Review Article

My Approach to HFpEF Considering Ventricular-Arterial Coupling and Ventricular Interdependence

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Abstract

Heart failure (HF) is a serious public health issue that impacts the mortality and morbidity of the global population. The prevalence of heart failure with preserved ejection fraction (HFpEF) is clearly increasing, associated with population aging, obesity, sedentary lifestyle, and cardiometabolic diseases. It is one of the most urgent diagnostic and therapeutic challenges nowadays. Additionally, the obesity phenotype of HFpEF may be associated with HF and occurs as a result of several mechanisms that are deleterious to cardiac function, including the direct action of epicardial adipose tissue (EAT), causing direct restraint of the pericardium and ventricular interdependence, with significant hemodynamic repercussions, decline in functional capacity, and a worse prognosis. The estimation of ventricular-arterial coupling (VAC) in a non-invasive manner by echocardiography allows a better understanding of the interaction between the heart and the arterial system by monitoring hemodynamic changes, which can guide medical therapy and have an impact on prognosis. Although these tools and parameters are promising, new technologies, such as artificial intelligence and machine learning, must be used to enable the applicability of VAC in clinical practice. Further studies are key to standardizing new methods and values in this context.

Introduction

Heart failure (HF) is a serious public health issue that affects millions of individuals worldwide and has a considerable impact on mortality and quality of life. Although epidemiological data indicate that the global incidence of HF tends to decrease, the prevalence of heart failure with preserved ejection fraction (HFpEF) continues to grow, being associated with population aging, obesity, sedentary lifestyle, and cardiometabolic diseases.[1-3]

The pathophysiology of HFpEF is associated with the primary morbidities that cause cardiac and vascular aggression from a chronic pro-inflammatory state. More specifically, this cardiac structural and functional impairment results from a complex interaction between metabolic abnormalities, damage to microcirculation, changes in the functioning of cellular organelles, autonomic dysfunction, exacerbation of the activity of the renin-angiotensin-aldosterone system (RAAS), and maladaptive immune responses.[4,5]

The diagnosis of HFpEF is challenging in most cases and is usually obtained in the advanced stages of the disease, which limits the therapeutic results. In summary, HFpEF can be diagnosed in the presence of clinical evidence of HF, left ventricular ejection fraction (LVEF) ≥ 50%, and evidence of elevated filling pressures and/or cardiac structural alteration. Therefore, a thorough clinical evaluation, echocardiographic examination, and natriuretic peptide levels remain fundamental diagnostic resources.[6]

Thus, HFpEF is one of the most pressing diagnostic and therapeutic challenges nowadays, considering its increasing prevalence, underdiagnosis, poor prognosis, limited therapeutic options, and considerable impact on healthcare systems.

HFpEF with obesity phenotype

HFpEF is characterized by the coexistence of multiple cardiac and non-cardiac diseases. In this way, distinct clinical phenotypes can be identified and determined by different risk factors, comorbidities, left ventricular (LV) remodeling, hemodynamic pattern, and organ dysfunction (Table 1).[6,7] Obesity, in addition to being unequivocally associated with systemic arterial hypertension (SAH), diabetes mellitus (DM), and insulin resistance, has been identified as the primary cause of HF, mediated by several elements that are deleterious to cardiac function due to altered cardiometabolism and direct restraint of the pericardium (epicardial fat), as well as systemic effects on the lung, skeletal muscle, kidney, and liver because of systemic inflammation, neurohormonal activation, autonomic dysregulation, and altered hemodynamic load (Table 1).[7-13]

Recent studies on obesity have given greater attention to the location of fat than to the amount of fat itself since subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and epicardial adipose tissue (EAT) contribute differently to the overall cardiovascular risk (Figure 1).[12,14,15] EAT may

Keywords

Obesity Phenotipe; Ventricular-Arterial Coupling; Ventricular Interdependence

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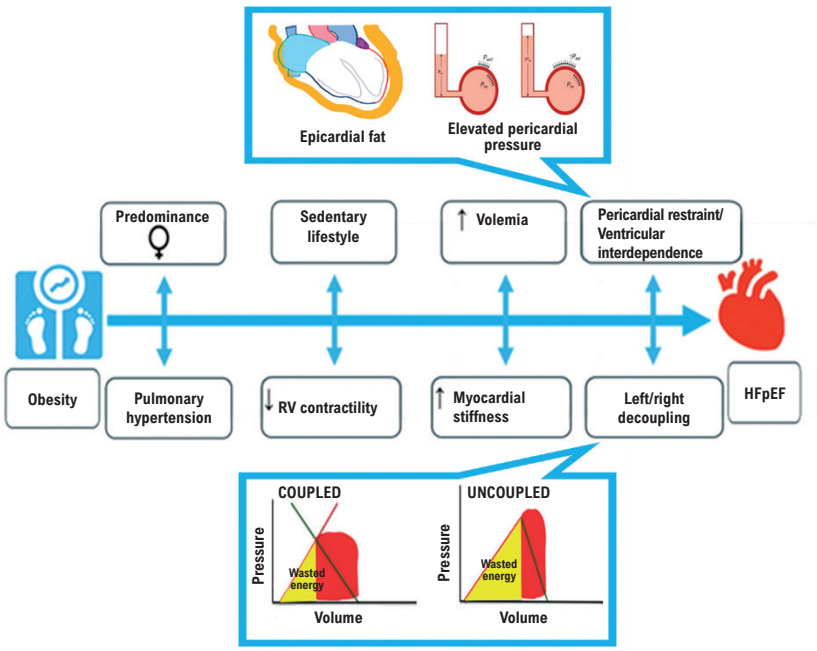
Central Illustration: My Approach to HFpEF Considering Ventricular-Arterial Coupling and Ventricular Interdependence



