Review Article

Invasive Hemodynamic Monitoring in the Diagnosis of Heart Failure with Preserved Ejection Fraction

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome that has a negative impact on quality of life and life expectancy of patients, with high hospitalization and mortality rates. HFpEF is a highly prevalent disease, probably due to the increase in the prevalence of common risk factors, such as advanced age, female sex, arterial hypertension, diabetes, renal failure and obesity.[1,2] It is estimated that nearly half of heart failure patients have preserved ejection fraction, defined as a left ventricular (LV) ejection fraction (LVEF) ≥50%. Despite the publication of numerous original articles, reviews, books and guidelines, there are still doubts and controversies regarding the real incidence, etiopathogenesis, pathophysiology, prognosis, and mainly the difficulties in the correct diagnosis of HFpEF by non-invasive methods. In this paper, we will describe the importance of the invasive hemodynamic monitoring (IHM) for the correct diagnosis of HFpEF.[1-4]

Non-invasive diagnosis of heart failure with preserved ejection fraction

Before addressing the role of IHM in the diagnosis of HFpEF, we will briefly consider the non-invasive methods available for this purpose and highlight their main limitations.[5,6]

Because of the difficulty or even impossibility of a clinical differential diagnosis between HFpEF and heart failure with reduced ejection fraction (HFrEF), all guidelines recommend the use of two-dimensional color Doppler for a detailed evaluation of diastolic function.[6-9] In the assessment of diastolic function, we will analyze several echocardiographic parameters (mitral flow, tissue doppler, left atrial volume and area, pulmonary artery pressure), which, when combined, allow the diagnosis of HFpEF.[6-8,10]

Analysis of mitral flow is the first step in the assessment of diastolic function in patients with sinus rhythm. By Doppler echocardiography, it is possible to determine the early wave (E wave) and the late wave (A wave) of LV filling.[10] E wave represents the rapid filling by difference of pressure, and the A wave represents active filling by atrial contraction. Diastole is analyzed by the relationship between E and A waves together with the deceleration time of E wave. E wave velocity can be analyzed in conjunction with tissue Doppler as we will see below. In healthy subjects, the ratio between the velocities of the E and A waves – the e/a ratio – is greater 1.0. Aging is associated with stiffening of the left ventricle, leading to a decrease in E wave velocity and lower deceleration time of the wave, and an increase in A wave velocity resulting in a E/A ratio lower than 1.0. This pattern of filling is known as change of relaxation, which does not imply a pathology *per se*, and, in most patients, does not indicate an increase in filling pressure or in LV end-diastolic pressure.

In patients with a reduction in LV compliance and increased LV diastolic pressure, a rapid equalization of left atrial and LV pressures is observed, resulting in early interruption of blood flow. Consequently, there is an increase in E wave velocity and decrease in deceleration time, associated with a reduction in A wave velocity. With these changes, the LV filling pattern becomes similar to the normal pattern and named as pseudonormal pattern, which probably indicates the presence of pathological diastolic dysfunction. The differentiation between the pseudonormal and normal patterns can be made by the Valsalva maneuver, with the increase of diastolic and LV filling pressures. These mitral flow changes tend to become more pronounced, with an increase in the E/A ratio (to values greater than 2.0), greater reduction in the E wave deceleration time and A wave velocity, characterizing the restrictive pattern of LV filling, which also results in probable pathological diastolic dysfunction.[11,12] Notably, the analysis of the E/A ratio has important limitations in the diagnosis of HFpEF for depending on several variables, including heart rate, arrhythmia, preload (blood volume), and afterload (hypertension). Therefore, this analysis is only accurate in patients with sinus rhythm and normal heart rate.[10,11]

Tissue Doppler echocardiography measures the velocity of basal myocardium displacement and mitral ring motion. Tissue Doppler curves are obtained from the apical four chamber view, in the septal and lateral mitral ring, where three wave velocities can be determined: early diastolic wave (e′), end diastolic wave (a′) and systolic wave (s). In case of altered relaxation, e wave velocity is reduced, regardless of LV filling pressures. The greatest importance of this method in the assessment of diastolic function is that it allows concomitant analysis of Doppler indices of mitral inflow, particularly mitral E wave and e′ wave (septal, lateral or medial) of tissue Doppler imaging. The E/e′ ratio has been used as an indirect measure of pulmonary capillary pressure or LV end diastolic pressure. Nevertheless, in HFpEF patients, the analysis of ventricular filling parameters, including the E/e′ ratio, compared with filling pressure measures obtained from simultaneous IHM

Keywords

Heart Failure; Heart Failure, Diastolic; Diagnosis.

