² at a mean BSA of 1.98 ± 0.21 m² were observed. Thus, our findings are consistent with the results of the meta-analysis, despite a slightly less pronounced reduction in LVeDD. In contrast, compared with the present study, smaller studies assessing patients as early as the first three months after TAVI did not document a positive effect on improvements in LVEF or LVeSD and LVeDD.[6,20] One of these studies also documented a reduction in IVSD of 1.4 mm, which was similar to that observed in our study.[6] Other parameters evaluated in some studies include left ventricular volume, for which a significant reduction has also been reported following AVR.[5] More recent studies have increasingly evaluated left ventricular global longitudinal strain, the change of which after aortic valve replacement appears to be a more sensitive predictor of long-term patient survival compared with LVEF.[6,16] Assessment of left ventricular hypertrophy and its reverse remodeling may be further influenced by comorbidities, particularly arterial hypertension, the effects of which on the left ventricle resemble those observed in aortic stenosis.[6] Some studies have differentiated left ventricular remodeling according to etiology, demonstrating that AS predominantly leads to a shift of the LV left–right axis with a decrease in short-axis eccentricity, whereas hypertension is more commonly associated with septal thickening. Furthermore, it has been documented that the left–right axis shift is not reversible following AVR.[2] Such complex assessments require prospective inclusion of these parameters, which was not feasible in the present retrospective analysis. Another group of parameters includes echocardiographic measures directly quantifying diastolic dysfunction. Among the most objective parameters of left ventricular diastolic dysfunction is the E/e′ ratio, with more recent data suggesting that averaged e′ provides greater diagnostic accuracy than assessment of septal or lateral e′ alone. In our study, this approach confirmed a favorable effect of aortic valve replacement on the E/e′ ratio, whereas not all previous studies have reported similar findings.[6]

Echocardiographic changes reflecting reverse left ventricular remodeling can be detected as early as one month after aortic valve replacement.[5] However, the temporal evolution of several ECHO parameters during the first year after surgery may be inconsistent. According to a meta-analysis focused on left ventricular remodeling after aortic valve replacement, a more pronounced reduction in LVM and LVeDD has been documented at six months compared with measurements obtained at three and twelve months following the procedure.[5] On the other hand, other authors have suggested that changes observed three months after TAVI may already be very similar to the final extent of reverse remodeling observed one year after the intervention.[6] However, their study did not demonstrate reductions in LVeSD and LVeDD, nor improvements in LVEF or the E/e′ ratio three months after TAVI.[6] In contrast, our study, which assessed ECHO parameters one year after SAVR, demonstrated a positive effect of surgical intervention across these parameters.

Prosthesis size and reverse remodeling

Patient–prosthesis mismatch (PPM) was first described in 1978 by Rahimtoola and represents an imbalance between the hemodynamic performance of the implanted prosthetic valve and the patient's cardiac output requirements. As outlined in the Introduction, severe PPM is typically defined by an indexed effective orifice area of less than 0.65 cm²/m².[10,11] In the presence of patient–prosthesis mismatch, the prosthetic valve functions normally but provides a relatively small effective orifice area in relation to the patient's body surface area, and this condition may occur after both surgical and transcatheter aortic valve replacement.[22] PARTNER studies that also evaluated patient–prosthesis mismatch identified only ECHO defined severe PPM as a risk factor for a higher incidence of primary endpoints, including death and hospitalization for heart failure. A statistically significant difference was demonstrated not only in comparison with no PPM (severe PPM vs. no PPM, p <0.001) but also in comparison with moderate PPM (severe PPM vs. moderate PPM, p = 0.02).[13] One smaller study even reported a higher incidence of reoperation in patients without PPM compared with those with moderate PPM (10-year cumulative incidence of reoperation: 8.3% for no PPM vs. 6.7% for moderate PPM).[12] Previous studies have more frequently focused on the impact of PPM on postoperative outcomes rather than on the effect of absolute prosthetic valve size or iGOA beyond the threshold of PPM. In contrast to the aforementioned lower risk of reoperation observed in patients with moderate PPM compared with those with larger aortic valve area, functional outcomes appear less favorable. A smaller increase in LVEF has been reported in patients with PPM compared with those without PPM one year after TAVI (1.9 ± 21.3% vs. 8.2 ± 30.1%, p = 0.045). In addition, a statistically significant effect on left ventricle global longitudinal strain has been documented.[16] The presence of patient–prosthesis mismatch is associated with worse survival after aortic valve replacement (hazard ratio 3.56, 95% CI 1.37–9.25; p = 0.009), a finding that is widely accepted and well documented in the scientific literature.[14] In the present cohort, however, only 4 of 216 patients exhibited a postoperative aortic valve area measured by ECHO ≤0.85 cm², and thus 98% of patients did not meet the criteria for PPM (unpublished data). Consequently, the present study focuses on evaluating the effect of iGOA above the PPM threshold. Direct comparison with studies primarily addressing PPM may therefore be limited and should be interpreted with caution. In our previous study, we demonstrated that implantation of a larger bioprosthetic valve was associated with better survival compared with a smaller bioprosthetic valve, even beyond the thresholds defining patient–prosthesis mismatch. In contrast, this association was not observed for mechanical prostheses.[15] The literature indicates that patient–prosthesis mismatch is associated with a 2.5-fold increase in the risk of structural valve deterioration.[11,23] This may subsequently adversely affect patient survival even in the absence of an impact on early postoperative reverse left ventricular remodeling. It therefore remained unclear whether smaller prosthetic valves lead to insufficient reverse myocardial remodeling or whether they are more prone to structural valve deterioration with subsequent recurrence of aortic stenosis. Our results demonstrate that, in the absence of PPM, larger indexed geometric orifice area of the implanted prosthesis is associated with greater improvement in parameters of RLVR,

particularly LVeSD and LVeDD, and borderline improvement in LVEF, compared with smaller iGOA. Based on this favorable remodeling effect, a subsequent beneficial impact on the incidence of heart failure and long-term survival may be anticipated, despite the absence of a detectable effect on short-term survival in the present study.

Conclusion

ECHO assessment performed one year after AVR for AS demonstrated a statistically significant improvement in iAVA, mean and peak transaortic pressure gradients, and a reduction in aortic valve jet velocity. The observed changes further indicate the presence of reverse left ventricular remodeling, documented by a statistically significant increase in LVEF and reductions in IVSD, iLVeSD, iLVeDD, and LVMi. Improvements in left atrial parameters were also observed, reflected by a reduction in left atrial diameter, along with improved left ventricular diastolic filling as indicated by a statistically significant decrease in the E/e′ ratio.

The present study confirms a beneficial effect of implantation of a larger valve prosthesis on more pronounced improvements in several left heart parameters, particularly iLVeSD and iLVeDD, with borderline but not statistically significant effects on LVEF and LAVi. Similarly, a nonsignificant trend toward greater LVMi reduction was observed with larger iGOA. However, no positive effect of larger prosthetic valve implantation on short-term patient survival was demonstrated.

Conflict of interest

The authors declare that there are no financial or personal relationships that could inappropriately influence (bias) the work reported in this manuscript. The authors confirm that they have no conflicts of interest relevant to the content of this article.

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Ethical statement

The processing of the retrospective study was approved by the Ethics Committee in compliance with the principles of the Declaration of Helsinki and ICH Guidelines for Good Clinical Practice and applicable regulatory requirements (protocol code: A2082025 and date of approval: August 22. 2025).

Informed consent

During hospitalization, patients provided written consent for the healthcare received. According to the recommendation of the Ethics Committee, due to the retrospective nature of the study, no further patient consents were required.

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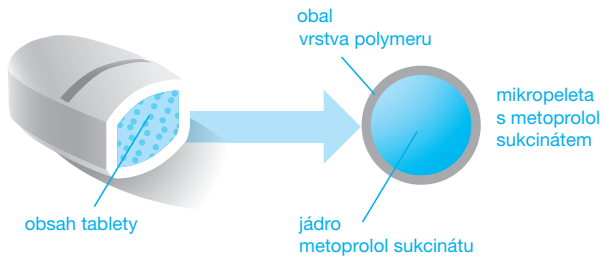
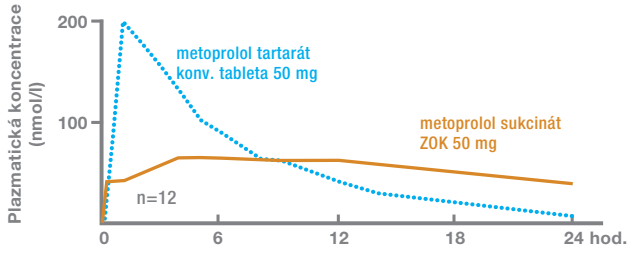


Upraveno dle Plosker GL, Clissold SP. Drugs 1992;43:382-414

Dávkování 1× denně
Stabilní plazmatická koncentrace 24 hodin[1, 3]



Upraveno dle Wieselgren I et al, J Clin Pharmacol 1990;30:S28 -32

Dávkování 1× denně[1]

Podávání léku 1× denně zlepšuje compliance pacientů.

Řízené uvolňování[1]

Potahované tablety s prodlouženým uvolňováním obsahují několik stovek mikropelet s jantaranem metoprololu. Každá mikropeleta je potažena vrstvou polymeru, která řídí rychlost uvolňování. Po spolknutí se tableta rychle rozpadá a mikropelety se dispergují v gastrointestinálním traktu a uvolňují léčivou látku po dobu asi 20 hodin. Tak je dosaženo rovnoměrných plazmatických koncentrací metoprololu po dobu 24 hodin (na rozdíl od konvenčních tablet s metoprololem).[1]

Dávkování u 7 schválených indikací[1]

Chronické srdeční selhání[1]

Doporučená počáteční dávka přípravku po dobu prvních dvou týdnů je 25 mg jednou denně. U pacientů třídy III-IV podle NYHA se doporučuje počáteční dávka 12,5 mg jednou denně po dobu prvního týdne. Doporučuje se dávku vždy po 14 dnech zvýšit na dvojnásobnou až na cílovou dávku 200 mg jednou denně (nebo nižší maximálně tolerovanou dávku.

Hypertenze[1]

50 mg 1× denně mírná až středně těžká hypertenze, 100–200 mg 1× denně při potřebě zvýšení dávky nebo kombinace s jinými antihypertenzívy.

Udržovací léčba po infarktu myokardu[1]

200 mg 1× denně

Angina pectoris[1]

100–200 mg 1× denně, lze kombinovat s jinými antianginózními léčivy

Srdeční arytmie[1]

100–200 mg 1× denně

Funkční srdeční poruchy s palpitacemi[1]

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Profylaxe migrény[1]

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Datum výroby materiálu: březen 2024. Kód materiálu: CZ-BET-2024-02-inzerce. **Tento materiál je určený pro odbornou veřejnost a interní účely společnosti.**

1. SPC Betaloc ZOK březen 2021 **2.** Plosker GL, Clissold SP. Drugs 1992;43:382-414. **3.** Wieselgren I et al, J Clin Pharmacol 1990;30:S28-32.

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Ventricular Arrhythmias in Electrolyte Imbalance

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Refrakterní perioda
Ryanodinové receptory

SOUHRN

Cíl: Cílem studie bylo analyzovat patofyziologické mechanismy, elektrokardiografické projevy a terapeutické přístupy související s komorovými arytmiemi způsobenými elektrolytovou nerovnováhou, se zvláštním důrazem na poruchy draslíku, hořčíku a vápníku a jejich roli v arytmogenezi a klinickém hodnocení rizika.
Soubor a metodika: Systematický přehled literatury byl proveden v souladu s doporučeními PRISMA 2020. Vědecké publikace z let 2019–2025 byly vyhledávány v databázích PubMed/MEDLINE, Scopus, Web of Science a Google Scholar. Výzkumná otázka byla strukturována pomocí rámce PICO se zaměřením na dospělé pacienty s poruchami elektrolytů a rozvojem komorových arytmií. Z původně identifikovaných 1 847 záznamů byly po vícestupňovém screeningu odstraněny duplicity a nerelevantní studie. Padesát dva publikací splnilo kritéria pro zařazení a bylo analyzováno. Extrahovaná data zahrnovala koncentrace elektrolytů, elektrofyziologické mechanismy, elektrokardiografické ukazatele, terapeutické intervence a klinické výsledky. Vzhledem k heterogenitě studií byla místo metaanalýzy použita tematická syntéza.
Výsledky: Bylo zjištěno, že poruchy elektrolytů významně ovlivňují elektrofyziologii myokardu a zvyšují riziko komorových arytmií. Hypokalemie přispívá k arytmogenezi prostřednictvím dysfunkce draslíkových kanálů a prodloužení repolarizace, což podporuje vznik časných a opožděných následných depolarizací. Nerovnováha hořčíku a vápníku ovlivňuje L-typ vápníkových kanálů a ryanodinové receptory, čímž vytváří podmínky pro polymorfní komorovou tachykardii, včetně torsades de pointes. Nejvyšší arytmogenní riziko se vyskytuje při kombinovaném nedostatku draslíku a hořčíku (K^+ < 2,8 mmol/L a Mg^{2+} < 0,6 mmol/l). Kontinuální monitorování srdeční činnosti odhalilo klinicky významné arytmie přibližně u 30 % vysoce rizikových pacientů ve srovnání s 6 % při standardním sledování.
Závěr: Elektrolytová nerovnováha představuje významný reverzibilní faktor ve vývoji komorových arytmií. Včasná laboratorní diagnostika, elektrokardiografické monitorování a individualizované korekční protokoly, včetně suplementace draslíku a terapie hořčíkem, jsou zásadní pro snížení arytmického rizika a prevenci náhlé srdeční smrti.

Keywords:
Hypocalcaemia
Hypokalaemia
Hypomagnesaemia
Refractory period
Ryanodine receptors

ABSTRACT

Aim: The aim of the study was to analyse the pathophysiological mechanisms, electrocardiographic manifestations, and therapeutic approaches related to ventricular arrhythmias caused by electrolyte imbalance, with emphasis on disturbances of potassium, magnesium, and calcium and their role in arrhythmogenesis and clinical risk assessment.
Methods: A systematic literature review was conducted following PRISMA 2020 guidelines. Scientific publications from 2019–2025 were searched in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The research question was structured using the PICO framework focusing on adult patients with electrolyte disturbances and the development of ventricular arrhythmias. From 1,847 initially identified records, duplicates and irrelevant studies were excluded through multi-stage screening. Fifty-two publications met the inclusion criteria and were analysed. Data extraction included electrolyte concentrations, electrophysiological mechanisms, electrocardiographic indicators, therapeutic interventions, and clinical outcomes. Because of heterogeneity among the studies, thematic synthesis was applied instead of meta-analysis.
Results: Electrolyte disturbances were found to significantly influence myocardial electrophysiology and increase the risk of ventricular arrhythmias. Hypokalaemia contributes to arrhythmogenesis through dysfunction of potassium channels and prolongation of repolarisation, promoting early and delayed afterdepolarisations. Imbalances in magnesium and calcium affect L-type calcium channels and ryanodine receptors, creating conditions for polymorphic ventricular tachycardia, including torsades de pointes. The highest arrhythmogenic risk occurs in combined potassium and magnesium deficiency (K^+ <2.8 mmol/L and

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Mg^{2+} <0.6 mmol/L). Continuous cardiac monitoring detected clinically significant arrhythmias in approximately 30% of high-risk patients compared with 6% under standard observation.
Conclusions: Electrolyte imbalance is a major reversible factor in the development of ventricular arrhythmias. Early laboratory detection, electrocardiographic monitoring, and individualised correction protocols, including potassium supplementation and magnesium therapy, are essential for reducing arrhythmic risk and preventing sudden cardiac death.

Introduction

Electrolyte imbalance is a common cause of life-threatening ventricular arrhythmias, as changes in potassium, magnesium, and calcium levels directly affect myocardial electrical stability. Timely recognition and correction of electrolyte disturbances are critical for preventing sudden cardiac death, particularly in patients with concomitant cardiac pathology.

The increased incidence of ventricular arrhythmias in patients with electrolyte imbalance has been widely documented in clinical and observational studies. In particular, disturbances in potassium, magnesium, and calcium levels have been identified as key factors affecting myocardial electrical stability and predisposing patients to life-threatening arrhythmias. Studies conducted in patients with myocardial infarction and chronic kidney disease have demonstrated that electrolyte abnormalities significantly increase arrhythmic risk and contribute to adverse clinical outcomes.

At the same time, existing research has primarily focused on isolated electrolyte disturbances, especially hypokalaemia, while comparatively less attention has been given to the combined effects of multiple electrolyte imbalances. Clinical observations indicate that interactions between potassium, magnesium, and calcium disturbances may exert synergistic effects on arrhythmogenesis, yet these interactions remain insufficiently systematised in the literature.

Furthermore, several methodological limitations are evident across existing studies, including small sample sizes, lack of longitudinal follow-up, and limited integration of electrophysiological, clinical, and diagnostic data. These limitations restrict the generalisability of findings and hinder the development of a comprehensive understanding of arrhythmogenic mechanisms in electrolyte imbalance.

Despite detailed pathophysiological insights, the lack of quantitative correlations between the type of imbalance and arrhythmia frequency restricts clinical applicability.

The role of hypokalaemia as a cause of acquired long-QT syndrome was illustrated by Pintaningrum and Pramana[3] in a clinical case of a female patient with hypokalaemia and hyponatraemia who developed ventricular arrhythmia with a prolonged QTc interval (exceeding 638 ms) according to Heart Rhythm Society standards. Following electrolyte correction, electrocardiogram/electrocardiography (ECG) parameters improved and arrhythmogenic manifestations resolved. Yet, the single-case design precluded generalisation of population-level risks. Electrolyte profiles in patients with confirmed ventricular tachycardia or fibrillation were explored by Laslett et al.[4], comparing clinical and biochemical characteristics in VT/VF patients with heart failure. Hypokalaemia occurred significantly more often in the VT/VF group, with severe hypokalaemia (K <3.0 mmol/L) linked to gastrointestinal losses and higher diuretic doses. Hypomagnesaemia was less frequent but present in both cohorts. The study lacked follow-up data on how electrolyte correction affected arrhythmia recurrence.

Inflammatory cytokines and their role in atrial fibrillation in Coronavirus Disease 2019 (COVID-19) patients remain an emerging issue in cardiology. Tcholadze et al.[5] conducted a retrospective cohort study at Chapidze Hospital, Tbilisi, involving 100 inpatients aged 40–80 years with COVID-19. Significantly elevated interleukin-6 ($p = 0.024$), C-reactive protein ($p = 0.001$), and ferritin ($p < 0.001$) levels were found in those with atrial fibrillation, along with longer hospitalization and lower oxygen saturation. Limitations included small sample size and absence of long-term electrolyte monitoring. Exercise testing for detecting ventricular extrasystoles in athletes was used to differentiate benign from potentially dangerous arrhythmias. Chutkerashvili et al.[6] retrospectively analysed 855 athletes at Tbilisi State Medical University: 91 (10.6%) exhibited ventricular arrhythmias on resting and/or stress ECGs. The study demonstrated that exercise testing enhances screening potential by unmasking latent arrhythmogenic substrates via adrenergic stimulation. However, its retrospective nature and lack of electrolyte assessment during exertion limited conclusions.

The long-term impact of interleukin-6 on cardiovascular outcomes post-COVID-19 was examined by Tcholadze et al.[7] through a longitudinal study at Chapidze Heart Hospital, comparing in-hospital and six-month post-recovery data. Elevated IL-6 levels during acute infection correlated with increased cardiovascular risk, suggesting that cytokine-mediated systemic inflammation exacerbates cardiac complications. Limitations included short follow-up and insufficient data on electrolyte imbalance. The historical contribution of Georgian cardiologists to hypertension research was revisited by Pagava et al.[8], which introduced the "reversible" and "latent" forms. The study underscored that hypertension prevalence in Georgia remains a major public health issue, though its historical focus lacked experimental data and relevance to electrolyte balance.

Therefore, this study aims to provide a comprehensive and structured synthesis of current scientific evidence on ventricular arrhythmias associated with electrolyte imbalance, integrating pathophysiological mechanisms, clinical manifestations, and therapeutic strategies. The study seeks to systematize available data, identify key patterns of arrhythmogenesis, and highlight gaps that require further investigation.

Materials and methods

This study is a systematic literature review conducted in accordance with the PRISMA 2020 recommendations, covering the period from 2019 to 2025 to analyse current scientific evidence on ventricular arrhythmias in the context of electrolyte imbalance. While the formal systematic search was limited to publications from 2019 to 2025, several earlier studies were additionally included to provide essential theoretical and clinical background. These sources were not part of the systematic selection process but were incorporated selectively to support the interpretation of mechanisms and to ensure conceptual continuity within the analysis. The research question was formulated using the PICO framework: in publications investigating adult patients with electrolyte disturbances (hypo-/hyperkalaemia, hypomagnesaemia, hypo-/hypercalcaemia) (P – population), how do changes in electrolyte concentrations influence the occurrence and progression of ventricular arrhythmias (O – outcome) through pathophysiological mechanisms, electrocardiographic diagnostic criteria, and therapeutic strategies?

A systematic search was performed in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar during December 2024 – January 2025. The search strategy combined the following terms: ("ventricular arrhythmia*" OR "ventricular tachycardia" OR "torsades de pointes" OR "ventricular fibrillation") AND ("electrolyte imbalance" OR "hypokalaemia" OR "hyperkalaemia" OR "hypomagnesaemia" OR "hypocalcaemia" OR "potassium" OR "magnesium" OR "calcium") AND ("pathophysiology" OR "mechanism*" OR "diagnosis" OR "treatment" OR "management"). In PubMed, Medical Subject Headings (MeSH) terms were applied, including "Arrhythmias, Cardiac/etiology" and "Water-Electrolyte Imbalance/complications". In addition, manual searches of the reference lists of selected articles were undertaken to identify relevant sources that might have been missed by electronic screening, including earlier foundational studies necessary for contextual and theoretical clarification.

Inclusion criteria were: original studies, clinical case reports with detailed mechanistic descriptions, systematic reviews, and meta-analyses published in English in peer-reviewed journals that examined the relationship between disturbances in potassium, magnesium, calcium, or sodium concentrations and the development of ventricular arrhythmias; studies containing quantitative or qualitative data on electrophysiological mechanisms at the level of ion channels, electrocardiographic markers, or therapeutic approaches; studies in adult populations or with findings that could be extrapolated to adults. Exclusion criteria were: publications dealing exclusively with atrial arrhythmias; animal studies without translational relevance to clinical practice; studies with insufficient methodological description; duplicate publications; works in which electrolyte disturbances were only briefly mentioned; publications in languages other than English; and conference abstracts without full text.

The initial search identified 1,847 records across the four databases. After a multi-stage selection process, as depict-

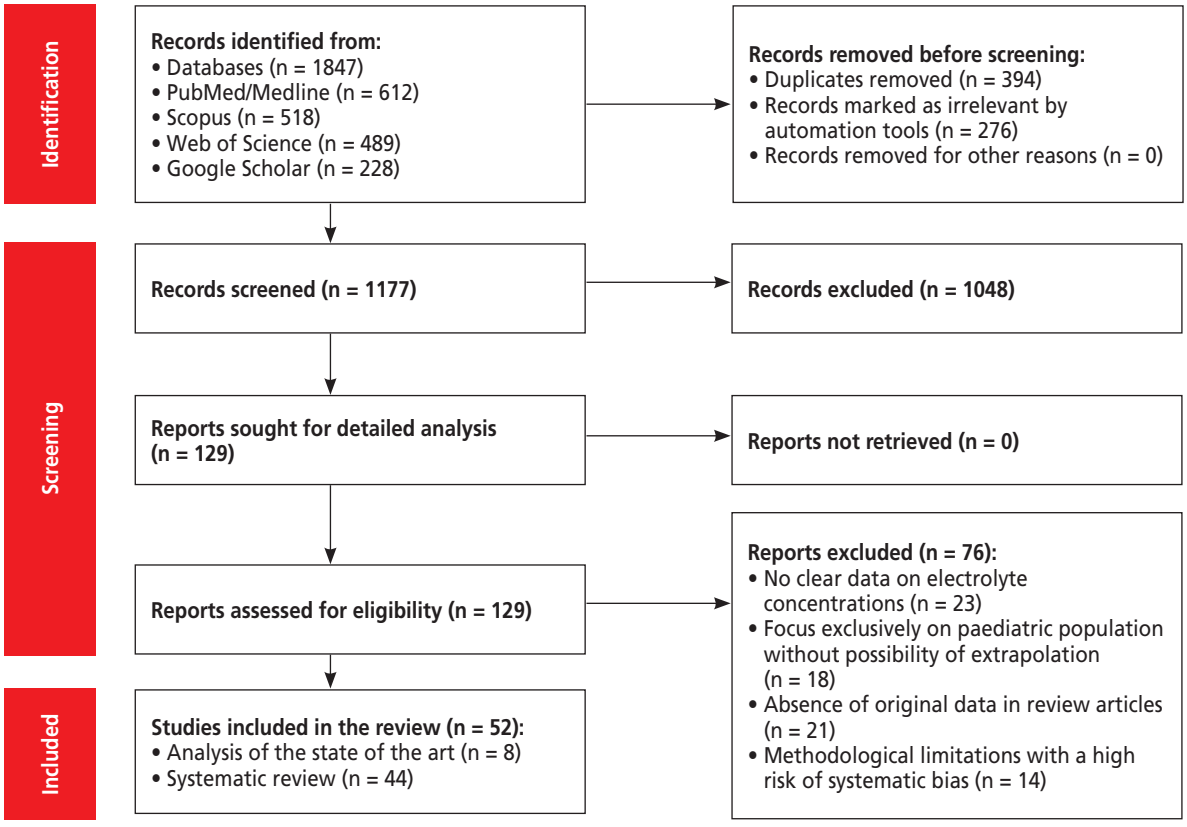

Fig. 1 – Flow diagram of source selection for the systematic review according to PRISMA 2020 methodology. Source: compiled by the author.

ed in **Figure 1**, 52 sources remained. Of the 52 studies included after screening, 44 were incorporated into the final systematic synthesis, while 8 were used selectively to provide contextual background and support the introductory overview of the topic. These 8 sources were not analysed as part of the formal systematic review but were included to enhance the conceptual framing of the study.

Study selection was performed independently by two reviewers using Mendeley Desktop 1.19.8 for reference management and documentation of the process; discrepancies were resolved by consensus or by consulting a third expert.

Data extraction was carried out independently by two reviewers using a standardised form that included: bibliographic details; study design, and population characteristics (sample size, age, sex, comorbidities); type and severity of electrolyte disturbance with specific concentrations in mmol/L; pathophysiological mechanisms (identified ion channels, changes in membrane potential, type of afterdepolarisation); clinical manifestations and diagnostic parameters (type of ventricular arrhythmia, ECG QT/QTc changes, wave morphology, monitoring methods); therapeutic interventions (route of administration, doses, infusion rates, concomitant therapy); and clinical outcomes (effectiveness of correction, recurrence rates, complications, mortality). For quantitative variables, means and standard deviations were extracted; for categorical variables, absolute frequencies and percentages. Disagreements in extracted data were resolved by re-examining the original publication until agreement was reached.

Methodological quality of included studies was assessed independently by two reviewers using validated tools appropriate to study design. The Newcastle-Ottawa Scale was used for observational studies, evaluating participant selection, group comparability, and outcome assessment (maximum 9 points). Case reports were assessed with the CAse REport guidelines (CARE), evaluating completeness of history, clinical presentation, diagnosis, and therapy. Systematic reviews were appraised using A MeaSurement Tool to Assess systematic Reviews (AMSTAR-2), which assesses 16 domains of methodological quality. Quality assessments informed the interpretation of evidence reliability, identification of potential sources of bias, and formulation of well-founded conclusions.

Due to substantial heterogeneity among the included studies, a meta-analysis was not undertaken; instead, thematic synthesis was applied. Extracted data were coded using a mixed inductive–deductive approach, assigning initial descriptive codes to discrete information fragments that were then grouped into higher-order descriptive themes. In the final stage, descriptive themes were integrated into three analytical categories: pathophysiological mechanisms by which electrolyte imbalance precipitates ventricular arrhythmias; clinical manifestations and electrocardiographic diagnosis in specific electrolyte disorders; and therapeutic strategies for correcting imbalance and pharmacological management of arrhythmias. Quantitative parameters were summarised in comparative tables of critical electrolyte concentrations, electrocardiographic indices, pharmacological dosages, and clinical outcomes, facilitating the identification of patterns and knowledge gaps.

Results and discussion

Pathophysiological mechanisms by which electrolyte imbalance precipitates ventricular arrhythmias

Between 2019 and 2025 it was established that hypokalaemia induced hyperpolarisation of the cardiomyocyte resting membrane potential through reduced IK1 current activity mediated by Kir2.1 channels. This decreased the stability of the membrane potential and increased cellular excitability. At the molecular level, such changes were attributable to mutations in the *KCNJ2* gene, which encodes Kir2.1. These mutations led to structural destabilisation of the channel, impairing its conductance and configuration in both the open and closed states.[9]

Electrophysiologically, hypokalaemia prolonged the action potential – particularly the repolarisation phase – thereby provoking early afterdepolarisations (EADs) through prolonged opening of L-type calcium channels. Excessive accumulation of calcium ions in the sarcoplasmic reticulum resulted in their spontaneous diastolic release via ryanodine receptors (RyR2), generating delayed afterdepolarisations (DADs) and promoting triggered activity.[10] In addition, hypokalaemia altered repolarisation gradients across layers of the ventricular myocardium, creating heterogeneity in action potential duration and strengthening substrates for re-entry. Bioengineered models based on human pluripotent stem cells showed that hypokalaemia reduced both longitudinal and transverse conduction velocities, shortened the effective refractory period from 242 to 165 ms, and increased calcium transient amplitude and action potential duration. These changes favoured re-entry by decreasing the wavelength of excitation and destabilising the depolarisation-repolarisation process.[11] Investigation of the functional role of the K2P1 channel demonstrated that, under hypokalaemic conditions, this channel altered ion selectivity and began to conduct inward Na^+ current, leading to spontaneous depolarisation of the resting potential, initiation of action potentials, and development of extrasystolic activity. In transgenic mice with cardiac expression of human K2P1, hypokalaemia more frequently led to ventricular extrasystoles, paroxysmal ventricular tachycardia, and ventricular fibrillation, confirming the arrhythmogenic role of this channel.[12] Thus, hypokalaemia initiated a complex set of disturbances encompassing resting potential hyperpolarisation, action potential prolongation, shortening of the refractory period, cellular calcium overload, and the creation of a heterogeneous electrophysiological substrate conducive to re-entry. Key contributors to these processes were changes in the function of the Kir2.1 and K2P1 potassium channels, alongside secondary alterations in calcium and sodium currents.

Calcium and magnesium imbalance modulated the electrophysiological properties of ventricular cardiomyocytes at the cellular level by affecting depolarisation-repolarisation dynamics and promoting polymorphic ventricular tachycardias of the torsades de pointes type through several interrelated mechanisms. Mutations in the ryanodine receptor (RyR2), the principal calcium-release channel of the sarcoplasmic reticulum, increased the likelihood of spontaneous diastolic calcium release, elicit-

ing DADs that act as triggers for arrhythmias. In a mouse model with the RyR2×R2474S mutation, Borile et al.[13] observed synchronous calcium release in adjacent cardiomyocytes, fostering electrical instability at the tissue level by overcoming intercellular electrotonic coupling. Another study showed that EADs can generate local regions with a resting potential above 0 mV and, given an appropriate tissue geometry with concave boundaries, can produce triggered activity capable of initiating recurrent re-entry tachycardia. Using computational modelling, Tsumoto et al.[14] found that chain-like emergence of EADs in clustered cardiomyocytes created directed electrical activity that facilitated torsades de pointes, particularly in the setting of a prolonged QT interval.

García-Cano et al.[15] reported in a clinical case that an *RYR2* gene mutation led to raised intracellular calcium concentration, resulting in delayed afterdepolarisations (DADs) and, consequently, triggered activity. This indicated dysfunction of sarcoplasmic reticulum calcium channels and involvement of the Na^+/Ca^{2+} exchanger in arrhythmia development. The observation suggested the possible presence of a latent catecholaminergic polymorphic ventricular tachycardia (CPVT) phenotype with a benign clinical course but a propensity to arrhythmogenesis during physical exertion. From the channelopathy perspective, Lerman et al.[16] emphasised the role of disordered calcium homeostasis – specifically, sarcoplasmic reticulum calcium overload and spontaneous Ca^{2+} release – which activated the Na^+/Ca^{2+} exchanger and produced DADs. At the same time, a reduced repolarisation reserve and increased late plateau inward current promoted the occurrence of EADs, which were directly implicated in the development of torsades de pointes within the framework of long-QT syndrome. Thus, calcium and magnesium imbalance affected the function of L-type calcium channels and RyR2 receptors, fostered spontaneous calcium release, EADs and DADs, and together created the conditions for triggered activity and the emergence of polymorphic ventricular tachycardia of the torsades de pointes type.

Hypernatraemia and hyponatraemia modulated the electrophysiological properties of ventricular cardiomyocytes by influencing the transmembrane potential, sodium-channel function and myocardial automaticity, notably by generating ectopic foci of excitation. Using two detailed mathematical models of cardiomyocytes, Verkerk and Wilders[17] showed in cellular electrophysiology simulations that hypernatraemia promoted hyperpolarisation of the resting membrane potential, increased the amplitude of calcium oscillations, raised the rate of depolarisation and augmented Na^+/K^+ pump current, while reducing the rapid and slow delayed rectifier potassium currents – ultimately prolonging the action potential. Importantly, these effects were marked only at extreme sodium levels, whereas changes were minor with moderate deviations. Timilsina et al.[18] described cases of transient atrial fibrillation arising during correction of chronic hypernatraemia in elderly patients without a prior history of arrhythmia. The authors hypothesised that sodium fluctuations during rehydration might provoke atrial stretch via preload changes, activating stretch-sensitive ion channels implicated in generating ectopic impulses. This pointed to a link between alterations in sodium balance and triggered activity, although the mechanism requires further confirmation.

Brown et al.[19] noted that even slight deviations in sodium concentration can modify neuromuscular transmission and lower the excitation threshold, while hyponatraemia is typically associated with generalised membrane depolarisation and a reduced transmembrane potential difference, promoting spontaneous activity – particularly under myocardial hypoxia or ischaemia. They emphasised that the electrophysiological consequences of disturbed sodium homeostasis occur in close interaction with other electrolyte abnormalities, especially hypokalaemia and hypocalcaemia, which together prolong repolarisation and increase the risk of late afterdepolarisations. Moreover, in a sepsis model, Castello et al.[20] showed that both hypernatraemia and moderate to severe hyponatraemia were associated with higher mortality at days 7 and 30. This indicated that sodium-balance disorders induce systemic changes, including effects on cardiac excitability and automaticity, particularly in critical illness. The authors highlighted that these disturbances may serve as markers of disease severity and predict the development of life-threatening arrhythmias. In summary, hypernatraemia and hyponatraemia alter the transmembrane potential of ventricular cardiomyocytes and sodium-channel activity, promote triggered activity and ectopic foci – especially in combined electrolyte disturbances such as hypokalaemia – and are therefore integrally linked to mechanisms of arrhythmogenesis.

Combined electrolyte disturbances exerted a synergistic arrhythmogenic effect at the levels of ion channels, gap junctions, and intercellular conductivity in the ventricular myocardium through several mechanisms that promoted fatal ventricular arrhythmias. A key role in disrupting the heart's electrical integrity was played by dysfunction of gap junctions formed by the protein Cx43. As shown by Yang et al.[21], after myocardial infarction Cx43 undergoes post-translational modifications and remodelling that impair its localisation and function, reduce intercellular electrical conductance, and facilitate ventricular tachyarrhythmias. These processes were potentiated by changes in Cx43 expression and phosphorylation that produced electrical disorganisation of the tissue. Ion channels – particularly calcium, sodium and potassium channels – also contributed to forming an arrhythmogenic substrate. Ma et al.[22] demonstrated that CaMKII activation disrupts ionic homeostasis by regulating sodium, potassium and calcium currents, thereby generating early and late afterdepolarisations. These electrical disturbances markedly increased the likelihood of initiating ventricular arrhythmias against a background of electrolyte imbalance.

Gap-junction dysfunction caused by fibrosis or inflammation likewise reduced electrical coupling and led to conduction anisotropy. Kléber and Jin[23] showed that reduced gap-junction conductance, combined with microscopic structural non-uniformity of the tissue, greatly heightens the risk of disorganised impulse propagation – particularly where electrolyte disturbances exacerbate functional disintegration between cardiomyocytes. A particularly critical pattern for fatal arrhythmias was the combination of hypokalaemia and hypocalcaemia, which prolonged action-potential duration and impaired

Table 1 – Comparative characteristics of electrophysiological changes in different types of electrolyte disturbance

Type of electrolyte imbalance	Effect on resting potential (mV)	Effect on QT/QTc duration	Specific ion channels	Primary mechanism of arrhythmogenesis	Typical ventricular arrhythmias	Critical concentrations (mmol/L)	Risk of torsades de pointes
Hypokalaemia	Hyperpolarisation (–90 to –100 mV)	QT prolongation by 50–120 ms per 1 mmol/L ↓ K^+	IKr, IKs, IK1, Kir2.1	Delayed repolarisation, EADs, triggered activity	PVCs, non-sustained ventricular tachycardia (NSVT), TdP, VF	<2.5 (moderate), <2.0 (high)	High (QTc >500 ms)
Hyperkalaemia	Depolarisation (–70 to –55 mV)	QT shortening, QRS >130 ms	INa, IK1, Kir2.1	Reduced excitability, slowed conduction, re-entry	Broad-complex VT, sine-wave pattern, VF, asystole	>6.5 (moderate), >7.5 (high), >8.5 (critical)	Low
Hypomagnesaemia	Mild hyperpolarisation (≈–85 mV)	QT prolongation by 40–90 ms	TRPM6/7, IKr, ICa-L	IKr block, Ca^{2+}-dependent EADs/DADs, increased triggered activity	TdP, polymorphic VT, PVCs, VF	<0.7 (moderate), <0.5 (high risk)	Very high
Hypocalcaemia	Mild depolarisation (≈–75 mV)	QT prolongation by 40–100 ms (ST segment)	ICa-L, RyR2	Prolonged action-potential plateau, EADs	Monomorphic VT, TdP (less common), PVCs	<1.8 (total Ca^{2+}), <0.9 (ionised)	Moderate
Hypercalcaemia	Mild hyperpolarisation	QT shortening <360 ms	ICa-L, RyR2, Ca^{2+} pumps	Shortened phase 2, ↑ automaticity, lower depolarisation threshold	PVCs, VT (with cardiac glycosides)	>2.8 (total), >1.4 (ionised)	Low
Hyponatraemia	Depolarisation (–75 to –65 mV)	Variable QT	INa (SCN5A), Na^+/K^+-ATPase	Reduced phase – 0 upstroke, conduction disturbance	Broad PVCs, NSVT, VT	<125 (severe), <115 (critical)	Low–moderate
K^+ < 2.8 + Mg^{2+} < 0.6	Marked hyperpolarisation (<–100 mV)	QT >550–600 ms	IKr, IK1, TRPM6/7	Profound repolarisation delay, multiple EADs, synergistic phase-3 prolongation	TdP, refractory polymorphic VT, VF	K^+ <2.8 + Mg^{2+} <0.6	Critically high

Source: compiled by the author based on Pintaningrum and Pramana[3], Brown et al.[25], Liu et al.[26]

repolarisation against a background of reduced sodium–potassium exchange and intracellular calcium overload. As demonstrated by Padget et al.[24], in acute viral infection – where Cx43 is modified and ion channels are disrupted – there was reduced conductance, prolonged action potentials and electrical instability even before any structural cardiomyopathy appeared. This confirmed that, even in the absence of significant myocardial remodelling, the combination of ion-channel changes and impaired intercellular communication creates a powerful arrhythmogenic substrate. Hence, the synergistic effect of combined electrolyte disturbances in the ventricular myocardium is realised through concurrent dysfunction of ion channels, Cx43-dependent gap junctions and tissue organisation, establishing the conditions for initiation and maintenance of ventricular arrhythmias, with particularly dangerous patterns involving hypokalaemia, hypocalcaemia and heightened CaMKII activity.

Studies have confirmed that different types of electrolyte disturbance exert specific effects on myocardial electrophysiology by altering resting potential parameters, the duration of repolarisation and ionic currents, thereby creating conditions for ventricular arrhythmias of varying severity. **Table 1** presents an updated comparative profile of these changes according to recent evidence.

Analysis of **Table 1** revealed a clear trend towards increased arrhythmogenic risk where repolarisation processes are impaired, particularly with combined potassium and magnesium deficiency. Determinants in such states include not only absolute concentration decreases but also their interaction with blockade of potassium and calcium currents, which promotes early afterdepolarisations. These changes generally occur without substantial structural myocardial remodelling but markedly destabilise electrophysiological integrity. Notably, even small shifts in membrane potential can reduce excitability or slow conduction – preconditions for re-entry mechanisms – seen particularly in hyperkalaemia and hyponatraemia. Despite a lower risk of torsades de pointes in these settings, their potential lethality is high due to asystole or ventricular fibrillation. Overall, the greatest clinical danger is posed by combined ionic deficits that create a polymodal arrhythmogenic substrate – characterised by delayed repolarisation, early and late afterdepolarisations, conduction disturbances, and pronounced abnormalities of automaticity.

Clinical manifestations and electrocardiographic diagnosis of ventricular arrhythmias in specific electrolyte disorders

Khan et al.[28] showed that hypokalaemia leads to sequential, quantitatively measurable ECG changes, from T-wave flattening at potassium <3.5 mmol/L and the appearance of U-waves at <3.0 mmol/L to marked QTc prolongation >500 ms when potassium falls below 2.5 mmol/L.

The authors identified a clear correlation between decreasing potassium and increasing T-peak to U-end distance, reflecting ventricular repolarisation heterogeneity and an elevated risk of polymorphic ventricular tachycardia. Tsai et al.[27] described the dynamics of ECG changes in severe hyperkalaemia (K^+ >7.5 mmol/L), including progressive P-wave disappearance, QRS widening beyond 160 ms, and the development of a sine-wave pattern preceding ventricular fibrillation.

These changes were accompanied by tall, symmetrical T-waves in the anterior precordial leads from K^+ >6.0 mmol/L. The authors stressed that the transition from a normal ECG to a sine-wave pattern occurs rapidly and demands immediate intervention, as the presence of this pattern signals a high risk of sudden asystole.

The review by Teymouri et al.[29] confirmed that hypokalaemia manifests with variability in T- and U-wave amplitude and morphology, with a tendency for T- and U-wave fusion in patients with concomitant QT prolongation. In hyperkalaemia, the principal early marker is a tall, symmetrical T-wave, whereas a falling R-wave amplitude and progressive QRS widening are markers of progression to instability. The authors proposed an "electrocardiographic spectrum" concept, within which the trajectory of changes enables risk stratification. Based on patients with renal failure, Varga et al.[30] showed that ECG changes in hyperkalaemia do not always correlate with absolute potassium levels, particularly in chronically adapted patients. Nevertheless, diffuse tall, symmetrical T-waves, reduced or absent P-waves, QRS >140 ms, and a sine-wave pattern had high specificity for identifying patients at immediate risk of life-threatening arrhythmias. They also noted that interpretation must account for clinical context, the rate of electrolyte change, and any pre-existing conduction system disease. Thus, the nature and sequence of ECG changes in hypo- and hyperkalaemia correlate both with potassium concentration and its dynamics, allowing the ECG to serve as a tool not only for diagnosis but also for risk stratification of fatal ventricular arrhythmias.

Clinical manifestations and ECG markers of ventricular arrhythmias due to hypomagnesaemia and hypocalcaemia are closely tied to repolarisation changes, increased QT dispersion, T-wave alternans, and the emergence of early or late afterdepolarisations, creating a favourable substrate for arrhythmogenic events. Yang et al.[31] showed that in isolated hypomagnesaemia, QTc, T-peak to T-end interval (Tpe) interval, and the Tpe/QT ratio increased significantly, indicating heightened repolarisation dispersion, a key factor in arrhythmia formation. QRS duration and PR interval remained unchanged, excluding intraventricular conduction delay as the cause of these changes. Kulkarni et al.[32] investigated T-wave alternans (TWA) as a reliable marker of electrical instability. They reported that spatially discordant repolarisation alternans – that is, asynchronous changes in action-potential duration in adjacent myocardial regions – creates conditions for the re-entry mechanism underlying ventricular tachycardia and fibrillation. This phenomenon is associated with increased repolarisation dispersion and is a salient element of arrhythmogenic pathophysiology in electrolyte deficiency.