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Development and progression of HFpEF with obesity phenotype. The implications for ventricular interdependence and VAC are highlighted. Source: Adapted from Borlaug et al., 2023.[13]

favor the onset of HFpEF due to pro-inflammatory paracrine effects, lipid infiltration, and pericardial restraint (Figure 1).[12,15]

It is worth emphasizing that, in HFpEF, arterial hypertension and other comorbidities coexist and lead to a scenario of chronic afterload elevation as a consequence of increased arterial stiffness and impaired vasodilation (dysregulation of the NO-sGC-cGMP-PKG pathway - nitric oxide, soluble guanylate cyclase, cyclic guanosine monophosphate, and protein kinase G), associated with an increase in blood volume and the appearance of early reflected pulse waves in the aorta (AO) (Figure 2). The stiffer (less compliant) artery causes a pulse wave that propagates at a higher speed, causing the corresponding reflex wave to return to the ascending AO earlier, still at the end of systole, with the aortic valve open. This results in an increase in systolic blood pressure (SBP), a reduction in diastolic blood pressure, and a reduction in coronary perfusion, i.e., a vicious cycle of progressive afterload increase and myocardial dysfunction (Figure 2). Ventricular-arterial coupling (VAC) has been used to assess the efficiency of the ventricular-arterial interaction process, and it also appears to represent an accurate marker of early LV dysfunction and potential therapeutic guidance in HFpEF.[13,16-22]

VAC

VAC assesses the relationship between two anatomically and functionally connected structures: the heart and the arteries. To investigate this interaction, a unit common to both systems is used: elastance, which measures changes in pressure for each unitary change in volume - unit: mmHg/ml. Originally, the elastance and VAC data came from the interpretation of the pressure-volume diagram of the cardiac cycle, derived from an invasive hemodynamic study (Figure 3).[16]

Arterial elastance (Ea) is defined as the ratio between ventricular end-systolic pressure and Stroke volume (ESP/Stroke volume), being influenced by vascular resistance, pulsatile load, and heart rate. It is characterized as an index of arterial load for the left ventricle. End-systolic elastance (Ees), usually known as ventricular elastance, is an index of LV contractility, independent of the load, and reflects the slope of the pressure-volume relationship curve at the end of systole (Figure 3), being the ratio between ventricular end-systolic pressure and ventricular end-systolic volume (ESP/ESV). The Ea/Ees ratio (ESP/Stroke volume)/(ESP/ESV) can be simplified as ESV/Stroke volume (removing ESP from the equation).[22]

VAC is defined as the ratio of Ea/Ees and investigates the contractile capacity of the heart and its ability to adapt to load impositions.[21] Previous studies have shown that the ideal VAC value, derived from the Ea/Ees ratio, should vary between 0.5 and 1, reflecting the state in which the LV systolic work is ideal (Figure 4). An Ea/Ees ratio > 1 suggests ventricular-arterial decoupling (Figure 4). Such ventricular-arterial incompatibility is frequently seen in HFpEF, being attributed to diastolic dysfunction induced by increased afterload and

Table 1 – Structural and functional changes in HFpEF

Cardiac Abnormality	Frequency, %
Alteration of LV geometry, concentric hypertrophy, or remodeling	60
Alteration of LV diastolic function (altered relaxation, increased stiffness)	80-90
Myocardial fibrosis	Mild 66 Moderate 17 Major 10
Microvascular myocardial dysfunction and/or reduced microvessel density	80
Increased LV stiffness	70
Left atrial enlargement and/or systolic and diastolic dysfunction	70
Increased epicardial fat	40-50 (patients with obesity)
Pericardial constriction with altered LV filling	30
Atrial fibrillation	40-50
Epicardial coronary artery disease	50-65
Pulmonary	
Post-capillary pulmonary hypertension or combined pre- and post-capillary pulmonary hypertension (group 2)	80
Pulmonary arterial, venous, and small vessel remodeling Restrictive pulmonary physiology	Mild 40-50 Moderate 10
Right heart	
RV diastolic dysfunction	50
RV enlargement and systolic dysfunction	30
Right atrial enlargement and/or right ventricular systolic/diastolic dysfunction	50
Vascular	
Increased arterial stiffness	70
Alteration of systemic microvascular function	70
Reduced systemic venous compliance and capacitance	70
Systemic	
Obesity	60-70
Dysglycemia/insulin resistance	60-70
Neurohumoral activation	30
Reduction of skeletal muscle and replacement with fat	60
Increased visceral fat	70
Renal	
Reduced glomerular filtration rate	60
Reduced sodium excretion	70
Hepatic	
Non-alcoholic fatty liver disease	40-50
Congestive liver disease	10

Table adapted from Redfield et al., 2023.[7] LV: left ventricle; RV: right ventricle.

subendocardial ischemia, and may be associated with a worse prognosis.[16]

Left VAC

The gold standard echocardiographic method for assessing LV-AO VAC is the so-called *single beat method*, developed by Chen et al.[23] (Figure 5). Simple non-invasive parameters that can be easily collected should be obtained: systolic and diastolic blood pressure, ejection volume, ejection fraction, pre-ejection period, and total ejection period. As the formulas are relatively complex, it is recommended to use an easy-to-use application (iElastance© - Apple iOS application)[24] (Figure 6), which yields fast and reliable results.

