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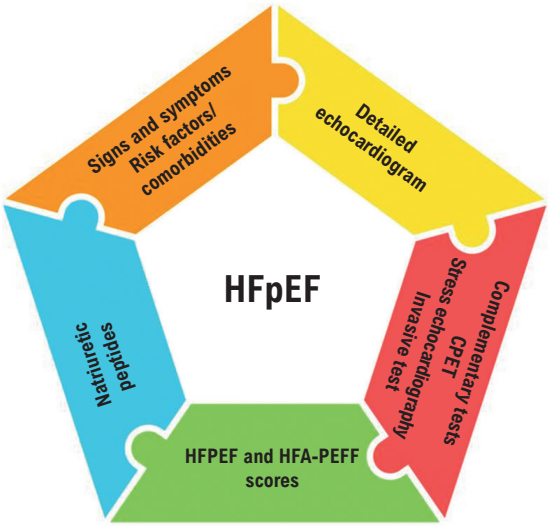

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Editorial

Lessons Learned from Community Studies of HFpEF – The Digitalis Study

Eduarda Corrêa Maia,[1] *Evandro Tinoco Mesquita,*[1] *Antonio José Lagoeiro Jorge,*[1] *Luiz Claudio Danzmann*[2,3]

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"Outpatient medicine is both science and art, as much science and art as hospital medicine, if indeed there is any difference between the two that is not based on pre-judged ideas."

Moacyr Scliar Physician and Public Health Specialist, Member of the Academia Brasileira de Letras

Medical education and, in particular, research in cardiovascular graduate programs have been developed within a segmented view, which reduces and disregards other aspects that constitute the individual, as well as the person beyond the disease. To correct and improve this view, we must understand the transformations that have occurred in medical education and in the health system rather than the privileges that constitute the current health scenario in Brazil. To this end, it is essential to understand the historical context of the changes in health education and medical education that led a group of researchers from the Fluminense Federal University (Universidade Federal Fluminense, UFF) to gain knowledge of heart failure (HF) in the city of Niterói, Brazil, which is the basis of the Digitalis study.[1,2]

Inspired by the importance of primary health care (PHC) in the Alma-Ata Declaration, which was adopted in 1978, projects aimed at improving health quality and access to health were planned and established with methods that included the entire community.[3] From this point onward, we were able to observe the development and implementation of the PHC model in Brazil and, especially, in the city of Niterói, which pioneered the implementation of the Family Health Program (FHP).[4] The FHP, which is based on the family medicine model from Cuba, consists of a team of general practitioners, led by a family doctor, that is responsible for the health of family groups in a given territory.[3,4]

The UFF has been participating in the reconstruction of PHC since its collaboration with the city of Niterói in the 1970s.[5,6] This collaboration began with the implementation of the program through changes in the medical curriculum, bringing new professionals, professors, and the UFF closer to PHC. This relationship promoted increased knowledge of the population of Niterói, especially of the approximately 150,000 inhabitants assisted by the FHP, which is the object of interest of the Digitalis study.[5,6]

To establish a relationship between PHC in Niterói and the UFF School of Medicine, professors with expertise in public health in Niterói played important roles in the development of the Niterói Project, as well as in the update of the UFF medical curriculum, reorganizing health in the municipality and structuring the FHP. Professor Hugo Tomassini, who helped develop the Niterói Project in the 1970s while he was Secretary of Health and later a professor at the UFF Institute of Community Health (currently known as the Institute of Collective Health), Maria Manuela Alves dos Santos, professor at the Community Health Institute, and professor Luis Santini, director of the School of Medicine at the time, were crucial for including the School of Medicine in the discussion about updating the medical curriculum regarding PHC practices and other changes in patient care management.[6]

Under these leaderships, PHC was established as a new field of practical activities in the School of Medicine through the creation of the Supervised Field Work discipline. This brought the academic curriculum closer to PHC and, consequently, to the reality of medical care in Niterói. The project subsequently expanded to integrated patient care with the involvement of research teams from UFF, further integrating the UFF with PHC. Dayse Mary da Silva Correia, a nursing professor at UFF, coordinated implementation logistics and the multidimensional evaluation of nursing diagnosis in PHC. Professor Maria Luiza Garcia Rosa was responsible for designing the project, and Professor José Antônio Lagoeiro's dissertation originated the Digitalis study.[6,7]