In a clinical study of patients with autosomal-dominant hypocalcaemia, Hartley et al.[33] found that sustained reductions in serum calcium and magnesium prolonged QTc via slowed repolarisation. Following correction with Encaleret, QTc normalised, indicating a direct dependence of repolarisation changes on calcium and magnesium levels, particularly through effects on L-type calcium chan-

nels and calcium-dependent inactivation. In addition, Reynard et al.[34] characterised ECG parameters reflecting both repolarisation (QTc, QT dispersion, Tpeak-Tend, TWA) and conduction (fragmented QRS, QRS dispersion). They noted that it is the combination of conduction and repolarisation abnormalities – captured, for example, by the electrophysiological balance index (QT/QRSd) – that heightens the risk of ventricular arrhythmias. These parameters not only identify individuals at increased risk of sudden cardiac death but also assist differential diagnosis of QT prolongation, including distinguishing electrolyte shifts from drug-induced or congenital long-QT syndromes. Therefore, hypomagnesaemia and hypocalcaemia are associated with pronounced alterations in ventricular repolarisation – manifesting as QTc prolongation, increased Tpe and Tpe/QT, T-wave alternans, and early afterdepolarisations – that create an arrhythmogenic substrate. Differential diagnosis of QT prolongation should be based on electrolyte status, medication history, assessment of TWA, and interval analysis considering heart rate and ECG wave morphology.

Between 2019 and 2025, multiple studies enabled quantitative and qualitative assessment of the diagnostic performance of cardiomonitoring methods – including Holter monitoring, telemetry, implantable devices, and electrophysiological study – for detecting ventricular arrhythmias, particularly those driven by electrolyte disturbances, and for monitoring the efficacy of their correction. In the randomised multicentre Telemedical cardiac risk assessment by implantable cardiac monitors in post-myocardial infarction patients (SMART-MI-DZHK9) trial, implantable cardiac monitors in patients with residual autonomic dysfunction after myocardial infarction detected prognostically significant ventricular arrhythmias in 30% of cases – substantially higher than the 6% seen with standard follow-up. Recorded events included ventricular fibrillation, ventricular tachycardia, and heart block, indicating high diagnostic sensitivity of these devices to subclinical rhythm disturbances potentially linked to impaired electrolyte homeostasis.[35]

In a clinical comparison of mobile telemetry and prolonged continuous ECG monitoring, the latter demonstrated a significantly higher detection rate of arrhythmias, including ventricular tachycardia (identified in 13 patients versus 7 with telemetry), indicating the superiority of continuous human signal analysis over algorithmic systems. In particular, continuous monitoring detected far more arrhythmic episodes overall – 61 versus 19 – which could be critical when evaluating the effectiveness of treatment for electrolyte disorders.[36] In a paediatric cohort of patients with hypertrophic cardiomyopathy, 72-hour Holter monitoring with telemetry revealed significant associations between sleep disturbances and an increased frequency of premature ventricular contractions and episodes of ventricular tachycardia. Although this study was conducted in a paediatric population, its inclusion is justified by the fact that the fundamental electrophysiological mechanisms underlying arrhythmogenesis–such as autonomic imbalance, ion-channel dysfunction, and electrolyte-related triggers–are consistent across age groups. Therefore, these findings are considered conceptually relevant for understanding arrhythmia mechanisms in adults, while acknowledging the limitations of direct clinical extrapolation. However, the extrapolation of paediatric data to adult populations should be interpreted with caution and considered as supportive rather than primary evidence.[37]

In an emergency department study, 24-hour Holter monitoring identified diagnostically significant arrhythmias in more than a quarter of patients presenting with syncope. Although results lacked clear diagnostic value in some cases, even non-specific changes predicted 30-day rehospitalisation, indicating latent risk and the potential role of electrolyte disturbances as arrhythmic triggers.[38–40] Thus, rhythm-monitoring methods – especially prolonged continuous ECG, implantable monitors, and telemetric systems – demonstrated high diagnostic capability for detecting ventricular arrhythmias associated with electrolyte imbalance and enabled assessment of therapeutic efficacy to reduce arrhythmic burden. **Table 2** summarises data from primary clinical and electrocardiographic studies on electrolyte disturbances and associated ventricular arrhythmias. It integrates reported ECG features, arrhythmia types, monitoring approaches, and clinically relevant diagnostic patterns described in the reviewed literature.

The analysis shows a clear correlation between the severity of electrolyte disturbance and the risk of life-threatening ventricular arrhythmias. The greatest danger is posed by combined potassium-magnesium disorders, severe hypokalaemia and hyperkalaemia, which are associated with unstable tachycardia phenotypes, electrical storms, and a need for continuous monitoring.[41–42] ECG changes progress from minimal to critical as electrolyte deficit worsens, reflecting a gradual rise in myocardial electrophysiological instability. It is also evident that key elements of risk stratification include not only classical ECG parameters (QTc, T–U waves, QRS width) but also contemporary methods such as T-wave alternans, beat-to-beat QT analysis, and telemetry, underscoring the growing role of dynamic, highly sensitive monitoring in identifying patients prone to fatal arrhythmias. The importance of metabolic and cardiac biomarkers (e.g., lactate, pH, troponins) is likewise increasing, especially in combined or severe disorders, indicating the need for a multidisciplinary monitoring approach that extends beyond ECG alone.[43,44] Overall, **Table 2** demonstrates that arrhythmic risk is determined by the intersection of four factors: depth of electrolyte imbalance, severity of ECG findings, arrhythmia type, and monitoring capabilities. It is the comprehensive assessment of these parameters that enables optimisation of patient management.

Notably, **Table 2** is intended as a structured analytical summary of patterns reported across the reviewed studies rather than as a formal diagnostic guideline. **Table 2** reflects synthesised evidence from relevant primary sources and should be interpreted as a comparative clinical framework rather than a normative protocol.

Therapeutic strategies for correcting electrolyte imbalance and pharmacological management of ventricular arrhythmias

Current clinical protocols for correcting hypokalaemia in patients with acute ventricular arrhythmias adopt an individualised approach that considers the degree of po-

Table 2 – Diagnostic criteria for ventricular arrhythmias in electrolyte imbalanc

Electrolyte disturbance	Concentration range	Specific ECG changes	Types of ventricular arrhythmia	Diagnostic monitoring methods	Risk class	Additional biomarkers	Recommended ECG monitoring frequency
Mild hypokalaemia	3.0–3.5 mmol/L	T-wave flattening, appearance of U-wave, ST up to 1 mm	Isolated PVCs (<30/hour), couplets	12-lead ECG, baseline monitoring	Low	Aldosterone, renin, creatinine, brain natriuretic peptide (BNP)	Every 24 h until normalisation
Moderate hypokalaemia	2.5–3.0 mmol/L	U >1 mm, QTc 470–500 ms, ST ↓ >1 mm, T inversion	Frequent PVCs, NSVT, bigeminy, trigeminy	24–48 h Holter, telemetry, TWA	Intermediate	Magnesium, troponin I (TnI), creatine kinase MB fraction (CK-MB), lactate, pH	Every 6–12 h + telemetry
Severe hypokalaemia	<2.5 mmol/L	QTc >500 ms, T-U fusion, QRS >100 ms	Polymorphic VT, TdP, VF, sustained VT	Continuous telemetry, intensive care unit (ICU) monitoring, defibrillation	High/Critical	Mg^{2+}, pH, lactate, troponin, digoxin	Continuous + ECG every 2–4 h
Moderate hyperkalaemia	5.5–6.5 mmol/L	T >10 mm, QT <360 ms, PR >200 ms	PVCs, idioventricular rhythm	12-lead ECG, baseline monitoring	Intermediate	Creatinine, urea, pH, glucose, CK	Every 4–6 h + after each intervention
Severe hyperkalaemia	>6.5 mmol/L	QRS >120 ms, sine-wave pattern, absent P	Broad-complex VT, VF, asystole, atrioventricular (AV) blocks	Continuous telemetry, ICU monitoring	High / critical	pH <7.2, creatinine, Ca^{2+}, glucose, insulin	ECG every 1–2 h
Hypomagnesaemia	<0.7 mmol/L	QTc 480–550 ms, T-U alternans, QT dispersion >80 ms	TdP (up to 80%), PVCs, polymorphic VT	Holter with QT-dispersion, TWA monitoring	High	K^+ (<3.0), calcium, albumin, phosphate	Every 4–6 h + 24-h Holter
Hypocalcaemia	<1.8 mmol/L (total) or <0.9 (ionised)	QTc prolongation 460–520 ms (via ST), narrow T	Monomorphic VT, rare TdP, PVCs	ECG + QT analysis, telemetry	Intermediate	Parathyroid hormone (PTH), vitamin D, Mg^{2+}, phosphate	Every 8–12 h
K^+ <2.8 + Mg^{2+} <0.6	K^+ <3.0 + Mg^{2+}<0.7	QTc >520 ms, marked T-U alternans	TdP, electrical storm (>3 VT/VF/24 h)	Beat-to-beat QT analysis, implantable cardioverter--defibrillator (ICD) monitoring, telemetry	Critical	pH, lactate, troponin, BNP, digoxin	Hourly ECG + continuous monitoring

Source: compiled by the author based on Khan et al.[28], Teymouri et al.[29], Yang et al.[31], Hartley et al.[33], Reynard et al.[34], Bauer et al.[35], Willcox et al.[36], and Lopes et al.[38].

tassium deficit, arrhythmic risk, concomitant electrolyte abnormalities, and patient status. Intravenous potassium is preferred in severe hypokalaemia (level <2.5 mmol/L) or when electrocardiographic changes are present, whereas oral administration is appropriate for mild or moderate deficits where intestinal absorption is intact. Amirnovin et al.[45] showed that a tiered intravenous potassium regimen in post-cardiac surgery patients achieved effective potassium elevation with minimal risk of hyperkalaemia, supporting structured protocols with controlled infusion rates and regular monitoring. Magnesium correction is integral when hypomagnesaemia drives renal potassium losses. As noted by Gaynor and Cornejo,[46] attempts to raise potassium without concurrent magnesium repletion may fail because magnesium deficiency promotes kaliuresis. The authors emphasised that intravenous magnesium – in the context of ventricular arrhythmias – raises the threshold for ventricular fibrillation, which is clinically significant in patients at high risk of life-threatening arrhythmias.

Monitoring recommendations included mandatory electrolyte checks with each potassium administration, at least daily for intravenous therapy, as described by Mustafa and Befkadu.[47] Protocols also mandated ECG surveillance when potassium infusion rates exceed 10 mmol/h because higher rates are associated with iatrogenic hyperkalaemia. The study showed that only 16% of patients with moderate or severe hypokalaemia received intravenous potassium and that concurrent monitoring was infrequently used, highlighting a need to improve protocol adherence. A specific clinical context was examined by Beaulieu and Kurczewski,[48] who studied electrolyte changes in neurosurgical patients undergoing therapeutic hypothermia. Despite a daily median potassium dose of 45 mmol, hypokalaemia persisted in 30% of cases, indicating reduced efficacy of standard regimens under specific physiological conditions. Magnesium levels, by contrast, remained stable with routine correction, underscoring the need for personalised electrolyte dosing in complex patients with secondary disturbances.[49] Thus, contemporary guidance for treating hypokalaemia in acute ventricular arrhythmias rests on the degree of deficit, route of administration, obligatory assessment of magnesium status, regular electrolyte and ECG monitoring, and avoidance of rapid unmonitored infusions. Individualised protocols support effective, safe therapy while preventing iatrogenic hyperkalaemia and potentially fatal arrhythmias.[50,51]

Intravenous magnesium sulphate remains a widely accepted first-line treatment in the emergency management of torsades de pointes (TdP) and other polymorphic ventricular tachycardias associated with QT prolongation. Antiarrhythmic mechanisms include reducing transmembrane calcium influx via L-type channels, stabilising myocardial cell membrane potential, and attenuating early afterdepolarisations, which is pivotal in preventing TdP.[52–54] Clinically, magnesium also shortens cardiomyocyte action-potential duration, thereby mitigating electrical instability. Matsuura et al.[55] reported a case of drug-induced QT prolongation with TdP unresponsive to a single 6 g magnesium dose; arrhythmia termination was achieved only after reaching an ionised magnesium level of 1.31 mmol/L via continuous infusion at 1 g/h, underscoring the importance of dynamic monitoring of ionised, rather than total, magnesium. In a clinical study by Narang and Ozcan,[56] intravenous magnesium sulphate combined with isoprenaline stabilised rhythm and abolished arrhythmia in patients with defibrillation-refractory TdP arising from combined electrolyte abnormalities, including hypomagnesaemia. Although dosing specifics were not given, high-dose use was justified in severe arrhythmogenic instability.

In a randomised controlled trial evaluating magnesium for ventricular arrhythmias in dogs, Schoeller et al.[57] showed that 0.1 mmol/kg (0.2 mEq/kg) magnesium sulphate significantly reduced ventricular ectopics and heart rate, though full conversion to sinus rhythm occurred in only two cases, suggesting a dose-dependent response and the need for human trials to confirm clinical utility. The antiarrhythmic mechanism of magnesium via calcium-channel blockade and membrane stabilisation is conserved among mammals, supporting cautious extrapolation of dose-response data to humans. In loperamide-induced TdP, Iqbal et al.[58] showed that intravenous magnesium 2 g effectively controlled ventricular tachycardias resistant to other treatments even when baseline electrolytes were normal, underscoring magnesium's versatility as baseline therapy in drug-induced QT-prolongation scenarios. Accordingly, magnesium sulphate is effective for terminating TdP regardless of the aetiology of QT prolongation – drug-induced, electrolyte-mediated, or idiopathic.[59] A bolus of 1–2 g with possible transition to continuous infusion (e.g., 1 g/h) tailored to clinical response and ionised magnesium level is considered optimal. Randomised trials and clinical cases support magnesium as first-line therapy in the emergency treatment of TdP, with emphasis on electrolyte monitoring and individualised dosing.

In patients with recurrent ventricular arrhythmias amid chronic or refractory electrolyte disturbances, interventional treatments – such as temporary pacing and ICD implantation – were justified based on clinical indications of rhythm instability unresponsive to medication.[60] In Tixier et al.,[61] temporary overdrive pacing was used to treat electrical storm in patients with ventricular fibrillation resistant to amiodarone, beta-blockers, and lidocaine. Temporary pacing reduced ventricular arrhythmia burden, particularly after recent ischaemic episodes, and served as a bridge to catheter ablation or optimisation of medical therapy, providing rapid electrophysiological stabilisation without major complications in most cases. Mitkowski[62] noted that ICD implantation for secondary prevention should proceed once reversible causes of arrhythmia have been excluded. In patients with chronic kidney disease (CKD), malabsorption, or endocrinopathies – where electrolyte imbalances are prolonged or recurrent – ICD placement was considered when the risk of recurrent life-threatening ventricular arrhythmias was high, accompanied by careful evaluation of the potential to restore electrolyte balance, particularly in reversible hypokalaemia or hypomagnesaemia.[63,64]

In a retrospective study, Meter and Borovac[65] described a case of refractory electrical storm after acute myocardial infarction in a patient with concomitant CKD. Temporary

ventricular overdrive pacing terminated arrhythmia unresponsive to drug therapy and served as a bridge to ICD implantation, confirming the utility of temporary pacing as bridging therapy in patients with severe electrolyte disturbances and high arrhythmic mortality risk. Analysis of Italy's national registry by Proclemer et al.[66] showed that ICD implantation for primary prevention predominated among heart-failure patients, with a substantial proportion also implanted for secondary prevention after cardiac arrest. In patients with comorbidities complicating electrolyte balance – including endocrine disorders and malabsorption syndromes – long-term management strategies combined ICD therapy, medication, electrolyte correction, and regular rhythm monitoring.

Correction of hypokalaemia and hypomagnesaemia in patients with ventricular arrhythmias requires a personalised strategy that accounts for the severity of imbalance, comorbidities, and risk of fatal complications. The choice between intravenous and oral administration, the necessity of concurrent magnesium correction, and continuous monitoring of treatment effectiveness enable stabilisation while avoiding iatrogenic hyperkalaemia. Interventional strategies such as temporary pacing and ICD implantation are justified in refractory or recurrent arrhythmias driven by chronic electrolyte disturbances and are complemented by long-term rhythm and metabolic control.

Conclusions

A systematic review of 52 scientific publications from 2019–2025 allowed for the synthesis of current evidence and the formulation of a conceptual framework describing ventricular arrhythmias in electrolyte imbalance. The study provides a structured summary of reported electrolyte thresholds and their potential association with arrhythmogenic risk.

Hypokalaemia is considered to contribute to a cascade of electrophysiological changes via Kir2.1 and K2P1 potassium-channel dysfunction, causing resting potential hyperpolarisation, action-potential prolongation, and critical shortening of the refractory period from 242 to 165 ms. Calcium and magnesium imbalance appears to modulate L-type calcium-channel and RyR2 receptor function, creating conditions for torsades de pointes through spontaneous diastolic calcium release. Combined potassium <2.8 mmol/L and magnesium <0.6 mmol/L may produce a synergistic arrhythmogenic effect via joint dysfunction of ion channels, Connexin-43-dependent gap junctions, and intercellular conductance, creating a critically high risk of fatal arrhythmias.

Systematisation of electrocardiographic markers revealed a clear correlation between imbalance severity and progression of ECG changes, enabling ECG-based risk stratification of sudden cardiac death. Hypokalaemia shows sequential changes from T-wave flattening below 3.5 mmol/L to QTc >500 ms below 2.5 mmol/L, while hyperkalaemia presents with tall, symmetrical T-waves above 6.0 mmol/L progressing to a sine-wave pattern. Prolonged cardiomonitoring detected prognostically significant ventricular arrhythmias in 30% of patients at risk of electrolyte imbalance compared with 6% under standard follow-up. Therapeutic protocols require an individualised approach with intravenous potassium at concentrations below 2.5 mmol/L, mandatory concurrent magnesium correction, and ECG monitoring when infusion rates exceed 10 mmol/h. Magnesium sulphate in a 1–2 g bolus remains first-line in emergency management of torsades de pointes, with monitoring of the ionised fraction.

Clinical implementation entails stratified monitoring protocols, comprehensive diagnostic panels including metabolic biomarkers, and personalised correction algorithms that account for comorbidities. A limitation of this review is substantial heterogeneity among included studies, precluding meta-analysis and quantitative estimation of therapeutic effect size. Future research should focus on addressing the key gaps identified in the current body of evidence. In particular, there is a need for prospective clinical studies evaluating the impact of combined electrolyte disturbances on the development and progression of ventricular arrhythmias, as most available data focus on isolated imbalances.

In addition, the literature demonstrates considerable variability in reported electrocardiographic thresholds, especially regarding QTc prolongation and its association with specific electrolyte levels, highlighting the need for standardisation of diagnostic criteria. Further investigation is also required to assess the long-term outcomes and recurrence rates of ventricular arrhythmias following correction of electrolyte imbalance, as current data are largely limited to acute clinical observations.

Finally, comparative studies evaluating the effectiveness of different cardiac monitoring strategies, including continuous ECG monitoring, telemetry, and implantable devices, are needed to determine optimal approaches for risk stratification and clinical management.

Conflict of interest
The author declares none.

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Ethical statement and consent to participate
All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Prior to the study, all patients signed a voluntary informed consent for participation in the study.

Consent for publication
All patients signed a voluntary informed consent to the processing of their personal data for the study.

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Původní sdělení | Original research article

The Value of Hypoxia Inducible Factor 1 alpha as a Biomarker for Stable Coronary Artery Disease Diagnosis and Risk Stratification

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SOUHRN

Kontext: Stabilní ischemická choroba srdeční (ICHS) představuje celosvětový zdravotní problém; proto vědci neustále pokračují v pátrání po důvěryhodných biomarkerech pro stanovení diagnózy ICHS a stratifikaci rizika. Primární regulátor buněčné odpovědi na hypoxii, hypoxií indukovatelný faktor-1 alfa (hypoxia inducible factor 1 alpha, HIF-1α), sice již byl důkladně zkoumán v kontextu akutních kardiovaskulárních příhod; nicméně jeho potenciální využití jako biomarkeru při stabilní ICHS dosud nebylo spolehlivě dokumentováno a je třeba jej teprve ověřit.
Cíle: Zhodnotit diagnostický a prognostický význam HIF-1α při stabilní ICHS a jeho korelaci se závažností onemocnění.
Pacienti a metody: Do této prospektivní studie bylo zařazeno 73 pacientů (50 mužů, 23 žen) s podezřením na ICHS, kteří byli vyšetřeni koronarograficky ve fakultní nemocnici ve městě Kená (Egypt) v období mezi srpnem 2024 a lednem 2025. Skupinu I (kontroly, n = 22) tvořili jedinci s normálním výsledkem koronarografie; ve skupině II (ICHS, n = 51) odhalilo koronarografické vyšetření alespoň 70% stenózu koronární tepny. Při rozšířené klasifikaci v rámci skupiny II se rozlišovalo postižení současně několika tepen (multi-vessel disease, MVD) (n = 29) a postižení jedné tepny (single-vessel disease, 1VD) (n = 22). Pro stanovení hodnot HIF-1α v plazmě byla použita ELISA; hodnotily se i Gensiniho skóre a další klinické údaje.
Výsledky: Ve srovnání s kontrolní skupinou byly průměrné hodnoty HIF-1α při ICHS značně vyšší (4,594 ± 3,101 ng/ml vs. 3,563 ± 0,5957 ng/ml; $p = 0,0265$). Větší statisticky významný rozdíl byl zaznamenán mezi podskupinou 1VD a kontrolní skupinou ($p = 0,0457$), a větší rozdíl – ne však statisticky významný – byl pozorován mezi podskupinou MVD a kontrolní skupinou ($p = 0,2652$). Vyšší průměrné hodnoty HIF-1α byly naměřeny u pacientů s chronickým celkovým uzávěrem (chronic total occlusion, CTO) (5,36 ± 3,7 ng/ml); tento rozdíl byl ve srovnání s hodnotami v kontrolní skupině statisticky významný, $p = 0,0310$. Hodnoty HIF-1α však statisticky významně nekorelovaly s Gensiniho skóre.
Závěr: Hodnoty HIF-1α byly vyšší při stabilní ICHS, zvláště při postižení jedné tepny a CTO; po adjustaci na věk, pohlaví a klinické faktory však tento rozdíl přestal být statisticky významný a nebyl nezávisle spojen se závažností postižení. Není pravděpodobné, že by HIF-1α mohl sloužit jako samostatný biomarker při stabilní ICHS, může však mít jistou úlohu v kombinaci s jinými biomarkery.

Keywords:
Biomarkers
Cardiovascular risk factors
Hypoxia-inducible factor 1-alpha
Stable coronary artery disease.

ABSTRACT

Background: Stable coronary artery disease (CAD) is a worldwide health concern, and trustworthy biomarkers for CAD diagnosis and risk assessment are still being investigated. The primary regulator of the cellular response to hypoxia, hypoxia inducible factor 1 alpha (HIF-1α), has been thoroughly investigated in the context of acute cardiovascular events; however, its function as a biomarker in stable CAD is less well-established and requires validation.
Objectives: To evaluate the diagnostic and prognostic significance of HIF-1α in stable CAD and its correlation with disease severity.

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Patients and methods: This prospective study comprised 73 patients (50 males, 23 females) with suspected CAD who had coronary angiography at Qena University Hospital from August 2024 to January 2025. Group I (normal control, n = 22) consisted of patients with normal coronary angiography, while Group II (CAD, n = 51) had coronary artery stenosis of at least 70%. Multi-vessel disease (MVD) (n = 29) and single-vessel disease (1VD) (n = 22) were the additional classifications given to Group II. ELISA was used to assess plasma HIF-1α levels, and Gensini scores and other clinical data were examined.

Results: Compared to the control group, the mean HIF-1α levels in CAD were considerably higher (4.594 ± 3.101 ng/ml vs. 3.563 ± 0.5957 ng/ml, $p = 0.0265$). A higher significant difference was noted between 1VD subgroup and control ($p = 0.0457$), but higher insignificant difference between MVD subgroup and control ($p = 0.2652$). Higher mean HIF-1α levels were observed in chronic total occlusion (CTO) patients (5.36 ± 3.7 ng/ml) and compared to the control group, this increase was significant, $p = 0.0310$. However, HIF-1α levels had no significant correlation with the Gensini score.

Conclusion: HIF-1α levels were higher in stable CAD especially in single-vessel disease and CTO but lost significance after adjustment for age, sex, and clinical factors and showed no independent association with disease severity. HIF-1α is unlikely to serve as a standalone biomarker in stable CAD but may have a possible role within a multi-biomarker approach.

Introduction

Stable coronary artery disease (CAD) is a common disorder characterized by the presence of atheromatous plaques in the coronary arteries, impairing blood flow to the heart. This disorder is one of the leading causes of morbidity and death worldwide.[1] The ISCHEMIA Trials biorepository analysis showed that biomarkers like high-sensitivity troponin T and NT-proBNP, when combined with clinical factors, CAD severity, and inducible ischemia, improve cardiovascular event prediction over a median follow-up of 3.5 years.[2] These markers, however, need further prospective validation, which emphasizes the necessity of investigating other options such hypoxia-inducible factor-1α (HIF-1α).

Gregg L. Semenza and Guang Wang identified the HIF transcriptional complex in 1995, and it is crucial for cellular oxygen sensing and hypoxia tolerance. HIF-1α regulates genes involved in angiogenesis, glycolysis, and cell survival. Semenza, William Kaelin Jr., and Peter J. Ratcliffe received the Lasker Award in 2016 for their work on HIF-1's role in adapting to hypoxic conditions. In 2019, they were together awarded the Nobel Prize in Physiology or Medicine for their Insights that improve understanding how HIF regulates cellular reactions to variable oxygen levels.[3]

HIF-1α is structurally a subunit of the HIF-1 transcription factor, which is made up of the constitutively produced HIF-1β subunit and the oxygen-sensitive HIF-1α subunit.[4] A number of functional domains are present in the HIF-1α protein, such as two PAS (Per-Arnt-Sim) domains for dimerization stability, an oxygen-dependent degradation domain (ODDD) for oxygen-sensitive regulation, two transactivation domains (TAD-N and TAD-C) that stimulate target gene transcription, and an N-terminal basic helix-loop-helix (bHLH) domain for DNA binding. Under normoxic circumstances, prolyl hydroxylase domain (PHD) enzymes hydroxylate proline residues in the ODDD, triggering recognition by the von Hippel–Lindau (VHL) protein and subsequent degradation. This hydroxylation, however, is prevented in hypoxic environments, allowing HIF-1α to solidify, go into the nucleus, dimerize with HIF-1β, and initiate the transcription of genes related to angiogenesis, glycolysis, and cell survival.[5,6]

In cardiovascular diseases, HIF-1α signaling supports ischemic adaptation through angiogenesis and metabolic shifts, yet its dysregulation is implicated in CAD progression, heart failure, and other conditions like cancer and peripheral artery disease.[7,8]

Despite its biological significance, the clinical utility of HIF-1α in stable CAD remains underexplored. Prior studies have largely focused on acute coronary syndromes or advanced multi-vessel disease, with limited attention to its role in stable CAD phenotypes like single-vessel disease or chronic total occlusion (CTO). Furthermore, small-scale studies and a lack of standardized protocols have hindered its translation into practice, leaving gaps in understanding its diagnostic and prognostic value, including its potential influence on plaque stability.[9]

The purpose of this research is to investigate the relationship between stable CAD and HIF-1α levels in individuals experiencing coronary angiography. Additionally, we seek to explore the correlation of HIF-1α with CAD severity, utilizing the Gensini score, left ventricular ejection fraction (LVEF), and clinical risk factors for a comprehensive assessment of disease burden. To our knowledge, this is the first study to specifically explore the diagnostic and prognostic significance of HIF-1α in stable CAD, highlighting its association with distinct obstructive CAD subtypes, offering novel insights into its value as a targeted biomarker for better disease management.

Patients and methods

Study design and setting

This cross-sectional, observational prospective study was carried out at the Cardiology Department, Qena University Hospital, between August 2024 and January 2025.

Study population

This study comprised 73 individuals with presumed stable CAD who were scheduled for diagnostic coronary angiography due to chest pain. After receiving written informed consent and clearance from South Valley University's Ethics Committee on Research on Humans, patients were enrolled. Assuming a moderate to large effect size (Cohen's d = 0.7–0.8) based on previous biomarker studies in CAD, the sample size was calculated using a power

analysis aiming for 80% power and a significance level (α) of 0.05 to detect significant changes in HIF-1α levels between CAD patients and controls. A minimum of 64 participants was required, and after screening 96 patients and applying exclusion criteria, 73 were included in the final analysis. Patients were categorized into two main groups based on their angiographic findings:

Group I (Normal Control Group, n = 22): Subjects with normal or non-obstructive coronary arteries (<70% stenosis in any epicardial coronary artery).

Group II (CAD Group, n = 51): Patients with ≥70% stenosis in at least one epicardial coronary artery on coronary angiography. This group was further subdivided into:

- Subgroup A (Single-Vessel Disease, n = 22): Patients with ≥70% stenosis in one major epicardial coronary artery.
- Subgroup B (Multi-Vessel Disease, n = 29): Patients with ≥70% stenosis in two or more major epicardial coronary arteries.

Inclusion criteria: Patients who satisfied all of the following requirements were eligible to participate in the study:

- 18 years of age or older.
- Suspected stable CAD, requiring coronary angiography for evaluation of chest pain.
- No prior history of myocardial infarction, revascularization, or other acute cardiac events in the last six months.
- LVEF (left ventricular ejection fraction) ≥50% with a sinus rhythm.
- Availability of blood samples without hemolysis, ensuring accurate biomarker analysis.

Exclusion criteria: Patients were excluded if they had any of the following:

- Acute coronary syndrome (ACS) (unstable angina, NSTEMI, or STEMI) within the past six months.
- History of coronary revascularization (CABG or PCI) within the past six months.
- Hemolyzed blood samples that could interfere with biomarker analysis.
- Severe comorbidities or systemic diseases, including: Chronic inflammatory or autoimmune diseases (e.g., rheumatoid arthritis, lupus), active infections or malignancies, chest disorders, moderate to severe valvular heart disease, atrial fibrillation or other significant arrhythmias, heart failure with reduced ejection fraction (LVEF <50%), thyroid dysfunction (hypothyroidism or hyperthyroidism), hematological disorders (e.g., anemia, coagulopathies), chronic kidney disease (eGFR <30 mL/min/1.73 m²) or hepatic dysfunction (cirrhosis, significant liver enzyme elevation).

Blood sample collection and HIF-1α measurement

Each participant who fasted for eight hours had two milliliters of venous blood extracted and placed in tubes containing EDTA. After centrifuging the samples for ten minutes at 3500 rpm, the separated plasma was aliquoted into one milliliter cryotubes and kept at –80 °C until biochemical analysis. ELISA assay kits from Bioassay Technology Laboratory (BT LAB, China, Catalogue No. E0422Hu) were used to determine the levels of plasma HIF-1α. The measurement was performed using a microplate ELISA reader (EMR-500, USA), with a sensitivity of 0.01 ng/mL and a standard curve range of 0.05–15 ng/mL. To minimize potential biases, laboratory personnel who performed HIF-1α measurements were blinded to patient clinical and angiographic data. Both the intra-assay and inter-assay precision were less than 8% and 10%, respectively.[10]

Demographic, clinical, and echocardiographic data collection

Demographic data such as age, sex, and body mass index (BMI) were recorded. Additionally recorded were clinical risk factors such as diabetes, hypertension, and a history of smoking. Furthermore, each participant's echocardiographic left ventricular ejection fraction (LVEF%) was determined. Echocardiographic assessment was done by a GE Vivid E95 ultrasound system (GE Healthcare, Chicago, IL, USA) guided by the American Society of Echocardiography recommendations.[11]

Coronary angiography and Gensini score calculation

Coronary angiography was done after admission via standard techniques to assess coronary artery status and classify disease severity based on the 2018 ESC/EACTS Guidelines for Revascularization of the myocardium. An experienced cardiologist, blinded to clinical and laboratory data, analyzed the findings. CTO (chronic total occlusion) is defined as an epicardial coronary artery occlusion without antegrade flow across the lesion and with a duration of ≥3 months. Patients with CTO classically have coronary collaterals distally on coronary angiography, however, these collaterals may not deliver enough blood flow to the myocardium, causing ischemia and anginal pain. The Gensini score was used to quantify coronary artery disease severity. Each lesion was assigned a score based on stenosis severity: 25% is equal to one point, 50% to two, 75% to four, 90% to eight, 99% to sixteen, and 100% to thirty-two points. This score was then multiplied by a weighting factor reflecting the lesion's anatomical location: Left main = 5, proximal LAD = 2.5, mid LAD = 1.5, distal LAD = 1, proximal LCX = 2.5, mid LCX = 2, distal LCX = 1, RCA = 1, major first diagonal, obtuse marginal and posterior descending artery = 1. The final Gensini score was the sum of all weighted lesion scores, providing a comprehensive assessment of coronary atherosclerosis.[12,13]

Study endpoints

The primary endpoint is to assess the correlation between the presence of coronary artery disease and HIF-1α levels.

Secondary endpoint: To evaluate the relationship between HIF-1α levels and individual clinical risk factors (e.g., smoking, diabetes, and hypertension), left ventricular ejection fraction (LVEF), and the severity of CAD as determined by the Gensini score.

Ethical considerations

The Ethics Committee on Research on Humans at South Valley University gave approval to the study protocol (SVU-MED-MBC004-MED018-4-25-1-4). The study adhered to the ethical principles outlined in the Declaration of Helsinki, and all participants provided informed consent before participation.

Statistical analysis

GraphPad InStat 3.10 (GraphPad Software, San Diego, CA, USA) was used for all statistical analyses. Continuous variables were tested for normality using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Normally distributed data are presented as mean ± standard deviation (SD), and non-normally distributed data as median (interquartile range, IQR). Categorical variables are expressed as frequencies and percentages. Between-group comparisons were performed using the unpaired t-test or Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Welch's adjustment was applied to the unpaired t-test when there were unequal variances. Correlations were assessed using Pearson or Spearman coefficients as appropriate. Multiple regression was used to evaluate the independent association of HIF-1α with CAD after adjustment for clinical factors. ROC analysis was performed to assess its diagnostic performance using the area under the curve. A *p*-value <0.05 was considered statistically significant.

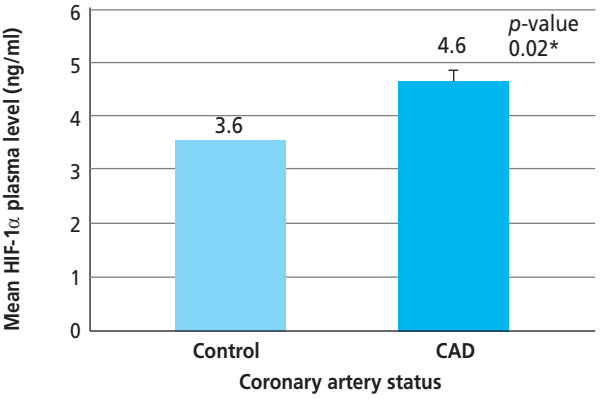

Fig. 1 – The difference between CAD and control groups in terms of baseline mean HIF-1α plasma levels. HIF-1α levels in CAD patients significantly increased compared to normal controls. CAD – coronary artery disease; HIF-1α – hypoxia inducible factor one alpha. * Significant p-value (<0.05). The two groups were statistically analyzed using the unpaired t-test with Welch's correction.

Results

A summary of the baseline demographic, clinical, biochemical, angiographic, and echocardiographic features is provided in **Table 1**, where:

- The CAD group was significantly older and had a higher proportion of males compared to the control group.
- The prevalence of diabetes mellitus (DM), hypertension (HTN), and smoking, as well as the mean BMI, was higher in the CAD group, though not statistically significant. This suggests a potential association between these factors and an increased risk of CAD.

HIF-1α levels in study groups

- The CAD group's mean HIF-1α levels were considerably higher than those of the control group (4.594 ± 3.101 ng/mL vs. 3.563 ± 0.5957 ng/mL, $p = 0.0265$), indicating that the raised HIF-1α level may be linked to the presence of CAD (**Fig. 1**).
- HIF-1α levels were considerably higher in subgroup A (single vessel disease) than in the control group (5.169 ± 3.506 ng/mL vs. 3.563 ± 0.5957 ng/mL, $p = 0.0457$).
- The HIF-1α levels in subgroup B (multi-vessel disease) were greater than those in the control group, but they were not statistically significant (4.158 ± 2.737 ng/mL vs. 3.563 ± 0.5957 ng/mL, $p = 0.2652$).

Table 1 – Comparison between the study groups regarding demographics, clinical, and biochemical data

Variables	Normal control (n = 22)	All CAD (n = 51)	Single-vessel disease (1VD) (n = 22)	Multi-vessel disease (MVD) (n = 29)	*p*-value (control vs. CAD)	*p*-value (IVD vs. MVD)
Age (years)	53.1 ± 8.7	58.1 ± 9.2	56.1 ± **8.2**	59.6 ± 9.8	**0.03***	0.2
Male sex (n, %)	10 (45%)	40 (78.4%)	18 (81%)	22 (75.8%)	**0.01***	0.7
BMI (Kg/m^2)	26.6 ± 3.6	27.3 ± 2.0	26.8 ± 2.0	27.5 ± 1.9	0.5	0.2
HTN (n, %)	7 (32%)	27 (52.9 %)	13 (59%)	14 (48%)	0.1	0.6
DM (n, %)	6 (27%)	24 (47%)	8 (36%)	16 (55%)	0.1	0.3
Smoking (n, %)	6 (27%)	25 (49%)	13 (59%)	12 (41%)	0.1	0.3
LVEF (%)	57.3 ± 4.1	56.5 ± 5.7	57.1 ± 6.4	56.2 ± 5.1	0.5	0.5
Gensini score (median)	–	36.0	24.0	**72.0**	–	< 0.001**
HIF-1α (ng/mL)	3.6 ± 0.6	4.6 ± 3.1	5.2 ± 3.5	4.2 ± 2.7	**0.03***	0.3

BMI – body mass index; CAD – coronary artery disease; DM – diabetes mellitus; 1VD, single-vessel disease; HIF-1α – hypoxia inducible factor one alpha; HTN – hypertension; LVEF – left ventricular ejection fraction; MVD – multi-vessel disease; n – number.
Continuous data expressed as mean ± SD, categorical data in the form of n (%). Comparison between the controls and all CAD groups was performed using unpaired t-test and Fisher's exact test, while HIF-1α *p*-value was done by unpaired t-test with Welch's correction.
** *P*-value represent the difference between 1VD and MVD subgroups in the median Gensini score and was highly significant (<0.001) in **bold**, done by unpaired t-test with Welch's correction. * Significant *p*-values are in **bold** (<0.05).

- Among CAD patients, those with chronic total occlusion (CTO) and coronary collaterals (n = 14, from subgroup A or B) exhibited the highest mean HIF-1α levels (5.36 ± 3.7 ng/mL) and when compared to the control group, this increase was significant, $p = 0.0310$.

Comparison within CAD subgroups

- Median Gensini scores were significantly higher in subgroup B (multi-vessel disease) compared to subgroup A (single vessel disease) (72 vs. 24, $p < 0.001$).
- HIF-1α levels in subgroups A and B did not differ significantly (5.169 ± 3.506 ng/mL vs. 4.158 ± 2.737 ng/mL, $p = 0.2702$).

Correlation analyses

No significant correlation was found between HIF-1α levels and: Gensini score (r = –0.03338, $p = 0.816$), age (r = –0.02256, $p = 0.8498$), BMI (r = 0.03735, $p = 0.7537$), diabetes (r = –0.0283, $p = 0.81$), smoking (r = 0.05733, $p = 0.63$), hypertension (r = 0.1089, $p = 0.41$), LVEF % (r = 0.09701, $p = 0.35$).

Multivariate and logistic regression analysis with confounder adjustment

A multiple regression model was used to evaluate the independent association of HIF-1α with CAD while adjusting for confounders. The model included age, sex, LVEF, BMI, diabetes mellitus, hypertension, and smoking as independent variables. It explained 25.68% of the variance in CAD ($R^2 = 0.2568$, $p = 0.0109$).

Confounder adjustment was performed by including clinically relevant covariates known to influence CAD risk. Diabetes mellitus ($p = 0.04$) and male sex ($p = 0.0180$) were significant predictors, while HIF-1α showed a positive but non-significant association ($p = 0.1803$). Other factors, including age, LVEF, BMI, hypertension, and smoking, did not reach statistical significance. Variance inflation factors (VIF <1.64) confirmed no multicollinearity, ensuring independent effects of each variable.

To address potential bias, additional adjustments were made using logistic regression, treating CAD as a categorical outcome (≥70% stenosis), The odds ratio (1.2380) suggests a modest increase in the likelihood of CAD with higher HIF-1α levels, but the confidence interval includes 1.0, and the *p*-value is not significant ($p = 0.0883$). Sensitivity analyses stratified the sample by diabetes status and sex to assess potential effect modification. Subgroup analyses evaluated differences in HIF-1α levels across CAD severity (Gensini score) (**Table 2 and Fig. 2**).

Despite not being a significant independent predictor, HIF-1α's association with obstructive CAD and its inclusion alongside established risk factors suggest its potential role in CAD risk assessment. To confirm these results, more research with larger sample sizes is required.

The ROC curve analysis demonstrated poor overall diagnostic performance for CAD (AUC = 0.510), with low sensitivity (35.29%) despite high specificity (95.45%). While high specificity suggests HIF-1α could help rule out CAD in specific cases, its low sensitivity limits its clinical utility as a standalone diagnostic marker. Additional studies are

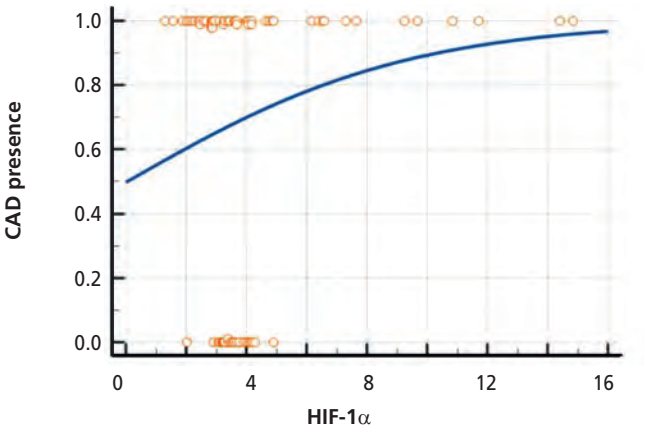

Fig. 2 – The relationship between HIF-1α levels and the existence of coronary artery disease (CAD) was assessed using logistic regression analysis. Although the *p*-value is not significant ($p = 0.09$), the odds ratio indicates a little increase in the risk of CAD with greater HIF-1α levels, and the confidence interval encompasses 1.0. CAD – coronary artery disease; HIF-1α – hypoxia inducible factor one alpha.

Table 2 – Multiple Regression Analysis of Predictors of CAD

Variable	Coefficient	Std. error	95% CI	t-ratio	*p*-value
Constant	–0.1	0.9	–1.8 to 1.7	0.1	1.0
HIF-1α	0.0	0.0	–0.0 to 0.1	1.4	0.2
Age	0.0	0.0	–0.0 to 0.0	1.1	0.3
LVEF	–0.0	0.0	–0.0 to 0.0	0.3	0.7
BMI	–0.0	0.0	–0.0 to 0.0	0.0	1.0
DM	0.2	0.1	0.0 to 0.5	**2.0**	*0.049
HTN	0.1	0.1	–0.1 to 0.4	1.3	0.2
Smoking	0.1	0.1	–0.2 to 0.4	0.8	0.5
Male sex	0.3	0.1	0.1 to 0.6	**2.4**	**0.02***

BMI – body mass index; CAD – coronary artery disease; CI – confidence interval; DM – diabetes mellitus; HIF-1α – hypoxia inducible factor one alpha; HTN – hypertension; LVEF – left ventricular ejection fraction.
* Significant *p*-values (<0.05) are in **bold**.

HIF-1α – hypoxia inducible factor one alpha.

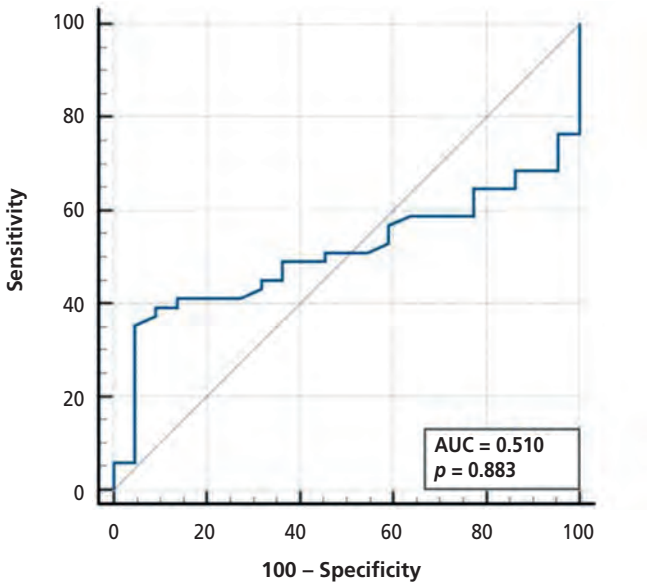

Fig. 3 – The ROC curve analysis demonstrated poor overall diagnostic performance for CAD (AUC = 0.510), with low sensitivity (35.29%) despite high specificity (95.45%).

necessary to decide whether HIF-1α could be integrated into multi-biomarker models to improve diagnostic accuracy (**Fig. 3**).