The proposed normal value for Ea is 2.2 (±0.8) mmHg/ml, and for Ees is 2.3 (±1.0) mmHg/ml.

$$Ea = (SBP \times 0.9) / Stroke\ Volume$$

$$Ees = [DBP - (E(nor)(est) \times SBP \times 0.9)]/E(nor)(est) \times Stroke\ Volume$$

where *DBP* and *SBP* are the diastolic and systolic cuff blood pressures, measured through the upper arm; *E(nor)(est)* is the normalized ventricular elastance, estimated at the beginning of ejection; and *Stroke volume* is derived from the product of the VTI (velocity-time integral) of the Doppler spectrum of the LV outflow tract flow by the measured LV outflow tract diameter.[22] Using the dedicated application avoids complex and time-consuming calculations. The user simply fills in the fields with the requested data: SBP (mmHg), diastolic blood pressure (mmHg), LV ejection fraction (%), stroke volume (ml), pre-ejection time (ms), and total ejection time (ms) (Figure 5). The result is immediate with the values of: Ea, Ees, and VAC (Figure 6).

Several methodologies have emerged to assess LV-AO VAC using echocardiography. The measurement of pulse wave velocity (PWV) appears to comprehensively represent arterial load (arterial stiffness, aortic impedance, and early reflected waves) (Figure 2), associated with the measurement of the global longitudinal strain (GLS) of the LV as a marker of myocardial performance. Therefore, the use of the PWV/

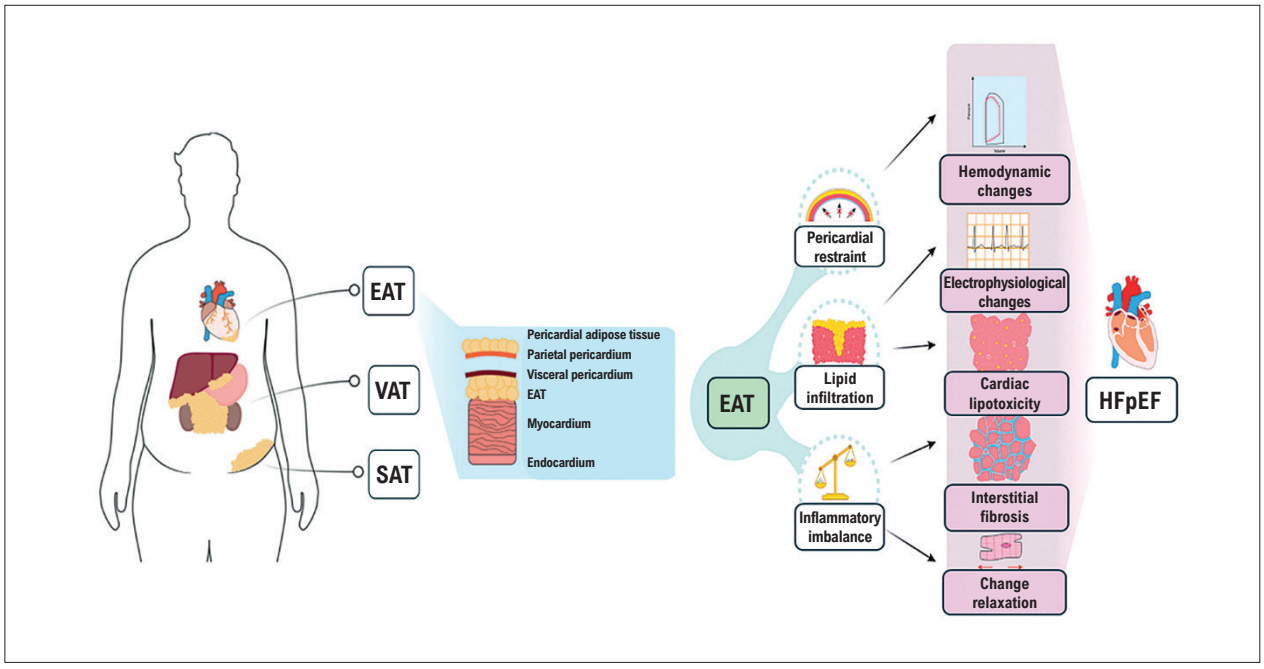

Figure 1 – *Different locations where fat can be deposited and the pathological potential of EAT. Source: Adapted from Dronkers et al., 2024.[12] EAT: epicardial adipose tissue; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; HFpEF: heart failure with preserved ejection fraction.*

