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Inappropriate left ventricular hypertrophy as a tool for risk stratification in patients with essential hypertension

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SOUHRN

Navrhujeme alternativní způsob predikce vhodné velikosti hmoty levé komory (LK) u osob s normálním krevním tlakem (TK) a arteriální hypertenzí. V naší studii jsme hodnotili i případné souvislosti mezi novým ukazatelem nevhodné velikosti hmoty LK a vznikem infarktu myokardu (IM), cévních mozkových příhod (CMP) a perzistentní fibrilace síní (FS).
Studie probíhala ve dvou fázích. V první bylo vyšetřeno 630 neléčených hypertoniků a 206 normotoniků měřením TK v ordinaci lékaře, echokardiograficky, ambulantním monitorováním TK (AMTK) a neinvazivní analýzou centrální pulsové vlny (central pulse wave analysis, CPWA). Byla nalezena středně významná korelace ($r = 0{,}58$; $p = 0{,}002$) mezi indexem hmoty levé komory (left ventricular mass index, LVMI) na jedné straně a součinem systolického TK (STK) a end-diastolického rozměru (end-diastolic dimension, EDD) levé komory na straně druhé. Tato korelace byla podstatně těsnější než korelace LVMI s každým výše uvedeným prediktorem zvlášť, a navíc nebyla méně spolehlivá (inferiorní) než současná metoda výpočtu nevhodné LVM. Prokázali jsme, že navržený výpočet by bylo možno zpřesnit použitím AMTK nebo neinvazivní CPWA. Ve druhé fázi studie bylo 132 pacientů s esenciální hypertenzí opakovaně odesílaných do nemocnice rozděleno podle vhodnosti LVMI. U všech byly v průběhu pěti let zaznamenány příhody jako IM, CMP nebo perzistentní FS. Podle našich údajů byla nevhodná LVMI spojena s vyšším rizikem IM, zvláště u pacientů bez hypertrofie LK.

ABSTRACT

The alternative method of appropriate left ventricular mass prediction in subjects with normal BP and arterial hypertension was proposed. Also the associations of new indicator of LVM inappropriateness with myocardial infarction, stroke and persistent atrial fibrillation were studied.
The study consisted of 2 stages. On the first stage 630 untreated hypertensive patients and 206 normotensive persons were studied using methods of office blood pressure (OBP) measurement, echocardiography, ambulatory blood pressure monitoring (ABPM) and noninvasive central pulse wave analysis (CPWA). Moderate significant correlation ($r = 0.58$; $p = 0.002$) between the left ventricular mass index (LVMI) and the product of systolic blood pressure (SBP) and end diastolic dimension (EDD) was found. This correlation was substantially stronger than correlations of LVMI with each of the above mentioned predictors apart and, besides, it was non-inferior compared with existing method for calculation of inappropriate LVM. We established that proposed formula could be improved by using ABPM or noninvasive CPWA parameters. On the second stage of the study 132 patients with essential hypertension, who repeatedly referred to the hospital, were divided depending on LVMI appropriateness. In all of them such events as myocardial infarction (MI), stroke or permanent AF during the period of ≈5 years were recorded. According to our data, inappropriate LVMI was associated with a higher risk of MI especially in patients without LV hypertrophy.

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Hemodynamic load is one of the main components, which determines the myocardial mass. An increase in blood pressure is a cause of myocardium overload in patients with arterial hypertension, that is why the interest to the relationship between blood pressure and myocardial mass is still unabated. Left ventricular mass is an important indicator of the severity of hypertensive heart disease. It reflects the individual measure of cardiovascular risk. This fact is well-known and lies in the basis of some prognostic tools such as Framingham Score. But in some cases the usual cut-off levels of left ventricular hypertrophy do not reflect the individual risk. It was shown that determination of inappropriateness of myocardial mass to the load had additional benefits concerning the risk stratification in patients with arterial hypertension [1].The most widespread algorithm for calculating of inappropriate left ventricular mass was proposed at the end of the 90s [2]. The idea that product of stroke volume and systolic blood pressure predicts left ventricular mass (LVM) is lying in its basis. Stroke volume could be calculated according to the data obtained using echocardiography, and systolic blood pressure – by office BP measurement (OBP). This method of calculation of inappropriate LVM was used in some later researches [3,4]. There were some attempts to adopt original equations for local population [5] and to improve it, for example, by using ambulatory BP monitoring (ABPM) [6]. Novel study shows the correlation of inappropriate LVM with enhanced accumulation of advanced glycation end products in skin [7].