Discussion

Hypoxia-inducible factor 1-alpha (HIF-1α) is considered as a crucial modulator of cellular response to hypoxia, stimulates angiogenesis, vascular remodeling, and metabolic changes. Studies by **Akbaş et al. (2021)** and **Liu et al. (2013)** have shown that HIF-1α is upregulated in acute ischemic events and is associated with coronary collateral development, reinforcing its role in ischemic adaptation, aligning with our study.[14,15]

But it's still unknown how HIF-1α contributes to stable CAD. Our findings, consistent with those of **Czibik et al. (2008)**, suggest that in chronic ischemia, HIF-1α activation may be insufficient to sustain significant hypoxic signaling. This is supported by demonstrating lower transcriptional activity of HIF-1α in stable CAD compared to acute settings, likely due to differences in ischemic stress thresholds. Moreover, stable CAD may involve compensatory mechanisms such as collateral circulation and metabolic reprogramming, which reduce the extent of HIF-1α activation. These results could explain our observation of high but not statistically significant levels of HIF-1α in CAD patients with multivessel disease.[16]

Additional mechanistic insights suggest that HIF-1α exerts its effects in CAD through both protective and pathological pathways. **Vink et al. (2007)** found that HIF-1α is associated with an inflammatory plaque phenotype and is upregulated in activated macrophages, indicating its involvement in both protective angiogenesis and pathological inflammation in atherosclerosis.[17] Additionally, **DeNiro et al. (2013)** demonstrated that vascular endothelial growth factor (VEGF) can activate the NF–κB signaling pathway, linking HIF-1α-induced angiogenesis to inflammatory processes. These interactions suggest that elevated HIF-1α in chronic hypoxia may lead to maladaptive vascular changes, including endothelial dysfunction and plaque instability, complicating its role as a straightforward biomarker.[18]

The potential diagnostic value of HIF-1α in CAD remains debated. Although HIF-1α levels were higher among the included CAD patients, especially in those with single-vessel disease and chronic total occlusion (CTO), our research revealed that these levels did not correspond to the severity of the disease. HIF-1α levels may be higher in single-vessel CAD due to acute localized ischemia, which activates hypoxic signaling. Multi-vessel CAD often develops collateral circulation which may explain reducing ischemic damage and HIF-1α activation in stable multi-vessel CAD patients. Plaque instability and acute inflammation may be another explanation, further increasing HIF-1α levels. This aligns with **Akbaş et al. (2021)**, who reported elevated but statistically non-significant HIF-1α levels in acute coronary syndrome (ACS), possibly due to localized ischemia, immediate medical therapy, or sample size limitations, suggesting variability in its diagnostic reliability.[14]

The findings of **Qin et al. (2024)** further illustrate this variability. Their study identified a HIF-1α cutoff for diagnosing coronary artery calcification (CAC) in non-dialysis CKD patients, with high specificity and moderate sensitivity. In contrast, our study showed poor diagnostic performance of HIF-1α for CAD (AUC = 0.510), suggesting that its clinical utility may be context-dependent, influenced by disease mechanisms such as vascular calcification versus atherosclerotic plaque burden. Both studies confirmed the higher prevalence of males and older patients in disease groups.[19]

Similarly, while **Gharib et al. (2022)** linked elevated HIF-1α to coronary complications in diabetes, our findings did not establish it as an independent risk factor for CAD. **López-Reyes et al. (2014)** found that HIF1A polymorphisms modulate metabolic risk and the HIF1A rs2057482 polymorphism may account for population-level variations in HIF-1α expression and CAD susceptibility since it is linked to the risk of developing early coronary artery disease as well as certain metabolic and cardiovascular risk factors.[20,21]

In patients with notable coronary artery stenosis, **Song-Ming et al. (2008)** discovered a robust correlation between the presence and degree of coronary collaterals and greater HIF-1α expression at both the protein and mRNA levels. This in agreement with our research findings that elevated HIF-1α levels were observed in obstructive CAD, particularly CTO cases that often involve collateral development. However, no direct correlation was found between HIF-1α levels and disease severity or collateral grading.[22]

Stojanovic et al. (2021) identified renalase as a hypoxia-responsive gene linked to HIF-1α, promoting cardiac protection. These results lend credence to a wider function of hypoxia-related markers in the prediction of is-

chemia. However, our study suggests that HIF-1α alone lacks sufficient discriminatory power for stable CAD risk stratification.[23]

Limitations and future directions

This study has several limitations. Single center study and the relatively small sample size may restrict the generalizability of findings to broader CAD populations. The cross-sectional design precludes causal inferences between HIF-1α levels and CAD severity and limits our ability to assess dynamic changes in HIF-1α over time or in response to treatment. While we adjusted for age, sex, diabetes, hypertension, smoking, BMI, and LVEF, other potential confounders—such as genetic polymorphisms (e.g., HIF-1α gene variants), additional comorbidities (e.g., chronic kidney disease, dyslipidemia), and medications (e.g., statins, beta-blockers, or antiplatelets)—were not accounted for, despite their possible influence on HIF-1α expression and CAD severity. Furthermore, ethnic variability and genetic differences across populations were not fully explored, potentially limiting applicability to diverse groups. To confirm these results and clarify the clinical significance of HIF-1α in CAD, larger, long-term investigations with more diverse populations and balanced gender representation are required.

Future studies should use larger, multicenter cohorts and longitudinal follow-up to validate HIF-1α as a potential biomarker and to see how HIF-1α changes through different stages of CAD. It will also be important to look at how HIF-1α works alongside other biomarkers such as sST2, hsTnT, NT-proBNP, GDF-15, NF-κB, and YKL-40, which are already linked to CAD progression. Research on HIF-1α gene variations and how they affect disease severity in different populations is also needed. Our results suggest that HIF-1α may play a role in stable CAD, but it does not seem useful on its own as a diagnostic or prognostic marker. A combined multi-biomarker and mechanistic approach may help define its real value in CAD.

Conclusion

HIF-1α levels were higher in patients with stable CAD compared to controls, with numerically higher values in single-vessel disease and chronic total occlusion. These differences, however, were no longer significant after adjustment for age, sex, and other clinical factors. HIF-1α did not correlate with angiographic disease severity and did not independently predict the presence of CAD. The results indicate that HIF-1α is not suitable as a standalone diagnostic or prognostic biomarker in stable CAD, although it may still contribute as one element within a broader multi-biomarker strategy. Larger and better-controlled studies are needed to define its potential role.

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No conflict to declare.

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The authors collectively contributed to the manuscript's content, including design, data collection, analysis, and preparation, as well as the revision of the study.

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Původní sdělení | Original research article

Circulating microRNA-29 Reflects Remodeling-Related Ventricular Changes in Ischemic Dilated Cardiomyopathy

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miR-29
Remodelace komor

SOUHRN

Kontext: Fibrotická remodelace je typickou známkou ischemické dilatační kardiomyopatie (IDKM). Z několika malých nekódujících molekul RNA (microRNA, miR) podílejících se na regulaci extracelulární matrix byla v experimentu miR-29 spojena s expresí kolagenu a transformujícího růstového faktoru β/skupiny proteinů podílejících se na transdukci signálů a regulaci transkripce (transforming growth factor-β/mothers against decapentaplegic homolog 3 related signaling). Profil cirkulující miR-29 při IDKM u člověka a její vztah se strukturou a funkcí dosud nebyly dostatečně popsány. Smyslem této studie bylo kvantifikovat hodnoty miR-29 v plazmě pacientů s IDKM a zjistit, zda se cirkulující miR-29 shodují se zavedenými echokardiografickými ukazateli nepříznivé remodelace komor.
Metody: Do této studie bylo zařazeno 46 pacientů s angiograficky potvrzenou IDKM a 30 zdravých jedinců. Exprese miR-29 v plazmě se určovala metodou RT-qPCR s normalizací miR-103. Při echokardiografickém vyšetření se měřily ejekční frakce (EF), průměr levé komory na konci diastoly (left-ventricular end-diastolic diameter, LVEDD) a průměr levé komory na konci systoly (left-ventricular end-systolic diameter, LVESD). Srovnali jsme obě skupiny, použili Spearmanovy korelace a provedli analýzu ROC a multivariační regresní analýzu.
Výsledky: Hodnoty miR-29 v plazmě byly vyšší při IDKM než u kontrol ($p < 0{,}001$). Diskriminační analýza prokázala příznivou schopnost odlišení skupiny s IDKM od kontrolní skupiny (AUC = 0,87; 95% CI 0,78–0,94). Ve skupině pacientů s IDKM korelovaly hodnoty miR-29 negativně s EF (r = –0,34; $p = 0{,}021$) a pozitivně s LVEDD (r = +0,557; $p < 0{,}001$) i LVESD (r = +0,571; $p < 0{,}001$). V multivariačních modelech zůstávala hodnota log10(miR-29) nezávisle spojena s EF (β = –1,05 % na každé zvýšení 1-log10; $p = 0{,}0227$) a s LVEDD (β = +2,14 mm na každé zvýšení 1-log10; $p < 0{,}001$).
Závěry: Při ischemické dilatační kardiomyopatii je cirkulující miR-29 spojena s nepříznivou dilatací komory a sníženou systolickou funkcí. Tato zjištění ukazují, že cirkulující miR-29 odráží molekulární aktivitu související s remodelací a je spojena regulací extracelulární matrix; uvedená zjištění mohou tak umožnit přesnější poznání remodelační biologie a posloužit jako základ pro formulaci hypotéz budoucích studií zkoumajících stratifikaci pacientů a léčebných postupů zaměřených na signální dráhy.

Keywords:
Extracellular matrix
Echocardiographic indices
Ischemic dilated cardiomyopathy
miR-29
Ventricular remodeling

ABSTRACT

Background: Fibrotic remodeling is a hallmark of ischemic dilated cardiomyopathy (IDCM). Among microRNAs (miR) implicated in extracellular matrix regulation, miR-29 has been experimentally linked to collagen expression and transforming growth factor-β / mothers against decapentaplegic homolog 3 related signaling. However, its circulating profile in human IDCM and its relationship with ventricular structure and function remain insufficiently characterized. The purpose of this study is to quantify plasma miR-29 in patients with IDCM and examine whether circulating miR-29 aligns with established echocardiographic indices of adverse ventricular remodeling.
Methods: This study included 46 angiographically confirmed IDCM patients and 30 healthy individuals. Plasma miR-29 expression was assessed using RT-qPCR with miR-103 normalization. Echocardiographic measurements included ejection fraction (EF), left-ventricular end-diastolic diameter (LVEDD), and left-ventricular end-systolic diameter (LVESD). Group comparisons, Spearman correlations, ROC analysis, and multivariable regression were performed.

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Results: Plasma miR-29 levels were higher in IDCM compared with controls (p <0.001). Discriminatory analysis demonstrated good discriminative performance between IDCM group and control (AUC = 0.87, 95% CI 0.78 – 0.94). Within IDCM patients, miR-29 correlated inversely with EF (r = –0.34, p = 0.021) and positively with LVEDD (r = +0.557, p <0.001) and LVESD (r = +0.571, p <0.001). In multivariable models, $\log_{10}$(miR-29) remained independently associated with EF (β = –1.05% per 1-log10 increase, p = 0.0227) and LVEDD (β = +2.14 mm per 1-$\log_{10}$ increase, p <0.001).
Conclusions: Circulating miR-29 is associated with adverse ventricular dilation and reduced systolic function in ischemic dilated cardiomyopathy. These findings indicate that circulating miR-29 reflects remodeling-related molecular activity linked to extracellular matrix regulation and may provide additional molecular insight into remodeling biology, serving as a hypothesis-generating signal for future studies exploring patient stratification and pathway-directed therapeutic approaches.

Introduction

Heart failure (HF) remains a major global health burden, and despite therapeutic progress, its rates of hospitalization, morbidity, and mortality continue to rise worldwide.[1,2] Among the principal causes of chronic HF, IDCM occupies a central position.[3] IDCM develops from recurrent or unresolved myocardial ischemia, culminating in necrosis, scar formation, and diffuse fibrosis that ultimately promote left-ventricular (LV) dilation and impaired systolic function.[3,4] Fibrotic remodeling represents a key determinant of structural deterioration and clinical outcome in ischemic heart disease, yet detecting early or evolving fibrosis remains challenging because conventional tools rely primarily on advanced imaging or invasive sampling.[5,6] These limitations have intensified interest in circulating molecular biomarkers capable of identifying fibrosis-driven remodeling in a non-invasive and clinically applicable manner.[7]

MicroRNAs (miRNAs) are short, non-coding RNAs that regulate gene expression post-transcriptionally by binding to target mRNAs and influencing translation and stability, reflecting changes in regulatory networks rather than simply downstream protein release.[8,9] They participate in many of the cellular responses that shape cardiac injury and repair including inflammation, angiogenesis, necrosis, hypertrophy, and matrix remodeling and influence multiple pathways involved in post-ischemic ventricular adaptation.[10,11] Their stability in the circulation and predictable detectability makes plasma miRNAs promising indicators of underlying myocardial pathology offering potential insight into underlying myocardial dysfunction.[12,13]

miR-29 is one of several circulating microRNAs detectable in peripheral blood that exhibit remarkable stability, often through encapsulation within extracellular vesicles or binding to protective proteins, making it feasible indicator of gene-regulatory programs engaged during disease progression.[14] Preclinical and cellular studies demonstrate that miR-29 directly represses multiple profibrotic ECM genes, including collagens such as Collagen Type I Alpha 1 (COL1A1) and Collagen Type III Alpha 1 (COL3A1), and that its downregulation is associated with increased collagen expression in fibrotic models, supporting an antifibrotic regulatory role.[15,16] miR-29 expression is tightly modulated by the transforming growth factor-β (TGF-β) / mothers against decapentaplegic homolog 3 (Smad3) signaling axis, a central pathway involved in maladaptive myocardial fibrotic remodeling.[17] Importantly, while these mechanistic data establish miR-29 as a regulator of ECM-related pathways at the tissue level, the extent to which circulating miR-29 reflects myocardial remodeling processes in human cardiomyopathy remains uncertain with previous studies focused on diagnostic classification or heterogeneous heart-failure populations.[13,15,18] To our knowledge, no prior study has specifically examined the association between circulating miR-29 and echocardiographic markers of remodeling severity in IDCM.

Given this consideration, we evaluated circulating miR-29 expression in patients with angiographically confirmed IDCM. The objective of this study was to examine the relationship between plasma miR-29 levels and echocardiographic indices of left-ventricular structure and systolic function, in order to assess whether circulating miR-29 is associated with remodeling patterns commonly linked to fibrotic processes in patients with IDCM.

Material and methods

Study setting and design

The objective of this study was to determine circulating miR-29 levels in patients with IDCM and examine their association with echocardiographic indicators of ventricular remodeling.

Study population

A total of 76 participants were included and allocated into the following groups:

1. **IDCM Group (n = 46)**
   All IDCM patients had prior coronary angiography confirming significant obstructive coronary artery disease consistent with an ischemic etiology. Patients who had undergone revascularization were included, provided that angiographic evidence of prior infarction or residual disease was present. Cases with recent or acute myocardial infarction were excluded to avoid acute-phase changes in circulating miRNAs. IDCM patients had left ventricular ejection fraction (EF) <40% with echocardiographic evidence of chamber dilation (LV end-diastolic diameter [LVEDD] >58 mm, consistent with echocardiographic reference values).

2. **Control Group (n = 30)**
   Controls consisted of healthy, age- and sex-matched volunteers with normal clinical examination and echocardiography.

Exclusion criteria
Exclusion criteria included EF >40%, LVEDD <58 mm, recent or acute myocardial infarction, significant valvular pathology, hypertrophic or restrictive cardiomyopathy, drug-induced or chemotherapy-related cardiomyopathy, isolated right-sided failure, chronic renal or hepatic dysfunction, hematologic and autoimmune diseases, and any acute or chronic inflammatory condition.

Echocardiographic evaluation
All subjects underwent transthoracic echocardiography according to standardized imaging protocols.
- EF was calculated using biplane Simpson method.
- LVEDD and LVESD were measured using M-mode imaging in the parasternal long-axis view.

Measurements adhered to American Society of Echocardiography guidelines, and sonographers were blinded to miRNA results.[19]

Blood collection and sample handling
Peripheral venous blood (10 mL) was withdrawn from each participant.
- Plasma was isolated from EDTA tubes, centrifuged, and stored at –80 °C.
- Serum was collected separately for routine biochemical assessment.

Only plasma samples were used for miRNA analyses. Samples demonstrating hemolysis or poor quality were excluded before processing.

miRNA extraction and quantification
Total circulating miRNA was isolated using the miRNeasy Serum/Plasma Kit (Qiagen, Germany). RNA concentration and purity were verified spectrophotometrically; only samples with acceptable A260/A280 and A260/A230 ratios (1.8–2.1) were included.

cDNA synthesis was performed with the miRCURY LNA miRNA PCR Starter Kit (Qiagen). Quantitative real-time PCR (qRT-PCR) was conducted on the Rotor-Gene Q platform using miRCURY SYBR Green Master Mix. Circulating miR-29 was quantified using a miRCURY LNA–based qRT-PCR assay (Qiagen) specific for hsa-miR-29a-5p according to the manufacturer's instructions. All reactions were duplicated, with repeat analysis performed when replicate Ct values differed by more than 0.3. Melt-curve profiles confirmed specificity, and no-RT and no-template controls were included in each run.

Normalization and data processing
miR-29 expression was normalized to miR-103, selected for its validated stability across study groups. Relative expression was calculated using the 2^−ΔΔCt method (ΔCt = Ct_target – Ct_reference; ΔΔCt = ΔCt_sample – mean ΔCt_controls).[20]

Given the right-skewed nature of circulating miRNA data, log10-transformed values were used for correlation and ROC analyses, whereas untransformed 2^−ΔΔCt values were used for group comparisons for ease of interpretation. All qPCR procedures followed MIQE recommendations.21

Bias minimization
To reduce selection bias, consecutive eligible patients were enrolled, and stringent inclusion and exclusion criteria were applied. Control subjects were clinically screened to exclude any cardiovascular or inflammatory disease.

Laboratory personnel were blinded to clinical grouping. All assays were performed under uniform laboratory conditions. Hemolyzed or suboptimal samples were excluded. Data completeness was ensured before analysis, and missing data (<5%) were handled by case-wise exclusion.

Statistical analysis
Analyses were performed using IBM SPSS Statistics v27 (IBM Corp., NY, USA). Continuous variables were expressed as mean ± SD or median (IQR), depending on distribution; categorical variables were presented as counts and percentages.

Group differences were assessed using:
- independent t-test for normally distributed variables,
- Mann–Whitney U test for non-normal variables, and
- chi-square for categorical comparisons.

Associations between circulating miR-29 and echocardiographic measures (EF, LVEDD, LVESD) were explored using Spearman correlation.

Diagnostic performance of miR-29 for distinguishing IDCM from controls was evaluated using ROC analysis, reporting AUC, sensitivity, specificity, and optimal cutoff (Youden index). Bonferroni correction was applied where appropriate. A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics
The baseline clinical and echocardiographic characteristics of the study population are summarized in **Table 1**. A total of 76 participants were enrolled, including 46 patients with angiographically confirmed IDCM and 30 healthy controls. IDCM patients exhibited reduced EF and enlarged LV dimensions on echocardiography. Demographic and risk-factor distributions, as well as blood pressure, heart rate, and chamber measurements, are presented in **Table 1.**

Circulating miR-29 expression in IDCM vs controls
Plasma miR-29 expression was markedly higher in IDCM than controls (p <0.001). Because miR-29 values were right-skewed, $\log_{10}$ transformation confirmed stable group separation, indicating robust up-regulation. The median miR-29 level was 14.7 (IQR: 1.11–312.99) in IDCM and 2.96 (IQR: 0.740–4.756) in controls (**Table 2, Fig. 1**).

ROC analysis of circulating miR-29
ROC curve analysis demonstrated a good discriminatory ability of circulating miR-29 between IDCM patients and controls (AUC = 0.87, 95% CI: 0.78–0.94; **Table 3, Fig. 2**). An optimal cut-off value of 1.10 yielded a sensitivity of 74.1% and a specificity of 73.3%.

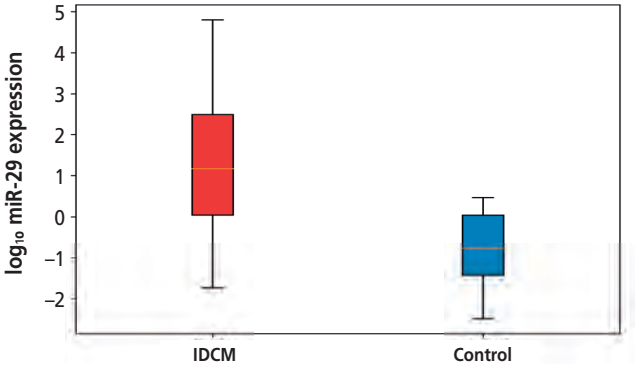

Fig. 1 – Comparison of circulating miR-29 between IDCM and control groups on log_{10} scale

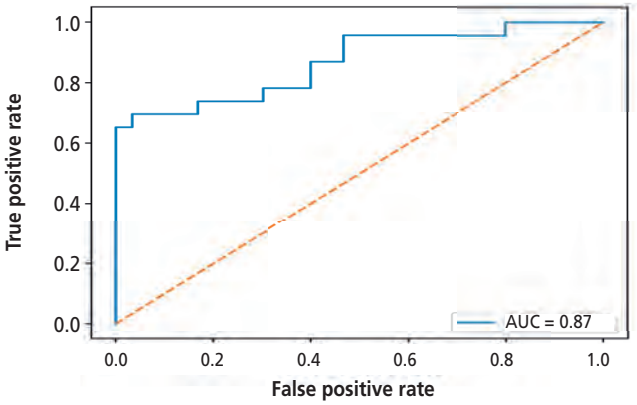

Fig. 2 – Receiver operating characteristic (ROC) analysis for circulating miR-29 in discriminating IDCM patients from healthy controls.

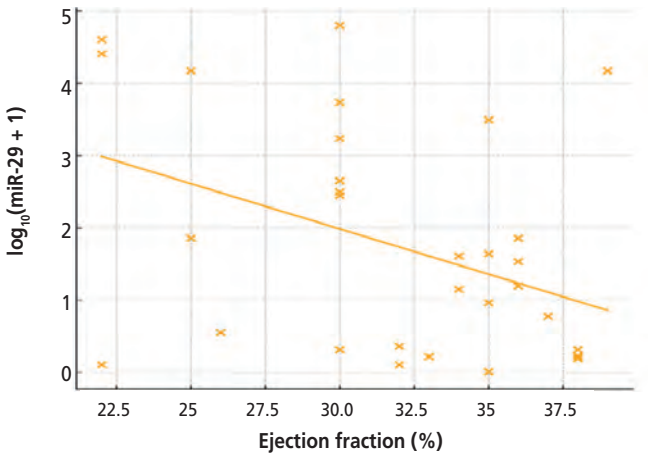

Fig. 3 – Relationship between log_{10}-transformed plasma miR-29 expression and EF in IDCM.

Table 3 – Discriminative (ROC) value of circulating miR-29 for diagnosis of ischemic IDCM

Parameter	Value
AUC (95% CI)	0.87 (0.62–0.85)
Optimal cutoff (miR-29)	1.10
Sensitivity (%)	74.1
Specificity (%)	73.3

The optimal cutoff value was determined using Youden's index. AUC – area under the ROC curve.

Table 1 – Baseline characteristics of IDCM patients and healthy controls

Variable	IDCM (n = 46)	Controls (n = 30)	*p*-value
Age (years), mean ± SD	58.61 ± 7.20	53.10 ± 7.90	0.03
Male sex, n (%)	30 (65.2%)	18 (60.0%)	0.63
HTN, n (%)	34 (73.9%)	0 (0.0%)	<0.001
DM, n (%)	18 (39.1%)	0 (0.0%)	<0.001
Current smoking, n (%)	30 (65.2%)	0 (0.0%)	<0.001
Heart rate (bpm), mean ± SD	81.22 ± 9.77	79.23 ± 12.54	0.47
Systolic BP (mmHg), mean ± SD	128.22 ± 12.09	112.83 ± 13.48	<0.001
Diastolic BP (mmHg), mean ± SD	80.26 ± 6.08	69.52 ± 7.38	<0.001
IVS thickness (mm), mean ± SD	8.9 ± 2.1	7.2 ± 2.5	0.003
LVEDD (mm), mean ± SD	66.43 ± 5.80	45.55 ± 5.67	<0.001
LVESD (mm), mean ± SD	56.54 ± 6.11	26.68 ± 9.32	<0.001
LVEF (%), mean ± SD	32.59 ± 4.57	62.45 ± 6.97	<0.001

Values are presented as mean ± SD or n (%). Continuous variables were compared using independent-samples t test. Categorical variables were compared using chi-square test.

Table 2 – Comparison of circulating miR-29 between IDCM and control groups

miR-29	Median (IQR)	IDCM (n = 46)	Control (n = 30)	*p*-value
		14.7 (1.11–312.99)	0.17 (0.04–1.10)	<0.001

Values expressed as median (IQR). Mann–Whitney U test was used to assess *p*-value.

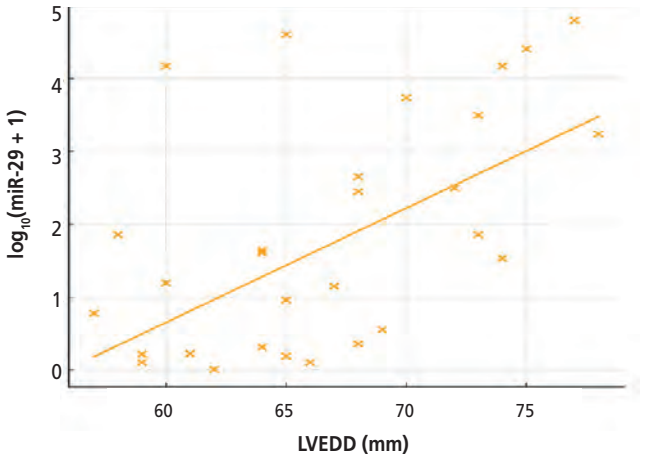

Fig. 4 – Relationship between log_{10}-transformed plasma miR-29 expression and LVEDD in IDCM.

Correlation with echocardiographic parameters

Table 4, and Figure 3 and 4 showed that miR29 was correlated negatively with EF (r = –0.340, p = 0.021) and positively with LVEDD (r = +0.557, p <0.001) and LVESD (r= +0.571, p <0.001).

These findings demonstrate a consistent remodeling pattern: higher miR-29 levels accompany greater chamber dilation and reduced systolic performance.

Multivariable analysis

To evaluate whether these associations were independent of clinical factors, multivariable linear regression models were constructed. After adjustment for age, HTN, DM, and sex, log_{10}(miR-29) remained significantly associated with both systolic function and chamber size. Each 1-log_{10} increase in miR-29 corresponded to a 1.05% lower EF (β = –1.05, p = 0.0227) and a 2.14-mm greater LVEDD (β = +2.14, p <0.001). None of the covariates showed significant associations with EF or LVEDD (**Table 5**).

Association with cardiovascular risk factors

Circulating miR-29 levels did not differ significantly according to the presence or absence of HTN (p = 0.43), DM (p = 0.69), or smoking (p = 0.22) (**Table 6**). These findings indicate that the elevation of circulating miR-29 in IDCM is independent of conventional cardiovascular risk factors.

Table 4 – Correlation between circulating miR-29 and echocardiographic parameters among IDCM patients

Parameter	Spearman r	*p*-value
Ejection fraction (EF)	–0.340	**0.021**
Left ventricular end-diastolic diameter (LVEDD)	+0.557	**<0.001**
Left ventricular end-systolic diameter (LVESD)	+0.571	**<0.001**

Associations evaluated using Spearman's rank correlation. Negative and positive correlation coefficients (r) indicate inverse and direct relationships, respectively.

Table 5 – Multivariable regression models showing independent predictors of EF and LVEDD

Model A: EF as outcome			
Variable	**Coefficient (β)**	**Std. error**	***p*-value**
Intercept	59.4743	7.2497	**<0.001**
log_{10}(miR-29)	–1.0503	0.4481	**0.0227**
Age	–0.0934	0.0893	0.3025
HTN	–1.3446	1.3572	0.3276
DM	–0.8829	1.3121	0.5088
Male sex	–0.5955	1.2363	0.6271
Model B LVEDD as outcome			
Variable	**Coefficient (β)**	**Std. error**	***p*-value**
Intercept	37.0922	3.8814	**<0.001**
log_{10}(miR-29)	+2.1402	0.2646	**<0.001**
Age	+0.0280	0.0471	0.5524
HTN	–0.1727	0.7158	0.8101
DM	–0.0777	0.6930	0.9114
Male sex	+0.5980	0.6487	0.3637

Table 6 – Comparison of circulating miR-29 levels according to clinical risk factors among IDCM patients

Risk Factor	Median (IQR) – yes	Median (IQR) – no	*p*-value
HTN	13.1 (1.0–313.0)	55.3 (2.5–322.7)	0.430
DM	8.2 (1.3–313.0)	23.9 (0.6–322.7)	0.693
Smoking	14.7 (0.7–227.9)	25.5 (4.1–6654.5)	0.217

Data are presented as median (interquartile range, IQR). Comparisons were performed using the Mann–Whitney U test).

Discussion

In our study, circulating miR-29 was significantly elevated in patients with IDCM and showed statistically significant associations with key echocardiographic indices of adverse remodeling. Its inverse correlation with LVEF, together with positive correlations with LVEDD and LVESD, suggests that higher circulating miR-29 levels are observed in parallel with greater ventricular dilation and more advanced systolic impairment.

Although direct fibrosis quantification with cardiac MRI or histology was unavailable, structural indices such as LV dilation and reduced EF are well-established indicators of chronic ischemic remodeling. In longstanding ischemic cardiomyopathy, chamber enlargement and systolic impairment are commonly associated with accumulated scar burden and altered ECM turnover.[3,22]

Circulating miR-29 levels do not necessarily mirror myocardial expression, as they are influenced by signals originating from multiple cell types and injury-related pathways.[23] Rather than serving as a direct surrogate for myocardial expression, circulating miR-29 may reflect the broader molecular environment of post-ischemic remodeling, integrating contributions from fibrosis, inflammation, and ECM turnover.[24,25] Experimental data show that

miRNAs can be exported via extracellular vesicles, released during apoptosis, or actively secreted in response to biomechanical stress or inflammatory signaling.[26,27] Such mechanisms have been described during cardiac injury and fibrosis, supporting the concept that elevations in plasma miR-29 may relate to enhanced ECM turnover or myocardial stress signaling rather than direct tissue expression.[28,29] In this context, circulating miR-29 provides complementary molecular insight into remodeling activity that is not fully captured by clinical assessment, echocardiographic indices, or conventional circulating biomarkers alone.[30]

The elevation of circulating miR-29 in IDCM is biologically plausible given its regulatory influence on major ECM components, including COL1A1, COL3A1, Fibrillin-1, and Elastin, with multiple experimental models demonstrating that suppressing miR-29 promotes collagen accumulation, whereas augmenting its activity can reduce fibrosis burden.[14,15] Chronic ischemia, neurohormonal activation, and scar maturation intensify TGF–β/Smad-mediated fibrotic signaling, which is a major upstream regulator of miR-29 expression.[3,31] Together, these mechanisms provide a coherent biological rationale for why circulating miR-29 may increase in parallel with fibrosis-linked remodeling in IDCM. Importantly, such elevations may reflect engagement of ECM–regulatory signaling or passive release from stressed myocardial tissue

The positive correlations between miR-29 and LVEDD/LVESD, together with its inverse relationship with EF, represent the most clinically relevant observations of this study. Ventricular dilation and systolic impairment are established downstream manifestations of chronic ischemic remodeling, in which ECM disorganization and fibrotic accumulation contribute to adverse chamber geometry and functional decline.[3,32] Ventricular dilation reflects progressive ECM disorganization, impaired architectural integrity, and maladaptive remodeling,[33,34] while lower EF in IDCM reflects both replacement fibrosis from prior infarction and diffuse interstitial fibrosis,[35,36] pathways that are plausibly influenced by ECM-modulating miRNAs such as miR-29. Accordingly, the observed associations between circulating miR-29 levels and LV geometry or systolic function support the concept that circulating microRNAs may serve as accessible indicators of underlying remodeling-related molecular pathways, rather than direct measures of myocardial fibrosis burden.

ROC analysis demonstrated good overall discriminatory performance of circulating miR-29 in distinguishing patients with IDCM from healthy controls. The observed sensitivity and specificity are consistent with the behavior of circulating microRNAs as biologically informative markers reflecting pathway-specific remodeling activity rather than broad disease screening tools.[37,38] In this context, the ROC findings support the interpretation of circulating miR-29 as a remodeling-associated, pathway-informative biomarker.

Circulating miR-29 levels were not significantly influenced by major clinical covariates, including HTN, DM, smoking status, or age. This relative independence from common cardiovascular risk factors reduces the likelihood that the observed associations are driven by systemic confounding, a known limitation in circulating miRNA research.[39] Importantly, the persistence of miR-29's associations with LVEDD and EF after multivariable adjustment strengthens the interpretation that circulating miR-29 relates to ventricular remodeling severity rather than nonspecific clinical burden.

While echocardiography remains central to phenotypic characterization, it does not capture the regulatory pathways driving remodeling progression. In this context, miR-29 provides insight into disease-relevant molecular signaling and ECM regulation, complementing structural and functional assessment without replacing established imaging or clinical markers.

In clinical terms, circulating miR-29, by reflecting engagement of ECM related regulatory pathways, may therefore serve as a molecular indicator of remodeling activity rather than a diagnostic or prognostic marker per se. Importantly, defining such molecular signatures may inform future studies aimed at stratifying patients according to dominant remodeling pathways and exploring pathway-directed therapeutic interventions.

Conclusions

Circulating miR-29 levels were significantly higher in patients with IDCM and were closely associated with indices of adverse ventricular remodeling, including LV dilation and reduced systolic function, independent of major clinical covariates. These findings suggest that miR-29 reflects remodeling-related molecular activity linked to ECM regulation and may provide additional molecular insight into remodeling biology, serving as a hypothesis-generating signal for future studies exploring patient stratification and pathway-directed therapeutic approaches.

Conflict of interest

The authors declare that they have no competing interests.

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Ethical statement

The study was approved by Ethics Committee of the National Research Centre – Ethics Committee: Medical Research Ethics Committee (MREC), National Research Centre (Approval number: 130601109).

Informed consent

Written informed consent was obtained from all individual participants included in the study.

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Původní sdělení | Original research article

Device Size/Septal Length as Predictors of Atrial Fibrillation After Percutaneous ASD Closure: 15-Year Follow-Up

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Klíčová slova:
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Velikost okluderu/celková délka septa

SOUHRN

Kontext: Ze sledování pacientů po perkutánním uzávěru defektu síňového septa (atrial septal defect, ASD) je známo, že dochází ke vzniku fibrilace síní (FS). Primárním cílem naší studie bylo zkoumat vznik a prediktory vzniku FS při dlouhodobém sledování pacientů po uzavření ASD.
Metody: Do studie bylo zařazeno 56 pacientů, u nichž byl mezi lety 2008 a 2010 na našem pracovišti proveden perkutánní uzávěr ASD. Sledovaná populace byla rozdělena do dvou skupin: s diagnózou FS a bez této diagnózy.
Výsledky: Ke vzniku FS došlo u 13 pacientů (dva muži, 11 žen; věk 41,02 ± 7,02 roku; ejekční frakce levé komory [EF LK] 62,39 ± 8,32 %); u 43 pacientů ke vzniku FS nedošlo (sedm mužů, 36 žen; věk 39,55 ± 9,26 roku; EF LK 64,76 ± 8,08 %). Regresní analýza prokázala, že nezávislým prediktorem vzniku FS je dlouhodobě pouze poměr velikosti okluderu a celkové délka septa.
Závěry: Podle této studie byl se vznikem FS v dlouhodobém horizontu spojen vyšší poměr velikosti okluderu a celkové délky septa. Doporučujeme, aby k uzavření defektu používali operatéři co nejmenší okludery.

Keywords:
Atrial fibrillation
Atrial septal defect
Device size/total septum length

ABSTRACT

Background: Atrial fibrillation (AF) is known to develop during the follow-up of patients who have undergone percutaneous atrial septal defect (ASD) closure. The primary aim of our study was to investigate the development and predictors of AF in the long-term follow-up of patients after ASD closure.
Methods: Fifty-six patients who underwent percutaneous ASD closure at our center between 2008 and 2010 were included in the study. The study population was divided into two groups: patients with and those without an AF diagnosis.
Result: There were 13 patients with AF (two males, 11 females; age = 41.02 ± 7.02 years; left ventricle ejection fraction [LVEF] = 62.39 ± 8.32%) and 43 patients without AF (seven males, 36 females; age = 39.55 ± 9.26 years; LVEF = 64.76 ± 8.08%). In regression analysis, only the device size/total septum length ratio was found to be an independent predictor of long-term AF development.
Conclusions: This study revealed that an increased device size/total septum length ratio was associated with the development of AF in the long term. We recommend that operators use the smallest size closure device that adequately covers the defect.

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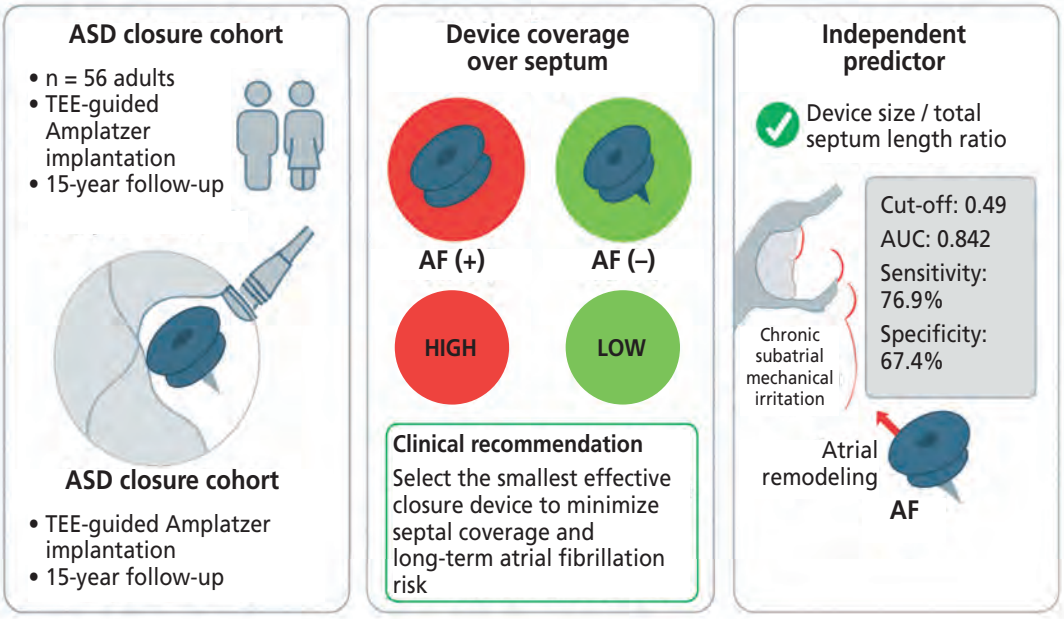
OVERSIZING OF SEPTAL OCCLUDER DEVICES PREDICTS LONG-TERM ATRIAL FIBRILLATION ASD CLOSURE



WHAT'S NEW?

- In patients with atrial septal defect (ASD), several echocardiographic parameters—including A-wave velocity, left ventricular ejection fraction, left atrial diameter, and ASD size—were significantly associated with long-term atrial fibrillation (AF) development.
- In addition to previous literature, our study demonstrated that the ratio of closure device diameter to total septal length is an independent predictor of late AF after transcatheter ASD closure.
- During long-term follow-up, pre-closure factors lost prognostic value, whereas the extent of interatrial septal coverage by the device became crucial. Therefore, operators should choose the smallest device ensuring complete closure to minimize AF risk.

Introduction

Atrial septal defect (ASD) is the most common congenital heart disease diagnosed in adults and is treated by interventional cardiologists.[1] Today, percutaneous closure is widely used and successfully used in line with current guidelines and under appropriate indications.[2] With increasing operator experience and newly developed devices, complications during percutaneous closure and in the acute phase are now more easily managed.[3] However, the long-term effects of these devices are still being investigated in current studies and meta-analyses.[4] The fact that these ASD closure devices remain in mechanical contact with the atria for an extended period suggests that they may predict the development of atrial arrhythmia in the long term, which has also been a main topic of research.[5] As the frequency of percutaneous ASD closure procedures continues to grow, identifying the development of AF and predicting which patients may develop it constitute important research topics. Some studies have demonstrated predictive parameters for AF based on follow-up duration, advanced age, or type of closure device.[6] Although the presence of an ASD with a clinically significant shunt size has been found to be a predictor for AF development,[3] some studies have reported that closure device size is not a predictor for AF development.[7]

Our hypothesis is that selecting the smallest device that can cover the patient's ASD may provide more effective protection against AF. Therefore, we calculated the device length/total septum length ratio, which was previously studied in a pediatric patient group.[8] In this study, we examined the average 15-year follow-up of patients who underwent percutaneous ASD closure in our clinic. We investigated the frequency of AF and echocardiographic and procedural technique-related factors, such as the device size/total septum length ratio, which would predict AF.

Material and methods

Study design and population

In this single-center, cross-sectional, retrospective study, patients who underwent percutaneous ASD closure in our center between 2008 and 2010 were reviewed, and 70 patients were identified. The baseline demographic data, echocardiography and 12-lead electrocardiogram findings, and anticoagulant use history of the patients were retrieved from the hospital information system. Twelve patients whose follow-up data within the last three months were not available and two patients with AF detected on their baseline electrocardiogram were excluded from the study. The remaining 56 patients were included in the

study and divided into two groups: those who developed AF and those who did not. To investigate the presence of AF, patients' ECGs from the past 3 months were reviewed, and AF was considered present if detected. For patients whose ECGs did not reveal AF, their Holter monitoring from the past 3 months was reviewed, if available. If Holter monitoring was not available, patients were called for a follow-up appointment, and the presence or absence of AF was determined based on 24-hour Holter monitoring. The study protocol was approved by the local ethics committee in accordance with the Declaration of Helsinki and good clinical practice guidelines.

Echocardiographic evaluation

Echocardiographic examinations were performed using the Philips IE33 system (Philips Medical Systems, Andover, MA, USA). Left ventricular ejection fraction (LVEF) was calculated using the Simpson biplane method. Measurements of the left atrial diameter, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal thickness, and posterior wall thickness were obtained from the parasternal long-axis view.

In the apical four-chamber view, the right atrial diameter, right ventricular basal diameter (RV-BD), and total septum length were measured. Mitral early diastolic filling velocity (E wave), late diastolic filling velocity (A wave), and the mitral annular early diastolic velocity (E′ wave) obtained from the lateral mitral annulus using tissue Doppler imaging were recorded. Tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode at the junction of the right ventricular lateral wall and the tricuspid annulus.

The right ventricular outflow tract (RVOT) diameter and RVOT velocity-time integral (RVOT-VTI) were measured in the parasternal short-axis view, whereas the left ventricular outflow tract (LVOT) diameter was measured in the parasternal long-axis view. The LVOT velocity-time integral (LVOT-VTI) was obtained from the apical five-chamber view using pulsed-wave Doppler. The Qp/Qs ratio was calculated using the following formula: Qp = RVOT VTI × ϖ × (RVOT diameter/2)², Qs = LVOT VTI × ϖ × (LVOT diameter/2).² It was obtained by dividing Qp by Qs. Systolic pulmonary artery pressure (PAP) was calculated by adding estimated right atrial pressure to the pressure measurement taken with continuous wave Doppler over the tricuspid valve in the apical four-chamber view. ASD width was measured at three different angles via transesophageal echocardiography, with the largest measurement recorded. All echocardiograms followed the recommendations of the American Society of Echocardiography.

Reproducibility

Intraobserver variability was assessed by repeating all measurements on separate occasions. Interobserver variability was assessed by having a second observer, blinded to the clinical data and initial echocardiographic results, repeat the measurements (M.G.Y).

Device information

All patients were treated under conscious sedation in the catheterization laboratory under the guidance of transesophageal echocardiography. An appropriately sized Amplatzer septal occluder device (AGA Medical Corp., Golden Valley, MN, USA) was implanted in the interatrial septum using a femoral access system. When selecting device dimensions, transesophageal echocardiography was performed, and ASD balloon sizing was also done during the procedure, supported by echocardiographic measurements.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test and homogeneity of variances tests were performed to examine parametric and non-parametric data distributions. The independent-samples t-test was used to compare two groups in terms of variables showing parametric distribution, and the Mann–Whitney U test was used to compare two groups in terms of variables that did not show a parametric distribution. Categorical variables were compared using the chi-square test. Univariable and multivariable logistic regression analyses were undertaken to determine predictive parameters of AF development. Receiver operating characteristic (ROC) analysis was used to determine the cut-off levels of the device size/total septum length ratio for predicting AF development. A *p*-value of <0.05 was considered statistically significant.