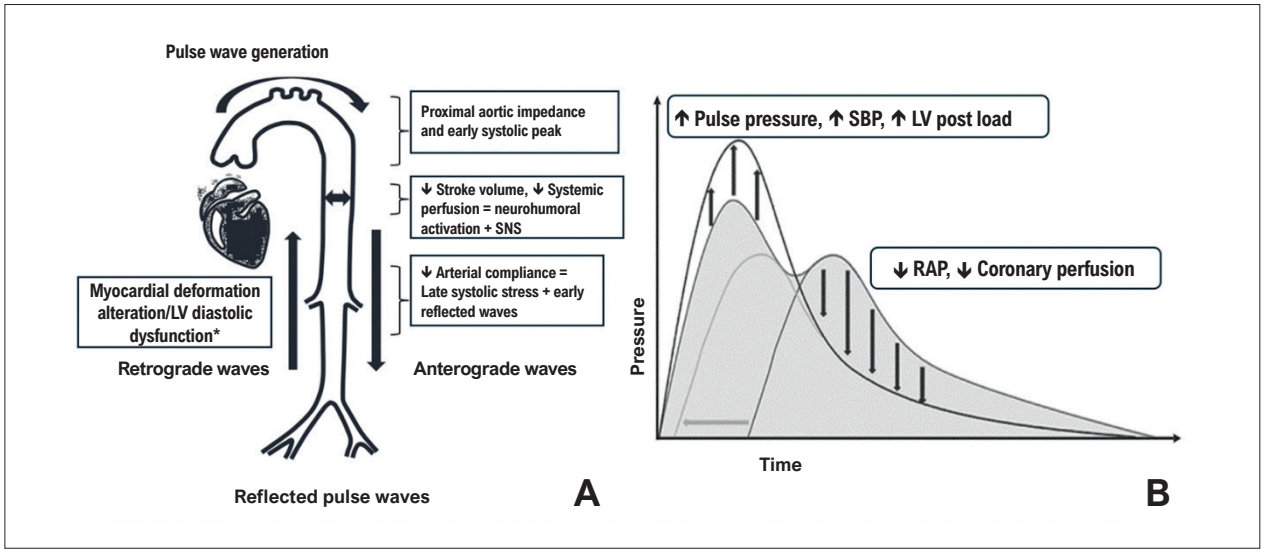

Figure 2 – *A: Pathophysiological mechanism that leads to LV dysfunction. B: Increased aortic stiffness and the emergence of early reflected waves that reach the heart at the end of systole, promoting increased pulse pressure, increased SBP, increased afterload, reduced diastolic blood pressure, and reduced coronary perfusion. Source: Adapted from Ikonomidis et al., 2019.[16] LV: left ventricle; SNS: sympathetic nervous system; SBP: systolic blood pressure; RAP: right atrial pressure.*

GLS ratio may be more appropriate in several scenarios to characterize VAC since it incorporates "gold standard" methods to assess arterial load (PWV) and LV contractility (GLS), with prognostic value.[16,22,25]

The use of 3D echocardiography to measure ventricular volumes, the use of myocardial work to analyze myocardial performance and the increasing incorporation of artificial intelligence and machine learning to calculate ventricular elastance (Ees) represent technical evolution and contribute to greater applicability of VAC in clinical practice in the future.[16,17] Studies will be necessary to standardize methods and values in this context.