The aim of this study was to propose alternative method of LVM prediction in subjects with normal BP and arterial hypertension through exploration of LVM relationship with different methods of blood pressure measurement and echocardiography data. Another goal was to establish prognostic meaning of new indicator of LVM inappropriateness concerning such events as myocardial infarction, stroke and persistent atrial fibrillation.

Materials and methods

Design of the study was approved by local ethic committee. All participants signed the informed consent form. The study consisted of two stages.

On the first stage untreated patients with arterial hypertension or persons without hypertension of both genders, aged 25 or more and those who signed informed consent form, took part in the study. The main goal of this stage was to determine the most applicable methods for inappropriate LVM calculation and compare them with the existing analogs. Exclusion criteria were as follows:

- Congenital or acquired heart defects.
- Systemic connective tissue diseases.
- Endocrine diseases excluding diabetes mellitus.
- Diabetes mellitus of type I or uncontrolled DM of type II.
- Chronic kidney diseases.
- Symptomatic arterial hypertension.
- Myocardiopathies of any genesis.
- Pulmonary hypertension.
- Hemodynamically significant arrhythmias including persistent AF, atrioventricular or sinoatrial blocks of the II–III degree.
- Unstable stenocardia at the day of involvement.

The results of echocardiography and blood pressure measurement of consecutive subjects with and without hypertension were collected in the data bank. There were 630 hypertensive untreated patients and 206 persons with normal BP. BP was estimated using methods of OBP, ambulatory blood pressure monitoring (ABPM) and central pulse wave analysis (CPWA). OBP was measured with "Omron MX3" device. Systolic (SBP) and diastolic blood pressure (DBP) were calculated as a mean of 2 consequent readings obtained on the arm with the higher values.

Echocardiography was performed in all subjects. LVM was calculated by ASE method using 2-D guided M-mode. LVM was indexed to the body surface calculated by Du Bois formula: $S\ (m^2) = W^{0.425} \times H^{0.725} \times 0.007184$. Another parameter of LV model was relative wall thickening (RWT) calculated as ratio of sum of LV walls thickness to the end diastolic dimension (EDD).

CPWA was performed in 278 persons: 150 hypertensive and 128 normotensive subjects. ABPM was also carried out in most of them (150 hypertensive and 50 normotensive subjects). Echocardiography, OBP measurement and CPWA were executed at the same day and ABPM – in a day or maximum in 3 days after other procedures. 278 participants underwent applanation tonometry of the radial artery with "Sphygmocor XCEL" equipment (AtCor Medical, Australia) for noninvasive CPWA. The pulse wave curve of the radial artery, obtained by Hi-Fi probe, was transformed into a central aortic pulse wave with the corresponding intra-aortic pressure values. Such parameters were used for the analysis:

CESBP – central end-systolic blood pressure
CSBP – central systolic blood pressure
CDBP – central diastolic blood pressure

ABPM was performed in 200 subjects with ABPM 4-01 device ("Meditech", Hungary). We obtained values of mean systolic and diastolic pressures during 24 h, including mean values for SBP and DBP in active and passive periods. Night decrease of BP – diurnal index (DI) and percentage of exceeding BP measurements – hypertension load indexes (HI) during active and passive period of the day were also calculated for SBP and DBP.

