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Ventricular-arterial coupling parameters and its prognostic value in patients with decompensated heart failure

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Aim. To assess ventricular-arterial coupling (VAC) parameters and their prognostic value in patients with decompensated heart failure (HF).

Material and methods. VAC parameters were evaluated upon admission using two-dimensional echocardiography in 355 patients hospitalized with decompensated HF. VAC was expressed as the ratio between arterial elastance (Ea) and end-systolic LV elastance (Ees). The optimal VAC range was considered 0,6-1,2. Parameters of left ventricular (LV) efficacy were calculated using the appropriate formulas. Differences were considered significant at p<0,05.

Results. The median values of Ea, Ees and VAC were 2,2 (1,7;2,9) mmHg/ml, 1,8 (1,0;3,0) mmHg/ml and 1,32 (0,75;2,21) respectively. In 63% of patients, VAC disorders were detected: 55% of patients had VAC >1,2 (predominantly patients with HF with reduced ejection fraction (HFrEF)-79%), 8% of patients had VAC <0,6 (all patients with HF with preserved ejection fraction (HFpEF)). Normal VAC was observed in 78%, 42%, and 1% of patients with HFpEF, HF with mid-range EF and HFrEF, respectively. There was significant correlation between Ea/Ees ratio and levels of NTproBNP (R=0,35), hematocrit (R=-0,29), hemoglobin (R=-0,26), pulmonary artery systolic pressure (PAPs) (R=0,18), dimensions of left atrium (R=0,32) and right ventricle (RV) (R=0,32).

After 6 months, rehospitalization with decompensated HF was recorded in 72 (20,3%) patients, 42 (11,8%) patients died. Ea decrease <2,2 mmHg/ml and PAPs increase >45 mmHg increased the risk of rehospitalization with decompensated HF and all-cause mortality 2,5 and 3,7 times, respectively.

Conclusion. Impaired VAC was diagnosed in 63% of patients with decompensated HF. However, the increased risk of all-cause mortality and rehospitalization with decompensated HF over the 6 months was associated with Ea decrease <2,2 mmHg/ml and PAPs increase >45 mmHg.

Key words: ventricular-arterial coupling, arterial elastance, ventricular elastance, heart failure.

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Ventricular-arterial coupling (VAC) is one of the main parameters of cardiac and aortic performance, and also plays an important role in representing the pathophysiology of cardiovascular diseases. VAC reflects how optimal is the transfer of stroke volume from the left ventricle (LV) to systemic arterial circulation [1]. Noninvasively, it is evaluated by the ratio of arterial elastance (Ea) to LV end-systolic elastance (Ees) [2]. Normal ranges of VAC varies from 0,6 to 1,2.

Elastance shows how much pressure will change when its volume changes. Ees reflects myocardial contractility and stiffness of LV [3]. Ea reflects a certain parameters characterizing arterial load: peripheral resistance, impedance, and systemic arterial compliance. As the disease progresses, both Ea and Ees can become abnormal, but the Ea/Ees ratio may remain within normal ranges.

The following parameters are used to describe LV energy: pressure-volume area (PVA), LV stroke work (SW), potential energy (PE), LV transfer efficiency (SW/PVA) (Figure 1).

PVA is circumscribed by three sides (the end-diastolic pressure–volume relation curve, the end-systolic PV relation (ESPVR) line and the systolic segment of the PV trajectory). PVA consists of two parts: the external mechanical work (the area within the PV trajectory) and the potential mechanical work (area underneath the ESPVR), which represents the PE that accumulates in the LV wall during systole [4].

Only exact concordance of Ees and Eas can lead to the most effective LV work to transfer the necessary blood volume against a certain pressure.

In patients with heart failure (HF) with reduced ejection fraction (HFrEF), an Ees decrease is observed due to a LV contractility reduction [5]. Decrease in cardiac output and increase in heart rate (HR) and peripheral resistance leads to an Ea increase. As a result, in this category of patients, the VAC increases by three to four times, the energy and mechanical work of the LV decreases, and the PE increases.

Patients with HF with preserved ejection fraction (HFpEF) have a lower VAC values compared with a healthy population due to an increase in Ea and Ees by about 40% and 50%, respectively. At the same time, adaptation reserves of external work increasing are reduced with an increase in load [6].