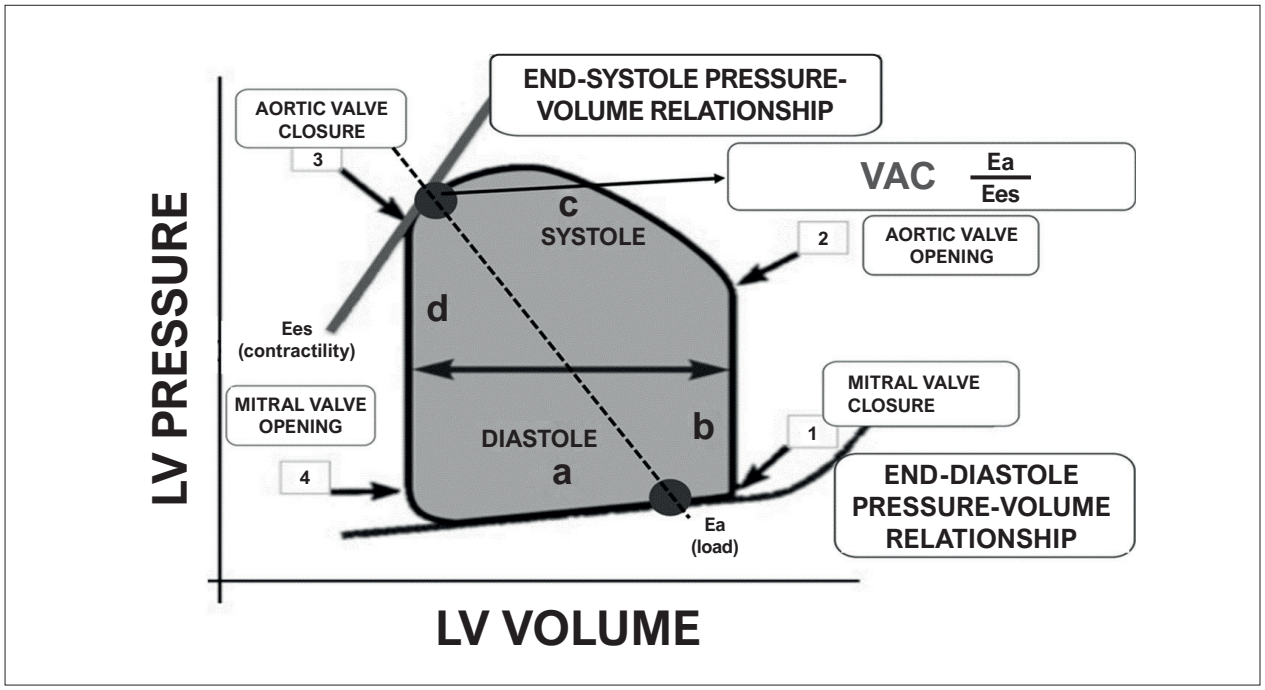

Figure 3 – *A classic Pressure-Volume diagram in the cardiac cycle demonstrating the Pressure-Volume relationship curves at the end of diastole and the Pressure-Volume relationship at the end of systole, determining Ea, Ees, and LV-AO VAC. Source: Adapted from Gamarra A et al., 2024.[17] Ea: arterial elastance; Ees: end-systolic elastance; LV: left ventricle; AO: aorta; VAC: ventricular-arterial coupling.*

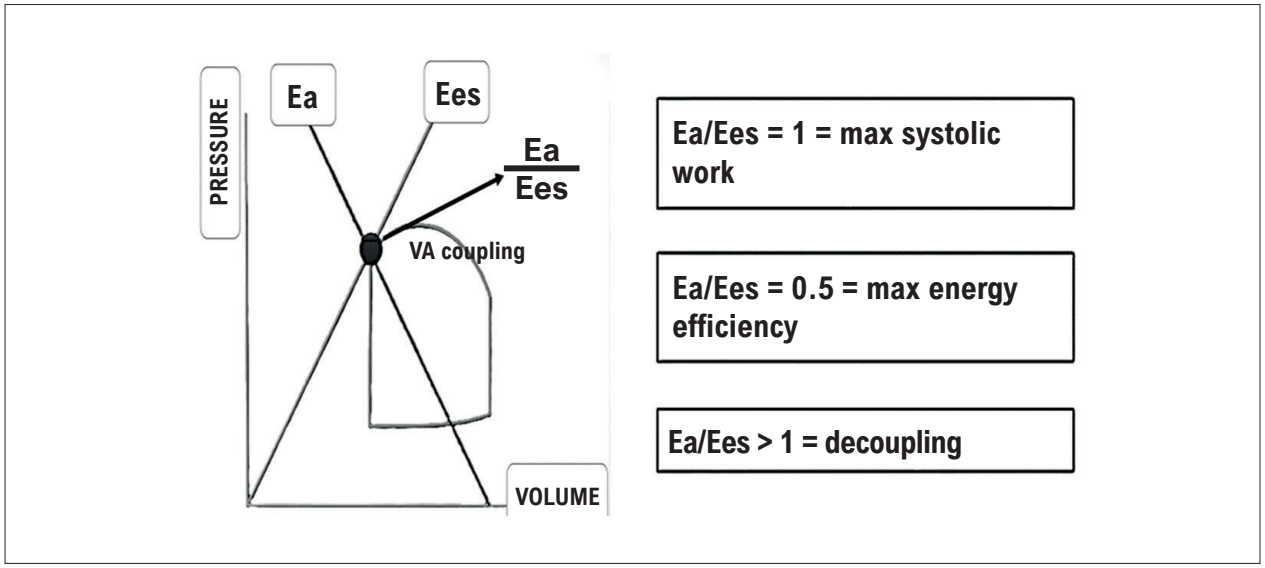

Figure 4 – *Assessment of energy efficiency in blood transfer from the ventricular to the arterial system by calculating VAC. Source: Adapted from Chirinos et al., 2013.[18] Ea: arterial elastance; Ees: end-systolic elastance; VE: left ventricle; VA: ventricular-arterial*

Right VAC

The TAPSE/PASP ratio (tricuspid annular plane systolic excursion/pulmonary artery systolic pressure) expresses the relationship between RV contractility and its afterload. It has been shown to have a good correlation with invasive methods deemed the "gold standard" for measuring RV (right ventricle)-PA (pulmonary artery) coupling. Consequently, the TAPSE/PASP ratio has been incorporated into the main guidelines for the assessment of RV and pulmonary hypertension.[26-28]

TAPSE is measured by M-mode echocardiography (Figure 7A) and assesses RV contractile function. To estimate RV afterload (PASP), the maximum velocity of the tricuspid