Results

The study included a total of 56 patients with a follow-up period of 15 (range: 14–16) years. Thirteen patients developed AF, resulting in an incidence of 23.2%. The patients were divided into two groups: those with and those without AF (of the 13 patients, 5 continued to have sinus rhythm after one paroxysmal AF attack; 4 patients were started on amiodarone for rhythm control due to recurrent paroxysmal AF attacks. Sinus rhythm was achieved in 2 patients after electrical cardioversion due to persistent AF. Two patients were diagnosed with permanent AF.) **Table 1** presents the comparison of the demographic data and baseline echocardiographic parameters between the two groups. Significant differences were found between the

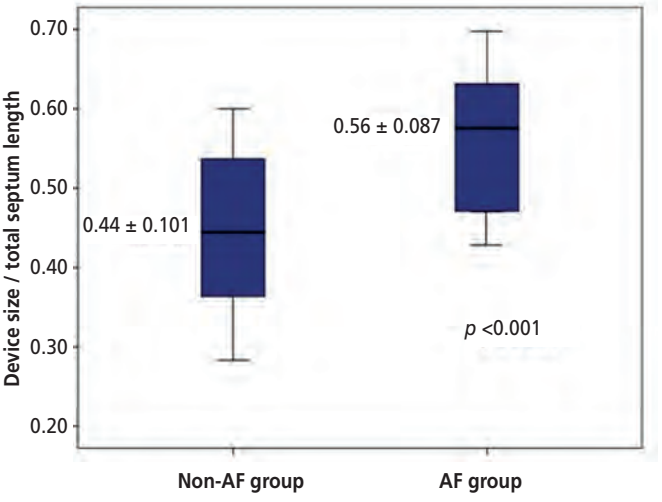


Fig. 1 – Relationship between the device size / total septum length ratio and the development of atrial fibrillation.

Table 1 – Clinical, echocardiographic, and implantable device characteristics of the study population

	AF group n = 13	Non-AF group n = 43	*p*-value
Age (years)	41.02 ± 7.02	39.55 ± 9.26	0.795
Gender (M/F)	2 / 11	7 / 36	0.655
HT (n)	2 (15.8%)	3 (6.9%)	0.580
DM (n)	1 (7.7%)	2 (4.65%)	0.555
CAD (n)	1 (7.7%)	2 (4.65%)	0.555
CVA (n)	0 (–)	0 (–)	–
LVEF (%)	62.39 ± 8.32	64.76 ± 8.08	0.180
LV-EDD (mm)	43.35 ± 7.44	42.38 ± 4.85	0.660
LV-ESD (mm)	27.43 ± 5.53	25.53 ± 4.62	0.250
LA (mm)	36.69 ± 5.41	33.44 ± 5.68	0.073
RA (mm)	45.84 ± 7.18	42.57 ± 8.10	0.197
RV – BD (mm)	42.38 ± 8.66	39.89 ± 7.12	0.137
IVS (mm)	9 (7.5–13)	9 (8–14)	0.298
PW (mm)	9 (7–13)	9 (7–12)	0.383
E wave (cm/s)	67 (50–125)	80 (45–120)	0.655
A wave (cm/s)	64 (40–83)	76 (43–104)	**0.018**
E' wave (cm/s)	16 ± 6.92	12.02 ± 4.79	0.052
sPAP (mmHg)	36.61 ± 5.31	34.88 ± 7.58	**0.009**
TAPSE (mm)	3.03 ± 0.44	2.91 ± 0.55	0.577
Qp/Qs	3.66 ± 1.21	3.03 ± 1.03	0.069
ASD size on TEE (mm)	23.41 ± 4.25	17.32 ± 5.97	**0.001**
Total septum length (mm)	50.33 ± 6.48	49.75 ± 6.61	0.781
Device size (mm)	28.30 ±5.40	22.12 ± 5.75	**0.001**
Device size / total septum length ratio	0.56 ± 0.087	0.44 ± 0.101	**<0.001**

A wave – late diastolic wave; CAD – coronary artery disease; CVA – cerebrovascular accident; DM – diabetes mellitus; E' – early diastolic myocardial velocity; E wave – early diastolic wave; HT – hypertension; IVS – interventricular septum; LA – left atrium, LV-EDD – left ventricular end-diastolic diameter; LVEF – left ventricular ejection fraction; LV-ESD – left ventricular end-systolic diameter; PW – posterior wall; Qp/Qs – ratio between pulmonary and systemic flow; RA – right atrium; RV-BD – right ventricle basal diameter; S' – tricuspid lateral wall annular systolic velocity; sPAP – systolic pulmonary artery pressure; TEE – transesophageal echocardiography.

Table 2 – Results of univariate and multivariate regression analyses showing the relationship between AF development and investigated parameters

	Univariable			Multivariable		
Variables	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
A wave (cm/sec)	0.014	0.001–0.655	**0.030**	0.020	0.004–9.471	0.073
LVEF (%)	1.094	1.010–1.185	**0.027**	1.066	0.917–1.239	0.404
LA (mm)	1.117	0.986–1.264	0.081	1.896	0.983–3.657	0.056
ASD size (mm)	1.235	1.066–1.430	**0.005**	0.739	0.469–1.666	0.194
Device size (mm)	1.218	1.062–1.396	**0.005**	0.885	0.582–1.344	0.565
Device size/total septum length ratio	1.028	1.014–1.072	**0.002**	1.066	1.010–1.112	**0.039**

AF – atrial fibrillation; ASD – atrial septal defect; A wave – late diastolic wave; CI – confidence interval; LA – left atrium; LVEF – left ventricular ejection fraction; OR – odds ratio.

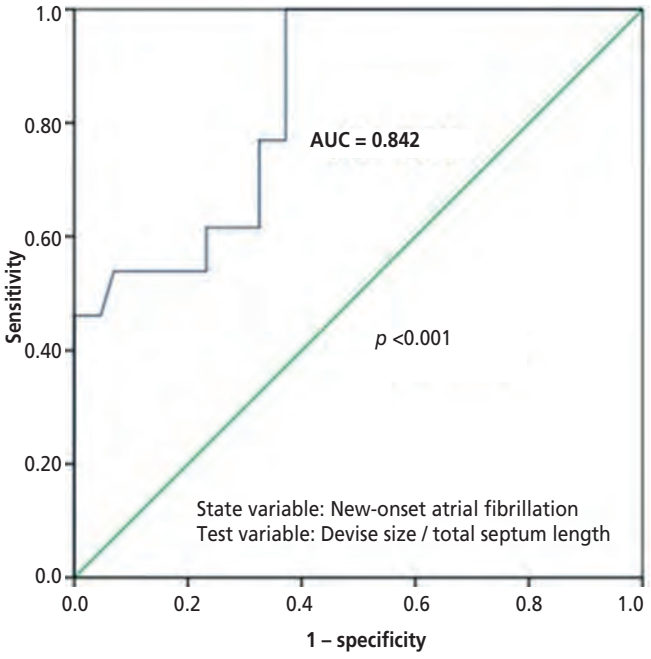


Fig. 2 – Receiver operating characteristic curve of the device size / total septum length ratio for predicting AF development.

groups in terms of A wave (p = 0.018), sPAP (p = 0.009), ASD size measured by transesophageal echocardiography (p = 0.001), device size (p = 0.001), and the device size/total septum length ratio (p <0.001; **Fig. 1**).

In regression analysis performed to determine the predictors of AF development during the 15-year follow-up, the A wave, LVEF, LA, ASD size, device size, and the device size/total septum length ratio were identified as dependent predictors in the univariable regression analysis (**Table 2**). According to the multivariable regression analysis, only the device size/total septum length ratio was an independent predictor. Receiver operating characteristic (ROC) analysis showed that the optimal cut-off value of the device size/total septum length ratio was 0.49 (area under the curve: 0.842, 95% confidence interval: 0.729–0.954, p <0.001; **Fig. 2**), with a sensitivity of 76.9% and a specificity of 67.4%.

During the annual follow-up, coronary artery disease was detected in one patient and hypertension in two patients in the AF group. In the group without AF, coronary artery disease was identified in two patients and hypertension in three patients. No cerebrovascular disease or mortality was observed in any patient.

Discussion

In this study, we examined the frequency and predictors of AF in the long-term follow-up of patients who underwent percutaneous ASD closure. Real-life data from our country shows that 2.7% of patients diagnosed with AF experience stroke and 7.5% die during a 12-month follow-up, which highlights the importance of diagnosing and treating AF.[9] We found that the frequency of AF development was 23.2% in our population. Previous studies have reported AF rates reaching 17–25% in the early period following ASD closure.[10] Abrahamyan et al., who conducted one of the longest follow-up studies available in the literature, reported an AF incidence of 14.9% with a mean follow-up of 10.6 years after ASD closure.[4] Our study covers an important period, with an average follow-up duration of 15 years. We believe that the high incidence of AF development (23.2%) in our study is due to this extended follow-up period.

While exploring predictors of AF following ASD closure, it is necessary to emphasize the importance of studies proving that ASD closure actually reduces the frequency of AF.[11] Pathophysiologically, the presence of ASD is known to lead to atrial structural and electrophysiologic remodeling, thereby triggering AF. Although the literature agrees that a large ASD can cause AF, there are conflicting results regarding whether the size of the device used during ASD closure can predict AF. For example, while Spies et al.[7] found no correlation between device length and AF development, Chiu et al., evaluating 517 patients, reported that device length was an important parameter for AF development.[12] In this study, we aimed to investigate whether device size played a significant role in AF development. We hypothesized that an increase in the ratio of device length to total septum could result in greater mechanical contact with the LA, affecting atrial contraction movement and potentially causing more electrophysiologic effects. Therefore, in addition to ASD size and device size, we calculated the device size/total septum length ratio. Our findings indicate that patients with a higher ratio experienced more frequent AF development in the long term.

In our study, ASD size and device size were also statistically significantly larger in the AF group, which aligns with expectations. However, in our regression analysis, only the device size/total septum length ratio emerged as a significant long-term predictor.

We also observed associations between AF and echocardiographic parameters such as PAP and A wave. The relationship between PAP and AF has been well-documented in previous publications in patients with ASD[13] and is consistent with our findings. The A wave, also known as the ventricular late diastolic wave, was first described as an indicator of atrial contraction strength and was found to be significantly reduced in patients with AF.[14] The relationship between A-wave reduction and AF development appears to be a logical consequence of flow physiology. In the regression analysis model, LA diameter did not emerge as an independent predictor. However, we included it in the regression analysis model both to demonstrate this and because it is one of the most important predictors of atrial fibrillation in the literature. We believe the reason why initial LA diameter was not found to be a long-term predictor of AF is that after ASD closure, the atria enter a new modeling process, and the initial LA diameter is no longer significant.

In our study, age did not significantly differ between the two groups. While age is generally considered an important parameter for AF in both the general population and ASD studies,[15,16] the narrow age range of our cohort and the absence of elderly patients may have mitigated age-related effects in our findings.

The literature also explores the relationship between different brands of ASD closure devices and AF.[3] However, in our study, only the Amplatzer septal occluder device was used, ensuring a homogeneous population.

The absence of differences between the two groups in terms of known risk factors for AF, such as hypertension and coronary artery disease, in our 15-year follow-up data allowed us to focus on baseline echocardiographic values as predictors. Our study provides valuable insights due to its extended follow-up period of 15 years, which is longer than most studies in the literature. We demonstrated the significance of the device size/total septum length ratio.

Previously identified predictors of AF were generally non-modifiable factors.[17] However, our findings suggest that more precise measurements during percutaneous ASD closure and careful selection of the smallest appropriate device may protect patients from AF development in the long term.

Study limitations

Our study had a single-center and retrospective design and was conducted with a relatively small number of patients. Age, hypertension, and various echocardiographic measurements, which are known predictors of AF, were not found to be statistically significant, likely due to the small sample size and the exclusion of patients with additional risk factors.

Conclusion

This study found that the long-term risk of AF increased as the device size/total septum length ratio increased in patients who underwent percutaneous ASD closure. To mitigate the risk of AF, we recommend that interventional cardiologists carefully measure ASD size and select the smallest appropriate device.

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Conflict of interest
There are no conflicts of interest in the conception or production of this study.

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Data availability statements
Data can be made available upon reasonable request.

Author contributions
All authors (1) contributed to the conceptualization and design, or acquisition of data, or analysis and interpretation of data; (2) drafted the article or revised it critically for important intellectual content; and (3) each author has read and approved the final version to be published.

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Původní sdělení | Original research article

Effect of Radial Artery Grafting on Clinical Outcomes After Coronary Artery Bypass Surgery: a Prospective Study on a Sample from Yemen

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Klíčová slova:
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SOUHRN

Kontext: Klíčovým faktorem ovlivňujícím klinické výsledky koronárního bypassu (coronary artery bypass grafting, CABG) je volba štěpu. Díky svým vynikajícím biologickým vlastnostem a průchodností ve srovnání se štěpy ze safény se postupem doby radiální tepna stala preferovaným tepenným štěpem, nicméně množství údajů z prospektivních studií popisujících krátkodobé klinické výsledky a obnovu funkcí spojených s použitím radiální tepny v rutinní klinické praxi je stále omezené.
Metody: Do této prospektivní deskriptivní studie byli zařazováni dospělí pacienti, u nichž byl proveden elektivní koronární bypass na vysoce specializovaném kardiochirurgickém pracovišti. Ve studii se shromažďovaly demografické, klinické, operační a postoperační údaje. Srdeční funkce se hodnotila elektrokardiograficky a transtorakální echokardiografií před výkonem a během následného sledování. Pacienti byli sledováni po dobu 3–6 měsíců. Hodnotily se klinické výsledky, pooperační komplikace, délka hospitalizace a pacientem uváděná kvalita života. Statistická analýza se prováděla pomocí neparametrických testů při statistické významnosti nastavené na hodnotu $p \leq 0{,}05$.
Výsledky: Do studie bylo zařazeno celkem 22 pacientů; sledování bylo dokončeno u všech. Štěpy z radiální tepny byly použity v 90,9 % případů. Statisticky významné pooperační zlepšení potvrdilo jak elektrokardiografické vyšetření, tak echokardiografie ($p < 0{,}001$). Méně závažné pooperační komplikace se vyskytly u 31,8 % pacientů; během sledování nedošlo k žádnému úmrtí, ani se nevyskytl žádný případ infarktu myokardu nebo cévní mozkové příhody. Kvalita života se zlepšila u 95,5 % pacientů. Celková úspěšnost výkonu dosáhla 90,9 %.
Závěry: Použití radiální tepny jako štěpu pro CABG bylo bezpečné a účinné a bylo spojeno se statisticky významným zlepšením srdeční funkce, nízkým výskytem komplikací a zlepšené krátkodobé kvality života. Tato zjištění podporují častější využívání radiální tepny jako štěpu u vhodných pacientů indikovaných k CABG.

ABSTRACT

Background: Conduit selection is a critical determinant of clinical outcomes following coronary artery bypass grafting (CABG). The radial artery has emerged as a preferred arterial conduit because of superior biological properties and patency compared with saphenous vein grafts. However, prospective data evaluating short-term clinical outcomes and functional recovery associated with radial artery use remain limited in routine clinical practice.
Methods: This prospective descriptive study included adult patients undergoing elective CABG at a tertiary cardiac surgery center. Demographic, clinical, operative, and postoperative data were collected. Cardiac function was assessed using electrocardiography and transthoracic echocardiography before surgery and during follow-up. Patients were followed for 3–6 months. Clinical outcomes, postoperative complications, hospital length of stay, and patient-reported quality of life were evaluated. Statistical analysis was performed using nonparametric tests, with a significance level set at $p \leq 0.05$.
Results: A total of 22 patients were included, all of whom completed follow-up. Radial artery grafts were utilized in 90.9% of cases. Significant postoperative improvement was observed in both electrocardiographic and echocardiographic findings ($p < 0.001$). Minor postoperative complications occurred in 31.8% of patients, with no reported cases of mortality, myocardial infarction, or stroke during the follow-up period. Quality of life improved in 95.5% of patients. The overall procedural success rate was 90.9%.
Conclusions: The use of the radial artery as a conduit in CABG was safe and effective, resulting in significant improvement in cardiac function, low complication rates, and enhanced short-term quality of life. These findings support broader adoption of the radial artery as a preferred arterial conduit in suitable patients undergoing CABG.

Keywords:
Coronary artery bypass grafting
Clinical outcomes
Radial artery graft

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Introduction

Though there is a noticeable advancement in the pharmacological therapy and percutaneous coronary intervention (PCI), the empirical findings show that coronary artery disease (CAD) continues to impose a considerable worldwide health burden. In addition, it has been established that CAD is among the leading causes of cardiovascular morbidity and mortality all over the world.[1–3] Although contemporary medical therapy and PCI have significantly improved outcomes in patients with stable and anatomically less complex disease, their benefits diminish as coronary complexity increases.[4] Consequently, in patients with multivessel CAD, left main coronary artery involvement, or diabetes mellitus, coronary artery bypass grafting (CABG) remains the most reliable and durable revascularization strategy.[5] This strategy offers superior long-term survival and sustained freedom from repeat revascularization.[6,7]

Importantly, the long-term success of CABG extends beyond operative technique and perioperative care. Rather, it is critically shaped by conduit selection, as graft durability directly influences postoperative survival, recurrent ischemia, the need for subsequent interventions, and long-term quality of life.[8,9] Among the available conduits, the left internal thoracic artery (LITA) has consistently demonstrated exceptional long-term patency and survival benefit and is therefore universally accepted as the gold-standard graft for revascularization of the left anterior descending artery.[8,10] In contrast, the optimal choice of a second conduit remains less clearly defined and continues to be the subject of active clinical investigation.[11]

For decades, the saphenous vein graft (SVG) has served as the default second conduit, largely due to its availability, ease of harvesting, and technical versatility.[12] However, mounting long-term evidence has revealed inherent biological limitations of venous grafts.[13] When exposed to systemic arterial pressure, SVGs are vulnerable to endothelial injury, intimal hyperplasia, and accelerated atherosclerotic change, processes that ultimately lead to progressive luminal narrowing and graft occlusion.[14–16] Indeed, angiographic studies have shown that up to 40–50% of SVGs may fail within a decade following CABG, thereby undermining long-term procedural durability and clinical benefit.[17,18]

By comparison, arterial conduits possess intrinsic biological characteristics that confer superior long-term performance.[19] These include preserved endothelial function, enhanced nitric oxide–mediated vasodilation, and greater resistance to atherosclerotic degeneration.[20,21] Within this context, the radial artery has emerged as a particularly compelling alternative.[22] Its favorable anatomical profile, appropriate luminal diameter, muscular wall composition, and capacity for physiological vasomotor adaptation render it well suited for coronary bypass grafting when carefully selected and supported by appropriate pharmacological management.[23,24]

Over the past two decades, a growing body of evidence from randomized controlled trials and large-scale observational studies has consistently demonstrated superior patency rates and improved clinical outcomes with radial artery grafts compared with SVGs.[25] Notably, the Radial Artery Patency Study and subsequent meta-analyses have reported significantly lower rates of graft occlusion and major adverse cardiac events among patients receiving radial artery conduits.[9,24,26] Furthermore, extended follow-up data suggest that radial artery use is associated with improved survival and a reduced need for repeat revascularization, particularly among younger patients and those with diabetes mellitus.[27]

In response to this accumulating evidence, contemporary international guidelines have increasingly endorsed the radial artery as the preferred second arterial conduit in suitable candidates undergoing CABG.[28] Both the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines now recommend radial artery grafting over saphenous vein use in the absence of contraindications, highlighting its long-term clinical.[29,30]

Despite strong evidentiary support and clear guideline endorsement, the adoption of radial artery grafting remains uneven across institutions and geographic regions.[26,31] This variability is particularly pronounced in low- and middle-income settings, where concerns related to surgical expertise, operative duration, vasospasm, and resource availability may limit routine implementation.[9] Moreover, although graft patency and long-term survival have been extensively examined, prospective data addressing short-term postoperative outcomes, functional recovery, and patient-reported quality of life in everyday clinical practice remain comparatively scarce.

Against this backdrop, the present study was designed to prospectively evaluate the safety and clinical effectiveness of radial artery grafting in patients undergoing elective CABG. Specifically, we sought to assess early postoperative cardiac function, perioperative complication rates, and short-term quality-of-life outcomes. We hypothesized that the use of the radial artery as a bypass conduit would be associated with favorable early clinical outcomes, a low complication profile, and meaningful improvements in short-term quality of life following CABG.

Patients and methods

Study design and setting

This study was designed as a prospective descriptive investigation conducted at a tertiary cardiac surgery center in Yemen. The study aimed to evaluate short-term clinical outcomes associated with the use of the radial artery as a conduit in coronary artery bypass grafting (CABG). The research protocol followed standard clinical research principles and reflected routine surgical practice at the study center.

Study population

Adult patients scheduled for elective CABG were consecutively screened for eligibility during the study period. Inclusion criteria comprised patients aged 35 years or older who were candidates for isolated elective CABG. Patients undergoing emergency surgery, those with a history of previous CABG, severe left ventricular dysfunction

(left ventricular ejection fraction <30%), significant valvular heart disease requiring surgical intervention, aortic pathology, or peripheral vascular disease affecting radial artery suitability were excluded. Patients unable or unwilling to provide informed consent were also excluded.

Preoperative assessment

All enrolled patients underwent comprehensive preoperative evaluation, including detailed medical history and physical examination. Cardiovascular risk factors such as diabetes mellitus, hypertension, hypercholesterolemia, smoking status, physical inactivity, and khat chewing were documented. Baseline investigations included electrocardiography, transthoracic echocardiography, laboratory testing, and coronary angiography. Radial artery suitability was assessed clinically, and Doppler ultrasonography was performed when indicated to confirm adequate collateral circulation and exclude arterial disease.

Surgical technique

All CABG procedures were performed through a standard median sternotomy under general anesthesia. The radial artery was harvested using an open, atraumatic technique with meticulous handling to minimize endothelial injury. Intraoperative antispasmodic measures were routinely employed. The radial artery graft was anastomosed to coronary vessels with significant stenosis to reduce the risk of competitive flow. The number and configuration of grafts were determined according to coronary anatomy and surgeon discretion.

Postoperative management and follow-up

Following surgery, patients were managed according to standard postoperative care protocols, including intensive care monitoring and guideline-directed medical therapy. Antiplatelet agents, statins, and other cardiovascular medications were prescribed unless contraindicated. Clinical assessments were between 3 and 6 months after surgery. Follow-up evaluations included physical examination, electrocardiography, echocardiography, and assessment of postoperative complications. Coronary computed tomography angiography was performed selectively to assess graft patency when clinically indicated.

Outcome measures

The primary outcome was overall procedural success, defined as survival without major adverse cardiac or cerebrovascular events and with objective improvement in cardiac function. Secondary outcomes included postoperative complications, length of hospital stay, need for repeat revascularization, graft patency when assessed, and patient-reported quality of life.

Data collection and management

Data were collected using a structured case report form and entered into a secure database. Data accuracy and completeness were verified prior to analysis. All patient identifiers were removed to ensure confidentiality.

Statistical analysis

Statistical analysis was performed using SPSS software. Continuous variables were summarized as means and standard deviations, while categorical variables were presented as frequencies and percentages. Preoperative and postoperative comparisons were conducted using the Wilcoxon signed-rank test. Associations between categorical variables were analyzed using the chi-square test, and correlations were evaluated using Pearson's correlation coefficient. All statistical tests were two-sided, and a p-value ≤ 0.05 was considered statistically significant.

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the institutional review board of the study center. Written informed consent was obtained from all participants prior to enrollment. Patient confidentiality and data protection were strictly maintained throughout the study.

Results

Patient enrollment and baseline characteristics

Table 1 presents the demographic characteristics and personal habits of the study participants. The mean age of the patients was 50.0 ± 10.5 years, with the majori-

Table 1 – Demographic characteristics of the study population (N = 22)

Variable	Category	n	%
Age (years)	<50	14	63.6
	≥50	8	36.4
	Mean ± SD	50.0 ± 10.5	—
Sex	Male	22	100
Body mass index (kg/m²)	Underweight (<18)	1	4.5
	Normal (18–24.9)	4	18.2
	Overweight (25–29.9)	14	63.6
	Obese (≥30)	3	13.6
	Mean ± SD	26.0 ± 3.5	—
Marital status	Married	19	86.4
	Divorced	3	13.6
Residence	Urban	14	63.6
	Rural	8	36.4
Smoking	Yes	14	63.6
	No	8	36.4
Tobacco powder use	Yes	10	45.5
	No	12	54.5
Regular exercise	Yes	4	18.2
	No	18	81.8
Khat chewing	Yes	17	77.3
	No	5	22.7
Regular medication use	Yes	5	22.7
	No	17	77.3

Table 2 – Post-surgery outcomes at ≥3 and 6 months (N = 22)

Follow--up period	Outcome	Category/Symptom	n	%
≥3 months	Clinical outcome	Improvement	21	95.5
		Wound infection	1	4.5
	Adverse events	Bleeding	0	0.0
		Stroke	0	0.0
		Myocardial infarction	0	0.0
		Heart failure	0	0.0
		Pericardial effusion	0	0.0
		Death	0	0.0
6 months	Complications	Yes	7	31.8
		No	15	68.2
	Symptoms	Chest pain	0	0.0
		Shortness of breath	0	0.0
		Palpitations	0	0.0
		Leg swelling	7	31.8
		Other	0	0.0

ty being younger than 50 years (63.6%). All participants were male. The mean body mass index (BMI) was 26.0 ± 3.5 kg/m²; most patients were classified as overweight (63.6%), while 13.6% were obese. The majority of patients were married (86.4%) and resided in urban areas (63.6%). Regarding personal habits, a high proportion of participants reported cigarette smoking (63.6%) and khat chewing (77.3%). Most patients did not engage in regular physical exercise (81.8%) and did not use medications regularly (77.3%). More than half of the participants reported no use of tobacco powder (54.5%).

Post-surgery evaluation (≥3 months)

Long-term postoperative outcomes, including both the three-month and six-month follow-ups, are summarized in **Table 2**. At three months post-surgery, the majority of patients exhibited clinical improvement (21 patients, 95.5%), while only one patient (4.5%) experienced a wound infection, which subsequently resolved with appropriate care. No adverse events such as bleeding, stroke, myocardial infarction, heart failure, pericardial effusion, or death were reported during this period.

At six months post-surgery, most patients continued to show favorable outcomes with no complications (15 patients, 68.2%). A minority of patients (7 patients, 31.8%) experienced complications, all of which were limited to leg swelling. No patients reported chest pain, shortness of breath, palpitations, or other cardiac-related symptoms, indicating sustained clinical stability and safety of the surgical procedure over time (**Fig. 1**).

Medical history, cardiovascular risk factors, and surgical characteristics

The medical history, cardiovascular risk factors, and surgical characteristics of the study population are summarized in **Table 3**. Among the 22 participants, common comorbidities included hypercholesterolemia (14 patients, 63.6%), diabetes mellitus (13 patients, 59.1%), physical inactivity (13 patients, 59.1%), obesity (9 patients, 40.9%), and hypertension (8 patients, 36.4%). These findings highlight the prevalence of modifiable and non--modifiable risk factors in this patient cohort.

Regarding surgical characteristics, radial artery grafts were employed in 20 patients (90.9%). In all cases where the radial artery was used, a single graft was implanted. Additional arterial or venous grafts were required in one patient (4.5%). No intraoperative mortality or major technical complications were reported, reflecting the safety and technical feasibility of the procedure.

Success rate after surgery

Overall, 20 patients (90.9%) were classified as having a successful surgical outcome, while 2 patients (9.1%) did not meet the success criteria (**Table 4**).

Cardiac function before and after surgery

Cardiac and vascular evaluations were performed preoperatively and postoperatively to assess the effectiveness of

Table 3 – Medical history, cardiovascular risk factors, and surgical characteristics

Category	Variable	Category/Outcome	n	%
Medical history & cardiovascular risk factors	Diabetes mellitus	—	13	59.1
	Hypertension	—	8	36.4
	Hypercholesterolemia	—	14	63.6
	Obesity	—	9	40.9
	Physical inactivity	—	13	59.1
Surgical characteristics	Radial artery graft used	Yes	20	90.9
		No	2	9.1
	Number of RA grafts	One	20	90.9
		None	2	9.1
	Additional grafts used	Yes	1	4.5
		No	21	95.5

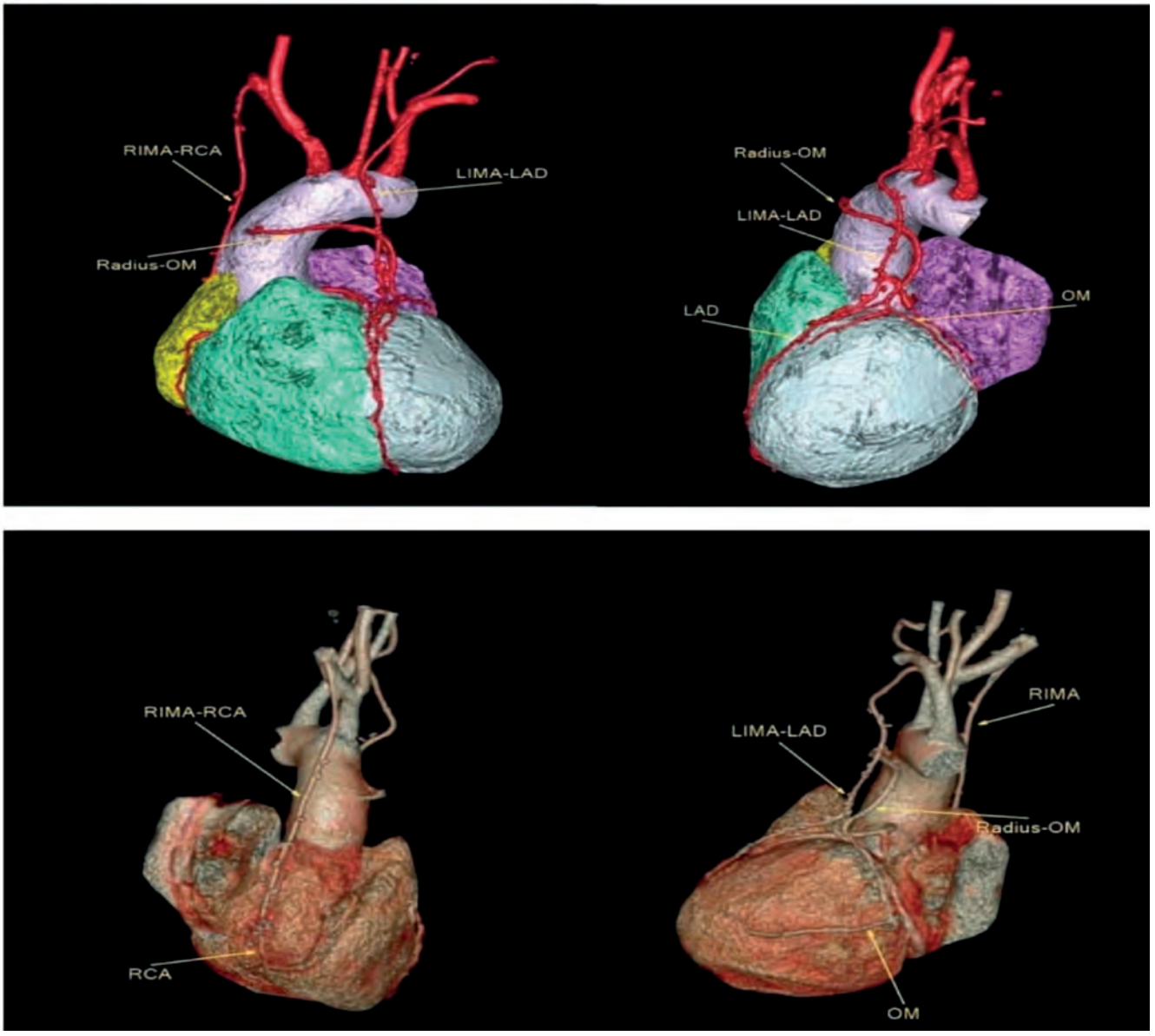

Fig. 1 – Complete revascularization after surgery using CT angiography.

coronary artery bypass grafting using radial artery grafts (**Table 5**).

Preoperative assessment revealed that the majority of patients had abnormal findings on electrocardiography (ECG) (21 patients, 95.5%), while only one patient (4.5%) demonstrated a normal ECG. Similarly, all participants (22 patients, 100%) had abnormal echocardiographic findings prior to surgery, indicating significant baseline cardiac dysfunction.

Postoperative assessments demonstrated marked improvement in cardiac function. All patients exhibited normal ECG and echocardiographic findings (22 patients, 100%). Additionally, postoperative Doppler ultrasonography of the upper limbs and abdominal ultrasonography were normal in all patients (100%), suggesting restoration of vascular integrity.

Regarding hospital stay, most patients were discharged within 10 days (13 patients, 59.1%), while a minority required hospitalization for more than 10 days (9 patients, 40.9%). These findings indicate that the surgical intervention resulted in substantial improvements in cardiac function, vascular status, and early postoperative recovery.

Mean differences in cardiac and vascular evaluations

Wilcoxon signed-rank test analysis demonstrated a statistically significant postoperative improvement in both ECG findings ($Z = -4.583$, $p < 0.001$) and echocardiographic parameters ($Z = -4.690$, $p < 0.001$), as summarized in **Table 6**. These results indicate a marked improvement in cardiac electrical and functional status following surgical intervention.

Post-operative outcomes

As shown in **Table 7**, it is noticed that in the early postoperative period (1 day to 3 months), the majority of patients

Table 4 – Success rate after surgery

Outcome	n	%
Success	20	90.9
Fail	2	9.1

Table 5 – Cardiac and vascular evaluations before and after surgery (N = 22)

Evaluation period	Variable	Category	n	%
Pre-surgery	ECG	Normal	1	4.5
		Abnormal	21	95.5
	Echocardiography	Normal	0	0.0
		Abnormal	22	100
Post-surgery	ECG	Normal	22	100
		Abnormal	0	0.0
	Echocardiography	Normal	22	100
		Abnormal	0	0.0
	Doppler U/S (upper limb)	Normal	22	100
		Abnormal	0	0.0
	Abdominal U/S	Normal	22	100
		Abnormal	0	0.0
	Hospital stays	≤10 days	13	59.1
		>10 days	9	40.9

Table 6 – Comparison of pre- and post-operative cardiac function (Wilcoxon test)

Variable	Z-value	*p*-value	Interpretation
ECG	–4.583	<0.001	Significant improvement
Echocardiography	–4.690	<0.001	Significant improvement

Table 7 – Post-operative outcomes

Category	Outcome	n	%
Early outcomes (1 day–3 months)	Clinical improvement	19	86.4
	Revascularization	2	9.1
	Irregular heartbeat	1	4.5
	Major complications	0	0
Medium-term outcomes (6 months)	Any complication	7	31.8
	Leg swelling	7	31.8
	Chest pain / MI / Stroke	0	0
Quality of life after surgery	Excellent	4	18.2
	Very good	17	77.3
	Good	1	4.5
	Fair / Poor	0	0
Overall, success rate	Successful	20	90.9
	Failed	2	9.1

Table 8 – Association between residence and surgical success

Residence	Success, n (%)	Failure, n (%)	χ^2	*p*-value
Urban	14 (63.6)	0 (0)	3.85	**0.050**
Rural	6 (27.3)	2 (9.1)		

Table 9 – Correlation between number of grafts and post-operative outcomes

Outcome variable	Pearson r	*p*-value
Hospital stays	0.177	0.431
Early outcomes (≤3 months)	0.000	1.000
Late outcomes (≥3 months)	**–0.836**	**<0.001**
Quality of life	–0.191	0.396

demonstrated favorable recovery. Clinical improvement was observed in 19 of the participants (86.4%), while revascularization was documented in 2 patients (9.1%). Only one patient (4.5%) experienced an irregular heartbeat, and there were no major complications during this interval, highlighting a generally positive short-term safety profile. At the medium-term follow-up at 6 months, 31.8% of patients (n = 7) reported complications, all of which were attributable to leg swelling; there were no events of chest pain, myocardial infarction, or stroke, indicating an absence of serious cardiopulmonary adverse outcomes in this cohort.

Assessment of quality-of-life following surgery revealed predominantly high patient-reported outcomes, with 4 patients (18.2%) rating their status as excellent, 17 (77.3%) as very good, and 1 (4.5%) as good; none of the patients reported fair or poor quality of life. Overall, the success rate of the surgical intervention was 90.9% (n=20), with a failure rate of 9.1% (n = 2), demonstrating a high level of clinical effectiveness within the studied sample.

Association between residence and surgical success

As noticed in **Table 8,** a statistically significant association was observed between place of residence and procedural success, with higher success rates among patients residing in urban areas ($\chi^2 = 3.85$, $p = 0.05$).

No significant associations were identified between procedural success and age, body mass index, marital status, educational level, smoking status, khat chewing, physical activity, or medication adherence.

Correlation between number of grafts and post-operative outcomes

As shown in **Table 9**, the findings of the Pearson correlation analysis demonstrated a strong negative correlation between the number of grafts implanted and late post-operative outcomes beyond three months (r = –0.836, p <0.001). No significant correlations were observed between the number of grafts and hospital length of stay, early postoperative outcomes, or postoperative quality of life.

Discussion

Principal findings

In this prospective cohort study, use of the radial artery as a conduit for elective coronary artery bypass grafting (CABG) was associated with excellent short-term clinical outcomes, including significant postoperative improvements in objective cardiac function measures, a low incidence of perioperative and early postoperative complications, the absence of major adverse cardiac and cerebrovascular events, and substantial enhancement in patient-reported quality of life. These data provide compelling evidence for the safety, procedural success, and clinical effectiveness of radial artery grafting in contemporary CABG practice.

Interpretation in the context of existing evidence

The normalization of electrocardiographic and echocardiographic parameters observed postoperatively in this study indicates effective myocardial revascularization and early functional recovery, consistent with the known biological advantages of arterial over venous conduits. Arterial grafts such as the radial artery maintain endothelial integrity, preserve nitric oxide–mediated vasomotion, and demonstrate greater resistance to intimal hyperplasia and atherosclerotic degeneration compared with saphenous vein grafts, supporting mechanistic plausibility for superior outcomes with arterial conduit.[20,21,32]

Randomized controlled trials and large observational studies have consistently demonstrated higher patency rates and improved clinical outcomes with radial artery grafts relative to saphenous vein grafts.[9,24,33] Long-term analyses further suggest that the use of the radial artery is associated with improved survival and reduced need for repeat revascularization, particularly in younger patients and those with diabetes mellitus.[27] Although the present study focused primarily on short-term outcomes, the favorable early functional recovery observed may represent an important mechanistic link between superior graft biology and improved long-term prognosis.

The low incidence of postoperative complications and the absence of mortality, myocardial infarction, or stroke during follow-up further support the safety profile of radial artery grafting.[34] Earlier concerns regarding radial artery vasospasm, technical complexity, and increased operative time have been largely mitigated through advances in harvesting techniques, atraumatic conduit handling, and routine use of perioperative antispasmodic therapy.[9,22,23,35] The application of these contemporary strategies in the present cohort likely contributed to the observed low complication rates and favorable outcomes.

Quality of life and patient-centered outcomes

An important and clinically relevant finding of this study is the substantial improvement in postoperative quality of life, with most patients reporting very good or excellent outcomes. While much of the existing literature has focused on angiographic graft patency and survival, patient-reported outcomes have received comparatively less attention. Nevertheless, quality of life and functional recovery are increasingly recognized as critical endpoints in cardiovascular surgery, particularly in the context of elective revascularization.[7,36,37]

The observed improvement in quality of life likely reflects effective symptom relief, enhanced myocardial perfusion, improved cardiac function, and an uncomplicated postoperative course. These findings are consistent with prior studies suggesting that arterial revascularization strategies may translate into better functional status and patient satisfaction, beyond traditional hard clinical endpoints.[9,38] From a patient-centered perspective, these outcomes are highly relevant, as they directly influence return to daily activities, adherence to secondary prevention, and overall well-being.[39]

Clinical implications

The findings of this study add to the growing body of evidence supporting the radial artery as the preferred second arterial conduit in CABG, as increasingly recommended by contemporary international guidelines.[29,30] In appropriately selected patients, radial artery grafting appears to provide effective myocardial revascularization without increasing perioperative risk, while offering meaningful improvements in early functional and quality-of--life outcomes.[39] These results support broader adoption of arterial revascularization strategies, particularly in centers seeking to optimize short-term recovery and patient satisfaction following CABG.

The observed association between urban residence and procedural success may reflect differences in healthcare access, postoperative follow-up, health literacy, and adherence to guideline-directed medical therapy. Although this finding should be interpreted cautiously due to potential confounding factors, it underscores the importance of structured postoperative care pathways and equitable access to follow-up services to ensure optimal outcomes across diverse patient populations.

Limitations

Several limitations of this study should be acknowledged. The relatively small sample size and single-center design may limit the generalizability of the findings, while the exclusive inclusion of male patients restricts applicability to female populations. In addition, the follow-up duration was insufficient to evaluate long-term graft patency and survival outcomes, which have been emphasized in prior studies. Routine postoperative angiographic assessment was not performed in all patients, and residual unmeasured confounding cannot be excluded.

The modest sample size should be interpreted within the context of the study's prospective design and clinical setting. This investigation was conducted at a single tertiary cardiac surgery center in a low-resource, conflict-affected environment, where the volume of elective coronary artery bypass grafting is inherently limited. Furthermore, stringent inclusion and exclusion criteria were applied to ensure patient safety and cohort homogeneity, particularly regarding elective surgery, radial artery suitability, and preserved left ventricular function.

Despite these constraints, the prospective nature of the study, complete follow-up of all enrolled patients,

and use of paired pre- and postoperative assessments enhanced internal validity and statistical efficiency. The large and statistically robust effect sizes observed for key outcomes, including electrocardiographic and echocardiographic improvement, indicate adequate sensitivity to detect clinically meaningful short-term changes. Importantly, the study was designed as a descriptive and exploratory investigation aimed at evaluating early safety, feasibility, and functional outcomes of radial artery grafting in routine clinical practice rather than providing definitive comparative or long-term efficacy estimates.

Accordingly, the findings should be considered hypothesis-generating and context-specific, offering valuable prospective evidence from an underrepresented setting. Larger multicenter studies with extended follow-up are warranted to confirm these results and to assess long-term graft patency and survival outcomes.

Conclusion

This prospective study demonstrates that the use of the radial artery as a conduit in coronary artery bypass grafting is safe and effective in routine clinical practice. Radial artery grafting was associated with significant postoperative improvement in objective measures of cardiac function, a low incidence of perioperative and short-term complications, and substantial enhancement in patient-reported quality of life. No major adverse cardiac or cerebrovascular events were observed during follow-up.

These findings support the role of the radial artery as a preferred arterial conduit in appropriately selected patients undergoing elective CABG. When combined with careful patient selection, meticulous surgical technique, and structured postoperative care, radial artery grafting can achieve high procedural success without increasing perioperative risk.

Although the follow-up period was limited and the study population was relatively small, the results are consistent with existing evidence cited in this manuscript and contribute context-specific prospective data on short-term outcomes following radial artery use in CABG. Larger, multicenter studies with longer follow-up are warranted to further evaluate long-term graft durability and survival outcomes.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

Ethical statement

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the institutional review board of the study center.

Informed consent

Written informed consent was obtained from all participants prior to enrollment. Patient confidentiality and data protection were strictly maintained throughout the study.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to ethical and privacy considerations, the data are not publicly available.

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Přehledový článek | Review article

Katetrizační léčba srdečního selhání

(Catheter-based therapy of heart failure)

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Klíčová slova:
Interatriální shunt
Katetrizační remodelace levé komory
Mezisíňová komunikace
Redukce plicnice

SOUHRN

Klinicky je testována řada nefarmakologických postupů, které ovlivňují rozličné patofyziologické mechanismy srdečního selhání. Metody se nacházejí v různém stadiu vývoje. V článku se zaměřujeme na katetrizační techniky léčby srdečního selhání, zejména na katetrizační remodelaci levé komory a mezisíňovou komunikaci. V případě katetrizační remodelace levé komory vykazují některé systémy nadějné výsledky u pečlivě vybraných pacientů v rukou zkušeného týmu. Mezisíňová komunikace se také zdá efektivní u určitých skupin nemocných se srdečním selháním, a to jak se zachovanou, tak sníženou ejekční frakcí levé komory.

Keywords:
Interatrial communication
Interatrial shunt
Pulmonary artery reduction
Transcatheter left ventricular remodeling

ABSTRACT

A number of non-pharmacological approaches that affect various pathophysiological mechanisms of heart failure are being clinically tested. These methods are at different stages of development. This article focuses on catheter-based techniques for the treatment of heart failure, especially catheter-based left ventricular remodeling and interatrial communication. Regarding catheter-based left ventricular remodeling, some systems have shown promising results in carefully selected patients when performed by an experienced team. Interatrial communication also appears to be effective in certain subgroups of patients with heart failure, both with preserved and reduced left ventricular ejection fraction.

Existuje řada katetrizačních technik, které lze využít v léčbě srdečního selhání. V širším pojetí mezi ně můžeme zahrnout i revaskularizační výkony (perkutánní koronární intervence) a katetrizační intervence na chlopních. Stále významnější místo v léčbě srdečního selhání zaujímá zejména edge-to-edge plastika atrioventrikulárních chlopní, především mitrální chlopně.

V článku se zaměřujeme na katetrizační techniky, které nejsou v tak širokém obecném povědomí, a to konkrétně na katetrizační remodelaci levé komory (LK), včetně remodelace LK pomocí redukce plicnice, a dále na mezisíňovou komunikaci (interatriální shunt).