It has been shown that an assessment of VAC has independent diagnostic and prognostic value and can be used to clarify risk and monitor therapeutic interventions. Thus, study of 41 patients with myocardial infarction showed an association between VAC and 5-year cardiovascular mortality (p=0,019) [7].

Thus, treatment aimed at improving the interaction between myocardial performance and vascular function can affect the progression of cardiovascular diseases [8, 9]. So, significant improvement in VAC and LV work during therapy in 42 patients with decompensate HF was noted [10].

The aim was to study the parameters of VAC and their effect on the prognosis in patients with decompensated HF (DHF).

Material and methods

The study included 355 patients hospitalized with DHF (median age 75 years; mainly men). Most subjects had a history of hypertension; half had a history of myocardial infarction; one in four had a history of chronic kidney disease and rehospitalizations for 12 months; the median of N-terminal pro-brain natriuretic peptide (NTproBNP) was 3763 pg/ml. There were following exclusion criteria: acute coronary syndrome; end-stage kidney and liver disease; cancer and autoimmune disease; edema of another nature. Classification of HF phenotypes was carried out depending on the LV ejection fraction (LVEF): <40% — HFrEF, 40-49% — HF with mid-range EF (HFmrEF), ⩾50% — HFpEF. Among patients with DHF, 44% had HFrEF, 20% — HFmrEF, and 36% — HFpEF. The median length of hospital stay was 9 (interquartile interval 7;10) days.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study. All participants gave written informed consent.

Echocardiographic parameters were evaluated for all patients using the Vivid 7 Ultrasound System (General Electric, USA).

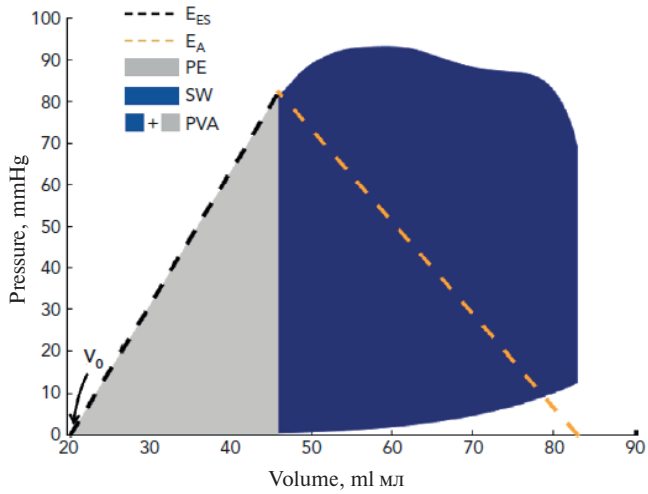

Figure 1. Pressure–volume loop analysis.
Abbreviations: Ea — arterial elastance, Ees — ventricular elastance, PE — potential energy, PVA — pressure-volume area, SW — stroke work [4].

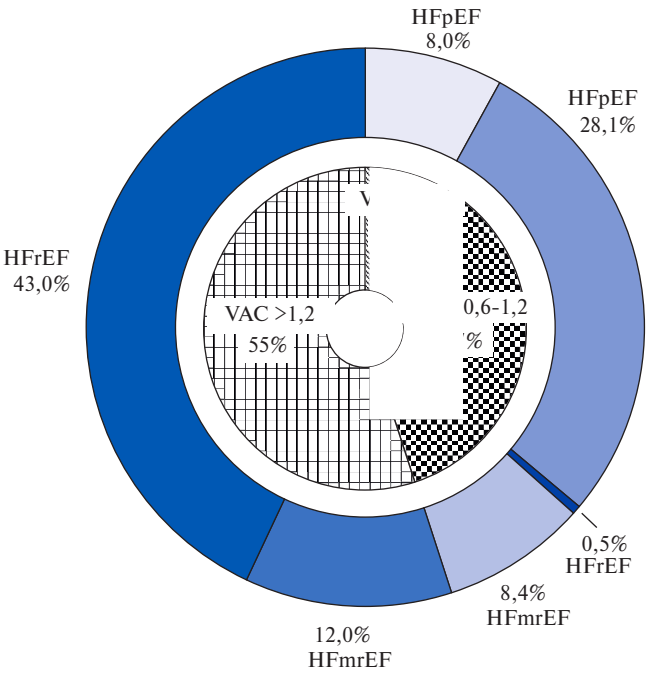

Figure 2. Distribution of HF phenotypes depending on the VAC.
Abbreviations: HFmrEF — heart failure with mid-range ejection fraction, HFpEF — heart failure with preserved ejection fraction, HFrEF — heart failure with reduced ejection fraction, VAC — ventricular-arterial coupling.