HF with preserved ejection fraction (HFpEF) is a cardiovascular condition with high costs and great impact on health systems around the world.[4,5,7] HFpEF is the most prevalent clinical presentation worldwide, accounting for 40%-50% of HF cases, leading to decreased quality of life and survival.[6-8] This condition is more prevalent in older people, women, and patients with diabetes, high blood pressure, or obesity.[9] In view of the epidemiological profile of public health service users, we noticed the importance of PHC in the diagnosis and initial management of HFpEF, as well as the relevance of cardiometabolic syndrome, which promotes the onset of HFpEF and is often observed in PHC,[10] and the high prevalence of cardiovascular diseases.[2,5,7]

In this sense, the changes in the profile of Brazilian cardiac patients required changes in primary cardiovascular care, which included the implementation of new protocols by the

Keywords

HFpEF; Family Health Program; Primary Care; Cardiology

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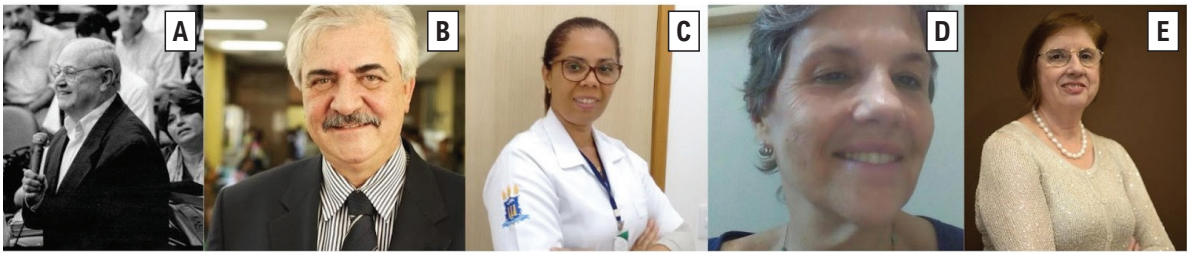

Figure 1 – *Professors Hugo Tomassini, Luiz Antonio Santini, Dayse Mary da Silva, Maria Luiza Garcia, and Maria Manuela Alves dos Santos. Hugo Coelho Barbosa Tomassini. Disponível em:https://www.abrasco.org.br/site/noticias/institucional/nosso-adeus-a-hugo-tomassini/ 52224/. Luiz Antonio Santini Rodrigues da Silva. Disponível em:https://tribunadaimprensalivre.com/dr-luiz-santini-carpe-diem-e-o-lema/. Dayse Mary da Silva Correia (Foto autoral). Maria Luiza Garcia Rosa (Foto autoral). Maria Manuela Pinto Carneiro Alves dos Santos. Disponível em:https://www.cmb.org.br/cmb/index.php/noticias/2408-superintendente-do-cba-e-eleita-pela-segunda-vez-uma-das-100-pessoas-mais-influentes-da-saude-no-brasil.*

Brazilian Ministry of Health. The need for data collection by region was highlighted, with targeted protocols and trained professionals for clinical recognition and appropriate management of these patients.[2,6]

Based on Portuguese physicians who observed an increase in HFpEF in PHC, several primary care patients with HFpEF were identified, and the knowledge of family doctors about the condition was evaluated. These actions resulted in the Digitalis study, a cross-sectional, epidemiological study conducted with all family medicine units in the city of Niterói, with a target population of 110,000 people aged > 45 years.[2] Professor Antonio José Lagoeiro Jorge was the principal investigator of HF in primary care; he disseminated knowledge by publishing data on HF in primary care, as well as on the importance of cardiac biomarkers and tissue Doppler echocardiography.[2,6]

This study allowed us to understand the profile of PHC users in Niterói and to establish preventive measures and early diagnosis in the FHP. The integration between family doctors and specialists is delayed by a lack of understanding of the role of each professional in the comprehensive care of cardiovascular patients. Establishing a relationship between doctors and PHC as early as medical education promotes better perception of the social role of the doctor, general practitioner, or specialist in the health of an entire community.[3,6]