Katetrizační remodelace levé komory

Srdeční selhání se sníženou ejekční frakcí je charakterizováno progresivní dilatací LK. Větší rozměr LK zvyšuje napětí její stěny (Laplaceův zákon), což přispívá k další progresi remodelace a zvyšuje energetické nároky myokardu. Principem katetrizační remodelace je ovlivnit příznivě geometrii LK, a snížit tak napětí její stěny, aby byly vytvořeny podmínky pro její reverzní remodelaci.[1]

Chirurgické remodelační operace LK jsou v různých modifikacích používány více než půl století. Tuto techniku rozvinul především francouzský kardiochirurg Vincent Dor.[2] Chirurgická ventrikuloplastika však představuje zpravidla

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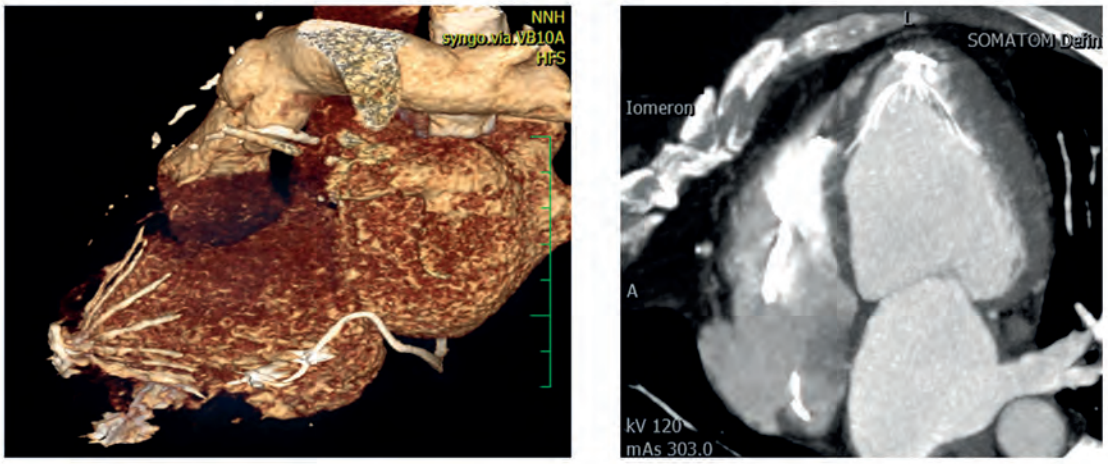
přidružený výkon doprovázející chirurgickou revaskularizaci myokardu, nikoli samostatnou nefarmakologickou léčbu srdečního selhání. Navíc evidence o přínosu chirurgické ventrikuloplastiky je rozporuplná. Největší randomizovaná klinická studie srovnávající samotnou chirurgickou revaskularizaci myokardu s chirurgickou revaskularizací myokardu doplněnou o ventrikuloplastiku u pacientů s výraznou poruchou kinetiky v oblasti přední stěny LK (STICH) neprokázala profit z konkomitantního remodelačního výkonu.[3] Ventrikuloplastikou se ale v této studii dosáhlo jen velmi malé redukce objemu LK, což bylo jedním z předmětů kritiky studie. *Post hoc* podskupinová analýza studie STICH a další data naznačila, že pokud se dosáhne remodelačním výkonem podstatnějšího snížení objemu LK, pacienti ze zákroku profitují.[4–9] Nicméně zásadním negativním aspektem chirurgické remodelace LK zůstává výrazná invazivnost výkonu.

V nedávné době byly testovány remodelační postupy, které spočívaly v komorové bandáži provedené z miniinvazivního chirurgického přístupu. Jednalo se např. o systémy VenTouch, CorCap nebo HeartNet.[10,11] V klinické praxi se nicméně neuplatnily pro absenci robustnějších dat o účinnosti.

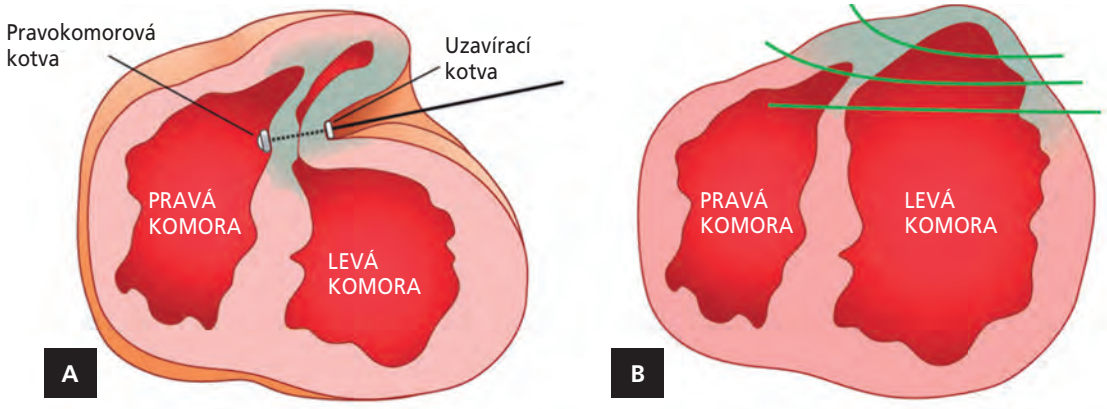
Současně byla a je vyvíjena řada dalších systémů, které pro remodelaci LK využívají čistě katetrizační, popřípadě hybridní přístup. U některých systémů byl již vývoj ukončen a do klinické praxe se neprosadily, u jiných výzkum stále pokračuje. Za zmínku stojí, že některé tyto systémy byly primárně určené pro léčbu sekundární mitrální regurgitace, ale prokázaly příznivý remodelační efekt i u pacientů se srdečním selháním bez významnější nedomykavosti na mitrální chlopni, např. systémy Carillon nebo AccuCinch. V dalším textu uvádíme příklady některých testovaných systémů.

Parachute

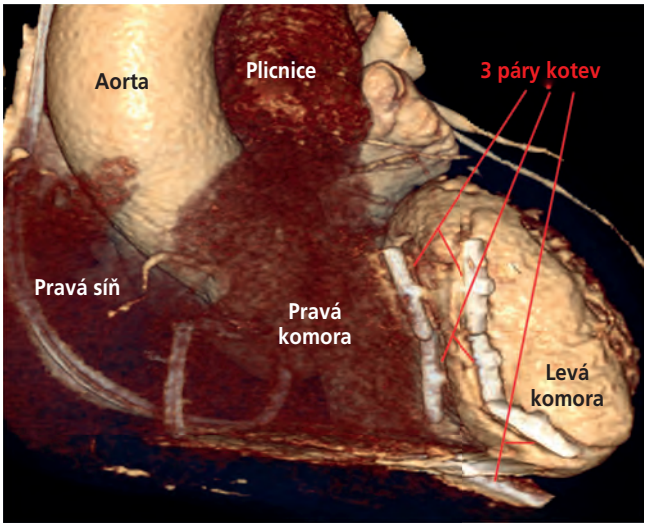
Principem intervence systémem Parachute (CardioKinetix, Menlo Park, USA) byla katetrizační okluze apikálního poinfarktového aneurysmatu LK pomocí implantátu tvaru rozepnutého deštníku (**obr. 1**).[12] Vývoj tohoto systému byl ukončen.



Obr. 1 – Vyšetření výpočetní tomografií po katetrizační okluzi apikálního aneurysmatu levé komory systémem Parachute (CardioKinetix). Vlevo trojrozměrná rekonstrukce, vpravo dvojrozměrné zobrazení ze čtyřdutinové projekce.[13]
(Zdroj: Radiodiagnostické oddělení, FNMH, pracoviště Homolka)



Obr. 2 – Schematické znázornění příčného řezu srdečními komorami se zobrazením exkluze jizevnaté tkáně (šedá barva) pomocí hybridního kotevního systému Revivent TC (A) a vyznačením (zeleně) různých způsobů naložení kotev tohoto systému (B).[13]



Obr. 3 – Stav po hybridní remodelaci systémem Revivent TC se znázorněním tří párů kotev. Vyšetření srdce výpočetní tomografií v trojrozměrné rekonstrukci. Upraveno podle Naar J et al. J Cardiovasc Transl Res 2021.[15] (Zdroj: Radiodiagnostické oddělení, FNMH, pracoviště Homolka)

Revivent TC

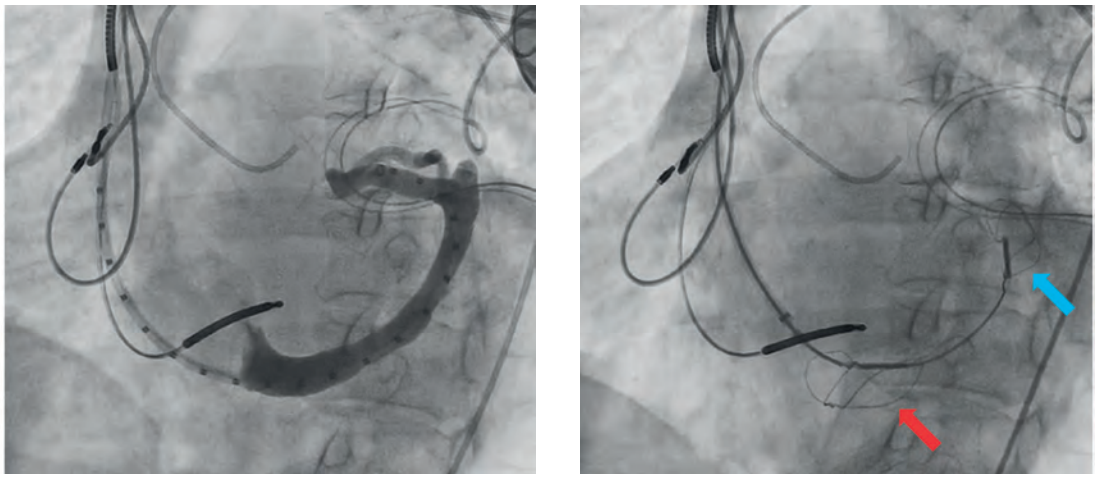
Remodelace systémem Revivent TC (Bioventrix, San Ramon, USA) je rovněž určena pro pacienty s ischemickou dysfunkcí LK, konkrétně pro nemocné s transmurální jizvou v povodí ramus interventricularis anterior. Spočívá v exkluzi jizevnaté tkáně pomocí dvojic kotev. Jedná se o výkon v pravém slova smyslu hybridní, kdy intervenční kardiolog zavádí katetrizačně cestou vena jugularis interna na pravokomorovou část interventrikulárního septa vnitřní kotvu a současně kardiochirurg nakládá z levostranné minitorakotomie protilehlou uzavírací kotvu (**obr. 2A**). V průměru se k remodelaci použije trojice kotev (**obr. 3**), přičemž některé kotvy (více apikální) lze naložit pouze chirurgicky epikardiálně, a to buď přes obě komory, nebo pouze přes LK (**obr. 2B**). Zákrok je prováděn v celkové anestezii na bijícím srdci, po výkonu pacienti užívají antikoagulační léčbu minimálně po dobu tří měsíců.

Dosavadní důkazy o účinnosti hybridní remodelace systémem Revivent TC vycházejí z menších nerandomizovaných studií. V první prospektivní multicentrické studii bylo na 86 pacientech se srdečním selháním s třídou NYHA (New York Heart Association) ≥ II a ejekční frakcí LK 15–45 % po roce sledování demonstrováno významné snížení objemů LK a zlepšení kvality života a tolerance zátěže. Nicméně pouze u 35 pacientů byl použit hybridní miniinvazivní přístup, ostatní pacienti byli operováni ze sternotomie.[14] Rovněž i my jsme prokázali na souboru 23 pacientů, kteří byli intervenováni hybridním přístupem, významné periprocedurální snížení objemů LK. Tento efekt přetrvával i po dobu pětiletého sledování.[15] Nejrozsáhlejší evidence o účinnosti a bezpečnosti systému Revivent TC pak pochází z prospektivní nerandomizované studie ALIVE (n = 126), která neprokázala zlepšení ve složeném klinickém cílovém ukazateli účinnosti.[16] Zajímavostí této studie je, že pacienti intervenovaní čistě chirurgickým přístupem (n = 23), tj. s naložením všech kotev miniinvazivním chirurgickým přístupem epikardiálně, vykazovali v porovnání s pacienty intervenovanými hybridním přístupem lepší výsledky, a to jak po stránce účinnosti, tak i bezpečnosti. Důvodem může být to, že hybridní remodelace tímto systémem vyžaduje určitou učební křivku a do studie ALIVE byla zařazena i nová centra. Nejčastější komplikací tohoto způsobu remodelace je zhoršení regurgitace na atrioventrikulárních chlopních, zejména trikuspidální.

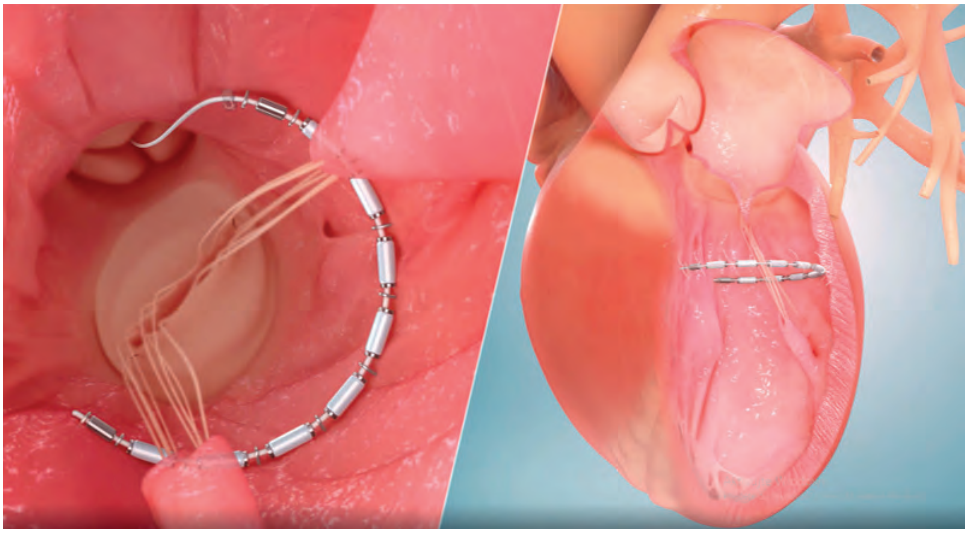
Další uváděné systémy se používají především ke katetrizační remodelaci LK, jejíž dysfunkce je neischemické etiologie.

Carillon

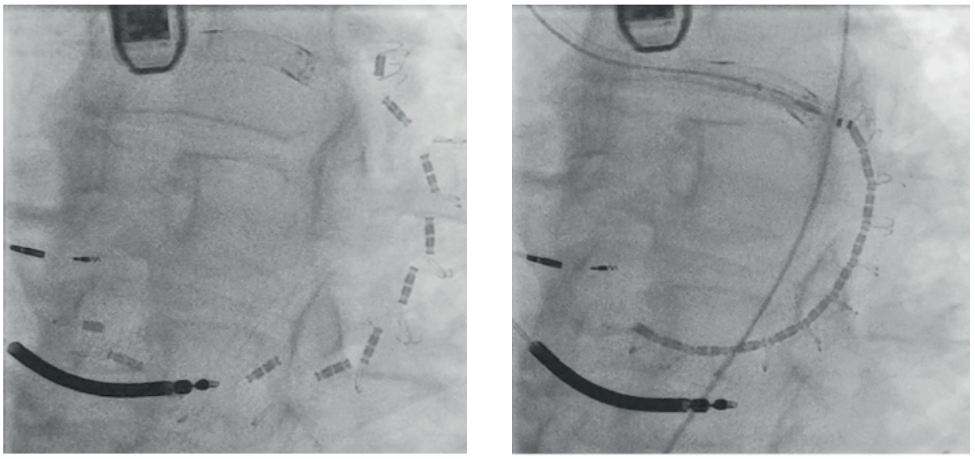
Podstatou remodelace systémem Carillon (Cardiac Dimensions, Kirkland, USA) je stažení LK na úrovni mitrálního prstence pomocí implantátu umístěného do koronárního sinu (**obr. 4**). Metaanalýza tří studií, z nichž jedna byla randomizovaná (REDUCE FMR), prokázala u pacientů s end-diastolickým rozměrem LK > 55 mm, NYHA třídou II–IV a mitrální regurgitací 2.–4. stupně nejen zmenšení významnosti mitrální regurgitace, ale také zlepšení morfologie LK a funkčních parametrů.[17,18]



Obr. 4 – Nalevo skiaskopie s angiografickým zobrazením koronárního sinu, napravo implantát Carillon zavedený v koronárním sinu. Červená šipka označuje proximální kotvu implantátu, modrá šipka distální kotvu implantátu. (Zdroj: Kardiologická klinika, 1. LF UK a FNMH, pracoviště Homolka)



Obr. 5 – Schematické znázornění katetrizační remodelace levé komory pomocí systému AccuCinch (Ancora Heart).[19]



Obr. 6 – Periprocedurální skiaskopie během implantace systému AccuCinch. Nalevo je situace po implantaci kotev před stažením, napravo pak po stažení propojovacího vlákna. Na obrázku je dále patrná jícnová echokardiografická sonda a síňová a defibrilační elektroda implantabilního kardioverteru-defibrilátoru. (Zdroj: Kardiologická klinika, 1. LF UK a FNMH, pracoviště Homolka)

AccuCinch

Remodelace LK systémem AccuCinch (Ancora Heart, Santa Clara, USA) je založena na implantaci série kotviček do myokardu bazálních segmentů volné stěny LK asi 1–2 cm pod úrovní mitrálního prstence. Kotvičky jsou propojeny spojovacím vláknem, na kterém jsou mezi kotvičkami rozmístěny podložky kontrastní pro rentgenové záření. Následným stažením propojovacího vlákna dojde ke změně geometrie (zmenšení obvodu) LK (**obr. 5**). Implantace systému je navigována skiaskopicky a pomocí jícnové echokardiografie (**obr. 6**). Přístup je katetrizační, ze společné femorální tepny (zavaděč 20 F), retrográdně, skrz aortální chlopeň.

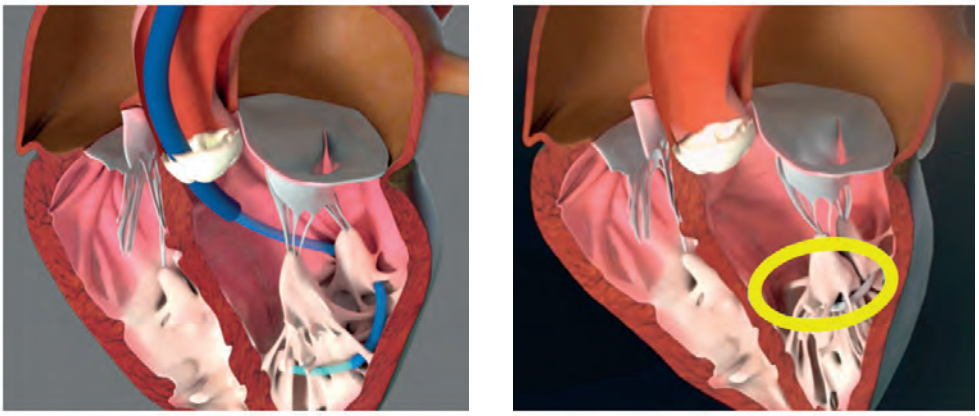
Data ze série 51 pacientů s ejekční frakcí LK 20–40 % a mitrální regurgitací do 2. stupně prokázala, že po 12 měsících od katetrizační remodelace LK systémem AccuCinch došlo k významnému snížení objemů LK, zlepšení kvality života a tolerance zátěže.[20] Příznivý remodelační efekt přetrvával i po dobu dvouletého sledování.[21] V současné době probíhá nábor do prospektivní randomizované klinické studie (CORCINCH-HF).

Vsling

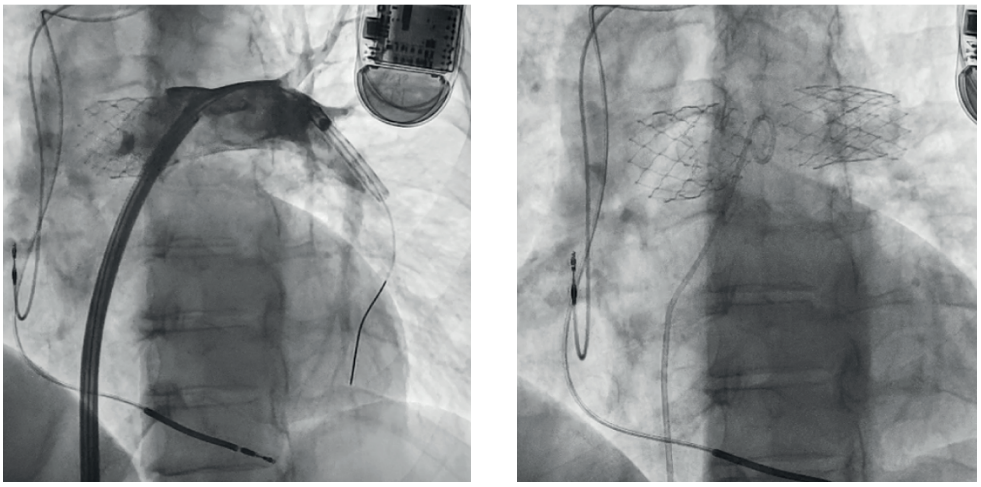
Systém Vsling (Cardiac Success, Yokneam, Izrael) představuje opět čistě katetrizační proceduru, jejímž principem je vzájemné přiblížení bazální části papilárních svalů mitrální chlopně pomocí goretexové bandáže (**obr. 7**). To vede nejen k lepší koaptaci cípů mitrální chlopně, ale i ke zmenšení obvodu bazální části LK.[23] Přístup je opět z femorální tepny, transaortálně. Tento systém je na počátku klinického hodnocení.

ContraBand

Remodealce LK pomocí systému ContraBand (Restore Medical, Or Yehuda, Izrael) spočívá v omezení průtoku plicním řečištěm zavedením implantátů do levé a pravé větve plicnice (**obr. 8**). Implantáty jsou samoexpandibilní, vnitřní kostra má nastavitelný průtokový kanál a zúžení lze



Obr. 7 – Schematické znázornění katetrizační remodelace levé komory pomocí systému Vsling (Cardiac Success). Na pravém obrázku žlutě označeno místo, kde je umístěna goretexová bandáž.[22]



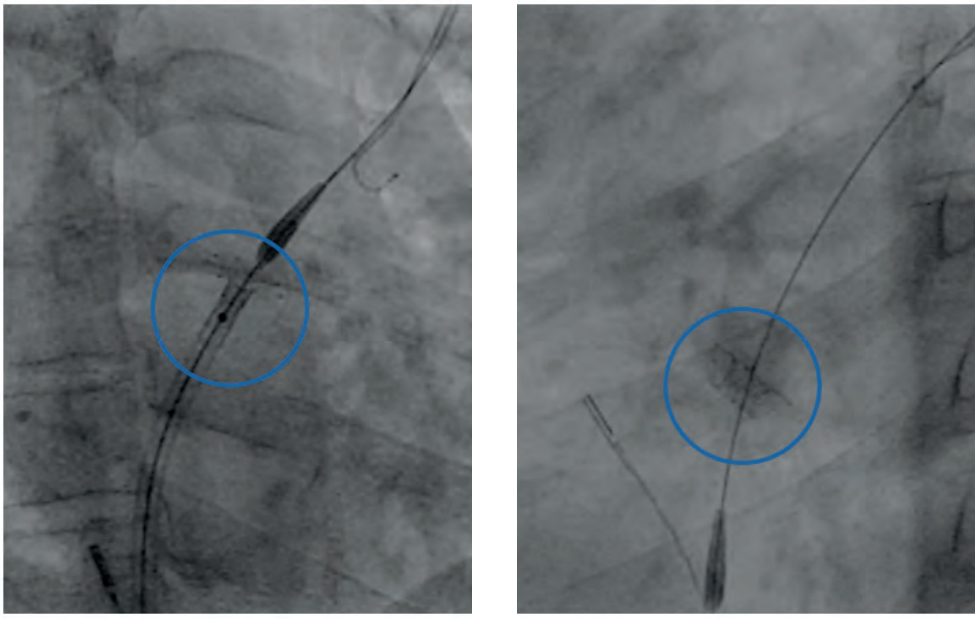
Obr. 8 – Periprocedurální skiaskopie při zavádění systému ContraBand (Restore Medical) pro katetrizační redukci plicnice. Na obrázku vlevo je situace po zavedení implantátu do pravé větve plicnice, probíhá angiografické vyšetření levé větve plicnice před uvolněním levostranného implantátu. Na obrázku vpravo jsou již rozvinuté implantáty v obou větvích plicnice. (Zdroj: Kardiologická klinika, 1. LF UK a FNMH, pracoviště Homolka)

zrušit balonkovým katétrem. Tento způsob remodelace je určen pro symptomatické pacienty se srdečním selháním se sníženou ejekční frakcí LK, kteří mají zachovanou systolickou funkci pravé komory. Odvážný koncept, který je na počátku klinického zkoušení, vychází z předpokladu, že zvýšením dotížení (afterloadu) pravé komory, a tím i systolického tlaku v pravé komoře dojde v systole komor k posunu mezikomorového septa do přirozenější anatomické polohy. Jinými slovy se předpokládá se, že negativní vliv tlakového zatížení pravé komory bude vykoupen zlepšením systolické funkce LK. První klinická data naznačují zlepšení funkčních parametrů a objemů LK při zachování systolické funkce pravé komory a určitý pozitivní vliv na zátěžovou hemodynamiku.[24]

Interatriální shunt

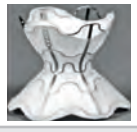
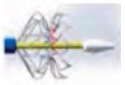
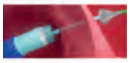
Podstatou je vytvoření permanentní mezisíňové komunikace o definovaném rozměru, většinou katetrizačním zavedením nitinolového implantátu (sloučenina niklu a titanu). Cílem této nefarmakologické léčby je snížit tlak v levé síni bez současného výraznějšího ovlivnění tlaku v pravé síni a objemového přetížení pravostranných oddílů. Hemodynamický, resp. i klinický efekt můžeme očekávat okamžitě. Tato strategie vychází z historických pozorování u pacientů s Lutembacherovým syndromem, tedy s kombinací mitrální stenózy a defektu na úrovni septa síní, u nichž docházelo v pozdějšímu nástupu symptomů z mitrální stenózy v porovnání s pacienty bez síňového defektu.[25]

Koncept má za sebou již řadu let vývoje. Prvním testovaným systémem byl implantát Interatrial Septal Device System (DC Devices, Tewksbury, USA, nyní Corvia) – **obr. 9** a **10**. Po preklinických zkouškách, kde byl definován rozměr zkratového ústí, byla na našem pracovišti provedena v roce 2013 první klinická implantace. Tato terapie byla primárně testována u pacientů se srdečním selháním se zachovanou nebo mírně sníženou ejekční frakcí a úvodní klinická data naznačovala pokles tlaku v zaklínění plicnice po výkonu i příznivý vliv na klinické parametry.[26,27] První randomizovaná klinická studie s falešnou procedu-



Obr. 9 – Periprocedurální skiaskopie při zavádění implantátu Interatrial Septal Device System (DC Devices) pro mezisíňový shunt. (Zdroj: Kardiologická klinika, 1. LF UK a FNMH, pracoviště Homolka)

Tabulka 1 – Systémy pro vytvoření mezisíňové komunikace testované u pacientů se srdečním selháním (převzato z Jagadeesan V, Gray WA, Shah SJ, et al. J Soc Cardiovasc Angiogr Interv 2023,[32] na základě licence Creative Commons CC-BY-NC-ND)

Zařízení/postup	Corvia	V-Wave	Occlutech	Edwards	Alleviant	NoYA	InterShunt
							
Typ	Implantát	Implantát	Implantát	Implantát	Postup	Postup	Postup
Charakteristika	Nitinolový stent	Nitinol/ PTFE tvaru přesýpacích hodin	Nitinolový oplet s centrálním otvorem	Trubicový nitinolový stent s retenčními rameny	Excizní katétr	Radiofrekvenční katétr	Řezný katétr
Průtok shuntu	LS → PS	LS → PS	LS → PS	LS → KS	LS → PS	LS → PS	LS → PS
Velikost shuntu	8 mm	5,1 mm	4, 6, 8, 10 mm	7 mm	6 mm	4–12 mm	6 mm
Stadium vývoje	Nábor do RCT dokončen, probíhá následná potvrzující RCT v podskupině respondérů	Nábor do RCT dokončen, pokračuje sledování	Probíhá nábor do RCT	Fáze 2 proveditelnosti / probíhá mechanistická RCT	Probíhá nábor do pilotní RCT	Probíhající otevřená studie	Malá pilotní studie u lidí

KS – koronární sinus; LS – levá síň; PS – pravá síň; PTFE – polytetrafluorethylen; RCT – randomizovaná kontrolovaná studie.

rou (REDUCE LAP-HF I, n = 44) potvrdila u této populace pacientů pokles tlaku v zaklínění plicnice v klidu i při zátěži po jednom měsíci.[28] V následné větší randomizované klinické studii s falešnou procedurou (REDUCE LAP-HF II, n = 626) nebyl po ročním ani dvouletém sledování pozorován rozdíl ve složeném primárním klinickém cílovém ukazateli. Z dílčích klinických parametrů došlo pouze ke zlepšení symptomů dle třídy NYHA.[29,30] Dle *post hoc* ana-

lýzy této studie se nicméně zdá, že by z intervence mohli profitovat jedinci s nižší plicní vaskulární rezistencí na vrcholu zátěže (< 1,74 WU). K průkazu této hypotézy byla uspořádána studie RESPONDER-HF.

Jiná prospektivní randomizovaná klinická studie s falešnou procedurou (RELIEVE-HF, n = 508), která zařadila pacienty se srdečním selháním napříč ejekční frakcí LK a ve které byl použit implantát Ventura (V-Wave, Cesarea, Izrael), rovněž neprokázala po dvou letech zlepšení v primárním kombinovaném klinickém cílovém ukazateli. Překvapivě však naznačila, že pacienti s ejekční frakcí LK < 40 % by mohli mít z této léčby prospěch.[31] Výzkum se proto nyní orientuje i na tuto subpopulaci pacientů se srdečním selháním.

Mimo dvou zmíněných implantátů byla a je testována řada dalších systémů. Kromě vytvoření zkratu na úrovni septa síní ve fossa ovalis existuje shunt propojující levou síň s koronárním sinem a také systémy, které spočívají ve stomizaci mezisíňového septa bez implantace cizorodého materiálu (**tabulka 1**).[32] Zajímavým technologickým konceptem je pak mezisíňový shunt Adona s nastavitelnou velikostí průtočného lumen a integrovaným tlakovým senzorem v levé i pravé síni (Adona Medical, Los Gatos, USA). Jedná se tedy o kombinaci terapeutického mezisíňového shuntu s implantabilním hemodynamickým monitorem. Tlakový senzor se dobíjí transkutánně a přes ústí implantátu lze provádět běžné levosíňové katetrizační intervence. První klinická implantace byla provedena v roce 2024 a systém je nyní testován u pacientů se srdečním selháním se zachovanou i sníženou ejekční frakcí (klinická studie ATHENS-HF).

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Přehledový článek | Review article

Ceramidy jako nové biomarkery kardiovaskulárních onemocnění

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SOUHRN

Kardiovaskulární onemocnění jsou celosvětově hlavní příčinou úmrtí. Tradiční kardiovaskulární rizikové faktory vysvětlují pouze 75 % rizika kardiovaskulárního onemocnění a expozice jednomu nebo více rizikovým faktorům je běžná i u jedinců, u kterých se nevyvinou žádné klinické projevy. Ceramidy jsou heterogenní skupinou bioaktivních membránových sfingolipidů, které hrají specializované regulační role v buněčném metabolismu. Ceramidy byly identifikovány jako nové biomarkery kardiovaskulárních onemocnění.

ABSTRACT

Cardiovascular disease is the leading cause of death globally. Traditional cardiovascular risk factors explain only 75% of the risk for cardiovascular disease and exposure to one or more vascular risk factors is common even in individuals who will not develop any clinical manifestations. Ceramides are a heterogeneous group of bioactive membrane sphingolipids that play specialized regulatory roles in cellular metabolism. Ceramides have been identified as novel biomarkers for cardiovascular diseases.

Úvod

Kardiovaskulární onemocnění (KVO) jsou celosvětově hlavní příčinou úmrtí a každoročně si vyžádají odhadem 19,8 milionu životů.[1] Tradiční kardiovaskulární (KV) rizikové faktory (např. hypertenze, diabetes, vysoký obsah lipoproteinů s nízkou hustotou, kouření, nadváha nebo obezita) vysvětlují pouze 75 % rizika KVO a vystavení jednomu nebo více vaskulárním rizikovým faktorům je běžné i u jedinců, u kterých se nevyvinou žádné klinické projevy.[2] Většina KV příhod je způsobena aterosklerózou, která se rozvíjí desítky let před klinickými příznaky a zákeřně postupuje do bodu, kdy ji lze pouze oddálit, ale nikoli zvrátit.[3–5] Proto je nezbytné identifikovat osoby s rizikem, aby se zabránilo vzniku KVO změnami životního stylu nebo lékařskou léčbou.

Ceramidy

Ceramidy jsou heterogenní skupinou bioaktivních membránových sfingolipidů, které hrají specializované regulační role v buněčném metabolismu v závislosti na charakteristické délce jejich mastných acylových řetězců a subcelulární distribuci.[5] Mají důležitou úlohu v mnoha buněčných funkcích, jako je apoptóza a zánět.[6] Během posledního desetiletí nové klinické údaje ukázaly, že ceramidy mají také diagnostickou hodnotu. Na základě četných publikovaných dat bylo vyvinuto a pro běžnou klinickou praxi adaptováno skóre rizika využívající koncentrace cirkulujících ceramidů. Sérové ceramidy se v současné době klinicky používají jako účinné stratifikátory rizika pro primární a sekundární prevenci aterosklerotických KVO, jako je ischemická choroba srdeční (ICHS), cévní onemocnění mozku, ale i srdeční selhání a fibrilace síní.[5,7–13]

Ceramidy a další sfingolipidy se obvykle kvantifikují kapalinovou chromatografií s tandemovou hmotnostní spektrometrií (liquid chromatography–tandem mass spectrometry, LC-MS/MS).[14] Obvykle se popisují počtem atomů uhlíku a dvojných vazeb v N-vázané mastné kyselině: například ceramidy C16:0 nebo C24:1. Tento popis ignoruje heterogenitu sfingoidního řetězce. Skutečný popis je však složitější a je nad rámec tohoto sdělení.

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Biosyntéza ceramidů a jejich metabolismus

Ceramidy jsou nezbytnými prekurzory většiny komplexních sfingolipidů, včetně sfingomyelinů, glukosylceramidů a sfingosinu. Tyto sfingolipidy jsou lokalizovány v lipidových dvojvrstvách, kde vykonávají četné strukturální funkce.[15,16]

Zvýšení koncentrace ceramidů mění propustnost buněčné membrány, což vede k hromadění LDL cholesterolu na stěnách cév. Tato akumulace zesiluje zánětlivý proces v cévní stěně, což podporuje apoptózu buněk hladkého svalstva cév a endoteliální dysfunkci. Obojí vede k nestabilitě a prasknutí aterosklerotického plátu.[17] Kromě aterosklerotického plaku dochází k této akumulaci v hladkých a kosterních svalech, což narušuje expresi glukózového transportéru typu 4 (GLUT4). To vede ke zhoršenému příjmu glukózy ve svalech a k inhibici syntézy glykogenu.[18] Ceramidy také stimulují apoptózu beta-buněk pankreatu, čímž přímo snižují produkci inzulinu.[19]

Akumulace ceramidů v tkáních má za následek metabolickou dysfunkci v mnoha orgánech a komplikace diabetu. Z dlouhodobého hlediska tyto účinky přispívají k patofyziologii diabetu 2. typu, ztučnění jater, hypertenzi, ateroskleróze a srdečnímu selhání (HF).[20,21]

Faktory ovlivňující koncentraci ceramidů v oběhu

Ceramidy se nacházejí v cirkulujících lipoproteinových částicích. Boon a kol. zjistili téměř rovnoměrné rozložení plazmatických ceramidů napříč částicemi, jako jsou lipoprotein s vysokou hustotou (HDL), lipoprotein s nízkou hustotou (LDL) a lipoprotein o velmi nízké hustotě (VLDL) s celkovým nárůstem ceramidů v plazmě obézních pacientů a pacientů s diabetem 2. typu.[22] Snížení počtu cirkulujících LDL částic, například inhibitory proprotein konvertázya subtilisin/kexin typu 9 (PCSK-9), snížilo koncentrace ceramidů v oběhu.[23] Ukázalo se také, že inhibitory syntézy cholesterolu, jako je rosuvastatin, účinně snižují koncentrace ceramidů v krvi.[24] Úbytek hmotnosti u diabetiků 2. typu změnou stravy nebo užíváním metforminu také vede ke snížení koncentrací ceramidů v plazmě.[22,25]

Ceramidy a kardiovaskulární riziko

Observační studie autorů Hilvo a Laaksonen jasně ukazují souvislost určitých poddruhů ceramidů se zvýšeným rizikem KV příhod.[8,9,26] Tyto studie vedly k vývoji dvou různých rizikových skóre ceramidů. Ceramidy C16:0, C18:0 a C24:1 popisují riziko KV příhod, nezávisle na dalších zjištěných KV rizikových faktorech u pacientů s onemocněním koronárních tepen. Je zajímavé, že souvislost zvýšených koncentrací ceramidu C18:0 se závažnými KV příhodami byla přítomna i u pacientů bez známé ICHS a byla nezávislá i na dalších KV rizikových faktorech.[27] Tyto výsledky byly potvrzeny také ve velké studii na úrovni běžné populace.[13] Poměry ceramidů byly významně spojeny se závažnými nežádoucími kardiovaskulárními příhodami (major adverse cardiovascular event, MACE), definovanými jako akutní infarkt myokardu, koronární revaskularizace (bypass nebo perkutánní intervence), cévní mozková příhoda nebo smrt nezávisle na LDL cholesterolu a konvenčních rizikových faktorech ICHS. Osoby v nejvyšším kvartilu skóre ceramidů měly téměř 1,5násobné riziko MACE, poměr rizik (HR) 1,47 (95% CI, 1,12–1,92).[13]

Predikce úmrtí z KV příčin u pacientů se stabilní ICHS a u pacientů s vyšším rizikem akutního koronárního syndromu (AKS) funguje i u pacientů, kteří jsou již léčeni statiny, a jsou proto potenciálním indikátorem reziduálního rizika.[8]

Další nedávné studie ukazují, že pacienti s nestabilní ICHS vykazovali zvýšené koncentrace ceramidů v plazmě (zejména C16:0, C18:0 a C24:1). Tyto molekuly jsou v současnosti považovány za nově vznikající biomarkery KVO.[9,10]

Současné výsledky nicméně zatím neprokazují kauzalitu. Nabízí se spekulovat, že ceramidy jsou spojeny s náchylností k plakům, protože je známo, že podporují mnoho centrálních aterosklerotických procesů, včetně agregace a absorpce lipoproteinů, zánětu, produkce superoxidových aniontů a apoptózy.[28–30] Několik enzymů syntézy sfingolipidů již bylo testováno jako potenciální cíle léčby, protože inhibice biosyntézy glykosfingolipidů prokazatelně snižuje aterosklerózu u myší.[31,32] Existují také důkazy o funkcích specifických pro délku řetězce ceramidů. Bylo prokázáno, že relativní nárůst druhů s dlouhým řetězcem (C16), ale nikoli druhů s velmi dlouhým řetězcem (C24-24:1), zprostředkovává inzulinovou rezistenci u myší.[33,34] A je zajímavé, že C18:1/C24:1 se chovají odlišně ve srovnání s C18:1/C24:0, což zdůrazňuje, že dochází také k další regulaci.[8] I když zmíněná studie odhaluje souvislost mezi ceramidy a KV příhodami, autoři naznačují směr budoucích výzkumů, které by zjistily, zda lze složení ceramidů ovlivnit a jak by se to mohlo projevit v kardiovaskulárním přínosu.

Testování ceramidů

Dle dostupných informací není pokročilé testování kardiovaskulárního rizika dostupné na většině pracovišť. Mayo Clinic nabízí krevní test, který měří plazmatické ceramidy. Tento test, dostupný prostřednictvím Mayo Clinic Laboratories, pomáhá lékařům předpovídat riziko nepříznivých srdečních příhod u pacientů s pokročilou ICHS a může být užitečný i pro další skupiny rizikových pacientů. Výsledky testu lze použít k lepšímu zacílení léčby a úpravy životního stylu, jako je dieta a cvičení.

Závěr

Ceramidy zlepšují hodnocení rizika aterosklerotických KV onemocnění nad rámec standardních rizikových faktorů. Mechanismy zahrnující souvislost ceramidů s KVO nejsou jisté, ale pravděpodobně zahrnují jejich propojení s lipidovými, aterosklerotickými a zánětlivými metabolickými drahami.[35] Zvýšené skóre ceramidů je robustním prediktorem KVO a závažných KV komplikací v populaci. Různé ceramidy cílí na různé složky lipidomické a zánětlivé kaskády a jejich kombinace do skóre optimalizuje jejich prognostický potenciál a usnadňuje využití lékařem a zjednodušuje interpretaci. Toto odůvodnění nakonec vedlo k použití ceramidového skóre k identifikaci a stratifikaci rizika pacientů s prokázanou, reziduální nebo suspektní ICHS, kteří by mohli vyžadovat agresivnější medikamentózní terapii.

Subklinická ateroskleróza předchází většině KV příhod a její detekce může zlepšit stratifikaci KV rizika. LDL cholesterol je rizikovým faktorem přímo zapojeným do rozvoje aterosklerotického plátu, a proto je důležitým terapeutickým cílem v klinické praxi. Dieta, změny životního stylu a užívání léků mohou vést k významnému a trvalému snížení plazmatických koncentrací LDL cholesterolu. KVO jsou však stále celosvětově jednou z hlavních příčin úmrtí, což naznačuje, že konvenční kontrola LDL cholesterolu nestačí; včasná detekce a prevence nestability aterosklerotického plátu tak může otevřít cestu k významnému snížení progrese onemocnění.

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Přehledový článek | Review article

Sekundárna prevencia ischemickej cievnej mozgovej príhody pri foramen ovale patens

(Secondary prevention of ischemic stroke in patent foramen ovale)

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SÚHRN

Foramen ovale patens (PFO) pravdepodobne zodpovedá za 5 % všetkých ischemických cievnych mozgových príhod (ICMP) a za 10 % ICMP v mladom a strednom veku 18–60 rokov.
Hodnotenie súvisu PFO a kryptogénnej ICMP je vždy len pravdepodobnostné. V súčasnosti sa za najlepší nástroj na hodnotenie tejto pravdepodobnosti považuje systém PASCAL (PFO-Associated Stroke Causal Likelihood). Ide o jednoduchý a efektívny nástroj na selekciu pacientov s najvyšším benefitom z katétrového uzáveru PFO a najnižším rizikom komplikácií. Klasifikácia PASCAL sa stanovuje pomocou RoPE skóre (Risk of Paradoxical Embolism) a echokardiografických rizikových charakteristík PFO – aneuryzmy predsieňového septa a intenzity pravo-ľavého skratu. Pomocou nej možno stanoviť 5 úrovní súvisu PFO s kryptogénnou ICMP – definitívny, vysoko pravdepodobný, pravdepodobný, možný a nepravdepodobný súvis. U pacientov vo veku 18 – 60 rokov s možným alebo pravdepodobným súvisom PFO s kryptogénnou ICMP sa odporúča po vylúčení iných príčin ICMP katétrový uzáver PFO a duálna protidoštičková liečba trvajúca 1 až 6 mesiacov s následnou mono protidoštičkovou liečbou 5 rokov. Z uzáveru PFO najviac profitujú pacienti s aneuryzmou predsieňového septa a/alebo veľkým pravo-ľavým skratom.

Keywords:
Ischemic stroke
PASCAL classification system
Patent foramen ovale
Transcatheter closure

ABSTRACT

Patent foramen ovale (PFO) is probably responsible for 5% of all ischemic strokes and 10% of strokes in young and middle-aged people aged 18–60 years. The assessment of the association between PFO and cryptogenic stroke is always only probabilistic. Currently, the best tool for assessing this probability is the PASCAL system (PFO-Associated Stroke Causal Likelihood).
It is a simple and effective tool for selecting patients who have the highest benefit from transcatheter closure of PFO and the lowest risk of complications. The PASCAL classification is determined using the RoPE score (Risk of Paradoxical Embolism) and echocardiographic risk characteristics of PFO – atrial septal aneurysm and right-left shunt intensity. It can be used to determine five levels of association between PFO and cryptogenic stroke: definite, highly probable, probable, possible, and unlikely association. In patients aged 18–60 years with a possible or probable association of PFO with cryptogenic stroke, transcatheter PFO closure and dual antiplatelet therapy for 1 to 6 months, followed by single antiplatelet therapy for 5 years, is recommended after exclusion of other causes of stroke. Patients with an atrial septal aneurysm and/or a large right-to-left shunt benefit most from PFO closure.