On the second stage 132 consecutive patients with essential hypertension (EH) (treated and untreated), which were referred for ECG examination repeatedly within one year or more, were assessed for new cases of myocardial infarction (MI), stroke or persistent atrial fibrillation (AF). All other inclusion-exclusion criteria were similar to the first stage of the study. The main task of this stage was to assess the association of LVM inappropriateness, calculated by original method, with such surrogate end-points as the risk of MI, stroke and persistent AF.

The median term of observation was 59.0 months (interquartile range 32.9–84.4 months). All patients were divided into group of patients with appropriate and inappropriate LVM index (LVMI) dependent on value of EDD × SBP/100.

Table 1 – Demographic, anthropometric and blood pressure characteristics of the control and the essential hypertension groups.

Parameters	CG	N	EH	N
Males (%)	56	206	50	630
Age, years (SD)	42.3 (10.3)	206	55.6 (10.8)*	630
Height, cm (SD)	171 (9)	206	170 (9)	630
Body mass, kg (SD)	76 (13)	206	90 (16)*	630
SBP, mmHg (SD)	126 (11)	206	153 (22)*	630
DBP, mmHg (SD)	75 (8)	206	87 (14)*	630
CESBP, mmHg (SD)	99 (9)	128	128 (21)*	150
CSBP, mmHg (SD)	96 (9)	128	125 (20)*	150
CDBP, mmHg (SD)	84 (8)	128	106 (13)*	150
SBP_{24h}, mmHg (SD)	109 (8)	128	142 (21) *	150
DBP_{24h}, mmHg (SD)	75 (7)	128	83 (13) *	150
SBP_{act}, mmHg (SD)	112 (8)	50	147 (23)*	150
DBP_{act}, mmHg (SD)	78 (7)	50	88 (16)*	150
SBP_{pass}, mmHg (SD)	103 (8)	50	132 (20) *	150
DBP_{pass}, mmHg (SD)	70(6)	50	81 (11) *	150
DIs, % (SD)	13 (6)	50	10 (7)	150
DId, % (SD)	14 (8)	50	12 (11)	150
HIs-act, % (SD)	15 (6)	50	61 (34)*	150
HId-act, % (SD)	10 (5)	50	56 (33)*	150
HIs-pas,% (SD)	18 (6)	50	66 (35)*	150
HId-pas,% (SD)	12 (6)	50	50 (34)*	150
EDD, mm (SD)	45.7 (4.3)	206	48.6 (5.2)	630
LVMI, g/m^2 (SD)	78 (29)	206	106 (34)*	630
RWT (SD)	0.41 (0.05)	206	0.48 (0.10)	630

CDBP – central diastolic blood pressure; CESBP – central end systolic blood pressure; CSBP – central systolic blood pressure; DBP – diastolic blood pressure; DBP_{24h} – mean DBP during 24 h; DBP_{act} – mean DBP during active period of the day; DBP_{pass} – mean DBP during passive period of the day; DId – diastolic diurnal index; DIs – systolic diurnal index; EDD – end diastolic diameter of left ventricle; HId-act – diastolic hypertension load index (%) during active period of the day; HId-pas – diastolic hypertension load index (%) during passive period of the day; HIs-act – systolic hypertension load index (%) during active period of the day; HIs-pas – systolic hypertension load index (%) during passive period of the day; LVMI – left ventricular mass index; RWT – relative wall thickness; SBP – systolic blood pressure; SBP_{24h} – mean SBP during 24 h; SBP_{act} – mean SBP during active period of the day; SBP_{pass} – mean SBP during passive period of the day; SD – standard deviation.

* Probability of differences based on Mann–Whitney test $p < 0.01$.

Statistical methods

All obtained data were processed by statistical methods preformed in "Statistica 8.0" application. Data were checked for normality by Kolmogorov–Smirnov and Lilliefors tests. Linear regression model was used for normally distributed data. Multiple regression method was applied for the creation of prediction models. Mann–Whitney test was used for paired comparison. Frequency tables and χ^2 test were applied for calculation of CV events odds risk.

Results and discussion

The main features of hypertensive (EH) and normotensive (CG) groups are performed in Table 1.