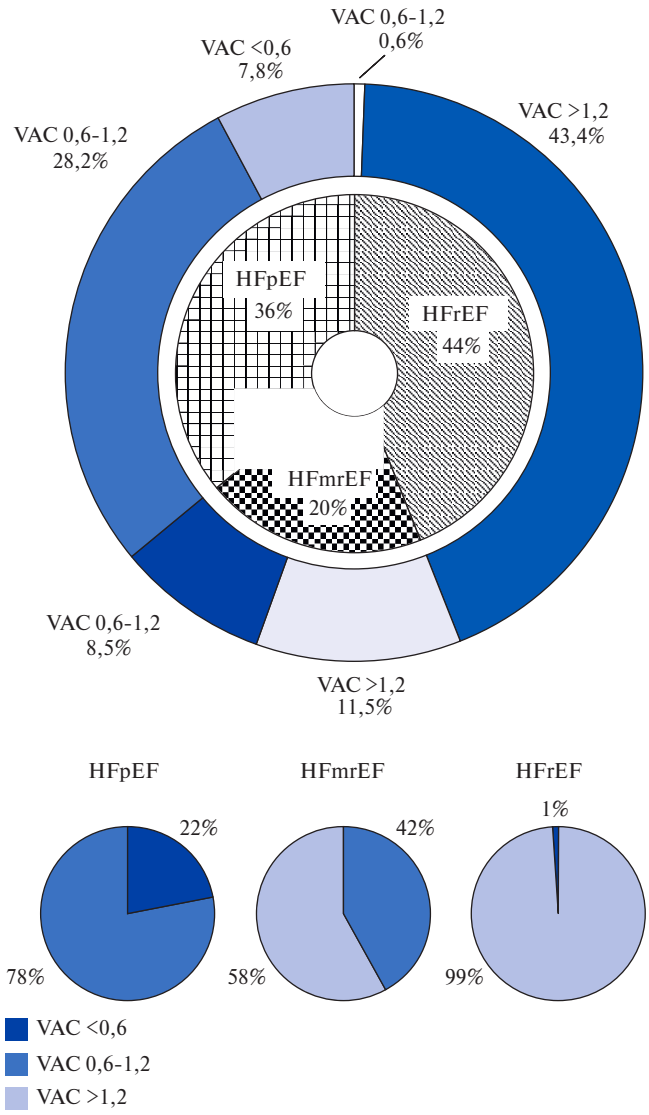

Figure 3. Distribution of VAC depending on the HF phenotypes.
Abbreviations: HFmrEF — heart failure with mid-range ejection fraction, HFpEF — heart failure with preserved ejection fraction, HFrEF — heart failure with reduced ejection fraction, VAC — ventricular-arterial coupling.

VAC was expressed as the ratio between Ea and Ees. Ees was obtained as the ratio of end systolic pressure (ESP) to end systolic volume (ESV); Ea was obtained as the ratio of ESP to stroke volume (SV). ESP was calculated as ESP=0,9 x systolic blood pressure (SBP).

The parameters characterizing LV energy were calculated:

Potential energy (PE): ESPxESV/2-EDPxESV/4, where EDP-end diastolic pressure;

External mechanical work, or stroke work (SW): SW=ESPxSV;

Pressure-volume area (PVA): PVA=SW+PE;

LV mechanical efficiency: SW/PVA.

After 6 months, adverse outcomes (rehospitalizations with DHF and all-cause mortality) were recorded by a structured telephone survey

Statistical processing was performed using the Statistica software for Windows (version 8.0). The type of distribution was determined by the Kolmogorov-Smirnov test and the Shapiro-Wilk test. To compare the quantitative characters in two different groups, the Mann-Whitney U test was used. For qualitative characters in two and three groups, the significance of differences was evaluated using the Pearson's chi-squared test. To assess the diagnostic effectiveness, ROC analysis with area under the curve (AUC) was used. The significance of differences in one group at different points was evaluated using the Wilcoxon test. Differences were considered significant at $p<0,05$. Kruskal-Wallis test was used for comparing the quantitative parameters in the three groups (lower significance level $p<0,017$).