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Foramen ovale patens (PFO) pravdepodobne zodpovedá za 5 % všetkých ischemických cievnych mozgových príhod (ICMP) a za 10 % ICMP v mladom a strednom veku 18 – 60 rokov.[1] Nález PFO u pacientov s ICMP však nemusí znamenať príčinnú súvislosť. PFO môže byť nevinný náhodný „bystander" bez súvisu s ICMP.

U pacientov po ICMP s PFO sa sumárne používa termín „PFO-associated stroke" (mozgová príhoda asociovaná s PFO) nezávisle od príčinnej súvislosti.[1]

Pravdepodobnostné charakteristiky súvisu PFO a kryptogénnej ICMP

U každého pacienta s ICMP je nevyhnutné stanoviť etiológiu príhody. Klasifikačné systémy TOAST, CCS a ASCOD rozlišujú 5 – 6 kategórií ICMP: 1. aterosklerotické (ateroskleróza veľkých artérií), 2. kardioembolické, 3. ochorenia malých ciev, 4. iné identifikovateľné príčiny (nonaterosklerotické arteriopatie vrátane vaskulitíd, hyperkoagulačné stavy), 5. artériová disekcia, 6. kryptogénne príčiny. Pri zvažovaní významu PFO pri ICMP treba v prvom kroku vylúčiť všetky etiológie sub 1. – 5. Po ich vylúčení ostáva 15 – 30 % pacientov s ICMP, ktorej etiológia je kryptogénna.[1] Časť týchto pacientov má PFO, ktoré môže a nemusí súvisieť s ICMP. Úlohou heart-brain teamu je posúdiť pravdepodobnosť súvisu PFO a ICMP a zvoliť najvhodnejšiu sekundárnu prevenciu.

Hodnotenie súvisu PFO a kryptogénnej ICMP je vždy len pravdepodobnostné. Podľa súčasných poznatkov existuje 5 kategórií nálezov, ktoré zvyšujú u pacientov s „PFO-associated stroke" príčinnú pravdepodobnosť:[1]

Aneuryzma predsieňového septa. Aneuryzma je definovaná ako protrúzia septum primum ≥ 10 mm do ľavej alebo pravej predsiene.[2] Ak septum kmitá medzi oboma predsieňami, sčíta sa súčet exkurzií konvexity septa do oboch predsení.

Veľký pravo-ľavý skrat via PFO. Skrat môže byť permanentný alebo len tranzitórny pri Valsalvovom alebo Müllerovom manévri. Müllerov manéver je opak Valsalvovho manévra. Ide o forsírované inspirium pri uzavretých dýchacích cestách (zatvorené ústa a zapchatý nos). Za veľký skrat sa obvykle považuje prienik > 20 mikrobublín do ľavej predsiene do 3 cyklov od opacifikácie pravej predsiene pri transezofagovej echokardiografii (TEE) alebo transtorakálnej echokardiografii (TTE). Pri stredne ťažkom skrate ide o prienik 10 – 20 mikrobublín.[2]

Súčasná žilová trombóza alebo jej rizikové faktory (hyperkoagulačné stavy, dehydratácia, imobilizácia, anamnéza predchádzajúcej flebotrombózy / pľúcnej embolie, anatomické príčiny venóznej kongescie).

Typické teritórium mozgového infarktu – izolované veľké hlboké infarkty, kombinované superficiálne – hlboké infarkty alebo malé distálne artérie (superficiálne infarkty). Pre príčinnú súvislosť PFO nesvedčia lakunárne infarkty.

Absencia rizikových faktorov aterosklerózy (vyšší vek, artériová hypertenzia, diabetes mellitus, hyperlipoproteinémia, fajčenie).

Tabuľka 1 – Kalkulácia skóre RoPE[3]

Charakteristika	Body
Bez anamnézy artériovej hypertenzie	1
Bez anamnézy diabetu mellitu	1
Bez anamnézy CMP alebo TIA	1
Nefajčiar	1
Kortikálny infarkt (CT, MR)	1
Vek (roky): 18 – 29	5
30 – 39	4
40 – 49	3
50 – 59	2
60 – 69	1
≥ 70	0

CMP – cievna mozgová príhoda; CT – počítačová tomografia; MR – magnetická rezonancia; TIA – tranzitórny ischemický atak.

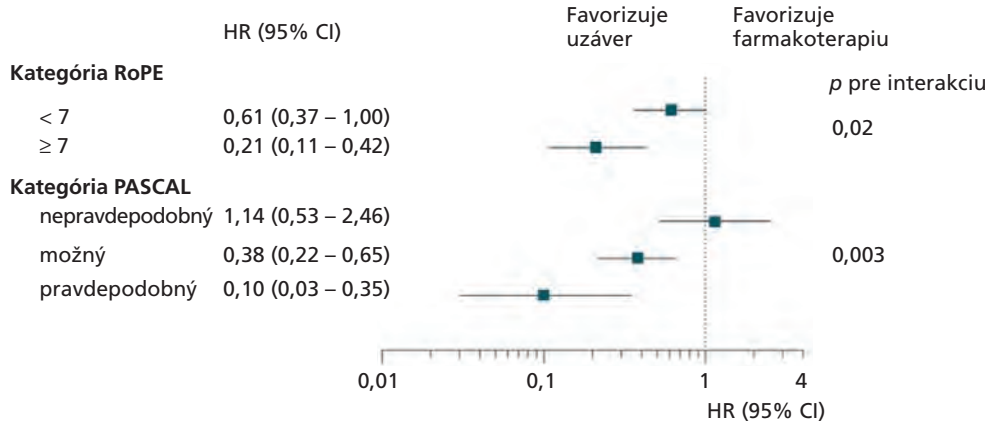
Stratégia hodnotenia príčinného vzťahu PFO a kryptogénnej ICMP

Posúdenie pravdepodobnosti súvisu PFO s ICMP má zásadný terapeutický dopad – zváženie katétrového uzáveru PFO. V súčasnosti sa za najlepší nástroj na hodnotenie príčinného súvisu PFO a za kľúčovú stratégiu na indikáciu katétrovej oklúzie pri „PFO-associated stroke" považuje systém PASCAL (PFO-Associated Stroke Causal Likelihood).[1]

Prvým krokom je stanovenie skóre RoPE (Risk of Paradoxical Embolism) (**tabuľka 1**).[3] Do skóre vstupujú charakteristiky uvedené sub 4. a 5. v predchádzajúcej kapitole.

Tabuľka 2 – Pravdepodobnosť súvisu foramen ovale patens (PFO) a ischemickej mozgovej/retinálnej príhody[1]

Riziko	Charakteristiky	Skóre RoPE	
		Nízke (< 7 bodov)	Vysoké (≥ 7 bodov)
Veľmi vysoké	Zaklinený trombus v PFO	Definitívna	Definitívna
Vysoké	1. Súčasná pulmonálna embolia alebo hlboká žilová trombóza predchádzajúca mozgovej príhode, kombinovaná s: 2a. PFO a aneuryzma predsieňového septa alebo 2b.veľký skrat via PFO	Pravdepodobná	Vysoko pravdepodobná
Intermediárne	1. PFO a aneuryzma predsieňového septa alebo 2. veľký skrat via PFO	Možná	Pravdepodobná
Nízke	Malý skrat via PFO bez aneuryzmy predsieňového septa	Nepravdepodobná	Možná



Obr. 1 – Pomer rizík (HR) rekurentnej ischemickej cievnej mozgovej príhody. Upravené podľa referencie 7.
CI – konfidenčný interval.

Ide o jednoduchý skórovací systém, ktorý hodnotí tzv. priraditeľnú pravdepodobnosť súvisu PFO a ICMP.[3] Čím je skóre vyššie, tým je vyššia pravdepodobnosť. Pravdepodobnosť zvyšujú nízky vek, absencia silných rizikových faktorov aterosklerózy a kortikálna lokalizácia infarktu. Skóre RoPE však nezahŕňa hodnotenie rizikových charakteristík samotného PFO ani viaceré klinické rizikové faktory.

Druhým krokom je posúdenie morfologických a funkčných charakteristík PFO – aneuryzmy predsieňového septa a intenzity pravo-ľavého skratu via PFO. Systém PASCAL preto požaduje vykonanie transtorakálnej alebo transezofagovej echokardiografie s i.v. kontrastnou látkou. Po echokardiografii a kalkulácii skóre RoPE je možné stanoviť 5 úrovní súvisu PFO s kryptogénnou ICMP – definitívny, vysoko pravdepodobný, pravdepodobný, možný a nepravdepodobný súvis (**tabuľka 2**). PASCAL integruje klinické charakteristiky, lokalizáciu mozgového infarktu podľa CT/MR a echokardiografické charakteristiky PFO.

Diskriminačný systém PASCAL možno použiť podľa autorov pri cerebrálnych a retinálnych infarktoch ale predpokladáme, že ho rovnako možno použiť aj pri periférnej embolizácii.[1]

Sekundárna prevencia ICMP pri PFO: katétrový uzáver vs antitrombotická liečba

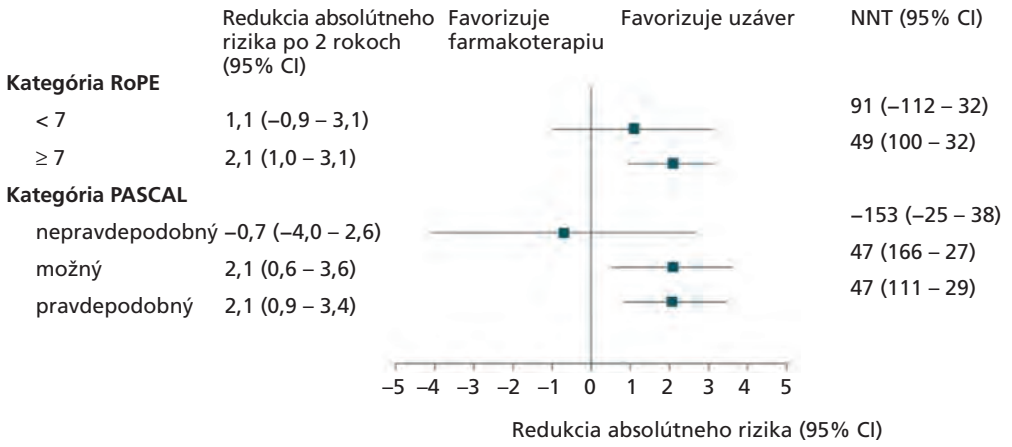
Do úvahy prichádza katétrová a/alebo medikamentózna liečba. Randomizované klinické štúdie (RCT) CLOSE, REDUCE a RESPECT dokázali, že u selektovaných pacientov s PFO a kryptogénnou ICMP je katétrový uzáver PFO + farmakoterapia superiórny oproti samotnej farmakoterapii v sekundárnej prevencii ICMP.[4–6]

Pacienti s „PFO-associated stroke" s aspoň pravdepodobným súvisom podľa systému PASCAL majú najvyššiu mieru profitu z katétrového uzáveru PFO. Tzv. SCOPE Consortium vykonalo analýzu dát všetkých 6 RCT, ktoré porovnávali v rokoch 2000–2017 katétrový uzáver PFO + farmakoterapia vs samotná farmakoterapia u pacientov s kryptogénnou ICMP.[7] Spolu šlo o 3 740 pacientov v štúdiách CLOSURE I, PC Trial, RESPECT, CLOSE, REDUCE a DEFENCE-PFO. Medián sledovania bol 57 mesiacov (interkvartilový rozptyl IQR 24 – 64). Pomer rizík (HR) recidívy ICMP silne závisel od klasifikácie PASCAL. Ak bol súvis nepravdepodobný, tak katétrový uzáver nemal žiadny významný efekt. Naopak, pri možnom a pravdepodobnom súvise bol benefit z katétrového uzáveru signifikantný. Pomery rizík a konfidenčné intervaly sú uvedené na **obrázku 1**. Tie isté tvrdenia v zmysle klinickej významnosti platili pre absolútnu mieru redukcie 2-ročného rizika rekurentnej ICMP (**obr. 2**). Pri nepravdepodobnom súvise nebola žiadna redukcia rizika. Naopak, pri možnom a pravdepodobnom súvise, bola významná redukcia absolútneho rizika.[7]

Často diskutovanou komplikáciou katétrového uzáveru PFO je indukcia fibrilácie predsiení *de novo*. Je zaujímavé, že aj výskyt fibrilácie evidentne súvisel s klasifikáciou PASCAL. Pri nízkej pravdepodobnosti bol výskyt po 45 dňoch od implantácie 4,41% (95% konfidenčný interval [CI] 1,02 % až 7,8 %), pri možnom súvise 1,53 % (95% CI 0,33 % až 2,72 %) a pri pravdepodobnom súvise bol výskyt najnižší 0,65% (95% CI –0,41 % až 1,71 %).[7]

Metaanalýza zistila, že prínos katétrového uzáveru PFO je veľmi heterogénny podľa klasifikácie PASCAL. Asi 15% pacientov, t.j. ktorých príčinný súvis bol nepravdepodobný, nemalo žiadny benefit. Podľa metaanalýzy nemožno predpokladať prínos katétrového uzáveru PFO u pacientov bez aneuryzmy predsieňového septa, bez skratu alebo len s malým skratom a zároveň s rizikovými faktormi aterosklerózy (skóre RoPE < 7). Naproti tomu pacienti s vysoko rizikovým PFO a absenciou rizikových faktorov aterosklerózy (skóre RoPE ≥ 7) mali redukciu relatívneho rizika až 90 %. Navyše pacienti, ktorí mali najvyšší benefit v zmysle redukcie rizika recidívy ICMP, mali zároveň aj najnižšie riziko fibrilácie predsiení.[7]

European Stroke Organisation (ESO) odporúča klasifikačný systém PASCAL na selekciu pacientov na oklúziu PFO. U pacientov vo veku 18 – 60 rokov s možným alebo pravdepodobným súvisom PFO s kryptogénnou ICMP od-



Obr. 2 – Redukcia absolútneho rizika rekurentnej ischemickej cievnej mozgovej príhody. Upravené podľa referencie 7. NNT – number needed to treat (počet pacientov potrebných na liečbu).

porúča katétrový uzáver + protidoštičkovú liečbu po vylúčení iných príčin ICMP.[2] Čiže už prítomnosť aneuryzmy predsieňového septa alebo veľkeho skratu via PFO bez akýchkoľvek iných podmienok považuje ESO za indikáciu katétrovej oklúzie PFO, lebo títo pacienti spĺňajú minimálne možný súvis PFO s kryptogénnou ICMP (pozri **tabuľku 2**).

Odporúčania ESO sú v zhode s odporúčaniami iných mienkotvorných spoločností – American Academy of Neurology 2020, Society for Cardiovascular Angiography & Interventions 2022, American Heart Association/American Stroke Association 2021.[8–10]

Ak je súvis PFO a ICMP nepravdepodobný, potom možno len podľa konsenzu expertov ESO (ale nie podľa výsledkov RCT) u pacientov vo veku 18 – 60 rokov odporučiť oklúziu PFO pri „rôznych kombináciách" situácií, poukazujúcich na vysokú pravdepodobnosť kauzality: venózny tromboembolizmus v blízkom časovom okne od indexovej ICMP, pľúcna artériová hypertenzia, sleep apnoe syndróm alebo iné hypoxemické stavy, asociované s PFO, Valsalvov manéver pred vznikom ICMP, anamnéza prolongovanej imobilizácie, aktuálny letecký transport, venózna trombofília, dekompresná choroba potápačov, syndróm platypnoe–ortodeoxia alebo Eustachova chlopňa. Čo znamenajú „rôzne kombinácie", nie je definované. U týchto pacientov je podľa nášho názoru potrebné individuálne a veľmi dôsledné zváženie indikácie uzáveru PFO „heart-brain teamom".

Pre optimálne načasovanie uzáveru PFO po ICMP nie je dostatočná medicína dôkazov. Podľa konsenzu panelu expertov ESO sa odporúča do 6 mesiacov, avšak podľa možnosti čím skôr.[2]

Vekový strop 60 rokov pre oklúziu PFO je arbitrárny, lebo nie je dostatok dát u pacientov nad 60 rokov. Štúdia DEFENCE-PFO totiž ako jediná RCT zahrnula aj pacientov starších ako 60 rokov (aj to len malý počet 34 pacientov).[11]

Po uzávere PFO sa odporúča duálna protidoštičková liečba (DAPT) 1 – 6 mesiacov s následnou mono protidoštičkovou liečbou 5 rokov.[2]

Optimálna medikamentózna liečba u pacientov s „PFO-associated stroke" nie je známa.[2] Zatiaľ žiadna RCT nedokázala superioritu antikoagulancií (vrátane direktných antikoagulancií [DOAC]) oproti protidoštičkovej liečbe. Metaanalýza štyroch RCT PICSS, CLOSE, NAVIGATE ESUS a RE-SPECT ESUS (vrátane 2 štúdií s DOAC), ktorá zahrnula 1 518 pacientov, dokázala nesignifikantný trend v prospech antikoagulancií.[1,12,13] ESO aktuálne neodporúča pri „PFO-associated stroke" dlhodobú antikoagulačnú liečbu, ak nie je pre ňu iná indikácia.[2]

U pacientov vo veku 18 – 60 rokov s možným alebo pravdepodobným súvisom PFO pretrváva neistota ohľadne benefitu a rizík pri porovnaní oklúzie PFO a dlhodobej antikoagulačnej liečby. Napriek tomu ESO odporúča uzáver PFO + protidoštičkovú liečbu vzhľadom na: 1. kumulatívne riziko veľkého krvácania pri antikoagulačnej terapii, 2. superioritu uzáveru PFO oproti antitrombotickej liečbe v RCT.[2]

U pacientov, ktorí odmietnu uzáver PFO, odporúča panel expertov ESO individuálnu voľbu antitrombotickej terapie v zmysle metaanalýz RCT a observačných štúdií. Antikoagulačná terapia má oproti protidoštičkovej liečbe nižšie očakávané riziko recidívy ICMP ale možný nárast veľkých krvácaní v dlhodobom horizonte.[2]

Treba uviesť, že všetky vyššie uvedené stanoviská sa týkajú len pacientov po ICMP, ale nie po TIA (tranzitórny ischemický atak). Pre „PFO-associated TIA" nie je totiž dostatok dôkazov, lebo pacientov s TIA zahrnula len štúdia CLOSURE.

Záver

Pacienti s „PFO-associated stroke" sú heterogénna populácia. Klasifikácia PASCAL je jednoduchý a efektívny nástroj na selekciu pacientov s najvyšším benefitom z katétrového uzáveru PFO a najnižším rizikom komplikácií. U pacientov vo veku 18-60 rokov s možným alebo pravdepodobným súvisom PFO s kryptogénnou ICMP sa odporúča katétrová oklúzia a protidoštičková liečba.

Umelá inteligencia bola použitá na jazykovú redakciu a kontrolu zrozumiteľnosti textu. Autor plne zodpovedá za obsah.

Prehlásenie
Rukopis nebol a nebude zadaný na uverejnenie v inom časopise.

Konflikt záujmov
Autor deklaruje, že nemá žiadny konflikt záujmov.

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Přehledový článek | Review article

Testosterone Replacement Therapy and Cardiovascular Safety: A Paradigm Shift in Cardiological Practice

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SOUHRN

Úvod: Hypogonadismus je častým, avšak často přehlíženým stavem u mužů s diabetem 2. typu, obezitou a kardiovaskulárním onemocněním. Nízké koncentrace testosteronu jsou spojeny s nepříznivým kardiometabolickým profilem a zvýšenou mortalitou. Testosteronová substituční terapie (TRT) byla však po dlouhou dobu vnímána s obavami z možného zvýšení kardiovaskulárního rizika, a to především na základě observačních studií s významnými metodologickými omezeními.
Cíl: Cílem tohoto přehledového článku je shrnout současné poznatky o vztahu testosteronu, hypogonadismu a kardiovaskulárního rizika, objasnit patofyziologické mechanismy působení testosteronu na kardiovaskulární systém a diskutovat klinický význam recentních důkazů o bezpečnosti testosteronové substituce, se zvláštním důrazem na studii TRAVERSE.
Metody: Byla provedena analýza dostupných observačních studií, metaanalýz a randomizovaných klinických studií hodnotících vztah hypogonadismu, testosteronové substituční terapie a kardiovaskulárních příhod se zaměřením na studii TRAVERSE jako dosud největší randomizovanou studii hodnotící kardiovaskulární bezpečnost TRT.
Výsledky: Hypogonadismus je vysoce prevalentní u mužů s diabetem 2. typu a obezitou a podílí se na rozvoji inzulinové rezistence, endoteliální dysfunkce, aterogenního lipidového profilu a chronického zánětu. Dřívější obavy z kardiovaskulárního rizika TRT vycházely převážně z observačních studií s významnými metodologickými limity. Randomizovaná studie TRAVERSE prokázala, že testosteronová substituční terapie u mužů s hypogonadismem a vysokým kardiovaskulárním rizikem nebyla spojena se zvýšeným výskytem závažných kardiovaskulárních příhod.
Závěr: Studie TRAVERSE poskytuje dosud nejpřesvědčivější důkaz o kardiovaskulární bezpečnosti testosteronové substituční terapie při správné indikaci a monitoraci. Hypogonadismus by měl být vnímán jako klinicky významný kardiometabolický rizikový faktor, nikoli pouze jako okrajový endokrinologický problém. Testosteronová substituce může být bezpečně zvažována i u pacientů se stabilním kardiovaskulárním onemocněním, avšak vyžaduje individualizovaný přístup a mezioborovou spolupráci.

ABSTRACT

Background: Hypogonadism is a common but frequently underdiagnosed condition in men with type 2 diabetes, obesity, and cardiovascular disease. Low testosterone levels are associated with an adverse cardiometabolic profile and increased mortality. However, testosterone replacement therapy (TRT) has long been considered potentially harmful with respect to cardiovascular risk, largely based on observational studies with significant methodological limitations.
Aim: To summarize current evidence on the relationship between testosterone, hypogonadism, and cardiovascular risk, to describe the pathophysiological mechanisms linking testosterone deficiency to cardiovascular disease, and to discuss the clinical implications of recent evidence on the cardiovascular safety of testosterone replacement therapy, with particular emphasis on the TRAVERSE trial.
Methods: A narrative review of observational studies, meta-analyses, and randomized controlled trials evaluating hypogonadism, testosterone replacement therapy, and cardiovascular outcomes was performed, with a focus on the TRAVERSE trial as the largest randomized study specifically designed to assess the cardiovascular safety of TRT.

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Results: Hypogonadism is highly prevalent in men with type 2 diabetes and obesity and contributes to insulin resistance, endothelial dysfunction, an atherogenic lipid profile, and chronic inflammation. Earlier concerns regarding cardiovascular risk associated with TRT were mainly derived from observational studies with substantial methodological limitations. The randomized TRAVERSE trial demonstrated that testosterone replacement therapy in men with hypogonadism and high cardiovascular risk was not associated with an increased incidence of major adverse cardiovascular events.
Conclusion: The TRAVERSE trial provides the most robust evidence to date supporting the cardiovascular safety of testosterone replacement therapy when appropriately indicated and monitored. Hypogonadism should be regarded as a clinically relevant cardiometabolic risk factor rather than a marginal endocrine condition. Testosterone replacement therapy may be safely considered in men with stable cardiovascular disease, emphasizing the need for individualized decision-making and interdisciplinary collaboration.

Introduction

Testosterone has traditionally been viewed primarily as a hormone responsible for male sexual function and reproductive health. However, this perspective does not reflect the current understanding of its complex biological effects. Testosterone plays a significant role in regulating energy metabolism, body composition, insulin sensitivity, inflammatory pathways, and the function of the cardiovascular system. Low testosterone levels have been associated with an increased incidence of obesity, type 2 diabetes (T2DM), metabolic syndrome, and atherosclerotic cardiovascular diseases.[1]

Hypogonadism, defined by a combination of low testosterone levels and the presence of clinical symptoms, is a common but often unrecognized condition in men with high cardiometabolic risk. Numerous observational studies have demonstrated that low testosterone concentrations are associated with increased overall and cardiovascular mortality, independent of age and traditional risk factors.[2] Nevertheless, testosterone replacement therapy (TRT) was for a long time approached with caution, especially within the cardiology community, primarily due to concerns about a potential increase in cardiovascular risk. These concerns stemmed from several observational studies published in the first half of the previous decade, which suggested a possible association between TRT and a higher incidence of major cardiovascular events.[3,4] As a result, there was significant therapeutic inertia and reluctance to indicate TRT in patients with existing cardiovascular disease or a high risk of its development. However, in recent years, there has been a substantial shift in understanding, thanks to new, methodologically robust clinical studies that allow for a more objective assessment of the cardiovascular safety of TRT.[5,6]

The aim of this review article is to summarize current evidence on the relationship between testosterone, hypogonadism, and cardiovascular risk, to clarify the pathophysiological mechanisms by which testosterone affects the cardiovascular system, and to critically evaluate the available data on the safety of testosterone replacement therapy, with particular emphasis on the recent randomized TRAVERSE trial, which represents a significant milestone in this field.

Prevalence of hypogonadism in patients with type 2 diabetes and obesity

Hypogonadism occurs significantly more often in men with type 2 diabetes and obesity than in the general population. Studies have confirmed that hypogonadism affects approximately 30–50% of men with T2DM, with prevalence increasing alongside greater insulin resistance and visceral obesity.[7–9]

Obesity, especially central obesity, plays a key role in the pathogenesis of hypogonadism. Increased aromatase activity in adipose tissue leads to higher conversion of testosterone to estradiol, which subsequently suppresses the hypothalamic–pituitary–gonadal axis. At the same time, insulin resistance, chronic subclinical inflammation, and altered gonadotropin secretion develop. This condition is often referred to as functional hypogonadism and is typical for patients with metabolic syndrome, T2DM, and cardiovascular disease.[10]

From a clinical perspective, the high prevalence of low testosterone in men with prediabetes is also significant. Men with impaired glucose tolerance or elevated fasting glucose have significantly lower total testosterone levels compared to normoglycemic individuals, even after adjusting for age and body weight. Thus, prediabetes represents a period during which hypogonadism and cardiometabolic risk mutually reinforce each other.[11]

Based on these findings, in 2018 the American Diabetes Association included recommendations to measure testosterone levels in men with diabetes and clinical symptoms of hypogonadism.[12] This fact underscores the growing importance of hypogonadism not only as an endocrinological issue but also as a cardiometabolic problem that should be considered in cardiology practice as well.

Understanding primary, secondary, and functional hypogonadism in clinical practice

From a clinical and pathophysiological standpoint, hypogonadism is a heterogeneous condition that can be divided into three basic categories: primary, secondary, and functional hypogonadism.

Primary (hypergonadotropic) hypogonadism is characterized by primary testicular failure, in which testosterone production decreases despite elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Typical causes include genetic syndromes, testicular

damage due to infection, radiotherapy or chemotherapy, and advanced age.[13]

Secondary (hypogonadotropic) hypogonadism arises from regulatory disorders at the level of the hypothalamus or pituitary gland. It is characterized by low or inappropriately normal levels of gonadotropins in the presence of low testosterone. This type of hypogonadism may occur with structural lesions of the central nervous system, hyperprolactinemia, or in connection with chronic systemic diseases.[13]

In addition to these classic forms, clinical practice is increasingly encountering so-called **functional hypogonadism**, which has a different pathophysiology and clinical consequences. Functional hypogonadism, often referred to as late-onset hypogonadism (LOH), is a potentially reversible condition closely associated with obesity, insulin resistance, chronic subclinical inflammation, and metabolic syndrome. Unlike primary and secondary hypogonadism, there is no structural disorder of the hypothalamic–pituitary–gonadal axis. Functional hypogonadism represents the most common form of low testosterone in men with type 2 diabetes and cardiovascular disease and is also a key link between hypogonadism and increased cardiovascular risk.[1,14]

Metabolic effects of testosterone and insulin resistance

One of the key mechanisms linking hypogonadism to cardiovascular risk is insulin resistance. Testosterone plays a crucial role in body fat distribution and the maintenance of muscle mass. Low levels of testosterone are associated with an increase in visceral adipose tissue, which is metabolically active and produces a range of pro-inflammatory mediators that promote insulin resistance.[15,16]

At the cellular level, testosterone increases the expression of the insulin receptor, insulin receptor substrate (IRS-1), and glucose transporter GLUT4 in muscle tissue, thereby improving insulin-dependent glucose uptake. Conversely, testosterone deficiency is associated with reduced muscle mass and a relative increase in fat mass, which further worsens insulin sensitivity and contributes to the development of hyperglycaemia.[17]

Testosterone, lipid metabolism, and atherogenic profile

Testosterone affects lipid metabolism through both direct and indirect mechanisms. Low levels of testosterone are associated with an atherogenic lipid profile characterized by elevated triglycerides, non-HDL cholesterol, and an unfavorable triglyceride/HDL ratio, which is considered a marker of insulin resistance and cardiovascular risk. An important aspect is the fact that testosterone influences not only individual lipid fractions but the entire spectrum of atherogenic lipoproteins. Non-HDL cholesterol, which includes all apoB-containing lipoproteins, is considered a better predictor of cardiovascular risk than LDL cholesterol alone, especially in patients with diabetes and hypertriglyceridemia. Hypogonadism is associated with increased levels of non-HDL cholesterol and remnant lipoproteins, which further promote atherogenesis.[18]

Vascular effects of testosterone and endothelial function

Testosterone has direct effects on the arterial wall. Both experimental and clinical studies have shown that testosterone acts as a vasodilator, primarily by stimulating the synthesis of nitric oxide (NO) in the endothelium and through a direct relaxing effect on vascular smooth muscle.[19,20] Low testosterone levels are associated with endothelial dysfunction, increased arterial stiffness, and impaired coronary vasodilation.[21,22] Endothelial dysfunction represents an early step in the development of atherosclerosis and is an independent predictor of cardiovascular events. Thus, hypogonadism may indirectly contribute to the progression of the atherosclerotic process even in its early stages.

Inflammation, immune response, and atherogenesis

Chronic low-grade inflammation is a key pathophysiological mechanism linking obesity, insulin resistance, and atherosclerosis. Hypogonadism is associated with elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF) and interleukin-6 (IL-6), as well as higher C-reactive protein (CRP) concentrations.[23]

In contrast, testosterone predominantly exerts immunomodulatory and anti-inflammatory effects. Testosterone replacement therapy has been associated in several studies with reduced levels of inflammatory markers and an improved inflammatory profile in patients with hypogonadism. These changes may contribute to slowing the progression of atherosclerosis and stabilizing atherosclerotic plaques.[23]

Electrophysiology and arrhythmogenesis

Testosterone influences ventricular repolarization. Hypogonadism is associated with a prolonged QTc interval, which is a known risk factor for Torsades de Pointes (TdP) and sudden cardiac death. It has been demonstrated that testosterone replacement therapy (TRT) shortens the QTc interval, suggesting a protective effect against ventricular arrhythmias through modulation of hERG potassium channels.[24–26]

Hematopoiesis and coagulation

The most common adverse effect of testosterone replacement therapy (TRT) is erythrocytosis. Testosterone stimulates the production of erythropoietin (EPO) and suppresses hepcidin, which increases iron utilization and the formation of red blood cells. Elevated hematocrit increases blood viscosity, which theoretically raises the risk of stasis and thrombosis. This is the main mechanism by

which the potential risk of venous thromboembolism (VTE) is explained.[27] In addition, testosterone has been reported to reduce platelet aggregation and the density of thromboxane A2 receptors, which could theoretically compensate for the risk of increased viscosity.[28]

The main systemic changes in untreated hypogonadism and after TRT, along with their cardiological implications, are summarized in **Table 1**.

Controversies surrounding testosterone replacement therapy and cardiovascular risk

Despite the growing evidence of the unfavorable cardiometabolic profile associated with hypogonadism, testosterone replacement therapy (TRT) was, for a long time, considered potentially risky in terms of cardiovascular safety. These concerns significantly influenced clinical practice, particularly in the field of cardiology, leading to caution or outright rejection of TRT for patients with existing cardiovascular disease.

A major turning point in the perception of TRT came after the publication of several observational studies in 2013–2014. The most frequently cited work is a retrospective analysis published by Vigen et al.,[3] which reported a higher incidence of a composite cardiovascular endpoint in men with low testosterone who had undergone coronary angiography and were treated with testosterone, compared to those untreated. Shortly thereafter, Finkle et al.[4] published a database-based analysis suggesting an increased risk of non-fatal myocardial infarction after initiating TRT, particularly in older men and in patients with pre-existing cardiovascular disease.

These studies attracted media and professional attention and led to regulatory actions, including warnings from the U.S. FDA (Food and Drug Administration) regarding the potential cardiovascular safety of testosterone products.[29] However, it is important to emphasize that both studies had significant methodological limitations that significantly constrain the interpretation of their findings. In contrast to the FDA, the EMA (European Medicines Agency) adopted a more cautious approach. After reviewing the available evidence, it stated that the data on increased cardiovascular risk are inconsistent, and the interpretation of these studies is therefore not definitive.[30]

The retrospective observational design represents the main weakness of most studies that highlighted a possible increase in cardiovascular risk associated with TRT. These works lacked randomization, testosterone treatment was not standardized, and the precise definition of hypogonadism was often missing. In many cases, it was unclear whether patients achieved physiological testosterone levels, or what their adherence to treatment was.

Another major issue was patient selection. The observed cohorts often included men with very high cardiovascular risk, polymorbid patients, and individuals shortly after acute cardiovascular events. These factors alone substantially increase the risk of cardiovascular events and can lead to so-called "confounding by indication", where treatment is prescribed to patients with poorer overall health status.

In addition, analytical errors were subsequently identified in some studies. In the case of the work by Vigen et al., the original results were subsequently corrected, with data reanalysis leading to a change in the direction of some conclusions. These circumstances further undermined the robustness of the initial claims about the increased cardiovascular risk of TRT.

In the following years, a number of meta-analyses were published that attempted to summarize the available data on the cardiovascular safety of testosterone replacement therapy. The results of these studies were heterogeneous and often depended on the included trials, duration of follow-up, and the definition of the assessed endpoints.[31–33] However, a common feature of most of these analyses was the absence of long-term randomized

Table 1 – Overview of the main systemic changes in untreated hypogonadism and after testosterone replacement therapy (TRT) and their possible cardiological implications

Parameter	Untreated hypogonadism (deficiency)	After testosterone replacement therapy (TRT)	Cardiology implications of TRT
Glucose metabolism[15–17]	Insulin resistance, high risk of progression to type 2 diabetes, higher HbA_{1c}	Increased insulin sensitivity, reduction in HbA_{1c}, potential remission of prediabetes	Reduced glucotoxicity and lower risk of microvascular complications
Body composition[16]	Accumulation of visceral fat, sarcopenia (loss of muscle mass), reduced basal metabolic rate	Reduction in fat mass (especially visceral), increase in lean (muscle) mass	Improved metabolic profile, reduced joint load, increased physical fitness
Inflammation[23]	Elevated pro-inflammatory cytokines (TNF , IL-6, CRP); chronic low-grade inflammation	Suppression of pro-inflammatory cytokines; reduction of systemic inflammation	Atherosclerotic plaque stabilization; reduced endothelial dysfunction
Hematopoiesis[27,28]	Frequent mild anemia (normocytic, normochromic); reduced oxygen-carrying capacity	Stimulation of erythropoiesis; increased hemoglobin and hematocrit	Improved tissue oxygenation (potential benefit in heart failure), but risk of hyperviscosity with overtreatment
Mental health and vitality[1]	Fatigue, reduced motivation, depression, lethargy ("metabolic fatigue")	Improvement in mood, energy, motivation, and libido	Better adherence to lifestyle measures (exercise, diet)

studies with sufficient statistical power to allow a definitive conclusion.

The ambiguous data led to significant caution in clinical practice regarding the indication of TRT, especially in patients with cardiovascular disease or those at high risk of developing it. This approach was understandable in the context of the "primum non nocere" principle; however, it may also have resulted in undertreatment of symptomatic patients with hypogonadism and in overlooking its potential impact on cardiometabolic health.

The lack of prospective randomized trials primarily designed to assess the cardiovascular safety of testosterone replacement therapy represented a major gap in the available evidence. This gap was filled only recently by the TRAVERSE study, which was specifically designed to assess the cardiovascular risks of TRT in men with hypogonadism and high cardiovascular risk.[34]

TRAVERSE Study

A major breakthrough in the assessment of the cardiovascular safety of testosterone replacement therapy was brought by the randomized, placebo-controlled TRAVERSE trial (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men), published in 2023.[6] The study was specifically designed to evaluate the relationship between TRT and the incidence of major adverse cardiovascular events in men with hypogonadism and concomitantly increased cardiovascular risk – precisely the population that has been the subject of the greatest concerns and controversies in clinical practice.

Study design and population characteristics

TRAVERSE was a multicenter, randomized, double-blind, placebo-controlled non-inferiority trial. The study enrolled 5,246 men aged 45–80 years with clinically and laboratory-confirmed hypogonadism, defined by two morning total testosterone levels below 300 ng/dl (≈10.4 nmol/l) and the presence of typical symptoms. The average BMI was 35 kg/m²; 70% had type 2 diabetes mellitus, and 90% had hypertension and dyslipidemia. Participants also had either established cardiovascular disease or were burdened with multiple cardiovascular risk factors.

Patients were randomized to daily application of transdermal 1.62% testosterone gel or placebo. The dose was titrated to maintain testosterone levels within the physiological range (350–750 ng/dl ≈ 12.1–26.0 nmol/l), which distinguishes this study from earlier works where supraphysiological peaks occurred, especially with injectable forms of therapy. The average duration of treatment was 21.7 months, and the mean follow-up period was 33 months.

Primary cardiovascular outcomes

The primary safety endpoint was the first occurrence of a major adverse cardiovascular event (MACE), defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The study clearly met the criteria for non-inferiority: the primary endpoint occurred in 7% of patients in the testosterone-treated group and 7.3% in the placebo group (hazard ratio 0.96; 95% CI 0.78–1.17; p <0.001 for non-inferiority). The results were consistent across each component of the primary endpoint and did not provide evidence of increased risk for cardiovascular mortality, myocardial infarction, or stroke. These data fundamentally refute concerns raised by earlier observational studies, especially the works by Vigen and Finkle.[3,4]

Following the publication of the TRAVERSE results, the FDA updated the labeling information for testosterone products and removed the boxed warning regarding increased cardiovascular risk.[35]

Secondary outcomes and safety signals

Secondary analyses provided clinically relevant details. Overall mortality and the need for coronary revascularization were comparable between the testosterone and placebo groups. On the other hand, a higher incidence of atrial fibrillation was observed in the testosterone-treated group (3.5% vs. 2.4%). There was also a slightly higher occurrence of acute kidney injury (2.3% vs. 1.5%) and pulmonary embolism (0.9% vs. 0.5%). Although the absolute differences were small, these findings highlight the necessity for careful monitoring, particularly of hematocrit and hydration, during testosterone therapy.[12]

The main cardiovascular outcomes and safety signals from the TRAVERSE study are summarized in **Table 2**.

Table 2 – TRAVERSE – overview of results and safety signals

Outcome	Testosterone vs. placebo	Hazard ratio (HR) / Result	Interpretation
All-cause mortality	Similar	0.96	TRT does not increase mortality.
Coronary revascularization	Similar	NS	No difference in the frequency of coronary revascularizations (PCI/CABG)
Atrial fibrillation (AFib)	3.5% vs. 2.4%	Increased risk	Higher incidence of atrial fibrillation; clinical vigilance recommended
Acute kidney injury (AKI)	2.3% vs. 1.5%	Increased risk	Statistically significant, but the absolute difference is small (<1%).
Pulmonary embolism (PE)	0.9% vs. 0.5%	Increased risk	Likely related to erythrocytosis

CABG – coronary artery bypass graft; HR – hazard ratio; NS – not statistically significant; PCI – percutaneous coronary intervention; TRT – testosterone replacement therapy.

Efficacy and non-sexual benefits of treatment

The TRAVERSE trial also provided data on the efficacy of TRT in non-sexual domains. Testosterone therapy led to the correction of anemia in hypogonadal men, which may be clinically significant especially for patients with heart failure or coronary artery disease. Metabolic benefits were further confirmed in substudies and related works, including the T4DM study, which showed that long-term TRT can slow or prevent the progression from prediabetes to type 2 diabetes.[36]

Summary of the significance of the TRAVERSE trial

The TRAVERSE trial provides the highest-quality and most robust evidence to date supporting the cardiovascular safety of testosterone replacement therapy when appropriately indicated, dosed, and monitored. Its findings offer a solid foundation for rational, individualized decision-making on TRT in men with hypogonadism and high cardiovascular risk within a multidisciplinary care framework.

TRAVERSE study in the context of current meta-analyses and consensus evidence

The most recent synthesis of available data on the cardiovascular safety of testosterone replacement therapy is presented in an updated systematic review and meta-analysis of placebo-controlled randomized clinical trials published in 2024, which now includes the results of the TRAVERSE study and thus allows its conclusions to be assessed in the context of the entire spectrum of randomized evidence. Out of a total of 3,615 identified works, 106 studies were included in the analysis, encompassing 8,126 men treated with testosterone and 7,310 patients in the placebo group.[5]

When evaluating major adverse cardiovascular events (MACE), no differences were found between the testosterone-treated group and the placebo group. An increased incidence of nonfatal arrhythmias and atrial fibrillation was observed only in a single study,[6] which had cardiovascular safety as its primary endpoint; however, this finding was not confirmed when all other studies were included in the meta-analysis. Additionally, no association was found between endogenous testosterone levels and the occurrence of atrial fibrillation after adjustment for confounding factors. The authors therefore conclude that testosterone replacement therapy is not associated with an increased risk of major adverse cardiovascular events.

Clinical implications: management of a cardiology patient with suspected hypogonadism

Although there is currently no standalone Czech guideline specifically addressing routine testosterone screening in men with type 2 diabetes, clinical practice in the Czech Republic is aligned with European and U.S. recommendations, including guidance from the European Association of Urology (EAU), the European Society of Endocrinology (ESE), and the American Diabetes Association (ADA), and applies a pragmatic symptom-based case-finding approach.

From a practical perspective, cardiologists should consider hypogonadism particularly in men with type 2 diabetes, obesity, metabolic syndrome, or chronic cardiovascular disease who also report symptoms such as persistent fatigue, reduced exercise tolerance, loss of muscle strength, or impaired quality of life. Alternatively, the Aging Males' Symptoms (AMS) questionnaire may be used to screen for symptoms suggestive of hypogonadism. In these cases, an appropriate first step may be a screening of morning total testosterone levels, followed by referral to an endocrinology evaluation if low values are repeatedly found.

For cardiologists, it is particularly important to recognize that the presence of stable cardiovascular disease by itself does not represent a contraindication to testosterone replacement therapy, provided that the treatment is indicated based on clinical symptoms and laboratory-confirmed hypogonadism. The TRAVERSE study was conducted precisely in a population of men with high cardiovascular risk, and it did not demonstrate any increase in the incidence of major cardiovascular events with testosterone treatment.

If TRT is initiated in a patient with cardiovascular risk factors, it should be accompanied by a clear monitoring plan. The goal is to maintain testosterone within the physiological range while minimizing specific risks. A practical monitoring framework (frequency of follow-ups and action thresholds) is provided in **Table 3**.[15]

Table 3 – Monitoring patients on TRT: what to monitor and when to intervene

Parameter	Frequency	Target / Action threshold	Rationale
Hematocrit	Baseline, 3–6 months, then annually	Hold therapy / reduce dose if **>54%**	Minimize hyperviscosity and thromboembolic risk (PE/DVT)
Prostate (PSA)	Baseline, 3–6 months, then annually	Refer to urology if PSA increase **>1.4 ng/mL/year**	Prostate safety surveillance (TRT does not cause cancer, but may unmask occult carcinoma).
Blood pressure	Every visit	Monitor for elevation	TRT may cause fluid retention / BP changes.
Lipid/Glucose	Annually	Monitor improvement	TRT improves metabolic profile (lower LDL, HbA_{1c}).
Cardiac rhythm	Every visit	Screening for atrial fibrillation	Signal from TRAVERSE for AFib; check pulse, obtain ECG if suspected.

AFib – atrial fibrillation; BP – blood pressure; DVT – deep vein thrombosis; $HbA1_c$ – glycated hemoglobin; LDL – low-density lipoprotein; PE – pulmonary embolism; PSA – prostate-specific antigen; TRT – testosterone replacement therapy.

Specific population: patients with heart failure

Men with heart failure represent a specific and clinically significant subgroup in whom hypogonadism occurs much more frequently than in the general population. Available data show that low testosterone levels can be found in approximately 30–50% of men with chronic heart failure, with prevalence increasing with disease severity. In this population, hypogonadism is associated with a worse prognosis, higher mortality, more frequent rehospitalisations, and reduced exercise tolerance.[37]

From a pathophysiological perspective, testosterone deficiency contributes to the development of muscle weakness, sarcopenia, and cardiac cachexia, all of which significantly affect the patient's functional status and quality of life. Low testosterone levels are also associated with insulin resistance, anemia, and inflammatory activation, which may contribute to the progression of heart failure independently of left ventricular ejection fraction.