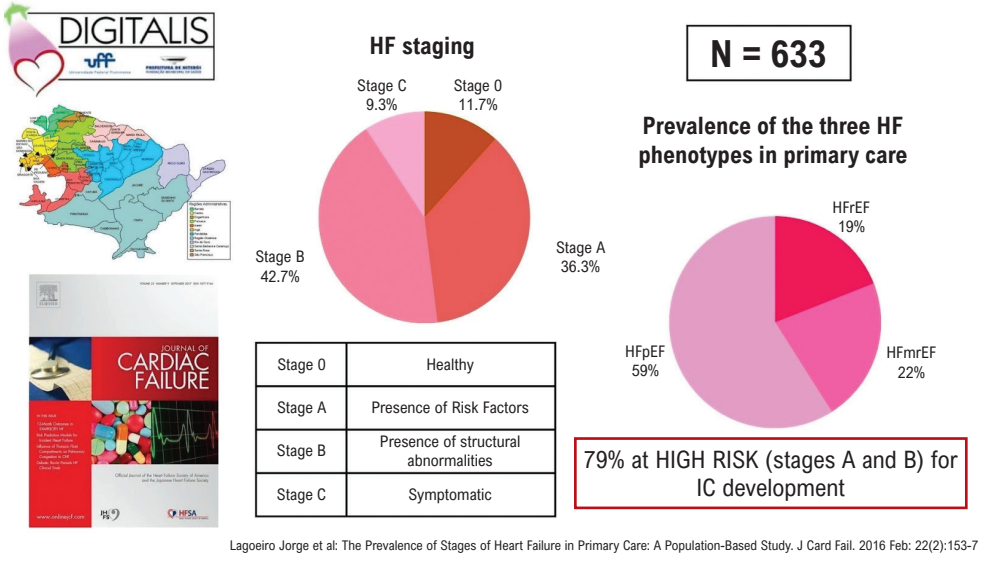

Figure 2 – *Findings of the Digitalis study. HF: heart failure; HFmrEF: heart failure with mild-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction. Prepared by the authors with data extracted from Jorge et al.[11]*

Editorial

In view of the aforementioned, the Digitalis study brought the Graduate Program in Cardiovascular Sciences at UFF closer to PHC in Niterói. The study is a legacy left by the graduate program to the population of Niterói that promotes the creation of a service focused on the epidemiological profile of patients using the public health system, allowing the creation of specific public policies for cardiovascular health in PHC in Niterói.

Therefore, the Digitalis Study associated the increased presence of comorbidities commonly associated with HFpEF with a significant prevalence of this syndrome in PHC within a modern diagnostic model using clinical, echocardiographic, and biomarker data. These data revealed the epidemiological importance of HFpEF in Brazil based on a reliable metric that has high potential for external validity for other outpatient settings in Brazil.

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Original Article

Efficacy of Different Cumulative Doses of Doxorubicin in the Induction of a Dilated Cardiomyopathy Model in Rats

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Abstract

Background: **Doxorubicin (DOXO) has been used to induce dilated cardiomyopathy (DCM) in experimental models.**

Objective: **To analyze cardiac changes after DOXO infusion and define the most effective protocol to reproduce an experimental model of DCM.**

Methods: **Male Wistar rats were divided into 4 groups and received increasing cumulative doses of DOXO (at a rate of 2 mg/kg/week) or saline solution: the control group (CTR) received saline solution, Group D-8 received a total infusion of 8 mg/kg, Group D-12 received 12 mg/kg, and Group D-16 received 6 mg/kg. All animals underwent echocardiography at baseline and after the end of infusion. The animals were then euthanized and cardiac tissue was collected for histological analysis.**

Results: **Mortality rates were 20% (D-8), 30% (D-12), and 67.6% (D-16). The 8 mg/kg dose was not associated with a significant reduction in left ventricular ejection fraction (LVEF) or an increase in left ventricular end-diastolic diameter (LVEDD). There was significant LVEF impairment with 12 mg/kg and 16 mg/kg doses compared to the control (68.3±5% vs 58.4±9%, $p < 0.01$, for CTR-12 vs D-12; and 66.0±6% vs 47.6±15%, $p < 0.01$, for CTR-16 vs D-16). Histological analyses revealed a greater percentage of fibrosis in D-12 (10.6±3.3%) and D-16 (9.8±2.3%) compared to CTR (2.3±1.0%), $p < 0.001$.**

Conclusions: **The DOXO dose of 16 mg/kg was associated with severe cardiac changes and high mortality. Thus, we propose a DOXO dose of 12 mg/kg as the most appropriate and effective for inducing DCM with an acceptable mortality rate.**

Keywords: **Doxorubicin; Cardiotoxicity; Heart Failure; Left Ventricular Dysfunction; Dilated Cardiomyopathy.**

Introduction

Animal models of cardiovascular disease are crucial for investigating pathophysiological mechanisms and testing new therapies.[1,2] Due to the high prevalence and clinical relevance of heart failure (HF) syndrome, several studies have described different models for analyzing this condition.[3-5] In this context, experimental HF models should mimic the major pathophysiological and morphological changes detected in humans, including cardiac remodeling, reduced ventricular function, hemodynamic changes such as reduced cardiac output and increased systemic vascular resistance, and histopathological changes. Over the last decades, several experimental models of acute and chronic HF with reduced ejection fraction have been developed to reproduce different aspects of dilated cardiomyopathy, a condition that can be induced by different events such as volume overload,[6] pressure overload by aortic constriction,[7] induction of arterial hypertension,[8] tachycardiomyopathy,[9,10] acute myocardial infarction,[11,12] and the use of cardiotoxic drugs such as propranolol, imipramine, and doxorubicin.[13,14]