Results

Patients hospitalized with DHF had the following medians of Ea, Ees and VAC: 2,2 (1,7; 2,9) mm Hg/ml, 1,8 (1,0; 3,0) mm Hg/ml and 1,32 (0,75; 2,21), respectively.

In 223 (63%) patients, there were VAC abnormalities (values outside the range of 0,6-1,2): VAC decrease (<0,6) was observed in 28 (8%) patients (all

Table 1

Differences between groups depending on the VAC

Parameter	VAC 0,6-1,2 (N=132)	VAC <0,6 (N=28)	VAC >1,2 (N=195)	p	r
SBP, mm Hg, (Me (IQR))	140 (130;160)	145 (130;170)§§	130 (114;150)**	<0,001	-0,24
SBP <110 mm Hg, n (%)	11 (8,3)	1 (3,6)	35 (17,9)	0,01	
Heart rate, bpm, (Me (IQR))	86 (74;100)	80 (70;90)§	94 (76;115)*	0,0007	0,20
NT-proBNP, pg/ml, (Me (IQR))	2884 (1489;4718)	2801 (929;4458)§	4458 (2855;5926)*	0,004	0,35
Hematocrit, (M±SD)	0,38±0,07	0,35±0,09§	0,41±0,07*	0,009	-0,29
LVEF, %, (Me (IQR))	55 (50;60)††	69 (68;72)§§§	33 (25;38)**	<0,001	-0,88
RV, cm, (Me (IQR))	3,0 (2,7;3,5)	3,0 (2,7;3,5)§	3,3 (3,0;3,7)**	<0,001	0,32
LA, cm, (Me (IQR))	4,5 (4,2;4,9)†	4,2 (4,0;4,7)§§§	4,8 (4,5;5,2)**	<0,001	0,32

Note: * — p<0,01, ** — p<0,001 — significance of differences compared with the group with normal (0,6-1,2) VAC, † — p<0,05, †† — p<0,001 — significance of differences compared with the group with reduced (<0,6) VAC, § — p<0,05, §§ — p<0,01, §§§ — p<0,001 — significance of differences compared with the group with increased (<1,2) VAC.

Abbreviations: LA — left atrium, LVEF — left ventricular ejection fraction, NT-proBNP — N-terminal pro-brain natriuretic peptide, RV — right ventricle, SBP — systolic blood pressure, VAC — ventricular-arterial coupling.

patients with HFpEF); VAC increase (>1,2) — in 195 (55%) patients (79% of patients with HFrEF) (Figure 2).

Only 2 (1%) patients with HFrEF, 30 (22%) patients with HFmrEF and 100 patients with HFpEF had normal VAC values (Figure 3).

Analysis of hemodynamic, laboratory, and echocardiographic data (Table 1) depending on the VAC showed that patients with VAC >1,2 compared with patients of the other two groups were characterized by higher values of NT-proBNP, hematocrit, heart rate, diameters of right ventricle (RV) and left atrium (LA), lower values of SBP and LVEF.

Comparison of VAC parameters depending on LVEF demonstrated that patients with HFrEF compared with patients with other HF phenotypes were characterized by the lowest Ees and highest VAC values. Patients with HFmrEF compared with HFpEF had lower Ees and higher VAC values (Figure 4). Patients with different phenotypes of HF (depending on LVEF) did not differ in Ea.

When studying the parameters of LV energy (Figure 5), it was found that as the LVEF decreased, an increase in potential energy was observed, as well as a decrease in the external work and mechanical efficiency of the LV.

In patients with VAC >1,2, the median length of hospital stay was 10 (8;12) days, in patients with VAC 0,6-1,2 — 9 (8;12) days, in patients with VAC <0,6 — 11 (8;14) days. No significant differences were found in the hospitalization length in patients with different VAC. During hospitalization, 1,5% of patients died.