Smaller randomized trials in stable patients with heart failure suggest that testosterone replacement therapy may lead to improvements in functional capacity, as assessed for example by the six-minute walk test or peak oxygen consumption (peak VO), as well as improvements in NYHA functional class. These benefits are typically not reflected in an improved ejection fraction, but are likely mediated by enhancements in peripheral muscle function, metabolic efficiency, and the anabolic state of the patient.[38–40]

However, increased caution is necessary. Testosterone can promote sodium and water retention, increasing the risk of volume overload, especially in patients with unstable or advanced heart failure. For this reason, testosterone replacement therapy should not be initiated in patients with decompensated heart failure or in NYHA class IV. In stable patients (NYHA I–III), TRT may be considered on an individual basis, ideally as part of multidisciplinary care approach and with careful clinical monitoring.[12]

Conclusion

Current evidence has fundamentally changed the perspective on the cardiovascular safety of testosterone replacement therapy (TRT). Hypogonadism is common in men with type 2 diabetes, obesity, and cardiovascular disease, and often represents part of a broader cardiometabolic phenotype associated with insulin resistance, dyslipidemia, endothelial dysfunction, and chronic inflammation.

Earlier concerns about the cardiovascular harms of TRT were based primarily on observational studies with significant methodological limitations. The TRAVERSE trial demonstrated the non-inferiority of TRT compared to placebo in the incidence of major adverse cardiovascular events (MACE). This represents a major shift in cardiology practice: stable cardiovascular disease itself is not a barrier to rationally guided TRT in symptomatic men with laboratory-confirmed hypogonadism.

When properly indicated and monitored, TRT in selected patients can provide not only non-sexual benefits (such as correction of anemia and improvement of metabolic profile) but also clinically meaningful improvements in vitality, functional capacity, and overall quality of life. In cases of stable heart failure (NYHA I–III), TRT may individually contribute to improved exercise tolerance and quality of life, while in decompensated heart failure (NYHA IV), TRT should not be initiated and its indication should be postponed until the condition is stabilized. In functional hypogonadism, TRT should be part of comprehensive care, including weight reduction and multidisciplinary collaboration.

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Přehledový článek | Review article

Saphenous Vein Graft in Coronary Artery Bypass Grafting (CABG) Surgery: Combating Thrombosis, Intimal Hyperplasia and Atherosclerosis in Maintaining Long-Term Graft Patency

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SOUHRN

Cíl: Vzhledem k zájmu o používání safény jako štěpu pro koronární bypass (coronary artery bypass graft, CABG) bylo cílem této studie získat další poznatky umožňující zdokonalit léčebný postup, a zabránit tak dalšímu poškození žilního štěpu safény (saphenous vein graft, SVG).
Metody: Tento komplexní přehled popisuje současné standardy, aktuální postupy při léčbě a výsledky koronárního bypassu s použitím SVG; zároveň představuje řadu metod a nových postupů s potenciálem zlepšit jak bezprostřední, tak dlouhodobou průchodnost štěpu, přináší poznatky o patofyziologii poškození SVG i jak mohou tyto poznatky ukázat na nové možnosti léčby případného poškození.
Výsledky: Odhojení SVG může být výsledkem trombózy, intimální hyperplazie a aterosklerózy. K akutní trombóze dochází v důsledku hyperkoagulability, patologie v oblasti spojky nebo z technických důvodů, jako jsou poškození štěpu a defekty anastomózy. Hlavními patofyziologickými faktory v rozvoji intimální hyperplazie jsou migrace a proliferace buněk hladkého svalstva cév (vascular smooth muscle cell, VSMC). Prvním krokem, který celý proces spouští, je dysfunkce nebo poškození endotelu při poškození cév. Tento přehled popisuje postupy od odebrání SVG až po jeho implantaci včetně výběru štěpu, způsobu jeho odběru, jeho důkladného vyšetření, konzervaci a implantaci štěpu s použitím speciálních pomůcek a vybavení. Přehled rovněž seznamuje čtenáře s farmakoterapií v různých stadiích implantace SVG s cílem zabránit rozvoji neointimální hyperplazie a její případné léčby.
Závěr: Zlepšení dlouhodobé průchodnosti SVG vyžaduje propojení optimalizovaných chirurgických postupů, přísných farmakoterapeutických režimů a nových doplňkových strategií. Pro snížení počtu případů odhojení SVG a delší přežívání pacientů s CABG je naprosto nezbytné pokračovat v translačním výzkumu v oblasti cévní biologie a biotechnologií.

Keywords:
Atherosclerosis
Coronary artery bypass graft surgery
Coronary artery disease
Graft patency
Intimal hyperplasia
Saphenous vein graft failure

ABSTRACT

Aim: Gaining further insight to enhance treatment to stop the progression of saphenous vein grafts (SVG) disease, given the interest in using saphenous veins as grafts in coronary artery bypass graft (CABG).
Methods: This comprehensive review synthesizes the current standards, contemporary treatment, and results related to coronary arterial bypass grafting using SVG, exploring a variety of methods and developments that have the potential to improve both immediate and long-term graft patency. Understanding pathophysiology of SVG disease and where it leads to suggest potential new treatments for the condition.
Results: Failure of SVG can be the results of thrombosis, intimal hyperplasia, and atherosclerosis. Acute thrombosis caused by hypercoagulability, conduit-related pathology, or technical such as graft trauma and anastomotic defects. The migration and proliferation of vascular smooth muscle cells (VSMCs) in the tunica intima layer is the main pathophysiology of intimal hyperplasia. Endothelial dysfunction or damage from vascular injury is the first step that sets off the process. This review narrates SVG graft-to-implant strategies that include graft selection, harvesting technique, careful graft assessment techniques, graft preservation, and technology-assisted techniques. The review also covers pharmacotherapy that targets distinct stages of the SVG condition to prevent and treat neointimal hyperplasia.
Conclusion: Improving long-term SVG patency requires integration of optimized surgical techniques, rigorous pharmacological regimens, and novel adjunctive strategies. Continued translational research into vascular biology and biotechnology is crucial to reducing SVG failure rates and improving patient survival after CABG.

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Introduction

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide, with an estimated 17.9 million deaths annually, representing nearly one-third of all global deaths.[1] The global economic impact of CAD is immense, driven by costs of hospitalizations, loss of productivity, and long-term management.[2] Despite extensive progress in preventive cardiology—including statins, antihypertensive therapy, antiplatelets, and smoking cessation—CAD incidence continues to rise in parallel with aging populations, sedentary lifestyles, obesity, and diabetes.[3]

For more than four decades, coronary artery bypass grafting (CABG) has been the gold standard of surgical revascularization for patients with advanced or complex CAD, particularly those with left main stenosis, three-vessel disease, diffuse atherosclerosis, or diabetes mellitus.[4] The SYNTAX, FREEDOM, and EXCEL trials have consistently demonstrated the survival and repeat-revascularization advantage of CABG over percutaneous coronary intervention (PCI) in these populations.[5–7] While PCI offers less invasiveness, CABG remains superior for long-term durability of revascularization.

The choice of conduit is central to CABG outcomes. The left internal mammary artery (LIMA) to the left anterior descending artery (LAD) is universally considered the "gold standard" anastomosis, with patency rates exceeding 90% at 10–15 years.[8] However, the saphenous vein graft (SVG) continues to be the most widely used conduit globally because of its availability, length, ease of harvest, and ability to reach multiple distal coronary targets. In fact, more than 70–80% of CABG procedures worldwide still use SVGs in some capacity.[9]

Yet, SVGs represent the Achilles heel of CABG. While LIMA durability is excellent, SVG patency rates drop steeply over time—10–15% occlude within the first year, and up to 50% fail within 10 years.[10,11] The main drivers are acute thrombosis, intimal hyperplasia, and accelerated atherosclerosis. These processes are influenced by a combination of patient-related risk factors (e.g., diabetes, smoking), technical issues (harvesting trauma, preservation), and biological mechanisms (endothelial dysfunction, smooth muscle proliferation, oxidative stress).[12]

Understanding the mechanisms of SVG failure has driven numerous innovations, from no-touch harvesting techniques, advanced preservation solutions, and pharmacological strategies (dual antiplatelet therapy, statins, PCSK9 inhibitors), to novel adjunct technologies such as external stents and bioengineered grafts.[13–16] Yet, despite these efforts, SVG disease remains a major determinant of long-term CABG outcomes.

This review synthesizes recent global evidence on SVG disease, covering pathophysiology, risk factors, surgical strategies, pharmacological therapy, technological adjuncts, outcomes, and future perspectives, with a focus on both international data and regional experiences.

Historical perspective of CABG And SVG

The history of CABG is rooted in the pioneering work of René Favaloro at the Cleveland Clinic in the late 1960s, who performed the first successful CABG using autologous saphenous vein grafts. Early results were revolutionary, providing surgical treatment for previously untreatable coronary artery disease. During the 1970s and 1980s, CABG expanded worldwide, rapidly becoming one of the most common performed major surgeries. In those early decades, SVGs were the default conduit. They were easy to harvest, versatile in length, and familiar to surgeons. Initial short-term outcomes were excellent, with high rates of symptom relief and survival improvement. However, as long-term angiographic and clinical follow-up became available, it was increasingly evident that SVGs had limited durability compared with arterial conduits.[17]

By the 1980s, observational angiographic studies showed SVG patency rates of ~70% at 5 years, dropping to ~50% at 10 years, while LIMA patency exceeded 90% at 10 years. This realization spurred greater interest in arterial grafting strategies, particularly the right internal mammary artery (RIMA), radial artery, and gastroepiploic artery.[18]

Nevertheless, the SVG remained indispensable. Arterial conduits have limitations: the RIMA increases the risk of sternal wound complications, particularly in diabetic and obese patients; the radial artery is susceptible to vasospasm and is not suitable in all patients; and the gastroepiploic artery is technically demanding and infrequently used. Moreover, many patients requiring CABG have multivessel disease involving 3–4 targets, for which available arterial conduits are often insufficient. Consequently, current CABG strategies reflect a combination approach: a LIMA-to-LAD graft for durability, supplemented with SVGs to other coronary territories. Even in advanced centres advocating multi-arterial grafting, SVGs remain necessary in the majority cases.[19,20]

Pathophysiology of saphenous vein graft disease

SVG failure is a multifactorial, time-dependent process, classically divided into three phases:

1. Early failure (0–1 month): Acute thrombosis

Acute thrombosis occurs in ~10–15% of grafts. The most common causes were technical issues (conduit trauma, poor anastomosis), hypercoagulability, and low-flow states. The mechanism of acute thrombosis involved venous endothelium, graft that accustomed to low-pressure circulation undergoing injury under arterial pressure. The process causes endothelial denudation, platelet activation, and fibrin deposition (**Fig. 1**).[21,22]

2. Intermediate failure (1–12 months): Intimal hyperplasia

Intimal hyperplasia is the pathognomonic lesion of SVG disease. It represents the intermediate phase of graft failure, occurring after the initial risk of acute thrombosis but preceding late atherosclerosis. The process is primarily triggered by endothelial injury sustained during vein harvesting and implantation into the arterial circulation. The venous conduit, originally adapted to a low-pressure, low-flow environment, is suddenly exposed to arterial shear stress and pulsatile pressure, re-

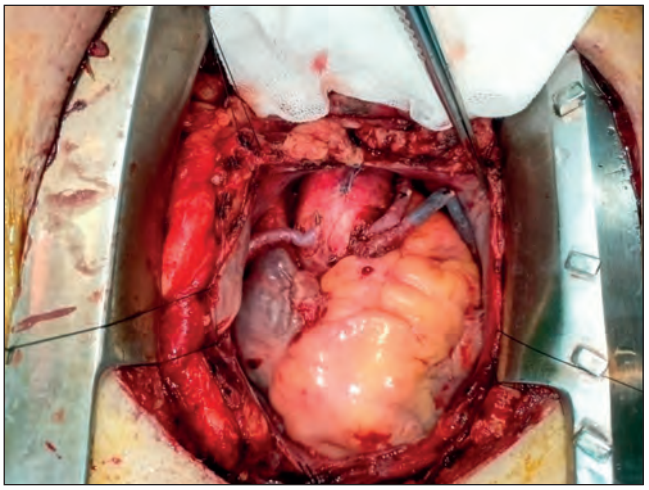

Fig. 1 – Aortocoronary bypass, operative field showing a saphenous vein graft with visible intraluminal thrombus.

sulting in endothelial denudation, platelet activation, and a cascade of inflammatory and proliferative signals. These early insults initiate vascular remodelling within the graft wall.[23]

Following endothelial injury, vascular smooth muscle cells (VSMCs) migrate from the media to the intima and undergo phenotypic modulation from a contractile to a synthetic state. In this state, VSMCs proliferate and secrete components of the extracellular matrix (ECM)—notably collagen, elastin, and proteoglycans—resulting in progressive intimal thickening. This neointimal formation narrows the graft lumen and increases vascular stiffness. Hemodynamic factors such as disturbed flow and oscillatory shear stress further promote VSMC proliferation and extracellular matrix deposition, reinforcing a cycle of maladaptive remodelling. Experimental and clinical studies have confirmed that the extent of intimal hyperplasia correlates strongly with graft stenosis and mid-term occlusion rates.[24,25]

Although intimal hyperplasia rarely causes acute graft occlusion, it establishes the pathological substrate for accelerated atherosclerosis within the vein graft. Thus, intimal hyperplasia is not only a hallmark lesion but also a pivotal transitional stage linking early mechanical and endothelial injury to the eventual development of graft atherosclerosis.

3. Late failure (>1 year): Accelerated atherosclerosis

Unlike native coronary atherosclerosis, SVG atherosclerosis is diffuse, concentric, and prone to plaque rupture. Histological features in SVG atherosclerosis are large lipid cores, thin fibrous caps, heavy inflammatory infiltrates. Late SVG failure clinically often presents as unstable angina, myocardial infarction, or distal embolization.[26]

Molecular mechanisms

The process of SVG disease begins with endothelial dysfunction, characterized by reduced bioavailability of nitric oxide (NO)—a key vasodilator—and concomitant upregulation of endothelin-1, reactive oxygen species (ROS), and other oxidative mediators. This imbalance leads to vasoconstriction, loss of anti-thrombotic surface properties, and promotion of a pro-inflammatory vascular milieu. The dysfunctional endothelium triggers inflammatory activation, during which cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) are released, inducing expression of adhesion molecules (VCAM-1, ICAM-1, and E-selectin). These molecules facilitate leukocyte adhesion, transmigration, and accumulation within the graft wall, initiating a chronic inflammatory response.[22,23]

Subsequently, vascular smooth muscle cells (VSMCs) within the media undergo phenotypic switching from a quiescent, contractile state to a synthetic phenotype capable of proliferation, migration into the intima, and secretion of extracellular matrix (ECM) proteins. This adaptive yet maladaptive remodelling response contributes to intimal hyperplasia, the hallmark intermediate lesion in SVG disease.[25]

Persistent oxidative stress further accelerates vascular injury: oxidized low-density lipoprotein (ox-LDL) particles are taken up by macrophages to form lipid-laden foam cells, which drive the development of atheromatous plaques within the graft. Over time, inflammatory cells and macrophages secrete matrix metalloproteinases (MMPs) that degrade ECM components such as collagen and elastin, leading to thinning of the fibrous cap and plaque instability, predisposing the vein graft to rupture and occlusive thrombosis.[23,27]

Hemodynamic factors

Veins are adapted to low-pressure and low-flow states. When saphenous veins are transposed into the arterial circulation, they are suddenly exposed to a hemodynamic environment for which they are not physiologically adapted. Normally accustomed to low-pressure and low-shear conditions, the venous endothelium experiences substantial mechanical stress when subjected to arterial shear and pulsatile pressure. Recent evidence demonstrates that this abrupt exposure induces endothelial injury and apoptosis mediated by mechanosensitive pathways such as the FGL2/FcγRIIB signaling cascade, leading to endothelial denudation and dysfunction. In addition, increased tangential stress and wall tension provoke maladaptive remodelling characterized by medial hypertrophy, smooth muscle cell activation, and extracellular matrix accumulation.[24,28]

Biomechanical and immunological studies further show that turbulent flow patterns at the graft–artery anastomosis amplify endothelial activation and inflammatory signaling, promoting smooth muscle migration and intimal hyperplasia. This combination of mechanical overload and inflammation drives concentric wall thickening and progressive luminal narrowing, setting the stage for vein graft disease. Together, these findings underscore that early hemodynamic mismatch—specifically increased shear stress, pulsatile arterial pressure, and disturbed flow—is the primary initiator of the structural and biological deterioration that ultimately compromises long-term graft patency.[29]

Risk factors for saphenous vein graft (SVG) failure

SVG patency is determined by a complex interaction between patient-specific, graft-specific, and surgical/technical factors. Understanding these risk factors enables surgeons to identify high-risk patients, tailor surgical strategies, and optimize postoperative care.

1. Patient-related risk factors

Diabetes mellitus

Chronic hyperglycaemia induces endothelial dysfunction, oxidative stress, and accumulation of advanced glycation end products, all of which accelerate smooth muscle proliferation and intimal hyperplasia. Histopathologic evidence further supports these findings, as patients with type II diabetes undergoing CABG exhibit characteristic structural changes within SVGs—such as intimal fibrosis, vacuolization of endothelial and smooth muscle cells, and pre-existing microvascular injury. Although the direct impact of these alterations on long-term graft patency remains to be fully clarified, they likely contribute to the heightened vulnerability of diabetic SVGs to early and progressive failure.[30]

Dyslipidaemia

Elevated low-density lipoprotein (LDL) cholesterol and persistent hypertriglyceridemia promote lipid infiltration and foam-cell formation within the SVG intima, accelerating graft atherosclerosis and luminal loss. Experimental and animal data show very rapid lipid accumulation and foam-cell development in veins graft exposed to hypercholesterolaemia, supporting a direct biological effect of circulating atherogenic lipoproteins on graft walls.[23,31]

Smoking

Smoking induces a cascade of vascular insults that directly compromise SVG integrity and long-term patency. Tobacco exposure increases oxidative stress and systemic inflammation, reduces endothelial nitric oxide bioavailability, and enhances platelet activation and aggregation, creating a prothrombotic and pro-inflammatory milieu within the graft. Clinical and observational studies consistently demonstrate that active smoking is associated with reduced graft patency and higher rates of adverse cardiovascular outcomes after CABG.[32]

Chronic kidney disease (CKD)

Chronic kidney disease promotes a pro-atherothrombotic vascular phenotype through persistent endothelial dysfunction (reduced NO signalling, impaired endothelial repair), chronic inflammation, and accelerated medial/intimal calcification. These mechanisms plausibly render saphenous vein grafts more susceptible to early neointimal hyperplasia and late atherosclerotic failure. Consistent with this biology, lower preoperative eGFR independently predicts higher SVG failure, contemporary reviews further confirm CKD as an adverse determinant of long-term post-CABG outcomes.[33,34]

Age and sex

Advanced age is associated with impaired saphenous vein graft (SVG) survival following coronary artery bypass grafting (CABG). Aging leads to progressive endothelial dysfunction characterized by decreased nitric oxide (NO) bioavailability, increased oxidative stress, and reduced endothelial regenerative capacity. Studies of human saphenous veins have shown that older donor age correlates with decreased endothelium-dependent relaxation and heightened susceptibility to intimal hyperplasia.[35]

Sex-based differences further influence graft outcomes. Several large observational cohorts have reported that women experience lower SVG patency and higher mortality after CABG compared with men. The underlying factors is poorly understood but this disparity maybe attributed in part to smaller coronary and conduit vessel diameters in women, which predispose to early graft thrombosis and competitive flow phenomena.[36–38]

Hypertension

Elevated and fluctuating arterial pressures expose the venous conduit—naturally adapted to low-pressure environments—to excessive hemodynamic stress, leading to endothelial injury, vascular smooth muscle cell proliferation, and maladaptive intimal hyperplasia. These processes accelerate graft wall remodelling and lumen narrowing. A recent retrospective study demonstrated that poor blood pressure control was significantly associated with lower long-term SVG patency following CABG, underscoring the role of hypertension as an independent predictor of graft failure. Chronic wall tension and disturbed flow patterns also promote atherogenesis and medial degeneration, further compromising graft durability.[39]

2. Graft-related risk factors

Vein quality

Pre-existing structural abnormalities in the saphenous vein, such as varicosities, thin vessel walls, or small luminal diameters, have been consistently associated with early thrombosis and late stenosis following coronary artery bypass grafting (CABG). These morphological changes reflect chronic venous remodelling and loss of medial smooth muscle integrity, predisposing the conduit to endothelial disruption and impaired adaptation to arterial pressure once grafted. Recent study reported that SVGs with diameters ≤2 mm exhibited markedly reduced long-term patency—approximately 55% at 10 years—compared with larger conduits (>2 mm, ≈88%), highlighting vessel size as a critical determinant of graft survival. Proper intraoperative vein assessment and selective harvesting of morphologically healthy segments are therefore essential to optimize long-term SVG performance.[23,40]

Conduit length and flow

Long and tortuous grafts are vulnerable mechanical-habitat risks: excessive graft length and tortuosity predispose the conduit to kinking, focal flow separation, and turbulence, which in turn amplify shear-stress abnormalities, endothelial dysfunction and focal intimal hyperplasia. Although conduit geometry is recognized as an im-

portant determinant of flow dynamics, recent literature highlights an ongoing evidence gap regarding the direct association between graft length and long-term patency. The specific contribution of graft length remains poorly defined and warrants further investigation. Preoperative ultrasonographic mapping of the great saphenous vein—assessing diameter, wall quality, and tortuosity—therefore remains a crucial step to optimize conduit selection, reduce wound morbidity, and potentially enhance long--term graft patency.[41,42]

3. Technical and perioperative factors

Harvesting technique

According to recent studies, conventional saphenous vein harvesting that strips the perivascular tissue and subjects the conduit to unregulated, high-pressure distension causes immediate structural and biological injury—mechanical trauma and endothelial denudation reduce nitric oxide bioavailability and expose subendothelial matrix, promoting platelet adhesion and acute thrombosis, while wall injury triggers vascular smooth muscle cell activation and intimal hyperplasia that accelerate graft stenosis. In contrast, "no-touch" or pedicled harvesting—where the vein is removed with its surrounding adipose and adventitia intact and handled minimally—has been associated with improved graft morphology and superior long-term patency, albeit at the cost of higher leg-wound morbidity in several series and registries. Endoscopic vein harvesting (EVH) reduces donor-site complications and wound morbidity compared with open techniques and is widely adopted, but operator technique matters: poorly performed EVH or excessive traction/distension during EVH can still produce endothelial injury.[43,44]

Therefore, many centres now emphasise a "soft-touch" conduit preparation strategy—defined by atraumatic handling, avoidance of high-pressure distension (use of low-pressure or no-pressure spasmolytic techniques), preservation of perivascular tissue when feasible, and standardised intraoperative graft assessment—to minimise endothelial and adventitial injury and optimise SVG performance. Contemporary guideline reviews and consensus statements recommend these pragmatic steps while acknowledging ongoing debates (and recent trial data) about the balance between patency gains and wound complications, and call for standardisation of harvesting and preparation protocols to improve reproducibility of outcomes.[45]

Preservation solution

Conventional storage media such as plain saline or heparinized autologous blood expose harvested SVG to a non-physiologic, unbuffered environment that promotes acidosis, oxidative stress, endothelial cell loss and impaired vasoreactivity, and several translational and clinical reports have linked saline storage to worse markers of endothelial injury. To mitigate these effects, investigators have evaluated a spectrum of preservation strategies such as simple buffered isotonic solutions and modified physiologic buffers that better maintain pH and ionic balance or specially formulated endothelial-damage-inhibitor (EDI) solutions such as DuraGraft that supply antioxidants and protective ions. Some others studied hospital-compounded recipes (for example the GALA solution: glutathione, L-ascorbic acid, L-arginine) tested in retrospective cohorts and early trials and organ-preservation-derived solutions (e.g., HTK/TiProtec-derivatives) that were developed to limit cold ischemia–reperfusion injury and have shown endothelial protection in experimental models. However, the clinical evidence remains heterogeneous and adequately powered trials with angiographic or functional graft--patency and hard clinical endpoints are limited.[46]

Anastomotic technique

Poorly constructed anastomoses—particularly those performed under excessive tension, with graft redundancy, twisting, or kinking—create local hemodynamic disturbances that manifest as flow separation, recirculation zones, and regions of low wall shear stress, which in turn accelerate early thrombosis and graft failure. Technical errors such as malalignment, adventitial injury, or mis--angle at the heel or toe of the graft further impair endothelial integrity and trigger platelet aggregation. Recent hemodynamic studies and clinical data confirm that non-physiologic geometry at the anastomosis correlates strongly with early occlusion risk. Competitive flow in terminal anastomoses of saphenous vein grafts, grafts with suboptimal configuration and moderate native coronary stenosis showed higher occlusion rates.[47,48]

In the realm of graft configurations, direct (single, end-to-side) SVG anastomoses remain the most common but may be vulnerable to competitive flow when the native target vessel stenosis is only moderate. Sequential grafting—where a single vein conduit supplies several distal anastomoses—has been shown to improve flow efficiency and reduce conduit waste in multivessel disease,

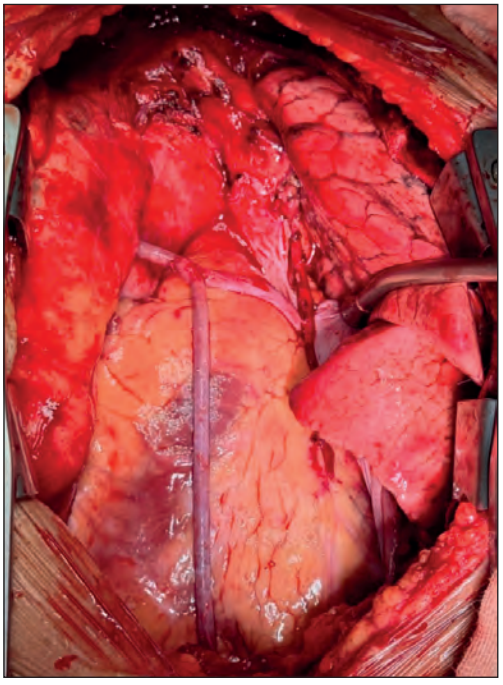

Fig. 2 – Y-graft of SVG in CABG.

though it demands technical precision. Composite graft configurations (e.g., Y- or T-grafts using a conduit such as the SVG or internal thoracic artery) are gaining interest for their potential to optimize inflow supply, reduce aortic manipulation and adapt to extended revascularization strategies. Recent found that a no-touch SVG used as a Y-composite graft demonstrated non-inferior one-year morphologic outcomes compared to an aortocoronary SVG configuration (**Fig. 2**).[49]

These findings reinforce that meticulous surgical technique—ensuring tension-free routing, minimal redundancy, proper alignment, anastomotic angle optimization, and configuration choice tailored to target morphology—is essential to minimize early thrombosis and preserve long-term SVG patency.

On-pump vs off-pump CABG

Off-pump coronary artery bypass grafting (OPCAB) may be associated with lower SVG patency when performed in the hands of less experienced surgeons or at lower-volume centres, although when performed in high-volume centres with experienced teams the long-term outcomes may be equivalent to on-pump CABG (ONCAB). Several randomised controlled trials (RCTs) and meta-analyses have shown that OPCAB is linked to a higher risk of graft occlusion with one updated meta-analysis reporting a relative risk (RR) of 1.40 (95% CI 1.23–1.59) for SVG occlusion in OPCAB vs ONCAB.[50]

The difference has been attributed in part to the technical challenges of performing distal anastomoses on a beating heart, potential incomplete revascularisation, fewer grafts per patient, and the steeper learning curve of OPCAB. Observational data also suggest that centres and surgeons with lower OPCAB volumes have worse outcomes and higher reintervention rates. On the other hand, recent analyses suggest that in centres with established OPCAB expertise and high annual volumes the SVG patency and overall outcomes approximate those of ONCAB.[51]

Therefore, when selecting OPCAB for a patient, the surgeon's experience and institutional volume should be taken into accounts, and intraoperative verification of graft quality (e.g., transit-time flow measurement) becomes particularly important to mitigate the higher risk of SVG failure.

Minimally invasive CABG and robotic CABG

In minimally invasive coronary artery bypass surgery, the use of SVG has demonstrated acceptable patency rates comparable to those achieved with conventional sternotomy approaches. Angiographic and computed tomography follow-up studies report early to mid-term SVG patency of approximately 80–90%, indicating that minimally invasive access does not compromise graft durability when proper harvesting and anastomotic techniques are applied.[52]

In robotic-assisted coronary artery bypass grafting (CABG) and totally endoscopic coronary artery bypass (TECAB), reported graft patency outcomes are generally favourable, primarily reflecting the routine use of the left internal mammary artery (LIMA) to the left anterior descending artery. The well-established durability of the LIMA conduit substantially influences overall patency results in these procedures. However, evidence specifically evaluating SVG patency in robotic CABG and TECAB remains limited. Although available data suggest acceptable early and mid-term SVG patency, further systematic follow-up is required to more clearly characterize long-term SVG outcomes in this minimally invasive context.[53]

Surgical strategies to improve SVG patency

Refinements in surgical technique are among the most effective interventions for improving SVG durability.

1. Vein harvesting techniques

Current studies emphasize that no touch harvesting is superior in terms of patency compared to conventional open harvesting. Endoscopic vein harvesting reduces wound complications and improves cosmetic. Early reports raised concerns about inferior patency, but other contemporary studies suggest equivalent outcomes when performed by experienced teams.

2. Preservation solutions

Traditionally, SVGs are stored in saline or blood during surgery. However, these solutions fail to prevent ischemic and oxidative injury. Buffered solutions (e.g., DuraGraft, Custodiol) provide antioxidant protection and maintain endothelial nitric oxide synthase (eNOS) activity, resulting in lower intimal hyperplasia.

3. Anastomotic technique

Sequential anastomosis can improve flow and reduce competitive flow, though carries risk of compromising multiple territories if the proximal graft fails. Individual grafting provides greater security but may sacrifice flow efficiency. Meticulous construction with avoidance of kinking, excessive tension, and precise suturing remains critical. Additionally, when a graft is anastomosed to a coronary vessel with only moderate stenosis (i.e., less-tight native flow resistance), the phenomenon of competitive flow from the native coronary reduces graft flow, increases the pulsatility index (PI) and retrograde flow fraction, and thereby augments the risk of early graft occlusion.

From a haemodynamic standpoint, computational modelling has demonstrated that increasing competitive flow (i.e., decreasing the severity of native stenosis) leads to lower time-averaged wall shear stress (TAWSS) and higher oscillatory shear index (OSI) in the graft, conditions known to promote endothelial dysfunction and subsequent occlusion.

4. Intraoperative graft flow measure

Intraoperative graft flow measurement has become a cornerstone in ensuring graft quality during CABG, especially for assessing the viability of SVGs and arterial grafts before chest closure. One of the most widely used tools is transittime flow measurement (TTFM), which quantifies the mean graft flow (MGF), calculates a pulsatility index (PI), assesses diastolic filling (DF) and may even incorporate advanced waveform analysis such as fast Fourier transform (FFT) to detect subtle anomalies.

Yet, intraoperative graft flow measurement should be considered a complement to, rather than a replacement for, surgical judgment. Surgeons are advised to measure flow under stable hemodynamic conditions, interpret the full waveform shape (not just single values), and revise grafts when persistently low flow, high PI or reverse flow are detected.

4. On-pump vs off-pump CABG

To improve SVG patency, the choice between on-pump and off-pump techniques should be guided by surgical expertise and patient characteristics. In the case of off--pump CABG, special attention should be paid to maintaining hemodynamic stability, avoiding target-vessel motion, and minimizing conduit trauma—factors that may explain the slightly higher graft failure rates when done in lower-volume centres. Indeed, a 2022 meta analysis found that overall graft patency and SVG patency were significantly *poorer* in off-pump vs on-pump CABG (RR ~1.32 for any graft occlusion; RR ~1.37 for SVG occlusion). Meanwhile other trial found *non-inferiority* of off-pump vs on-pump graft patency when performed by experienced surgeons.[50,54]

5. External stents and conduit supports

External stenting places a flexible scaffold around the SVG to limit outward dilation, reduce wall tension, and thereby blunt the mechanotransduction cascade that drives smooth muscle cell proliferation and intimal hyperplasia. Early human and preclinical data consistently show that external support produces more uniform lumens, less focal dilation, and significantly smaller intimal-hyperplasia areas and intima–media thickness versus unsupported SVGs. However, the translation from favourable vessel remodelling to hard clinical benefit remains incompletely proven.[55]

6. Other surgical innovations

Composite grafting — for example an internal mammary artery-based Y-graft that supplies both the LAD and an attached SVG — offers important technical and physiologic advantages: it reduces aortic manipulation (fewer proximal aortic anastomoses), provides competitive LIMA flow that can pressurize downstream conduits, and can improve run-off and shear stress patterns in the distal coronary bed. Using arterial inflow (RITA or LIMA) to supply an SVG limb (composite-grafts), which may improve SVG behaviour by exposing it to arterial nitric-oxide production and more favourable hemodynamic.[56]

Pharmacological therapies for SVG patency

While surgical technique is crucial, pharmacotherapy is equally important in preventing graft failure. Drugs act on the thrombotic, inflammatory, and proliferative pathways that drive SVG disease.[57]

1. Antiplatelet therapy

In clinical practice following CABG, aspirin remains the foundation of antiplatelet therapy: begin as soon as haemostasis is secured (ideally within 6 hours) to reduce early graft thrombosis, and plan for long-term daily aspirin to minimise graft occlusion and major adverse cardiac events (MACE). For patients at higher risk of SVG failure (e.g., multiple SVGs, poor graft flow, or concomitant acute coronary syndrome), consider dual antiplatelet therapy (DAPT) with aspirin + a $P2Y_{12}$ inhibitor for 12 months, provided bleeding risk is acceptable. For example, the DACAB trial showed that aspirin + ticagrelor improved SVG patency and reduced MACE up to five years versus aspirin alone.[57]

On the other hand, the POPular CABG trial found no significant improvement in SVG occlusion at 1 year and an increased bleeding trend with DAPT. Consequently, the decision to use DAPT should be individualised: assess patient-specific factors (bleeding risk, graft count, graft flow quality, comorbidities) and aim for shared decision-making, monitoring carefully for bleeding. In lower-risk patients (stable CAD, single SVG, no ACS), monotherapy with aspirin may suffice; in higher-risk cases the incremental benefit of DAPT may justify the bleeding risk, provided close follow-up is ensured. Regular review of antiplatelet strategy and adjustment based on renal function, haemodynamic changes, and concurrent therapies is advised.[58]

2. Lipid-Lowering Therapy

Statins

Intensive statin therapy has biological plausibility for protecting SVGs. Statins lower LDL-C and exert pleiotropic actions (anti-inflammatory, antithrombotic, improved endothelial function) that reduce lipid deposition, blunt expansive remodelling and intimal hyperplasia in veins conduits. Observational and randomized data have linked statin use and lower LDL levels with less SVG disease and smaller intimal hyperplasia on imaging. However, some findings imply that early LDL lowering alone may be insufficient to prevent the multifactorial process of early SVG failure (thrombosis, technical factors) and that benefits on atherosclerotic progression may emerge later.[59]

PCSK9 inhibitors

Trials testing intensive LDL lowering beyond statins (PCSK9 inhibitors) have directly addressed whether deeper LDL reduction with adding evolocumab to background statin therapy did not show a reduction in early SVG failure.[60]

3. Anticoagulation

Routine postoperative warfarin or other full-dose oral anticoagulation solely to improve SVG patency is not recommended because randomized trials and pooled analyses have not shown a consistent patency advantage that outweighs the clear increase in bleeding risk. When anticoagulation is required (for AF, mechanical valves, LV thrombus, etc.), clinicians must explicitly plan antithrombotic combinations because adding antiplatelet therapy increases bleeding risk. In exceptional situations (extensive endarterectomy, early graft thrombosis), consider individualized short-term anticoagulation with careful risk–benefit assessment and local multidisciplinary input.[61]

Future research direction

Anti-proliferative such as sirolimus analogues or other anti-proliferative drugs have been investigated for preventing intimal hyperplasia, but more research is needed to evaluate its potensial for SVG disease.[62] Polymeric external stents, in some recent studies show reduced intimal hyperplasia, but though long-term clinical benefit remains questionable.[63]

Bioengineered conduits, developed using decellularized scaffolds or synthetic polymers seeded with endothelial or stem-derived vascular cells, are under active preclinical and early translational evaluation. Current studies show encouraging biomechanical strength, biocompatibility, and the ability to remodel and integrate into host tissue, but long-term durability and thrombosis resistance remain key hurdles before clinical adoption. Emerging tissue-engineered vascular grafts (TEVGs) must demonstrate not only safety and manufacturability at scale, but patency rates at least equivalent to, if not better than SVG to become a viable alternative for CABG in routine practice.[64]

Conclusion

SVG failure remains a critical limitation of CABG. Although numerous innovations show promising potential to improve saphenous vein graft patency, current evidence consistently demonstrates that the most decisive determinants of long-term outcomes remain the fundamentals: high-quality surgical technique, thorough preoperative optimization, and appropriate, guideline-directed pharmacotherapy. In other words, while adjunctive technologies may enhance results in the future, the cornerstone of successful CABG today continues to rely on meticulous operative practice and comprehensive medical management.

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There is no conflict of interest

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Ethical statement
The work was carried out in compliance with the Declaration of Helsinki.

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Přehledový článek | Review article

Growth Differentiation Factor-15 and Cardiovascular Diseases: Biology, Clinical Implications, and Future Outlook

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SOUHRN

Růstový diferenciační faktor-15 (growth differentiation factor-15, GDF-15) je cytokin reagující na stres a spojovaný se zánětem, oxidačním stresem, metabolickou dysfunkcí a s poškozením tkání. V posledních 20 letech získal postavení významného biomarkeru u několika kardiovaskulárních onemocnění, jako jsou srdeční selhání, ischemická choroba srdeční, akutní koronární syndromy, vaskulární plicní onemocnění, arytmie, a u kardiometabolických onemocnění. Zvýšené hodnoty cirkulujícího GDF-15 předpovídají mortalitu, hospitalizaci pro srdeční selhání, opakované ischemické příhody a pravděpodobnost krvácení. Tento přehled shrnuje poznatky o biologii a patofyziologii GDF-15, jeho využití v diagnostice a prognostice, i uplatnění v léčbě a přináší i kritický pohled na současné mezery v důkazech a požadavky na další výzkum.

Keywords:
Cardiovascular diseases
Growth Differentiation Factor-15
Oxidative stress

ABSTRACT

Growth Differentiation Factor-15 (GDF-15) is a cytokine responsive to stress, linked to inflammation, oxidative stress, metabolic dysfunction, and tissue damage. In the past twenty years, it has become a significant biomarker in several cardiovascular diseases (CVDs), such as heart failure (HF), coronary artery disease, acute coronary syndromes, pulmonary vascular disease, arrhythmias, and cardiometabolic disorders. Increased circulating GDF-15 levels forecast mortality, hospitalisation due to HF, repeated ischaemic incidents, and the likelihood of haemorrhage. This review consolidates GDF-15 biology, pathophysiology, diagnostic and prognostic applications, and therapeutic implications and offers a critical evaluation of existing evidence gaps and future research requirements.

Introduction

GDF-15: biology and pathophysiology

Molecular architecture and regulation

GDF-15 is a member of the TGF-β superfamily and is produced as a precursor protein that undergoes proteolytic cleavage to generate a 25 kDa disulphide-linked dimer.[1] Its transcription necessitates two p53-responsive promoter sites, hence associating its expression with oxidative stress, mitochondrial malfunction, and DNA damage pathways.[2] The placenta is the primary generator of GDF-15, with levels significantly increasing throughout pregnancy.

Pathophysiological mechanisms

Inflammation and immune regulation

GDF-15 exhibits a dual and context-dependent function in the regulation of inflammation. In the case of acute tissue injury, it demonstrates anti-inflammatory effects by diminishing leukocyte integrin activation and restricting neutrophil recruitment, therefore averting excessive inflammatory cell infiltration and subsequent tissue damage.[1,2] These systems are believed to facilitate the prompt containment of harm and sustain cellular homeostasis. In chronic atherosclerotic disease, GDF-15 seems to transition towards a pro-inflammatory phenotype. Experimental and human evidence indicates that a sustained increase of GDF-15 may perpetuate low-grade inflammation, alter macrophage phenotype, and facilitate the growth and instability of atherosclerotic plaques.[1] This bidirectional behaviour highlights GDF-15's intricate role in cardiovascular (CV) inflammation, acting as both a protective and detrimental modulator based on the temporal and clinical context.

Cellular origins in health and disease

In pathological situations, GDF-15 is synthesised by: Cardiomyocytes during ischaemia and post-myocardial in-

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farction remodelling.[3–5] Endothelial cells and vascular smooth muscle cells in atherosclerotic plaques.[1] Adipose tissue acts as an adipokine during metabolic stress.[4] Extracardiac organs in chronic heart failure (HF).[5] In acute myocardial infarction, cardiac output predominates, but chronic HF redirects output to peripheral tissues, including the liver, kidneys, and skeletal muscle.[5]

Endothelial dysfunction and accelerated vascular senescence

An increasing amount of epidemiological evidence indicates that GDF-15 is significantly correlated with indicators of vascular ageing and endothelial dysfunction. Community-based cohort studies indicate that elevated circulating GDF-15 levels are associated with enhanced arterial stiffness, compromised endothelial nitric oxide-mediated vasodilation, and early structural vascular abnormalities. These associations endure following the adjustment for conventional CV risk variables, indicating that GDF-15 may signify early microvascular damage and endothelial ageing. Given that endothelial dysfunction precedes numerous CV disorders, GDF-15 may serve as a sentinel biomarker for vascular health, detecting subclinical alterations that occur prior to the manifestation of overt disease.[6–10]

Diagnostic and prognostic functions of disease category

Community-based populations

Extensive cohorts, such as Rancho Bernardo and Framingham, indicate that GDF-15 serves as a predictor:

- overall mortality,
- CV mortality,
- mortality associated with cancer,
- even subsequent to the adjustment for traditional biomarkers such as NT-proBNP, hs-troponin, and hs-CRP.[7–9]

Lifestyle variables, such as suboptimal CV health indicators and tobacco use, correlate with elevated GDF-15 levels.[11,12]

Oxidative and metabolic strain

GDF-15 is acutely responsive to oxidative and metabolic stress, serving as a circulating biomarker indicative of systemic physiological burden. Increased GDF-15 levels are strongly associated with heightened oxidative stress marker expression and metabolic dysregulation, signifying an augmented state of cellular damage and stress signalling. These correlations are routinely noted in illnesses such as chronic renal disease, diabetes, and obesity, where prolonged metabolic stress fosters chronic inflammation and mitochondrial impairment. GDF-15 functions as a sensitive marker of disrupted metabolic homeostasis, amalgamating signals from oxidative processes, inflammation, and organ stress into a singular measurable biomarker. This renders it especially beneficial for detecting persons predisposed to cardiometabolic decline prior to the onset of clinical symptoms.[12]

Myocardial remodelling

In chronic HF, GDF-15 is persistently increased and significantly correlated with detrimental myocardial remodelling. Elevated GDF-15 levels are associated with augmented myocardial fibrosis, compromised left ventricular (LV) systolic and diastolic function, and enhanced neurohormonal activation.[5] These alterations illustrate the interaction among mechanical stress, inflammation, oxidative injury, and cellular apoptosis that contribute to advancing cardiac injury. GDF-15 thereby consolidates many upstream damage pathways into a prognostic indicator that accurately reflects the extent of structural and functional heart decline. Consequently, it is widely acknowledged as a crucial biomarker of pathological remodelling and disease progression in chronic HF.

Coronary artery disease (CAD)

In patients with CAD, GDF-15 is independently correlated with: multivessel CAD, diabetes and renal impairment systemic inflammation

In the Heart and Soul Study, GDF-15 was a predictor of CV mortality, HF hospitalisations, and recurrent ischaemic episodes in stable CAD.

Acute coronary syndromes (ACS)

In FRISC-II, PLATO, and PROVE-IT TIMI-22:
GDF-15 surpasses hs-CRP, NT-proBNP, and cardiac troponins in multivariable models.[13–20] GDF-15 is a robust predictor of both short- and long-term mortality. The risk increases incrementally throughout tertiles (1.5%, 5%, 14.1%).[16] Continued increase following acute coronary syndrome indicates persistent remodelling and risk of HF.[16,21] Patients with GDF-15 levels over 1200–1800 ng/L derive the most advantage from early invasive intervention.[19,20]

Heart failure

Chronic HFrEF/HFpEF
GDF-15 is associated with:
HF severity (NYHA classification, congestion), BNP/NT-proBNP, high-sensitivity cardiac troponin T, inflammation, cachexia, renal impairment.[21]

In HFpEF, increased GDF-15 indicates systemic inflammation associated with comorbidities such as diabetes and hypertension (HT).[22]

Acute HF
In advanced heart failure necessitating mechanical circulatory support, GDF-15 levels decrease swiftly after LV assist device (LVAD) implantation, indicating early restoration of peripheral organ function rather than direct cardiac unloading—an effect not observed in natriuretic peptide levels like BNP.[23] GDF-15 serves as a significant prognostic marker in cardiogenic shock, with elevated levels predicting short-term mortality and reflecting the extent of systemic stress and multi-organ involvement.[24] The RELAX-AHF trial demonstrated that decreases in circulating GDF-15 during serelaxin therapy were significantly correlated with enhanced clinical outcomes, highlighting its efficacy as a dynamic biomarker for treatment response in acute heart failure.[25] These observations collectively underscore GDF-15 as a sensitive biomarker along the

continuum of acute and severe heart failure, including haemodynamic impairment, systemic inflammation, and organ dysfunction, into a singular prognostic indicator.