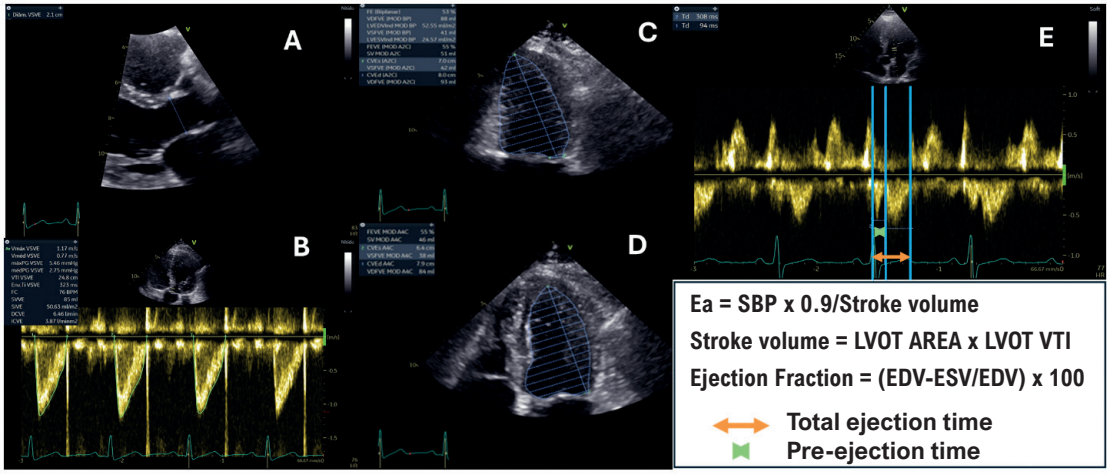

Figure 5 – *(A) Two-dimensional echocardiographic image in parasternal view, long axis, zooming in on the LV outflow tract diameter measurement. (B) VTI image of the Doppler spectrum of the LV outflow tract flow, which is obtained by tracing the fullest line of the spectrum to calculate the stroke volume. (C)/(D) Two-dimensional echocardiographic image in apical 4-chamber (D) and 2-chamber (C) views to obtain the LVEF value (Simpson method). (E) Apical 5-chamber view of the Doppler spectrum of the LV outflow tract flow and mitral inflow to obtain pre-ejection time (green) and total ejection time (orange). Ea: arterial elastance; SBP: systolic blood pressure; LVOT: left ventricular outflow tract; EDV: end-diastolic volume; ESV: end-systolic volume; VTI: velocity-time integral; LVEF: left ventricular ejection fraction.*

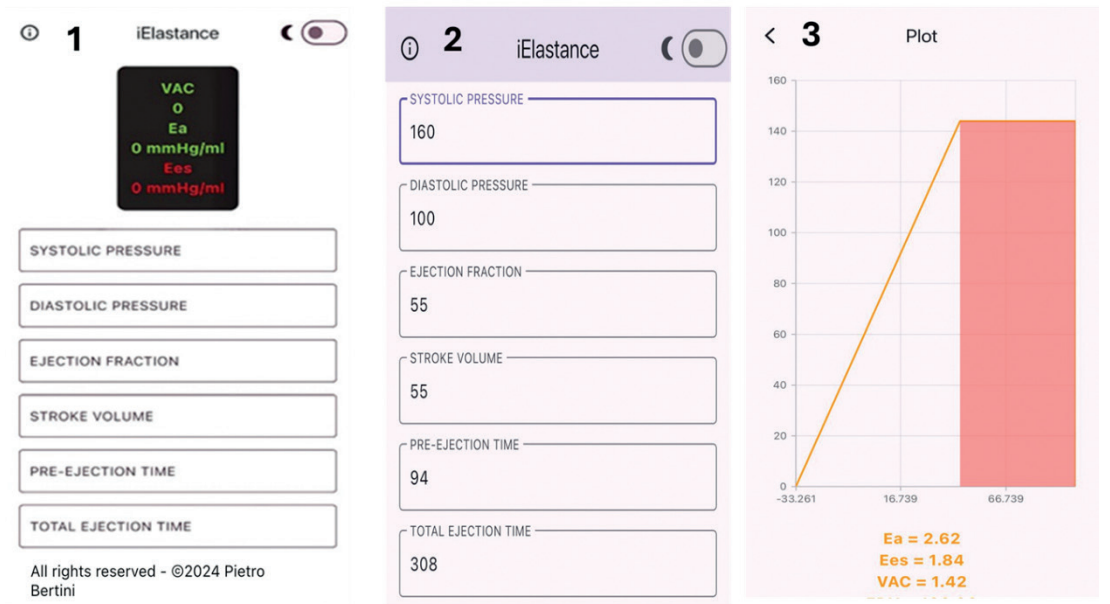

Figure 6 – *(1) Image reproduced from the mobile application showing how easy it is to use. It is only necessary to fill in the fields with the data obtained, as shown in Figure 5. (2) Practical example of filling in the fields. (3) Immediate result for Ea, Ees: end-systolic elastance, and VAC. Source: Bertini P. iElastance- Apple iOS App. Available at: https://apps.apple.com/br/app/ielastance/id556528864.*[24]

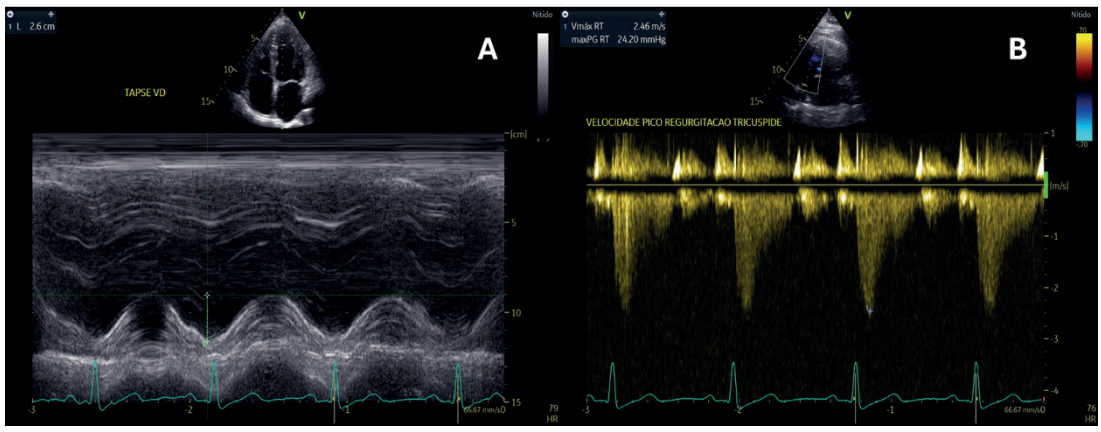

Figure 7 – *(A) Tricuspid annular displacement measured by M mode echocardiography - TAPSE. (B) Continuous Doppler spectral curve, demonstrating tricuspid regurgitation flow, allowing the systolic pressure in the pulmonary artery to be estimated. The TAPSE/PASP ratio estimates the value of RV-PA VAC. TAPSE: tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure; RV: right ventricle; PA: pulmonary artery.*