After 6 months, 42 (11,8%) patients died. Rehospitalizations with DHF was recorded in 72 (20,3%) patients. No significant differences were found in the VAC and LV energy between patients with/without adverse outcomes. Patients with adverse events had significantly lower Ea (2,1 (1,7; 2,8; 2,8) vs 2,3 (1,9; 3,0) mm Hg/ml, p=0,048) and Ees levels (1,5 (0,7; 2,5) vs 1,9 (1,0; 3,1) mm Hg/ml, p=0,03). Patients with adverse outcomes compared with patients without adverse outcomes were characterized by lower values of SBP (130 (115;150) vs 140 (130;160) mmHg), higher values of NT-proBNP (4687 (3277;6220) vs 3396 (1555;5052) pg/ml) and pulmonary artery systolic pressure (PASP) (53 (46;66) vs 45 (34;64) mmHg), larger RV dimensions (3,3 (3,0;3,7) vs 3,0 (2,8;3,5) cm).

In multivariate analysis, independent predictors of adverse outcomes were Ea (β=-0,63), PASP (β=1,02). Using ROC analysis, the following threshold values for Ea and PASP were obtained, indicating an unfavorable prognosis: decrease in Ea <2,2 mm Hg/ml and increase in PASP >45 mm Hg raised the risk of rehospitalizations with DHF and all-cause mortality by 2,5 and 3,7 times, respectively (Table 2).

Discussion

The results of our study showed that more than half of patients hospitalized with DHF have a VAC abnormalities: 55% — increased, 8% — reduced.

According to a study of 72 patients with stable HF and LVEF >45% (all had a history of hypertension, more than half (62%) were women, mean age 71 years), a decrease in VAC was observed in 52% of patients [11]. In our study, patients with HFpEF were characterized by a normal and reduced VAC (78 and 22%, respectively). An increase in the proportion of patients with normal VAC and DHF may be associ-