We studied pair correlations of LVMI and its possible predictors among anthropometric data and some other parameters. These results are reflected in Table 2.

We noted significant correlations of LVMI with age, SBP, DBP and EDD. As for EDD the result is predictable, because LVMI depends on EDD. But the fact that the strength and significance of correlation of EDD and SBP product with LVMI occurred more pronounced than each of them alone was rather unexpected.

Fig. 1 demonstrates the relationship between actual values of LVMI and parameter of EDD × SBP/100.

This correlation had a high confidential level as for the entire model ($p < 0.001$), for the regression coefficient and intercept ($p < 0.001$ for both).

We hypothesized that the actual LVMI value could be inappropriate to the certain BP level if it exceeded 95%

Table 2 – Correlation coefficients between LVMI and its probable predictors.

Predictors	*r*	*p*
Age	0.14	<0.001
Height	0.03	0,38
Weight	0.03	0.30
SBP	0.38	0.03
DBP	0.11	0.002
EDD	0.45	0.72
SBP × EDD	0.58	0.002
SBP_{24h}	0.21	0.04
DBP_{24h}	0.15	0.08
SBP_{act}	0.28	0.014
DBP_{act}	0.24	0.13
SBP_{pass}	0.27	0.53
DBP_{pass}	0.18	0.67
DIs	–0.34	0.002
DId	–0.45	<0.001
HIs-act	0.22	0.06
HIs-pas	0.32	0.004
HId-act	0.01	0.9
HId-pas	0.22	0.06
CESBP	0.40	0.009
CSBP	0.41	0.008
CDBP	0.25	0.11

confidential interval (95% CI) of EDD × SBP/100. After calculations of 95% CI, values of EDD × SBP/100 exceeded more than 41% were determined as cut-off values for inappropriate left ventricular hypertrophy. We found that in persons with normal BP and hypertension the correlation coefficients of actual LVMI and EDD × SBP/100 were similar: in the control group it was 0.59 and in EH group – 0.57 ($p < 0.001$ for both). According to that fact we have made an assumption that EDD × SBP/100 value could be applied as a universal indicator (for normo- and hypertensive subjects of any gender) of inappropriate left ventricular mass. The model for calculation of cut-off value for LVMI was

(1),

where LVMI – left ventricular mass index (g/m^2), EDD – end diastolic dimension (mm), SBP – office systolic blood pressure (mm Hg)

Also we believed that if predicted values obtained by proposed model had correlation coefficient with LVMI similar to the values obtained by MAVI method, proposed model could have a similar prognostic significance. Calculations of inappropriate LVM based on MAVI equation were the following:

(2)

where LVM – predicted left ventricular mass, SW – stroke work, calculated as and "gender" is equal to 1 for males and 2 for females.

After calculations we determined that predicted values in persons with hypertension correlated with actual LVM similar to the values obtained by original method ($r = 0.59$; $p < 0.001$ and $r = 0.57$; $p < 0.001$, respectively). It was found that there was a strong pair correlation ($r = 0.79$; $p < 0.001$) between predicted values obtained by both methods.

Table 3 – Anthropometric features in patients with appropriate and inappropriate LVMI.

Feature	Appropriate LVMI (SD) (*n* = 51)	Inappropriate LVMI (SD) (*n* = 81)	*p*
Age, years	48.6 (8.5)	49.7 (8.6)	>0.05
EH beginning, years	35.2 (12.4)	37.8 (11.7)	>0.05
EH duration, years	13.6 (9.3)	12.3 (9.0)	>0.05
SBP, mmHg	171 (35)	150 (26)	0.0006
DBP, mmHg	94 (15)	88 (16)	0.04
BMI, kg/m^2	31.6 (3.8)	31.3 (4.7)	>0.05

Table 4 – Incidence of cardiovascular events in patients with appropriate and inappropriate LVMI.