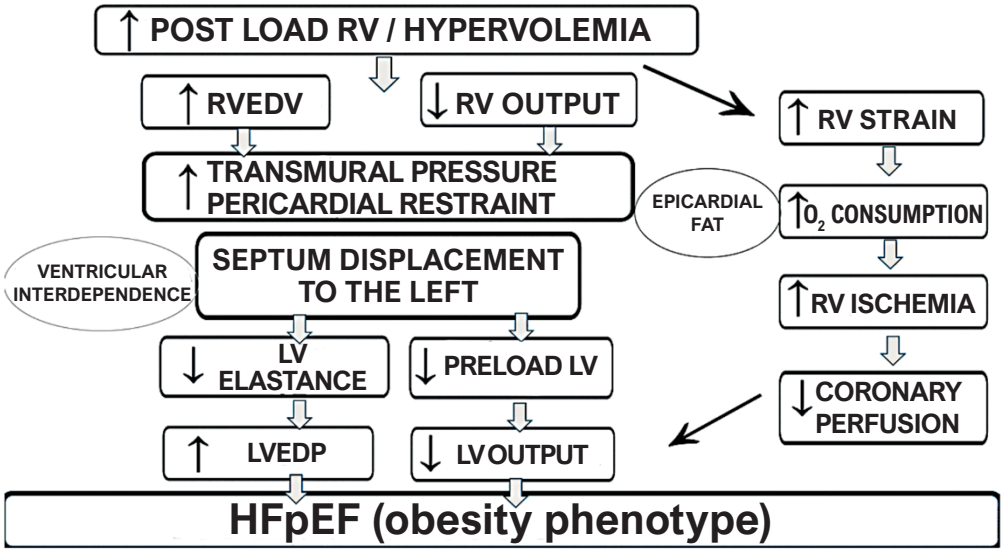

Figure 8 – *A proposed hemodynamic mechanism for HFpEF with obesity phenotype. LV: left ventricle; RV: right ventricle; O_2: oxygen; LVEDP: left ventricular end-diastolic pressure; RVEDV: right ventricular end-diastolic volume.*

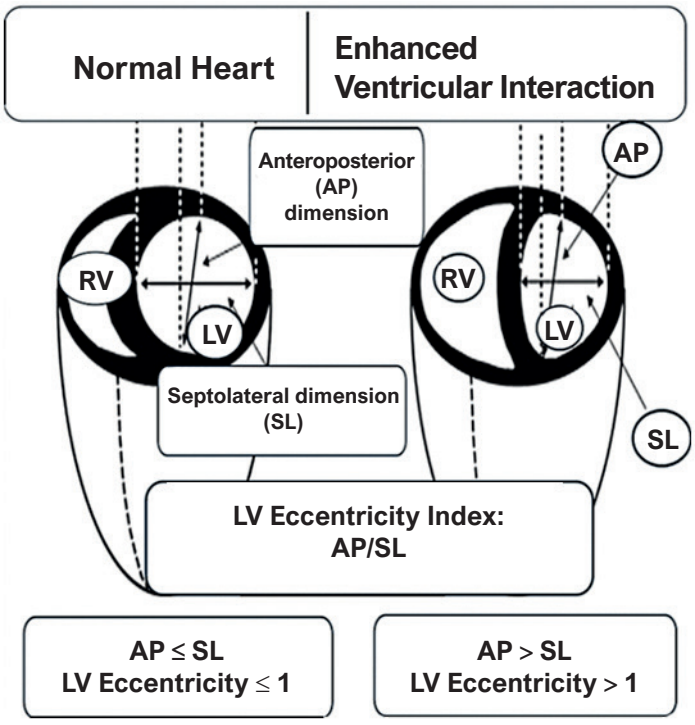

Figure 9 – *Illustration showing an increase in the LV eccentricity index due to ventricular interdependence, as proposed for HFpEF with obesity phenotype. Source: modified Borlaug et al., 2019.[39]*

regurgitation jet is determined by analyzing the continuous Doppler spectral curve and adding the right atrial pressure (RAP), which is estimated by observing the inferior vena cava. As a result, the RVSP (right ventricular systolic pressure) is obtained, which is calculated using the modified Bernoulli equation: 4 x peak velocity (Figure 7B). In the absence of right ventricular outflow tract obstruction or pulmonary stenosis, RVSP is equal to the PASP.