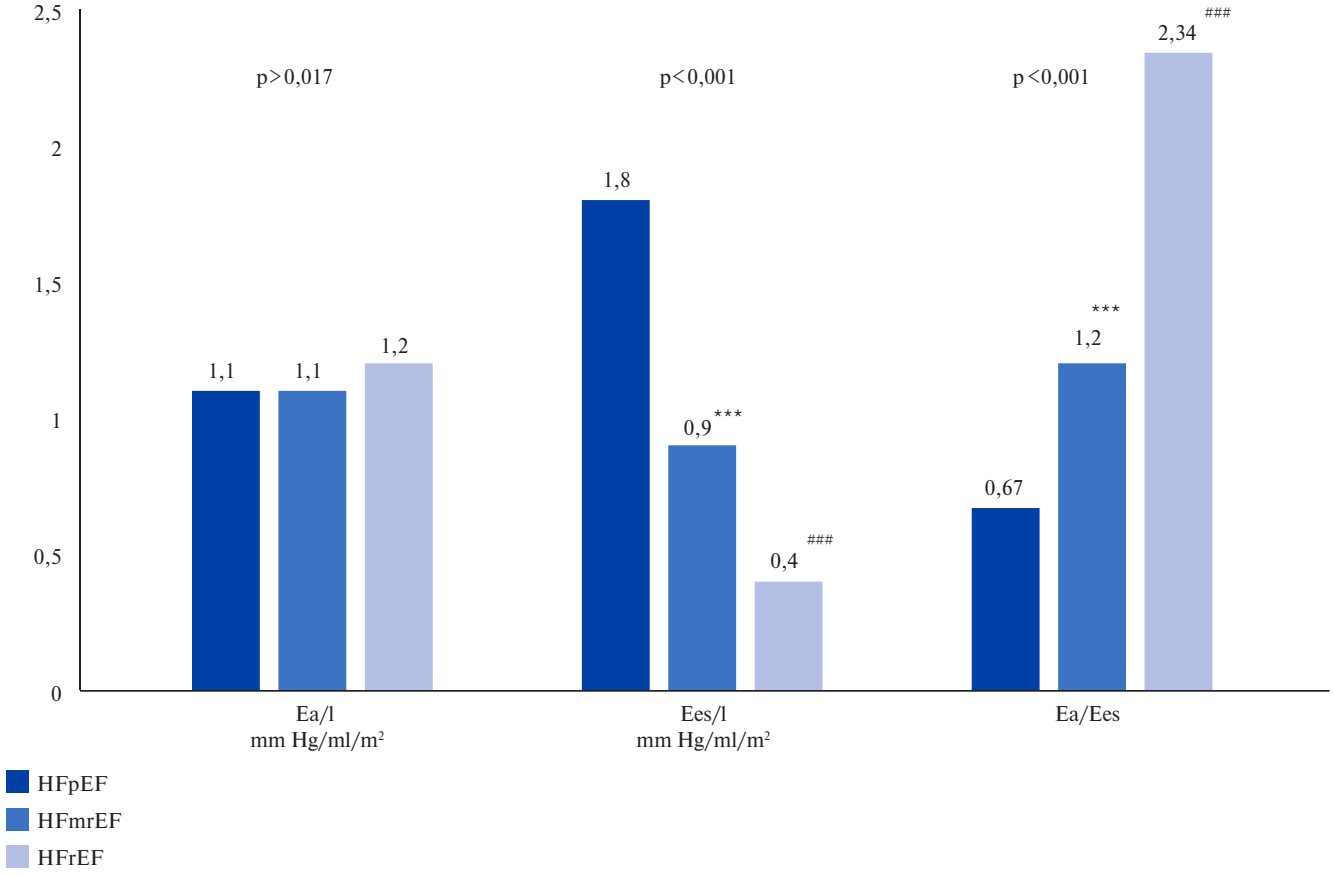

Figure 4. Characteristics of VAC parameters depending on LVEF.
Note: *** — p<0,001 - significance of differences compared with the HFpEF group, ### — p<0,001 — significance of differences compared with the HFmrEF and HFpEF groups.
Abbreviations: Ea — arterial elastance, Ees — ventricular elastance, HFmrEF — heart failure with mid-range ejection fraction, HFpEF — heart failure with preserved ejection fraction, HFrEF — heart failure with reduced ejection fraction, VAC — ventricular-arterial coupling.

ated with the "pseudonormalization" of the VAC. This phenomenon is characterized by normal VAC for LVEF of 45-54% in combination with more severe clinical HF manifestations (increased NT-proBNP levels and 6-minute walk distance).

In a study of 96 patients with stable HFrEF <40% (all patients with hypertension, mean age 63 years, 56% men), 87% of patients had a VAC >1,2 [11]. In our study, 99% of patients with decompensated HFrEF had a VAC increase. It is likely that the increase in the proportion of patients with an elevated VAC is associated with more severe structural and functional changes in the myocardium with DHF.

In a study of 466 patients with HFrEF (median follow-up 3,4 years), an association of VAC with the functional class of HF, NT-proBNP increase, and adverse outcomes (death, heart transplantation, LV assist device implantation, cardiovascular hospitalization) was revealed [12].

In a study of 891 patients with a previously diagnosed or suspected coronary artery disease who have negative stress echocardiography, VAC was measured at peak stress and at rest. It was found that all-cause mortality was higher in patients with impaired VAC reserve [13].

In our study, there were no significant differences in the VAC values in groups with/without rehospitalizations with DHF or all-cause death after follow-up of 6 months. In multivariate analysis, independent predictors of unfavorable prognosis were Ea (β=-0,63) and PASP (β=1,02).

According to published data, a decrease in arterial elasticity in HF is associated with several mechanisms, such as abnormal smooth muscle tone, a decrease in elastin/collagen of arterial wall, and a change in vessel geometry [1]. Since the LV and arterial work are interconnected, a decrease in afterload and cardiac output in severe HFrEF leads to mean BP reduction, resulting in a decrease in arterial elastance [14]. The afterload reduction may be partially caused by vasodilators.

In our study, it was found that in patients with DHF, the arterial elastance has a greater effect on the