Doxorubicin (DOXO), an anthracycline antineoplastic agent, is one of the drugs most frequently employed by investigators to induce dilated cardiomyopathy and HF.[15-21] DOXO is associated with dose-dependent cardiotoxicity, which may ultimately progress to HF. However, there is wide variation among protocols regarding the total cumulative dose of DOXO, the interval between doses, and the duration required to induce cardiopathy. In addition, the efficacy of these models in producing structural and functional changes that are consistent with those detected in human dilated cardiomyopathy while inducing acceptable mortality rates has not been clearly defined.

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To understand these findings in greater depth, the present study aims to investigate the morphological and functional cardiac changes induced by different cumulative doses of DOXO in rats in terms of the associated mortality rate and to define the most effective and high-yield induction protocol that would reproduce an experimental model of non-ischemic dilated cardiomyopathy.

Methods

Animals

Adult male rats with a mean body weight of 250 g were obtained from the Central Animal House of the Ribeirao Preto Medical School, Universidade de São Paulo (FMRP-USP). They were maintained in a climate controlled environment on a 12-h light/dark cycle with free access to water and standard chow. The number of animals allocated to each experimental group was based on previous studies and (an expectation of high mortality, especially in the groups that received DOXO infusion. This expectation was based on a series of prior reports in the literature on the use of DOXO to induce non-ischemic dilated cardiomyopathy, in which mortality was around 50 to 60%.[15,22] The Research Ethics Committee at FMRP approved all experimental procedures (protocol No. 041/2005).

Chemical products

Adriablastin® RD (doxorubicin chloride) was purchased from Pfizer (Pharmacia, Milan, Italy), dissolved in saline solution (10 mg/100 mL), and administered by intravenous injection. In addition, intramuscular injections of ketamine hydrochloride (Vetbrands, Jacareí, SP, Brazil) and xylazine (Calier, Les Franqueses del Vallés, Barcelona, Spain) were used for anesthesia.

Experimental protocol

A total of 60 animals were randomly divided into 3 experimental groups and 1 control group without specific criteria, receiving intravenous infusions with increasing cumulative doses at a rate of 2 mg/kg/week of DOXO or saline solution: Group D-8 (n = 20 animals) received a total infusion of 8 mg/kg over 4 weeks, D-12 (n = 30 animals) received a total infusion of 12 mg/kg for 6 weeks, and D-16 (n = 28 animals) received a total infusion of 16 mg/kg over 8 weeks. The control group (CTR) consisted of 8 animals matched for age that received 0.9% NaCl solution of the same volume as the DOXO infusion for 8 weeks.

All animals underwent, at baseline and 2 weeks after the end of infusion, an in vivo assessment of ventricular function by echocardiography. Then, they were euthanized for histological assessment and quantitative analysis of collagen areas.

The animals were kept in cages with members of the same group. All of them were submitted to the same stress conditions and order of measurements to minimize potential confounders. All procedures were performed under anesthesia to reduce stress and pain. There was no restriction on feed and water.

Echocardiographic assessment of ventricular remodeling and function

Cardiac function was evaluated at baseline and after DOXO treatment by 2D echocardiography, as previously described.[23]

After sedation with ketamine and xylazine (20 and 8 mg/kg), the echocardiogram was recorded using a Sonos 5500 Philips (Andover, MA, USA) high-resolution two-dimensional echocardiography system with a 15-MHz high-frequency linear transducer. Using the parasternal window to obtain long-axis and short-axis images of the left ventricle (LV) at the papillary level, M-mode images were used to measure the interventricular septum, LV posterior wall thickness, and LV end-diastolic (LVEDD) and end-systolic (LVESD) dimensions. The diastolic diameter of the LV was measured at the maximum ventricular diastolic dimension, and systolic LV dimension was obtained during the maximum inward motion of the septum and posterior wall.

LV ejection fraction (LVEF) was calculated by the two-dimensional method, in which a two-dimensional LV shortening area was measured from the apical, subcostal, and, particularly, short axis views. In addition, images of left ventricular endocardial areas in diastole and systole were digitalized and measured offline. The shortening area was determined by the formula: EF (2D) = (EDA-ESA)/EDA, in which EDA and ESA are the end-diastolic and end-systolic areas, respectively.