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Manuscript received August 22, 2022, revised manuscript September 13, 2022, accepted September 13, 2022

DOI: https://doi.org/10.36660/abc.20220059

has low, or at most, moderate predictive value in estimating filling pressure.[13,14] E/e′ ratio has weak correlation with hemodynamic measures, especially when the ratio is below 15. It is worth mentioning that calculation of the E/e′ ratio depends on an adequate echocardiographic window and presence of sinus rhythm and is influenced by valvular changes such as mitral annular calcification and mitral insufficiency, both common in the elderly.[12-14]

All these echocardiographic parameters may not be altered at rest and in this case should be interpreted with caution. Most patients with HFpEF experience symptoms with activity only due to increases in filling pressure. Thus, the measurement of echocardiographic parameters, particularly the E/e′ ratio during exercise (diastolic stress test) is more sensitive and can be useful in the assessment of these patients. While the E/′e′ ratio is not affected during exercise in healthy individuals, it increases in patients with LV diastolic function, with a correlation with filling pressure and pulmonary pressure increases. Therefore, diastolic stress test should be considered for patients with a HFpEF phenotype, clinical presentation of heart failure and E/e′ ration lower than 15.[13-18] Performance of lung ultrasound concomitantly with diastolic stress test may help to detect pulmonary congestion with an elevation of pulmonary capillary pressure.[19] Limitations of stress echocardiography include its unavailability as a routine test in most echocardiography laboratory, poor echocardiographic window, dependence on operator experience in obtaining the hemodynamic parameters, and the fact that the quality of images is affected by tachypnea during exercise. Only 50% of patients undergoing stress echocardiography have adequate echocardiographic window. In addition, atrial fibrillation is a limiting factor that corroborates the poor accuracy of echocardiogram in assessing filling pressure during stress.[12,13]

In light of limitations of invasive methods here described and the lack of consensus about the best way to diagnose HFpEF, some authors have tried to establish uniform criteria in this regard. Considering the difficulties in confirming the non-invasive diagnosis of HFpEF, diagnostic scores are important to strengthen a clinical suspicion and screen eligible patients for IHM.[20,21]

The H2FPEF score is the most widely used scoring system (Table 1), as it can be easily and accurately calculated.[19] The score was developed in a cohort of patients with unexplained dyspnea who were referred for right heart catheterization and stress test. The score includes six clinical and echocardiographic variables: age >60 years, body mass index (BMI) >30 kg/m², arterial hypertension (treatment with ≥2 antihypertensives), atrial fibrillation (permanent or paroxysmal), echocardiographic E/e′ ratio >9 and echocardiographically derived systolic pulmonary artery pressure >35 mmHg. The presence of atrial fibrillation yields 3 points, a BMI > 30 kg/m² yields 2 points, and the other criteria yield 1 point. The H2FPEF had good discriminatory ability (area under the ROC curve of 0.84) and higher sensitivity and specificity to exclude or confirm HFpEF as compared with the HFA-PEFF score.[23] Since the HFpEF score estimates disease likelihood, the instrument can be used to effectively rule out the disease among patients with low scores (0 or 1), and confirm the diagnosis of HF2pEF with reasonably certainty in

Table 1 – H2FPEF score for the diagnosis of heart failure with preserved ejection fraction

	Clinical variables	Values	Points
H2	Body weight (Heavy)	BMI > 30kg/m²	2
	Arterial hypertension	≥ anti-hypertensives	1
F	Atrial fibrillation	Paroxysmal or persistent	3
P	Pulmonary hypertension	PASP ≥35mmHg	1
E	Elder	> 60 anos	1
F	Filling Pressure	E/e´> 9	1