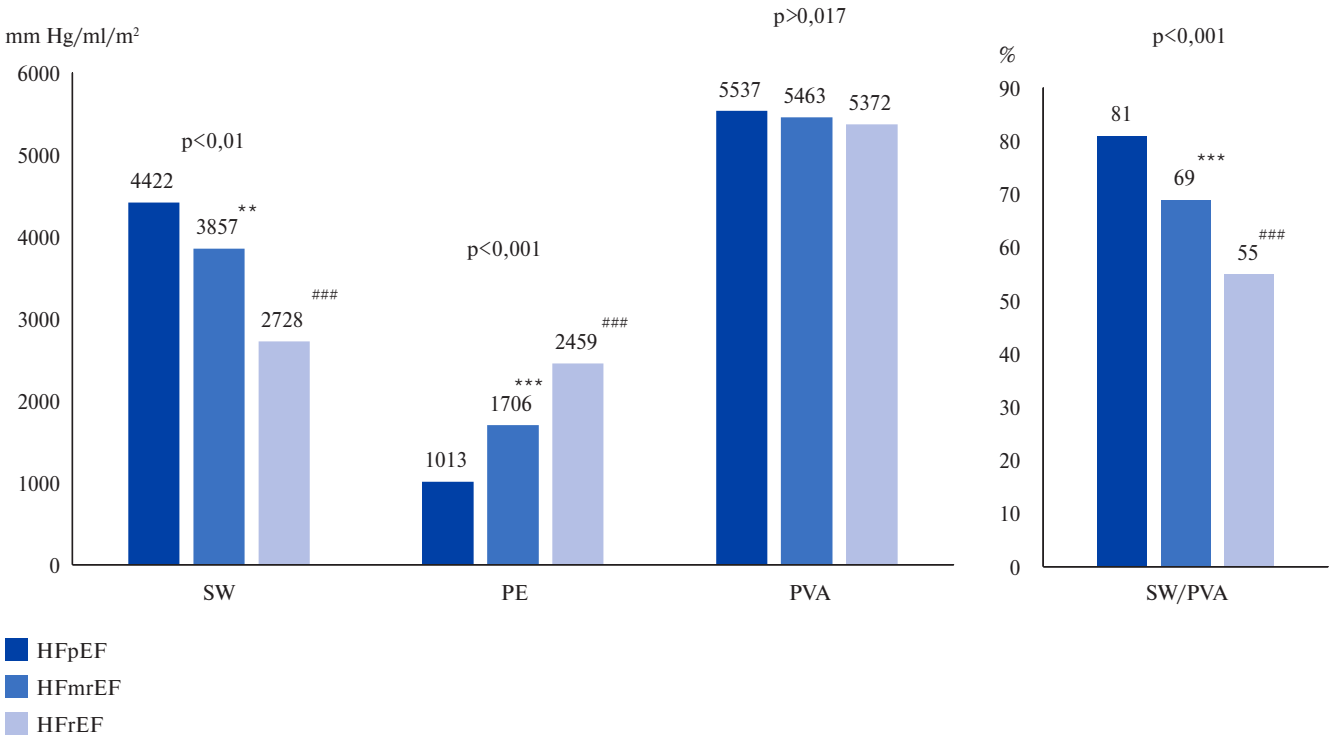

Figure 5. Characteristics of LV energy depending on LVEF.
Note: ** — p<0,01, *** — p<0,001 — significance of differences compared with the HFpEF group, ### — p<0,001 — significance of differences compared with the HFmrEF and HFpEF groups.
Abbreviations: HFmrEF — heart failure with mid-range ejection fraction, HFpEF — heart failure with preserved ejection fraction, HFrEF — heart failure with reduced ejection fraction, PE — potential energy, PVA — pressure-volume area, SW — stroke work, VAC — ventricular-arterial coupling.

Table 2

Predictors of unfavorable prognosis based on ROC analysis

Parameter	Threshold value	AUC	95% CI	Sensitivity, %	Specificity, %	OR
Ea	<2,2	0,593	1,39-4,34	63,6	57,6	2,5
PASP	>45	0,634	1,74-7,45	75,9	51,3	3,7

Abbreviations: AUC — area under the curve, CI — confidence interval, Ea — arterial elastance, OR — odds ratio, PASP — pulmonary artery systolic pressure.

unfavorable prognosis than the LV end-systolic elastance. These data also confirm an aggressive load reduction in acute HF and show that LV resistance has less pathophysiological significance than arterial elasticity.

Study limitations. One of the limitations is that at the hospitalization, there may have been some delays in performing examinations related to the severity of the patient's condition. Also, given the large number of patients with atrial fibrillation, the assessment of central BP was carried out using an equation, and not using applanation tonometry. In addition, we evaluated the outcomes after 6 months. Probably, longer follow-up in this category of patients is necessary in order to fully assess the VAC effect on the prognosis.

Conclusion

The results of our study confirm the impaired cardiovascular function in patients with DHF. With disease progression, Ea and Ees may deviate from normal values, and the ratio of Ea/Ees may be close to normal values. Therefore, the measurement of each component of this ratio can describe and quantify the interaction of the heart and blood vessels. In our study, the VAC parameters are associated with a risk of adverse outcomes in the studied population. Thus, treatment aimed at improving VAC by enhancement of both or each of its components can delay the progression of HF and possibly improve prognosis.

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