CV event		Appropr. LVMI (*n* = 51)	Inapprop. LVMI (*n* = 81)	OR	χ^2 *p*
MI	Yes	2	13	4.70	0.03
	No	48	66		
Stroke/TIA	Yes	11	26	1.74	0.23
	No	39	53		
AF	Yes	15	20	0.72	0.28
	No	33	61		

AF – atrial fibrillation; MI – myocardial infarction; OR – odds ratio; TIA – transitional ischemic attack; χ^2 *p* – accuracy of OR based on χ^2 criterion.

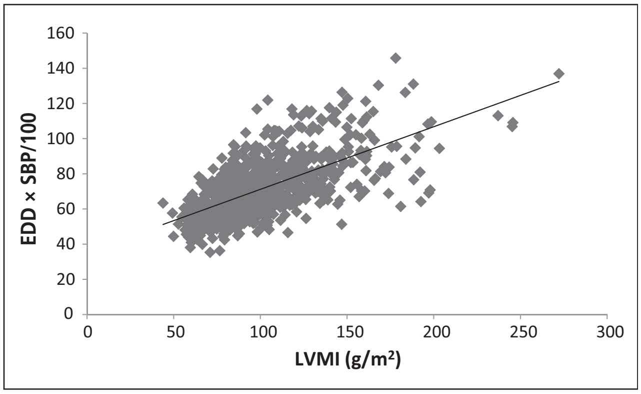

Fig. 1 – Correlation of actual LVMI and EDD × SBP/100.

We tried to improve our model by using of ABPM and CPWA parameters. Some weak, but significant correlations of ABPM parameters with LVMI, were found (Table 2). SBP_{daily}, DId were the most significant predictors. It was revealed that the correlation of LVMI with product of SBP_{daily}, DId and EDD ($r = 0.64$; $p < 0.001$) was more pronounced than with product of EDD and SBP ($r = 0.56$; $p = 0.01$). Moreover, it was noted that R^2 for the model using ABPM parameters rose from 0.31 to 0.41.

(3)

where LVMI – left ventricular mass index (g/m²), EDD – end diastolic dimension (mm), SBP_{daily} – daily systolic blood pressure (mm Hg)

The next step was to shift from OBP to CPWA values in equation for inappropriate LVMI calculation. CSBP had the most significant correlation with LVMI, that is why our attention was focused mainly on this parameter. Use of CSBP values instead of SBP in Eq. (1) improved the power of model from 0.56 to 0.74 ($p < 0.001$ for both).

On the next stage we studied the role of inappropriate LVMI in patients using retrospective analysis of medical history. There were 132 hypertensive patients divided in 2 groups: with appropriate (51 persons) and inappropriate LVMI (81 persons). The majority of anthropometric data in both groups were similar, excluding SBP and DBP (Table 3).

All main classes of antihypertensive drugs and their combinations were used for patients' treatment: ACE inhibitors, AT_1 receptors antagonists, diuretics, calcium antagonists and beta-blockers. There were 34 naive patients and 98 on treatment regimen.

We provided the semi-quantitative scale for the assessment of AHT effectiveness:

0 – Ineffective AHT: patient noticed no BP decrease by home self-assessment. OBP was over target goal.

1 – Moderate effectiveness of AHT: decrease in BP self-assessment within 15%. OBP was over target goal.

2 – Effective AHT: self-assessment and OBP data was below target goal.

56 patients were referred to ineffective AHT, including 34 without any treatment and 22 with non-effective AHT; 56 – to the group with moderate effect of AHT and 20 – to the group with enough effect of treatment. The analysis of AHT showed similar average estimate of AHT effectiveness in both groups (with appropriate and inappropriate LVMI): 0.72 and 0.85, respectively ($p > 0.05$ based on Mann–Whitney *U* test). Thus, both groups were very similar not only by their clinical characteristics, but also by the results of AHT. So, it allowed us to calculate odds ratio of cardiovascular events in patients with inappropriate LVMI (Table 4).

Inappropriate LVMI was associated with a 4.7 fold risk of MI, but was not associated with stroke or persistent AF. Moreover, inappropriate LVMI was revealed in 7 of 15 patients with new MI and no signs of LV hypertrophy assessed by routine method. Thus, we supposed the important prognostic meaning of LVMI inappropriateness for hypertensive patients without LV hypertrophy.