Total score									
0	1	2	3	4	5	6	7	8	9
0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	0.96	

BMI: body mass index; PASP: pulmonary artery systolic pressure

patients with high scores (>9). Therefore, the HF2pEF score should be used to identify patients with intermediate scores (2-9), who would require additional tests.[19,22,23]

Likelihood of HFpEF

Diagnostic apps may be useful in clinical practice, as they are based on scores that provide information about diagnostic probability of HFpEF with acceptable sensitivity and specificity. Hence, patients with high probability of diagnosis are identified, as well as patients with intermediate probability are screened for more meaningful tests, like the IHM, which provides direct measurements of filling pressures (pulmonary capillary pressure and/or LV end diastolic pressure) and pulmonary arterial pressure at rest and during exercise.[21]

IHM in HFpEF

Exertional dyspnea is a common condition in patients with cardiopulmonary diseases. To elucidate the etiology of dyspnea in clinical practice, we analyze epidemiological data and clinical history, and perform physical examination. Tests like spirometry, cardiopulmonary exercise test and imaging tests help in the diagnosis of diseases that affect the ventilatory function.[21,23] Echocardiography is always used in the cardiological assessment, but, unfortunately, is performed at resting conditions only. In addition, important limitations of the test are not usually considered, including a poor window (due to obesity, chest deformation, pulmonary hyperinflation), and especially atrial fibrillation, which hampers the analysis of diastolic function.[14-16]

The presence of HFpEF should always be considered to differentiate a pulmonary and cardiac cause of dyspnea, as it is responsible for 30-50% of the cases of dyspnea or pulmonary hypertension in patients undergoing IHM.[15,23,24] IHM at rest and during exercise is the best method to elucidate the causes of exertional dyspnea and pulmonary hypertension.

It is currently considered the gold standard for the diagnosis of HFpEF, allowing the direct measurement of ventricular filling pressure, pulmonary pressure, cardiac output, and pulmonary vascular resistance.[24-26] In addition, the method is very useful in patients with mixed diseases, like heart failure and pulmonary disease, as it informs us whether the most limiting factor for exercise has a predominantly cardiac or pulmonary cause.[15,25,26]

Current guidelines for the diagnosis of HFpEF highlight the limitations of echocardiographic data obtained at rest, due to its low sensitivity and low specificity, in addition to technical drawbacks in acquiring echocardiographic parameters for diastolic function assessment. Then, stress echocardiography has been recommended for the diagnosis of HFpEF, although several limitations still exist. Thus, the direct measurement of filling pressures at rest is the only instrument capable of excluding the diagnosis of HFpEF due to its high sensitivity (100%) and specificity (100%) values. Therefore, IHM at rest and during exercise is the only method able to confirm or refute the diagnosis of HFpEF.[22-26]

In addition to allowing an early diagnosis of HFpEF, the IHM provides important information about the severity and prognosis of HFpEF. Increased pulmonary capillary pressure during exercise and its relation to cardiac output are correlated with a worse prognosis in short and medium term.[27,28]

Invasive hemodynamic assessment at rest is useful in cases of hemodynamic abnormalities such as elevations in filling pressures. However, in cases of normal filling pressure, which do not exclude the diagnosis of HFpEF, the method has limited sensitivity, since in this situation, a rise in filling pressure only occurs with exercise.[25,26] Therefore, only IHM during exercise allows to confirm or to exclude HFpEF as the cause of dyspnea, with a sensitivity and specificity of 100%.[15,16,22,23] Although alternatives like acute volume overload and leg raise to increase venous return may be of some help, they should not replace the hemodynamic monitoring with exercise; these alternative strategies should be reserved for patients who cannot carry out exercises involving lower limbs and for dehydrated patients at resting blood pressure time.[29,30]

Indications for IHM in HFpEF

The management of all patients with HFpEF, elderly patients with unexplained pulmonary hypertension, and patients with unexplained dyspnea should be performed according to the flowcharts for HFpEF that include diagnostic scores and parameters for the assessment of diastolic function by echocardiography at rest or diastolic stress test.[21,23] In previous studies, approximately 50% of patients with an intermediate risk score who did not undergo IHM with exertion stress may have HFpEF.[15,16,25,26] The main indications for IHM are listed in Table 2.