Pulmonary vascular and right-heart pathology

GDF-15 improves risk stratification in several right-heart and pulmonary vascular conditions. In acute pulmonary embolism, increasing GDF-15 levels indicate individuals at increased risk for negative outcomes, offering additional predictive value beyond clinical evaluation alone.[26] In pulmonary arterial hypertension, GDF-15 is associated with disease severity and right-ventricular strain, perhaps surpassing natriuretic peptides in specific prediction models.[26,27] These relationships highlight its efficacy as a biomarker that encompasses cardiopulmonary stress, right-ventricular dysfunction, and systemic inflammatory activation.

Clinical applications and therapeutic consequences

Risk stratification and triage

Elevated GDF-15 levels identify patients with acute coronary syndrome who either derive greater advantages from early revascularisation or necessitate more rigorous antithrombotic treatment.[19, 20] In chronic HF, GDF-15 facilitates risk assessment and helps identify patients susceptible to unfavourable remodelling.

Prediction of bleeding risk

GDF-15 is a crucial element of bleeding-risk models established from the ARISTOTLE and RE-LY trials, exhibiting substantial predictive capability for major non-CABG-related haemorrhage and markedly enhancing risk classification beyond high-sensitivity cardiac troponins and conventional clinical variables. Increased GDF-15 levels predict bleeding problems in patients with ACS on dual antiplatelet therapy, hence identifying those at increased haemorrhagic risk during rigorous antithrombotic treatment.[28]

Assessment of treatment efficacy

Valsartan reduces BNP levels but does not affect GDF-15 (Val-HeFT), indicating distinct molecular processes.[21] Serelaxin induces swift decreases in GDF-15 during acute HF (RELAX-AHF).[25] Empagliflozin elevates GDF-15, signifying regulation of metabolic stress.[29]

Potential for therapeutic targeting

GDF-15 modulates appetite regulation and systemic metabolic management via the GFRAL–RET signalling pathway, indicating possible therapeutic implications in various interrelated domains. GDF-15's regulation of energy balance identifies it as a potential target for obesity and metabolic syndrome therapy. Furthermore, its pivotal position at the intersection of inflammation, metabolic stress, and cardiac dysfunction underscores the promise for therapeutic strategies targeting GDF-15 pathways to enhance outcomes in cardiometabolic disorders and HF.[30]

Cardiac arrhythmias

Individuals with lone atrial fibrillation (AF) or paroxysmal AF (PAF) frequently have elevated circulating GDF-15 levels, indicating increased atrial stress and systemic inflammation. These rises are associated with age, atrial dimensions, and structural atrial remodelling, indicating that GDF-15 may function as a sensitive measure of atrial substrate susceptibility. Besides basic atrial arrhythmias, GDF-15 has emerged as a prognostic indicator in non-ischaemic cardiomyopathy, with increased levels predicting severe arrhythmic events, including prolonged ventricular arrhythmias and the need for implantable cardioverter-defibrillator interventions. These data collectively demonstrate the promise of GDF-15 as a comprehensive biomarker connecting atrial disease, cardiac stress, and the risk of malignant arrhythmias (**Tables 1, 2**).[30,31]

Cardiometabolic and systemic disorders

Elevated levels are observed in individuals with metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and obesity, indicating underlying metabolic stress and inflammation.[30] Environmental and toxic exposures, including cadmium, correlate with substantial elevations in GDF-15, underscoring its responsiveness to oxidative and metabolic damage mechanisms.[32,33] GDF-15 is persistently increased in many cardiometabolic and systemic diseases. Increased circulating concentrations are correlated with the severity of diabetic foot ulcers, suggesting a potential role in wound-healing assessment and risk stratification.[34] Ultimately, it functions as a growth biomarker in congenital heart disease, especially in younger children when conventional dietary indicators are less dependable.[35] Moreover, GDF-15 functions as an autonomous predictor of coronary plaque burden in individuals with HIV, signifying its robust association with chronic inflammation and vascular injury.[36,37]

Constraints and prospective directions

Constraints

Primary limitations

The primary limitations of the existing evidence encompass the utilisation of different immunoassays and poor calibration across analytical platforms,[3] leading to heterogeneity in reported GDF-15 values. Threshold values vary significantly among research, restricting comparability and obstructing the formulation of standardised clinical cut-offs. Furthermore, the majority of accessible data originate from observational cohorts, which limits causal inference and heightens vulnerability to residual confounding.[7,16] Renal impairment, advanced age, and multimorbidity significantly affect circulating GDF-15 levels, confounding the interpretation and risk assessment across various individuals.[7,12] Ultimately, mechanistic pathways are inadequately comprehended in human studies, underscoring the necessity for more profound translational research to elucidate GDF-15's biological function in CV disease (CVD).

Table 1 – The main topic points of recent studies

Reference no.	Authors	Subjects	Main theme
Ref [30]	Dallmeier et al.	Patients with stable coronary heart disease	Baseline GDF-15 independently predicts CVE and 10-year total mortality. Despite adjusting for well-established cardiovascular risk variables and cardiac biomarkers, 12-month relative changes were associated with subsequent CVE and total mortality.
Ref [32]	Hagström et al.	Patients with acute coronary syndromes	Higher GDF-15 levels in ACS patients increase the risk of all kinds of severe non-CABG-related bleeding, spontaneous MI, stroke, CV and total mortality, and seem to improve risk stratification for CV-mortality and major bleeding beyond known risk factors.
Ref [34]	Schopfer et al.	Patients with stable ischemic heart disease	Higher GDF-15 levels predict major CV events in stable ischemic heart disease. Other risk factors may not explain GDF-15 risk.
Ref [35]	Fuernau et al.	Acute myocardial infarction patients	GDF-15 on admission independently predicts short-term mortality in infarct-related cardiogenic shock.
Ref [39]	Wallentin et al.	Patients with non-ST-elevation acute coronary syndrome	Lifetime perspective suggests early invasive therapy for most non-ST-elevation acute coronary syndrome patients.
Ref [42]	Chan et al.	Patients with heart failure	Inflammatory damage (GDF15) may be relevant in both HF syndromes beyond haemodynamic stress (NT-proBNP).
Ref [46]	Cotter et al.	Patients with heart failure	GDF-15 elevations, but not baseline amounts, were associated with worse RELAX-AHF outcomes. Serelaxin reduced GDF-15 more than placebo.
Ref [47]	Wollert et al.	Community-dwelling individuals	GDF-15 shows CV disease development, progression, and prognosis that clinical risk factors and other biomarkers cannot.
Ref [48]	Abu-Assi et al.	Patientss with acute coronary syndromes	An update on clinically utilised ACS bleeding risk ratings.
Ref [49]	Wallentin et al.	Patients with atrial fibrillation	GDF-15 causes atrial fibrillation-related haemorrhage, mortality, and stroke. N-terminal pro-brain natriuretic peptide and high-sensitivity troponin I did not influence bleeding or death.
Ref [50]	Hijazi et al.	Patients with atrial fibrillation	ABC-bleeding beat HAS-BLED and ORBIT scores and may assist atrial fibrillation patients choose anticoagulation.
Ref [51]	Kato et al.	Individual patient meta-analysis	GDF15 predicts ASCVD CV mortality and HHF. GDF-15 improves MI and stroke prognosis, but not ACS.
Ref [52]	Omar et al.	Patients with heart failure	Empagliflozin increased plasma GDF-15 in HFrEF patients without raising hsTNT or hsCRP
Ref [53]	Xiao et al.	Review	GDF-15-mediated energy control may treat glucolipid metabolic disorders (GLMD). GDF-15 increases appetite in patients with diabetes, obesity, non-alcoholic fatty liver disease (NAFLD), and other disorders. GDF-15's role in GLMD's pathophysiology may lead to a novel therapy

Knowledge deficiencies

Significant gaps persist in the existing comprehension of GDF-15, necessitating elucidation through forthcoming study. Inadequate characterisation of the longitudinal trajectories of circulating GDF-15 across various phases of cardiovascular and metabolic illnesses constrains its effectiveness for dynamic risk evaluation. Secondly, the absence of defined disease-specific reference ranges complicates the identification of clinically significant cut-off values for various illnesses. The molecular role of GDF-15 in critical disease processes—such as myocardial inflammation and fibrosis in HFpEF, atrial remodelling in AF, and vascular remodelling in pulmonary HT—remains little defined. The genetic regulation of GDF-15 expression, particularly the impact of single nucleotide polymorphisms, necessitates further examination to elucidate interindividual variability and heritable factors influencing circulating levels.[9]

Anticipated pathways

Future research must prioritise several critical domains to enhance the clinical and translational application of GDF-15. First, the development and universal adoption of standardised immunoassay platforms is essential to minimise inter-laboratory variability and enable reliable comparisons of results across studies. Secondly, incorporating GDF-15 into multi-omics frameworks—such as genomics, proteomics, metabolomics, and transcriptomics—could elucidate fundamental biological pathways and improve disease phenotyping. Third, clinical decision-support technologies based on machine learning that integrate GDF-15 could enhance personalised risk assessment and treatment stratification. Fourth, prospective clinical trials are necessary to assess GDF-15–guided management options and to ascertain its supplementary value in standard cardiovascular therapy. A thorough examination

Table 2 – The main topic points of recent studies

Reference no.	Authors	Subjects	Main theme
Ref [54]	Li et al.	Patients with "lone" atrial fibrillation	In AF of unknown aetiology (UeAF), plasma GDF-15 was higher than sinus rhythm and lower than paroxysmal AF (PAF). Left atrial diameter and age substantially influence GDF-15.
Ref [55]	Chen et al.	Patients with atrial fibrillation	In this community-based biracial group, greater GDF-15 concentrations independently predicted incident AF.
Ref [56]	Carballo-Casla et al.	Older adults	The metabolic syndrome raised elderly GDF-15 levels. Abdominal obesity, hyperglycemia, low HDL-cholesterol, and inflammation caused this link.
Ref [57]	García-Esquinas et al.	Non-smoking older adults	Cd exposure raises CVD risk. CD may boost GDF-15.
Ref [58]	Zang et al.	Ischemic Stroke patients	GDF-15 levels independently predicted poststroke depression (PSD) in acute ischemic stroke, suggesting it may be a PSD biomarker.
Ref [59]	Sendur et al.	Patients with diabetic foot ulcer	Diabetic foot ulcer patients have elevated GDF-15. Advanced lesions are more common. GDF-15 measurement may help treat diabetic foot ulcers.
Ref [60]	Paneitz et al.	Children with Congenital Heart Disease	GDF-15 is an important growth indicator in congenital cardiac disease (CHD) children, especially those under 2 with HF. Prealbumin has no long-term growth biomarker.
Ref [61]	May et al.	Patients with nonischemic dilated cardiomyopathy	Serum GDF-15 independently predicted major arrhythmic episodes and mortality in nonischemic HF patients on optimal medication treatment. This biomarker may stratify sudden death risk in this population.
Ref [62]	Asrih et al.	Patients with metabolic syndrome	Preclinical animal studies show that GDF15 mimics lower food intake and weight. Thus, GDF15 might fight global obesity.
Ref [63]	Tridamayanti et al.	Acute myocardial Infarction Patients	At 3 months, MI patients with elevated GDF-15 risked major cardiac adverse events (MACE).
Ref [64]	Royston et al.	People living with and without HIV	GDF-15 and smoking synergistically increase coronary plaque volume in people living with HIV (PLWH). GDF-15 levels independently predicted coronary artery plaques in HIV-negative individuals.
Ref [65]	Deng et al.	Patients With Chronic Obstructive Pulmonary Disease	Chronic obstructive pulmonary disease (COPD) patients may readily assess sarcopenia using serum GDF15 levels.
Ref [66]	Mei et al.	Patients with type 2 diabetes mellitus	CAD and diabetic patients exhibited differing GDF-15 and ApoB/ApoA1 levels. Diabetics may predict CAD using ApoB/ApoA1 and GDF-15.
Ref [67]	Duceppe et al.	Patients 45 years or older having major noncardiac surgery	GDF-15 accurately predicts 30-day major cardiovascular events and cardiac risk in noncardiac surgery patients.

of GFRAL–RET signalling and its regulatory mechanisms in cardiovascular pathology may provide potential treatment avenues.

Conclusion

GDF-15 is a reliable biomarker indicative of cardiometabolic stress, inflammation, vascular dysfunction, and detrimental remodelling. In specific cardiovascular contexts, elevated GDF-15 consistently predicts mortality, recurrent ischaemic events, the advancement of HF, and the risk of haemorrhage. Despite its established diagnostic and prognostic significance, considerable limitations—such as assay variability, insufficient mechanistic understanding, and a lack of standardised thresholds—hinder its practical application. Future mechanistic and interventional studies will ascertain whether GDF-15 may transition from a prognostic marker to a therapeutic target.

Conflict of interest
The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Diseminovaný epiteloidní hemangioendoteliom jako vzácná příčina nádorového postižení srdce

(Disseminated epithelioid hemangioendothelioma as a rare cause of heart neoplasm)

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Pozitronová emisní tomografie

SOUHRN

Epiteloidní hemangioendoteliom (EHE) je vzácný mezenchymální nádor vaskulárního původu s heterogenním klinickým průběhem. Nejčastěji postihuje játra, plíce, kosti a měkké tkáně, zatímco postižení srdce patří k mimořádně vzácným projevům tohoto onemocnění a může imitovat benigní primární srdeční tumory.
Prezentujeme případ 29letého muže bez významné osobní a rodinné anamnézy, který byl přijat pro postupně narůstající dušnost. Vstupní vyšetření prokázalo oboustranný pleurální výpotek, perikardiální výpotek a intrakavitální útvar levé síně o maximálním rozměru až 40 mm, který byl dle morfologie v echokardiografickém obraze suspektní z myxomu. Další zobrazovací vyšetření odhalila tumorózní expanzi zadního mediastina s infiltrací levé síně, postižení pleury, mnohočetná ložiska v plicním parenchymu a skeletu. Diferenciálněd iagnosticky bylo zvažováno hematologické onemocnění, které však nebylo potvrzeno. Definitivní diagnóza diseminovaného epiteloidního hemangioendoteliomu byla stanovena na základě histologického a imunohistochemického vyšetření kostní léze s pozitivitou markeru CAMTA1.[1]
Navzdory zahájení paliativní systémové léčby došlo k rychlé progresi onemocnění a pacient zemřel čtyři měsíce od stanovení diagnózy. Kazuistika poukazuje na nutnost zvažovat maligní etiologii i u zdánlivě typických intrakardiálních útvarů, zejména při přítomnosti systémových projevů. Multimodální zobrazovací přístup v kombinaci s histologickou verifikací je zásadní pro stanovení správné diagnózy.[1,2]

Keywords:
Echocardiography
Epithelioid hemangioendothelioma
Heart neoplasms
Mediastinal neoplasms
Positron-emission tomography

ABSTRACT

Epithelioid hemangioendothelioma (EHE) is a rare mesenchymal tumor of vascular origin with a heterogeneous clinical course. It most commonly affects the liver, lungs, bones, and soft tissues, whereas cardiac involvement is an exceptionally rare manifestation of the disease and may mimic benign primary cardiac tumors. We present the case of a 29-year-old man with no significant personal or family medical history who was admitted for progressively worsening dyspnea. Initial examination revealed bilateral pleural effusion, pericardial effusion, and an intracavitary mass in the left atrium measuring up to 40 mm, which was considered suspicious for a myxoma based on its echocardiographic morphology. Further imaging revealed a tumor mass in the posterior mediastinum infiltrating the left atrium, pleural involvement, and multiple lesions in the lung parenchyma and skeleton. A hematologic malignancy was considered in the differential diagnosis but was not confirmed. The definitive diagnosis of disseminated epithelioid hemangioendothelioma was established by histopathological and immunohistochemical examination of a bone lesion demonstrating CAMTA1 positivity.[1.]
Despite the initiation of palliative systemic therapy, the disease progressed rapidly, and the patient died four months after the diagnosis was established. This case highlights the need to consider a malignant etiology even in apparently typical intracardiac masses, particularly in the presence of systemic manifestations. A multimodality imaging approach combined with histopathological verification is essential for establishing the correct diagnosis.[1,2]

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Úvod

Epiteloidní hemangioendoteliom (EHE) je vzácný mezenchymální nádor vaskulárního původu s biologickým chováním na pomezí benigních hemangiomů a vysoce maligních angiosarkomů.[3] Incidence onemocnění se odhaduje přibližně na 1 případ na 1 000 000 obyvatel ročně. Klinický průběh je značně variabilní – od indolentních forem s dlouhodobým přežitím až po agresivní, rychle progredující diseminované onemocnění.

Epiteloidní hemangioendoteliom nejčastěji postihuje játra, plíce, kosti a měkké tkáně. Postižení srdce patří k mimořádně vzácným projevům tohoto onemocnění a v literatuře jsou popisovány pouze ojedinělé případy, převážně ve formě primárního srdečního nádoru.[4,5] Tyto případy mohou mít při včasné diagnóze a radikální chirurgické léčbě relativně příznivou prognózu.[4,6,7] U lokalizovaných forem epiteloidního hemangioendoteliomu, včetně vzácných primárních srdečních případů, je při technické možnosti kompletní chirurgické excize s negativními resekčními okraji (R0) popisována příznivější prognóza a chirurgická resekce je považována za kauzální léčbu.[4,6,7] Naopak sekundární srdeční postižení v rámci diseminovaného onemocnění je spojeno s nepříznivým průběhem a omezenými terapeutickými možnostmi.[6,8]

Diagnostika EHE je obtížná vzhledem k nespecifickým klinickým příznakům a variabilním nálezům při zobrazovacích vyšetřeních. Zásadní význam má histopatologické vyšetření doplněné imunohistochemií, přičemž pozitivita markeru CAMTA1 je považována za vysoce specifickou pro tuto jednotku.[1] Cílem této kazuistiky je prezentovat případ mladého pacienta s diseminovaným epiteloidním hemangioendoteliomem s postižením srdce, který byl iniciálně diagnosticky zvažován jako benigní primární srdeční nádor.

Popis případu

Devětadvacetiletý muž, dosud zdravý, bez významné osobní či rodinné anamnézy, byl přijat na kardiologickou kliniku pro postupně narůstající dušnost a celkovou slabost. Při vstupním klinickém vyšetření byly přítomny známky oboustranného pleurálního výpotku a tlumené srdeční ozvy. Pacient byl hemodynamicky stabilní, bez známek akutního srdečního selhání.

Transtorakální echokardiografie prokázala intrakavitální útvar levé síně o velikosti přibližně 25 × 40 mm, patrný v projekci parasternální dlouhá osa (parasternal long axis) (**obr. 1**). Útvar byl nepravidelného tvaru, bez jasně patrné stopky, částečně adherentní k zadní stěně levé síně. Současně byl přítomen perikardiální výpotek bez echokardiografických známek srdeční tamponády. Systolická funkce levé komory byla zachována, bez významné chlopenní patologie.

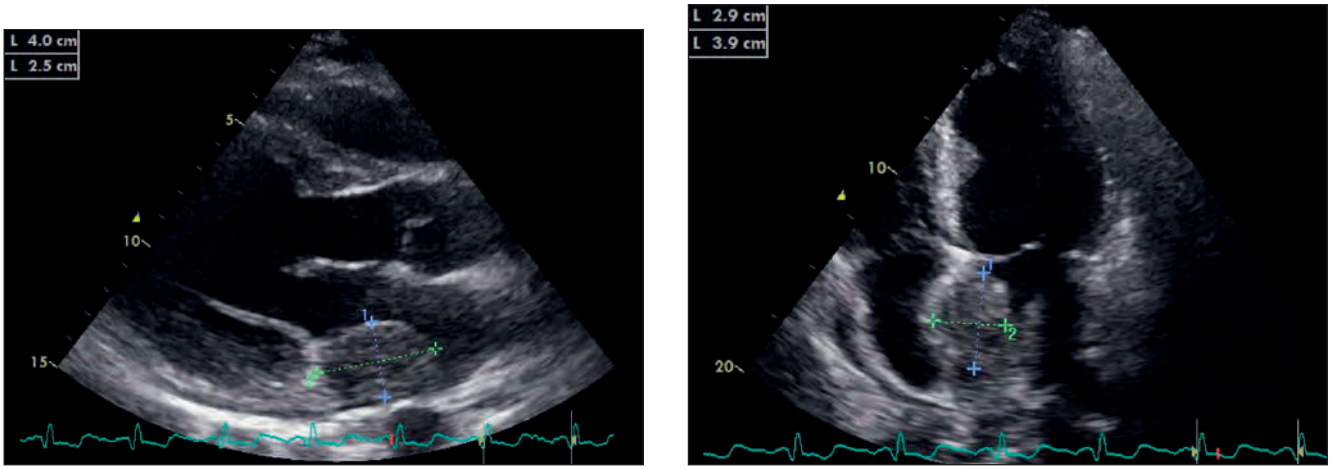
Vzhledem k lokalizaci a morfologii intrakardiální masy byla v diferenciální diagnostice primárně zvažována diagnóza myxomu levé síně. Přítomnost oboustranného pleurálního výpotku však vzbuzovala podezření na systémové onemocnění. Pleurální výpotek měl charakter exsudátu, cytologické a kultivační vyšetření bylo negativní, flowcytometrie neprokázala patologickou lymfoproliferaci.

CT vyšetření hrudníku prokázalo tumorózní expanzi zadního mediastina s infiltrací levé síně, dále infiltrativní postižení pleury, mediastinální lymfadenopatii a mnohočetná ložiska v plicním parenchymu a skeletu (**obr. 2**). Na základě těchto nálezů bylo vysloveno podezření na hematologickou malignitu, které však nebylo potvrzeno ani biopsií mediastinální lymfatické uzliny, ani vyšetřením kostní dřeně.

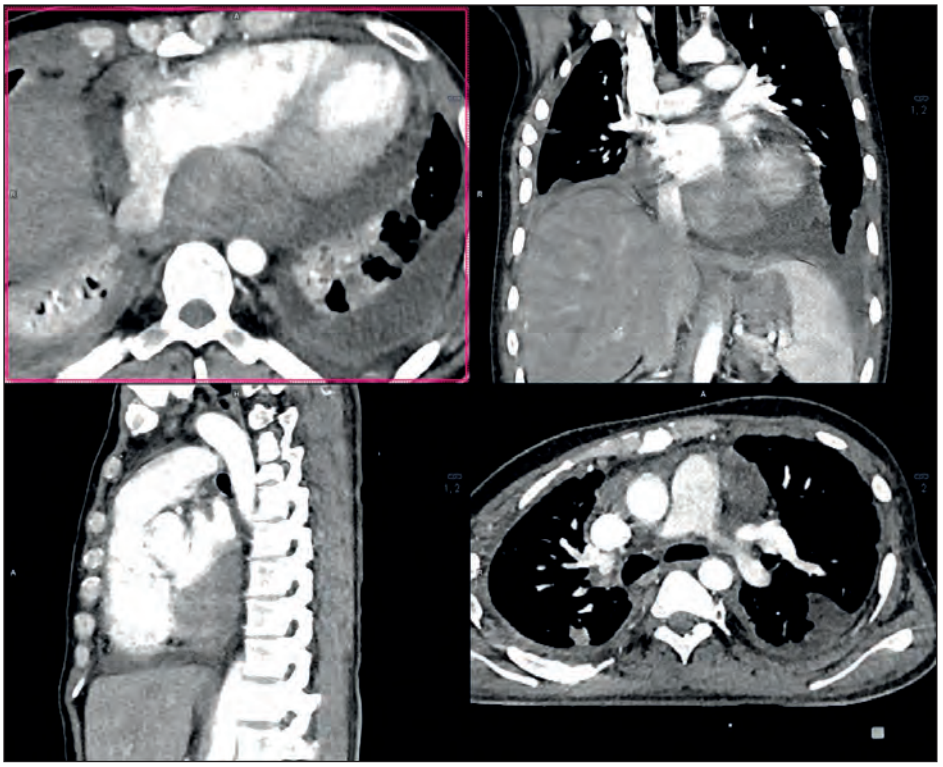
Výraznou akumulaci fluorodeoxyglukózy (FDG) v mediastinálních uzlinách, plicním parenchymu a skeletu prokázalo vyšetření pozitronovou emisní tomografií/výpočetní tomografií (PET/CT) (**obr. 3**). Jedno z metabolicky nejaktivnějších ložisek bylo lokalizováno v oblasti diafýzy humeru, odkud byla provedena cílená biopsie.

Histopatologické vyšetření kostní léze prokázalo infiltraci epiteloidními buňkami s eozinofilní cytoplazmou a fokální světlobuněčnou luminizací (**obr. 4**). Imunohistochemické vyšetření bylo pozitivní v markeru CAMTA1 (**obr. 5**), čímž byla potvrzena diagnóza epiteloidního hemangioendoteliomu.[1]

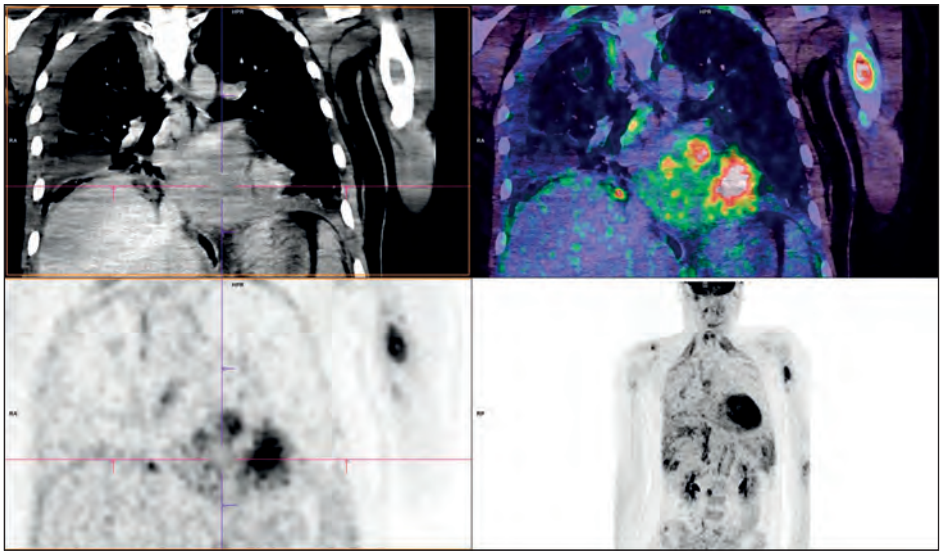
Na základě rozsahu postižení byla stanovena diagnóza diseminovaného epiteloidního hemangioendoteliomu s postižením srdce, plic, pleury, mediastina a skeletu. Pa-



Obr. 1 – Echokardiografický obraz intrakavitálního útvaru levé síně a perikardiálního výpotku v projekcích PLAX a A4C.



Obr. 2 – CT vyšetření hrudníku – objemný útvar za srdcem prominující do pravé síně. Oboustranný fluidotorax.

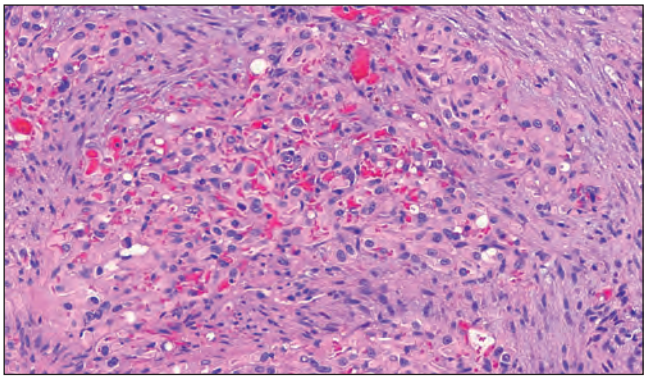


Obr. 3 – ^{18}F-FDG PET/CT – známky akumulace FDG v mediastinálním útvaru i uzlinách a drobné fokusy akumulace v pleurální dutině a kostech. FDG – fluorodeoxyglukóza; PET/CT – pozitronová emisní tomografie / výpočetní tomografie.

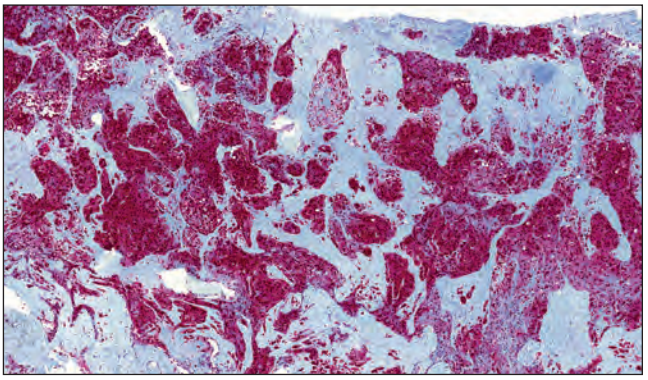
cient byl přeložen k další péči na Onkologickou a radioterapeutickou kliniku, kde byla zahájena paliativní chemoterapie doxorubicinem. Onemocnění však i přes léčbu rychle progredovalo a pacient zemřel přibližně čtyři měsíce od stanovení definitivní diagnózy.

Diskuse

Epiteloidní hemangioendoteliom představuje diagnosticky i terapeuticky náročnou jednotku s výrazně variabilním klinickým průběhem.[3,6] V prezentovaném případě byla nemoc manifestována intrakardiální masou levé síně, která byla při vstupním echokardiografickém vyšetření morfologicky kompatibilní s benigním primárním nádorem srdce, zejména myxomem. Tento fakt ilustruje



Obr. 4 – Buňky tumorózního ložiska s eozinofilní cytoplazmou a fokální světlobuněčnou luminizací při barvení hematoxylin-eosinem.



Obr. 5 – Pozitivní imunohistochemické vyšetření s protilátkou CAMTA1.

jedno z hlavních diagnostických úskalí EHE – schopnost imitovat běžnější a prognosticky příznivější srdeční léze.[4,5]

Zásadní roli v diagnostickém procesu sehrálo multimodalitní zobrazování. Zatímco echokardiografie umožnila detekci intrakardiální masy a posouzení jejího hemodynamického významu, CT vyšetření přineslo klíčové informace o extrakardiálním šíření procesu. PET/CT vyšetření následně umožnilo identifikaci metabolicky nejaktivnějšího ložiska vhodného k biopsii, což vedlo ke stanovení definitivní diagnózy.[2]

Definitivní diagnóza EHE byla potvrzena histopatologicky a imunohistochemicky s pozitivitou CAMTA1, která je považována za vysoce specifický marker tohoto onemocnění.[1] Prognóza EHE je významně závislá na rozsahu onemocnění v době diagnózy. Zatímco lokalizované formy mohou mít relativně příznivý průběh, diseminované onemocnění je spojeno s velmi nepříznivou prognózou a omezenými terapeutickými možnostmi.[6,8] U některých pacientů může být diseminovaný průběh komplikován závažnými systémovými projevy, včetně koagulačních komplikací, jak dokládají i recentní kazuistiky.[9]

Z hlediska léčby je u lokalizovaných forem epiteloidního hemangioendoteliomu, včetně vzácných primárních srdečních případů, považována kompletní chirurgická resekce s negativními resekčními okraji (R0) za kauzální léčbu a je spojována s příznivější prognózou.[4,6,7] Naproti tomu u diseminovaného onemocnění neexistuje standardní kurativní léčba a terapeutické možnosti jsou omezené. Systémová léčba má převážně paliativní charakter a zahrnuje zejména antracyklinové režimy (např. doxorubicin), taxany, interferon či antiangiogenní léčbu, přičemž efekt těchto postupů je variabilní a často omezený.[6,8]

Prezentovaný případ dokumentuje mimořádně vzácnou situaci, kdy je srdeční postižení součástí rozsáhlého diseminovaného epiteloidního hemangioendoteliomu. Kazuistika poukazuje na nutnost zvažovat maligní etiologii i u zdánlivě typických intrakardiálních útvarů, zejména pokud je přítomna systémová manifestace onemocnění.

Závěr

Diseminovaný epiteloidní hemangioendoteliom je vzácnou, avšak klinicky závažnou příčinou nádorového postižení srdce. Zobrazovací metody v kombinaci s histologickou verifikací jsou klíčové pro stanovení správné diagnózy.[1,2] Na tuto jednotku je nutné myslet zejména u mladších pacientů s atypickým průběhem a známkami diseminace do dalších orgánů.

Prohlášení autorů o možném střetu zájmů
Autoři prohlašují, že nemají žádný střet zájmů.

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Žádné

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Práce byla napsána v souladu s Helsinskou deklarací.

Informovaný souhlas
Nebylo třeba žádat o informovaný souhlas, protože v této kazuistice nebyly publikovány osobní údaje ani identifikovatelné fotografie pacienta.

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Memorandum o vzájemné spolupráci

Memorandum o vzájemné spolupráci mezi

1. Českou společností soudního lékařství a soudní toxikologie České **lékařské společnosti Jana Evangelisty Purkyně**
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Se sídlem: Sokolská 490/31, 120 00 Praha 2

a

2. Společností lékařské genetiky a genomiky České lékařské společnosti Jana Evangelisty Purkyně
Zastoupenou: prof. MUDr. Milanem Mackem, jr., DrSc., MHA, předsedou výboru SLG ČLS JEP
Se sídlem: Sokolská 490/31, 120 00 Praha 2

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3. Českou kardiologickou společností, z.s.
Zastoupenou: prof. MUDr. Petrem Ošťádalem, Ph.D., FESC, předsedou ČKS
Se sídlem: Netroufalky 6b, 625 00 Brno

a

4. Českou asociací preventivní kardiologie České kardiologické společnosti, z.s.
Zastoupenou: prof. MUDr. Milošem Táborským, CSc., FESC, FACC, MBA, předsedou ČAPK
Se sídlem: Netroufalky 6b, 625 00 Brno

(společně dále jen „smluvní strany Memoranda“)
uzavřeli níže uvedeného dne, měsíce a roku Memorandum o vzájemné spolupráci (dále jen „Memorandum“)

I.
Preambule:

Smluvní strany podpisem tohoto Memoranda deklarují společný zájem o vzájemnou spolupráci, a to především v oblasti diagnostiky kardiovaskulárních, geneticky podmíněných onemocnění u případů náhlé srdeční smrti, v problematice kardiovaskulární prevence u přímých příbuzných osob zemřelých náhlou srdeční smrtí z kardiovaskulárních příčin, vzdělávání odborné a laické veřejnosti a v dalších segmentech, s cílem dosáhnout optimální dostupnosti specializovaných genetických vyšetření v indikovaných případech jak pro *post mortem* vyšetření, tak pro žijící pacienty, zajištění metodiky vzájemného předávání pacientů včetně definice standardů reference a podpory všech odborností. Cílem je dlouhodobá kultivovaná odborná spolupráce všech zainteresovaných odborností ve prospěch pacientů.

II.
Obecné principy spolupráce založené na datech EBM:

1. Dědičná kardiovaskulární onemocnění (dědičné kardiomyopatie, dědičné arytmické syndromy, dědičné aortální syndromy často spojené s disekcí aorty či chlopenními vadami typu bikuspidální aortální chlopeň nebo prolaps mitrální chlopně) jsou spojena s rizikem náhlé srdeční smrti u jedinců do 50 let věku.
2. Náhlá srdeční smrt je často prvním a posledním příznakem onemocnění a zcela zásadní roli v jejím rozpoznání hraje pitva a rozvaha pitvajícího lékaře. Případy jsou ve většině případů pitvány v režimu zdravotní či soudní pitvy na pracovištích soudního lékařství, v případě delší dobu trvajícího přežívání po kardiopulmonální resuscitaci pak obvykle na pracovištích patologie.

Adresa pro korespondenci: Prof. MUDr. Miloš Táborský, CSc., FESC, FACC, MBA, Kardiologie Prof. Táborský s.r.o., Bieblova, 1047/6, 150 00 Praha 5, Česká republika, e-mail: milos.taborsky@seznam.cz
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III.

Logistika záchytu případu na soudním lékařství s indikací genetického vyšetření:

1. U případů náhlé srdeční smrti s podezřením na dědičné kardiovaskulární onemocnění je nezbytné standardizované provedení pitvy náhle zemřelé osoby, včetně spektra doplňujících laboratorních vyšetření. Při pitvě jsou v těchto případech odebírány nativní vzorky tkání (obvykle myokard a/nebo slezina) k případnému *post mortem* genetickému vyšetření.
2. Doporučení ke genetickému vyšetření vyslovuje pitvající lékař, pokud stanovil diagnózu či má podezření na dědičné kardiovaskulární onemocnění.
3. V případě jasně deklarovaného aktivního zájmu přímých příbuzných o zjištění příčiny smrti je povinností soudního lékaře rodinu zemřelého informovat o povaze onemocnění, vyžádat si písemný souhlas s *post mortem* genetickou analýzou u jejich zemřelého příbuzného a nabídnout jim ve formě předání informací možnost preventivního kardiologického vyšetření.
4. Vlastní indikace ke genetickému vyšetření musí být konzultována a potvrzena lékařským genetikem, který odpovídá za adekvátní interpretaci výsledků vyšetření.
5. Záchyt případu náhlé srdeční smrti s podezřením na dědičné kardiovaskulární onemocnění na soudnělékařském pracovišti by měl být dále konzultován se spolupracujícím kardiologem, který indikuje případná preventivní kardiologická vyšetření přímých příbuzných v případě jejich zájmu.
6. Spolupracující lékařský genetik i kardiolog by měli být plně informováni o zjištěných pitevních nálezech, vč. laboratorních vyšetření (zejména histologie). Pitvající lékař by měl být zpětně informován o výsledcích *post mortem* genetického vyšetření.
7. Indikaci případu k *post mortem* genetické analýze chápeme jako mezioborové komplexní vyšetření zaměřené především na prevenci u žijících přímých příbuzných.
8. Prosazujeme koncepci multidisciplinárního týmu. Péče o pacienty a jejich příbuzné s dědičným kardiovaskulárním onemocněním předpokládá úzkou multidisciplinární spolupráci dětských i dospělých kardiologů/arytmologů/kardiochirurgů s lékařskými a molekulárními genetiky, patology, soudními lékaři a lékaři intenzivní medicíny či akutní kardiologie, neurology, praktickými lékaři a psychology aj.

IV.

Logistika genetické péče v kardiologii:

1. Doporučení ke genetickému vyšetření stanoví u zemřelých pitvající soudní lékař.
2. Pitvající lékař zachová tkáň vhodnou k molekulárněgenetickému testování.
3. Pitvající lékař kontaktuje pozůstalé (je-li to možné) a informuje je o možné příčině náhlé smrti a vhodnosti kardiologického a genetického vyšetření (mají-li o tuto informaci zájem). Současně informuje i spádové mezioborové centrum či centrálního koordinátora posmrtné péče (scd@ikem.cz) o záchytu případu náhlé srdeční smrti.
4. Vlastní indikace ke genetickému vyšetření musí být potvrzena a vedena lékařským genetikem, který odpovídá za adekvátní interpretaci výsledků vyšetření. V budoucnosti se subjekty tohoto memoranda budou snažit o zjednodušení tohoto schématu u některých klinicky jasných diagnóz.
5. Prosazujeme koncepci multidisciplinárního týmu. Péče o pacienty a jejich příbuzné s dědičným kardiovaskulárním onemocněním předpokládá úzkou multidisciplinární spolupráci dětských i dospělých kardiologů/arytmologů/kardiochirurgů s lékařskými a molekulárními genetiky, patology, soudními lékaři a lékaři intenzivní medicíny či akutní kardiologie, neurology, praktickými lékaři a psychology aj.

V.

Principy spolupráce subjektů v rozšíření povědomí a dostupnosti kardiogenetického vyšetření:

1. Odborné společnosti se dohodly, že primárním cílem je dlouhodobá spolupráce zajišťující kontinuitu, rozšíření povědomí a dostupnosti genetického vyšetření v léčbě pacientů s dědičným kardiovaskulárním onemocněním s rizikem náhlého úmrtí.
2. Cílem společných aktivit je především zajištění regionální dostupnosti genetických vyšetření pro indikované pacienty, včetně *post mortem* vyšetření. Prosazujeme společně koncepci genetického poradenství, které by mělo být dostupné v každém kardiovaskulárním centru dle Věstníku MZČR KV centra (https://mzd.gov.cz/wp-content/uploads/2026/04/Seznam-KCdo-KCde-KKCdo-KKCdo-HTx-a-KKCde-HTx-duben-2026-v.-1.0.pdf). Tato skutečnost je i součástí Národního kardiovaskulárního plánu (https://mzd.gov.cz/narodni-kardiovaskularni-plan-cr-na-obdobi-2025-2035/).
3. Vytvoříme mapu specializovaných kardiologických pracovišť, která spolupracují v rámci multidisciplinárních týmů s lékařským genetikem a akreditovanou molekulárněgenetickou laboratoří. Tato mapa bude zveřejněna transparentně na webu Národního zdravotnického informačního portálu (NZIP) a také bude dostupná na webových stránkách odborných společností a sociálních sítích s cílem informovanosti jak lékařů, tak pacientů. Tato síť bude průběžně aktualizována na základě dohody odborných společností.
4. Aktivně spolupracujeme s pacientskými organizacemi, dominantně s Českou aliancí kardiovaskulárních onemocnění, z.s. (ČAKO), a se zainteresovanými pacientskými organizacemi sdruženými v České asociaci pro vzácná onemocnění (ČAVO).
5. Budeme vytvářet společná odborná stanoviska a publikovat je jako mezioborové dokumenty o spolupráci. Budeme spolupracovat se zainteresovanými Evropskými referenčními sítěmi pro vzácná onemocnění dle Věstníku 1/2022. Průběžně budou dle nových poznatků a studií tyto dokumenty aktualizovány.

VI.

Základní odborné dokumenty spolupracujících subjektů:

- Zeman M, Pohlová Kučerová Š, et al. Standardní operační a diagnostický postup na soudnělékařských pracovištích v případech náhlé srdeční smrti (NSS) u jedinců do 40 let věku. Soud lek 2023;68:2–10.
- Pohlová Kučerová Š, Krebsová A, et al. Výstupy multicentrické studie příčin náhlé srdeční smrti (SCD) v České republice a primární prevence srdeční zástavy u příbuzných. Soud lek. 2022;67:10–24.

- Krebsová A, Kutílková E, Kubánek M, et al. Genetické vyšetření v kardiologii: Aktualizované souhrnné vyjádření a doporučení odborníků pracovní skupiny kardiogenetiky při ČAPK/ČKS, SLG a ČSSL a ST při ČLS JEP. Cor Vasa 2025;67:511–534.
- Krebsová A, Kutílková E, Zoubková V, et al. Genetické vyšetření v kardiologii: Souhrnné vyjádření a doporučení odborníků Pracovní skupiny kardioge netiky při ČAPK/ČKS, SLG a ČSSL a ST při ČLS JEP. Cor Vasa 2023;65:798–805
- Votýpka P, Krebsová A, Norambuena-Poustková P, et al. Post-mortem genetic testing in sudden cardiac death and genetic screening of relatives at risk: lessons learned from a Czech pilot multidisciplinary study. Int J Legal Med. 2023 Nov;137(6):1787-1801.
- Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS/Asia Pacific Heart Rhythm Society (APHRS)/ Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the State of Genetic Testing for Cardiac Diseases. Heart Rhythm 2022;19:e1–e60.
- Zeppenfeld k, Tfelt-Hansen J, de Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2022;43:3997–4126.
- Verhagen JMA, Kempers M, Cozijnsen l, et al. Expert consensus recommendations on the cardiogenetic care for patients with thoracic aortic disease and their first-degree relatives. Int J Cardiol 2018;258:243– 248.
- Stiles MK, Wilde AAM, Abrams DJ, et al. 2020 APHRS/ HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. Heart Rhythm 2021;18:e1–e50.
- Escobar-Lopez l, Ochoa JP, Royuela A, et al. Clinical risk Score to Predict Pathogenic Genotypes in Patients With Dilated Cardiomyopathy. J Am Coll Cardiol 2022;80:1115–1126.
- Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478a–3490a.
- Adler A, Novelli V, Amin AS, et al. An International, multicentered, Evidence-based reappraisal of Genes reported to Cause Congenital long QT Syndrome. Circulation 2020;141:418–428.

VI.
Závěrečná ustanovení:

1. Smluvní strany Memoranda vyjadřují svou vůli vzájemně spolupracovat v oblasti vymezené tímto Memorandem způsobem uvedeným v čl. I– V.
2. Memorandum je projevem skutečné, svobodné a vážné vůle smluvních stran Memoranda.
3. Memorandum je vyhotoveno ve třech stejnopisech, z nichž každá smluvní strana Memoranda obdrží po jednom stejnopise.
4. Memorandum nabývá platnosti a účinnosti dnem podpisu všemi smluvními stranami Memoranda.

V Praze dne 30. 6. 2026

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ČESKÁ KARDIOLOGICKÁ SPOLEČNOST

XXIX.

KONFERENCE ČESKÉ ASOCIACE SRDEČNÍHO SELHÁNÍ

9.– 10. října 2026 | Hotel Passage, Brno

Jste srdečně zváni.

Možnost registrace a aktuální informace naleznete na **www.kardio-cz.cz**

Těšíme se na Vaši účast!