LVM estimation is one of the key points for patients' total risk assessment. It was shown that some additional benefit could be observed using inappropriate LVM calculation instead of routine LVM measurement. In the MAVI study the level of fatal and non-fatal events in patients with inappropriate hypertrophy was significantly higher than in those with appropriate or low myocardial mass. Also it was revealed that observed LVM/predicted LVM ratio, either in persons with or without hypertrophy, had additional predictive value [1]. We expected that as our method of inappropriate LVM assessment compared with MAVI method demonstrated similar correlation with observed LVM readings, it could have similar prognostic meaning. The influence of inappropriate LVMI on the incidence of secondary end-points during approximately 5 years proved this assumption. Significant association of inappropriate LVMI with the incidence of MI, especially among patients with normal LVMI was shown. Easy way of appropriate LVMI cut-off calculation by the formula: EDD × SBP/100 + 41% make it useful in the routine practice. We also demonstrated that additional benefit could be obtained by using ABPM data: SBP_{daily} and DId. Another way to predict inappropriate LVMI was to change SBP by CSBP readings of CPWA. It gave some additional increase of predicting power compared with SBP.

Conclusion

Preliminary results showed that alternative method of appropriate left ventricular hypertrophy prediction could be at least as good as the widespread method. We also believe that ABPM and CPWA could improve statistical reliability of appropriate LVM prediction. In particular, CSBP instead of SBP showed better power of correlation and DId gave a better power and significance of SBP × EDD product.

Limitations

The conclusions about predictive meaning of our method are based on correlation of well-known and proposed formulas and the results obtained in rather small prospective group with a few cardiovascular events. Another limitation is a secondary nature of end-points in our prospective study. Additional prospective studies using proposed formulas should be provided to prove the association of LVMI inappropriateness with primary end-points such as

CV mortality and total mortality, because they are preferable compared with the incidence of some secondary end-points.

Conflict of interest
None declared.

Funding body
None.

Ethical statement
Authors state that the research was conducted according to ethical standards.

Informed consent
Design of the study was approved by local ethic committee. All participants signed the informed consent form.

References

[1] G. de Simone, P. Verdecchia, S. Pede, et al., Prognosis of inappropriate left ventricular mass in hypertension. The MAVI study, Hypertension 40 (2002) 470–476.
[2] V. Palmieri, G. de Simone, M.J. Roman, et al., Ambulatory blood pressure and metabolic abnormalities in hypertensive subjects with inappropriately high LV mass, Hypertension 34 (1999) 1032–1040.
[3] H. Shemirani, R. Hemmati, A. Khoshravi, et al., Echocardiographic assessment of inappropriate left ventricular mass and left ventricular hypertrophy in patients with diastolic dysfunction, Journal of Research in Medical Sciences 17 (2012) 133–137.
[4] Y.H. Lim, J.U. Lee, K.S. Kim, et al., Association between inappropriateness of left ventricular mass and left ventricular diastolic dysfunction: a study using the tissue Doppler parameter, E/E0, Korean Circulation Journal 39 (2009) 138–144.
[5] J. Shin, K.S. Kim, S.K. Kim, et al., Influences of body size and cardiac workload on the left ventricular mass in healthy Korean adults with normal body weight and blood pressure, Korean Circulation Journal 35 (2005) 335–340.
[6] J. Shin, S.H. Ihm, W.B. Pyun, et al., Definition of inappropriate left ventricular mass index using ambulatory systolic blood pressure, a pilot study for the general population in Korea, Journal of the American Society of Hypertension 9 (4 Suppl.) (2015) e88–e89.
[7] C.C. Wang, Y.C. Wang, G.J. Wang, et al., Skin auto fluorescence is associated with inappropriate left ventricular mass and diastolic dysfunction in subjects at risk for cardiovascular disease, Cardiovascular Diabetology 16 (2017) 15.