Protocol of IHM in HFpEF

We adopt and recommend the HFpEF assessment protocol proposed by Borlaug et al.[15,16,25,26] (Table 3). It is recommended that the patient receives a brief training to perform exercises using an in-bed cycle ergometry, as it contributes to the venous return and increases the elevation in pulmonary capillary pressure (Figure 1). For obese patients who cannot tolerate the supine position, it is recommended to raise the head of the bed up to a 45-degree angle. Both situations should be carried out with the patient under continuous electrocardiographic monitoring and digital oximetry, breathing room temperature air. For patients with atrial fibrillation, it is recommended a good heart rate control before IHM, and that the patient is not dehydrated for excessive use of diuretics.

Table 2 – Main indications for invasive hemodynamic monitoring

1	Patients with a poor echocardiographic window for the assessment of diastolic function by resting echocardiography
2	Impossibility of obtaining reliable parameters by stress echocardiography
3	Patients with permanent atrial fibrillation
4	Patients with an intermediate H2FPEF score (4-8 points)
5	Patients with an E/e´ ratio between entre 9 and 15
6	Patients with pulmonary disease or mixed disease like CPOD that may be the cause of dyspnea
7	Dyspnea and/or pulmonary hypertension of unknown cause

CPOD: chronic pulmonary obstructive disease.

We now describe the steps involved in IHM in the diagnosis of HFpEF. The protocol recommends that the test is started with a workload of 20 watts for three minutes (first stage), followed by an increase to 40 watts for three minutes (second stage). Studies have shown that filling pressures rise to abnormal levels as early as at the end of the first stage[25,26] and rapidly return to baseline values after effort interruption (Figure 2).[31-33]

Interpretation of IHM

An adequate interpretation of the IHM results requires the analysis of curves of filling pressure, right cavity pressure, pulmonary pressure, and left ventricular end diastolic pressure, obtained preferably at the end of exhalation at rest and at maximum effort (Figure 3).

The integrated analysis of all hemodynamic parameters obtained both at rest and during exercise will allow confirmation or exclusion of HFpEF as the cause of symptoms. Values of left ventricular end diastolic pressure may replace pulmonary capillary pressure, especially in case of atrial fibrillation or of suboptimal quality of pulmonary capillary pressure curves due to the presence of V wave due to mitral regurgitation. The diagnosis of HFpEF is established when pulmonary capillary pressure ≥15mmHg at rest or ≥25 mmHg during exercise.[22-24,34] In case of atrial fibrillation, mean pressure of 10 consecutive cardiac cycles should be considered, and extrasystoles excluded. It is worth pointing out that normal blood pressure at rest do not rule out the diagnosis of HFpEF, and it is mandatory to repeat all measures during exercise.[25,26,33,35] If patients are not able to move their legs, arm exercises, volume overload test, passive leg raise maneuver or even a combination of these may be used as alternatives.[29,30,35,36]

Table 3 – Steps of the invasive hemodynamic monitoring in the diagnosis of heart failure with preserved ejection fraction

1	Puncture of the right internal jugular vein and placement of an 8F introducer for Swan-Ganz catheterization
2	Puncture of the right or left radial artery with a 5F introducer for catheterization of the left ventricular cavity with a 5F pigtail catheter and measurement of blood pressure and left ventricular end diastolic
3	Place the Swan-Ganz catheter in zone 2 to obtain pulmonary capillary wedge pressure (typical capillary pressure curve)
4	Install the pressure transducers, zeroed at the level of the mid-axillary line, for measurements of pressures in the right atrium, right ventricle and pulmonary artery, pulmonary capillary pressure and left ventricular end diastolic pressure and mean arterial pressure. Measures are taken according to cardiac cycle (at the end of ventricular diastole) and if possible, at the end of exhale
5	Measure baseline blood pressure and cardiac output at rest. In patients with atrial fibrillation, mean blood pressure should be obtained from 10 consecutive heart beats. Measurements are obtained by a polygraph and printed by a printer coupled to the system
6	Adjust the patient feet on the ergometer pedals and fix them with an adhesive tape
7	Initiate the exercise protocol at 20 Watts and 60 revolutions per minute (rpm) for three minutes, advance to the next stage (workload of 40 watts) for another three minutes. At patient's maximum effort or maximum tolerance, take blood pressure and cardiac output measurements
8	After five minutes at rest, take blood pressure measurements
9	As most patients have coronary disease risk factors, perform coronary cineangiography before removing the radial line
10	After the test, analyze pressure curves and cardiac output measurements, and calculate pulmonary vascular and systemic resistances, transpulmonary and pulmonary diastolic gradients, and eventual left ventricular gradient/end diastolic pressure
11	A diagnosis of HFpEF is confirmed by resting pulmonary capillary pressure or left ventricular end diastolic pressure ≥ 15 mmHg at rest and ≥ 25 mmHg during exercise