In HFpEF with obesity phenotype, right ventricular dysfunction results from several mechanisms acting on preload, afterload, and contractility of the right ventricle. Increased pulmonary pressure (combined pre- and post-capillary) is frequently present, as is right ventricular dilation, primary ventricular sarcomere dysfunction, pericardial constriction, and ventricular interdependence, which further aggravate biventricular filling and pulmonary hypertension.[27]

RV dysfunction is an independent predictor of mortality and hospitalization risk in HFpEF. Therefore, it should always be investigated. A TAPSE/PASP ratio < 0.48 mm/mmHg was associated with higher all-cause mortality and higher hospitalization for HF in a population with HF with preserved and reduced LVEF.[29] Another study has demonstrated that, in the subgroup of patients with HFpEF and pre-capillary pulmonary hypertension, a TAPSE/PASP ratio < 0.36 mm/mmHg was associated with poor clinical outcomes, but suggested that these individuals could respond more favorably to interventions targeting RV afterload.[30]

It is important to highlight that the RV-GSL/PASP ratio has also been used as an appropriate methodology to assess RV-PA coupling and has proven to be an accurate instrument for assessing patients in different scenarios.[26-28]

VAC X HFpEF

In the context of HFpEF, the calculation of the LVEF does not characterize broader aspects of the ventricular-arterial connection, particularly those related to afterload (Ea) or contractility (Ees), which are highly relevant for therapeutic management in patients with clinical symptoms of HF and preserved LVEF. In this scenario, Ees may be normal, while Ea may be increased, resulting in Ea/Ees > 1.0 (VA decoupling). However, Ea/Ees can often occur with a normal result (between 0.5 and 1.0), despite Ea and Ees being elevated. Therefore, it is crucial to identify the value of the elastances individually[22] (Figures 5 and 6). Some interventions have shown potential impact on elastances, in addition to improving VAC: antihypertensive drugs,[21] angiotensin receptor-neprilysin inhibitors (ARNIs),[31] sodium-glucose cotransporter-2 (SGLT2) inhibitors,[32] GLP-1 analogs,[33] and interleukin IL-1[34] and IL-12 inhibitors.[35]

The use of VAC to assess the population with HFpEF has proven to be an accurate tool for stratifying those individuals at greater risk. In a recent study involving patients with LVEF > 40%, it was shown that the subgroup of patients, despite having higher LVEF, had a greater degree of LV

hypertrophy, higher LV filling pressures, and a higher rate of LV-AO decoupling with a worse prognosis. On top of that, the subgroup that showed RV-PA decoupling, verified by the TAPSE/PASP ratio, also demonstrated a worse prognosis, regardless of LVEF values, E/e' ratio, and presence of atrial fibrillation.[34]

Pericardial restraint (HFpEF) X ventricular interdependence

Obese patients with HFpEF have peculiar pathophysiological characteristics, including hypervolemia, RV-PA decoupling, biventricular hypertrophy, right ventricular dysfunction, pre- and post-pulmonary capillary hypertension, elevated filling pressures in left chambers, and increased EAT[36] (Figure 8).

Due to its proximity to the myocardium, excess EAT can promote local inflammatory and mechanical constrictive effects on the cardiac muscle. Pericardial restraint associated with hypervolemia can increase pericardial pressure, promote competition for filling between the RV and LV, cause flattening of the ventricular septum, highlight ventricular interdependence, and lead to RV distension, reduced LV preload, increased LV end-diastolic pressure, and reduced cardiac output (Figure 8). On echocardiography, it is possible to quantify, using the parasternal short-axis plane, the LV eccentricity index, which becomes higher (LV eccentricity index > 1) (Figure 9) as greater pericardial constriction and higher intracardiac pressures are observed, including right atrial, pulmonary arterial, and RV end-diastolic pressures, which are concomitant with a significant reduction in functional physical capacity.[37-40]

Ventricular interdependence has been a therapeutic target of several current studies. Studies performing transcatheter interventions to reduce tricuspid regurgitation in patients with HFpEF have been designed to improve ventricular interdependence and increase LV filling.[40,41] Similarly, a pilot study has demonstrated the potential for surgical pericardiotomy in patients with HFpEF and restraint EAT.[42]

Final considerations

The magnitude of the global public health issue of HFpEF, in which obesity has a prevalence of approximately 70% (Table 1), has motivated, in recent years, a more specific investigation of the phenotype of subpopulations for better diagnostic, therapeutic, and prognostic results. Particular attention has been given to excess EAT in this population, which, associated with volume overload, can lead to pericardial restraint with ventricular interdependence, contributing to a more significant increase in left chamber filling pressures, worsening of pulmonary pressure, reduction in cardiac output, low physical capacity, and a worse prognosis. This hemodynamic condition can be identified by echocardiogram (LV eccentricity index > 1).

Non-invasive analysis of VAC by echocardiography appears to be a promising tool to assess hemodynamics in a more individualized manner and customize the treatment of patients with HFpEF. The single-beat echocardiographic method, coupled with a dedicated application, is becoming increasingly feasible. Besides, physicians are gaining more experience with this technology, having a better understanding of the complex interaction between the heart and the vessels. Yet, efforts to develop new methods must continue, both through advanced imaging techniques and new software solutions, artificial intelligence, and machine learning. It is clear that the earlier an accurate diagnosis, etiological definition, and severity estimation are made, and preventive and therapeutic efforts are implemented, the greater the benefits in terms of disease progression and the associated outcomes.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data and writing of the manuscript: Braga JCMS; critical revision of the manuscript for intellectual content: Braga JCMS, Assef JE, Guimarães Filho FV, Silva RAB.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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