HFpEF: heart failure with preserved ejection fraction.

Figure 1 – *Simulation of patient positioning for invasive hemodynamic monitoring in the diagnosis of heart failure with preserved ejection fraction.*

In conclusion, in light of the difficulties of establishing the diagnosis of HFpEF due to the low sensitivity and specificity of invasive methods, especially when of those performed at rest, IHM during exercise has emerged as the gold standard for the diagnosis of HFpEF because of objectivity of filling pressure measurements and high sensitivity and specificity rates, with positive and negative predictive values of nearly 100%.[32,33] This is a safe method that can be used in most patients with a HFpEF phenotype, including patients with an intermediate risk score, patients with dyspnea or pulmonary hypertension of unknown origin after non-invasive tests were performed.[23-25]

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Almeida DR, Andrade FA.

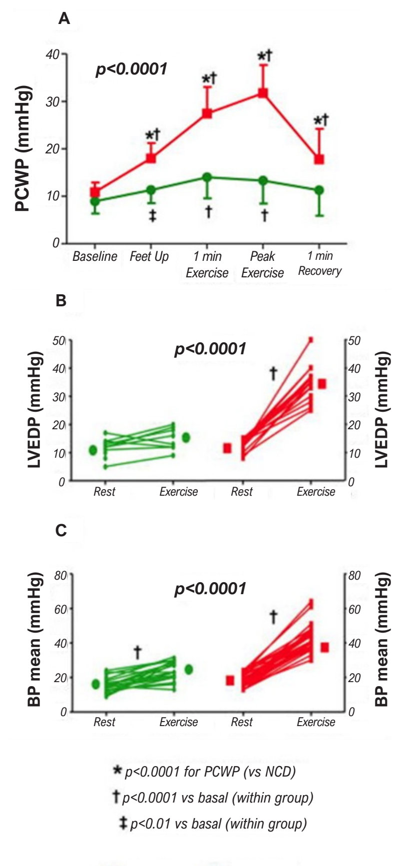

Figure 2 – *Temporal magnitude representation of the increase in pulmonary capillary pressure and left ventricular end diastolic pressure during exercise in patients with heart failure with preserved ejection fraction (Obokata et al. Circulation 2017; 135:825-38, authorized by the author). LVEDP: left ventricular end diastolic pressure; HFpEF: heart failure with preserved ejection fraction; BP: blood pressure; NCD: non-cardiac dyspnea.*

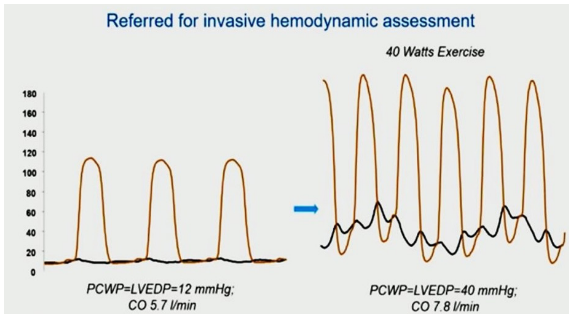

Figure 3 – *Representation of pulmonary capillary pressure (PCWP) and left ventricular end diastolic pressure (LVEDP) curves at rest and at maximum effort of a patient with heart failure with preserved ejection fraction; adapted from Barry et al.[25]*

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

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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