The images were recorded by an echocardiography technician experienced in laboratory work with small animals who was blinded to the groups during the offline analysis at the end of the study.

All measurements represented the mean of five consecutive cardiac cycles using the same transducer position and angle in the same image frame. The interval between two consecutive cardiac cycles was measured for calculating heart rate.

Histopathology – harvesting and preparation of hearts

Six animals randomly chosen from each group were used for histopathological analysis. The hearts were rapidly removed, rinsed in ice-cold 0.9% saline solution, and fixed as a whole by immersion in phosphate-buffered 10% formalin for 24 hours at 4°C for histological study. Both ventricles from each heart were isolated and cut into two fragments by a midventricular coronal section. Each block was serially cut in the same direction at a thickness of 4–7 μm appropriate for each stain, and sections were stained with hematoxylin and eosin (H&E) and picrosirius red.

Collagen quantification

The sections stained with picrosirius red were used to quantify the interstitial collagen volume fraction using Leica Qwin Software V 3.2.0 (Leica Imaging Systems Ltd., Cambridge, UK) together with a Leica DMR microscope (Leica Microsystems Wetzlar GmbH, Wetzlar, Switzerland), video camera (Leica DC300F, Leica Microsystems AG, Heerbrugg, Switzerland), and an online computer. Twenty

high-magnification fields (×400) of the LV free wall were randomly selected for each animal, and interstitial collagen volume fraction values were expressed as percentages of the total LV area.

Statistical analysis

Continuous variables are reported as means ± standard errors of the mean, and nominal variables are reported as absolute (n) and relative (%) frequencies. Data were analyzed using GraphPad Prism 4 (GraphPad Software Inc., San Diego, CA, USA). The Kolmogorov-Smirnov test was used to verify the Gaussian distribution of the variables. Student's t-test was used to compare the results between experimental and control groups. The Kruskal-Wallis nonparametric test, followed by Dunn's post-test, were used to evaluate the differences between the mean scores obtained at fibrosis quantification. Fischer's exact test was used to compare frequency distributions. The level of significance was set at $p < 0.05$, two-tailed in all analyses.

Results

Mortality

Two weeks after the end of the drug infusion period, in group D-8, four of the 20 animals that had started the experiment died (20%). In group D-12, mortality was 30% (9/30 animals), whereas mortality was extremely elevated in D-16: 67.6% (19/28 animals). No animals in the CTR group died (0%). A significant difference in mortality was detected only between group D-16 and its respective CTR group ($p < 0.001$), Figure 1.

Body weight

A significant reduction in body weight (compared to the respective controls) occurred in animals in group D-8 (368±32 g vs 444±19 g, $p < 0.01$), group D-12 (366±30 g vs 505±23 g, $p < 0.0001$), and group D-16 (331±21 g vs 534±29 g, $p < 0.0001$). This difference was progressively more evident with the increasing DOXO dose, since the control animals weighed, on average, 20%, 38%, and 61% more than animals in groups D-8, D-12, and D-16, respectively.

Functional and structural LV evaluation by echocardiography

Baseline evaluation: Baseline echocardiography data are presented in Table 1. No significant difference in echocardiography parameters was detected at baseline between groups ($p > 0.05$) before DOXO administration.

Evaluation after doxorubicin infusion: The echocardiography data obtained after DOXO infusion are presented in Table 2.

LVESD was larger in group D-16 compared to the respective control: 5.1±0.8 mm vs 4.3±0.5 mm, $p < 0.05$. This variable presented no differences in the remaining experimental groups. The final LVESDs of animals in the D-8, D-12, and D-16 groups were similar to those of their controls, $p > 0.05$.

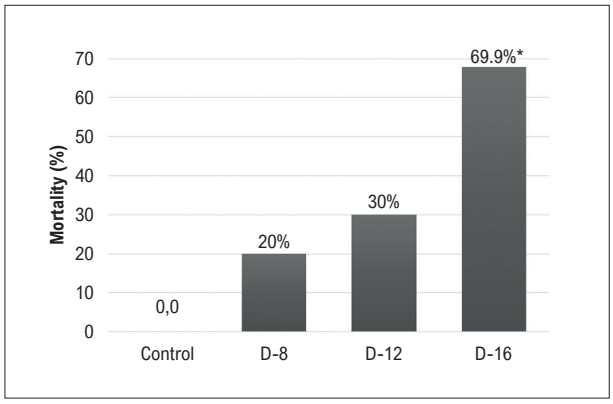

Figure 1 – *Mortality rate detected in the study groups (*p < 0.001 – Fisher's exact test).*

Table 1 – Baseline echocardiography parameters assessed in all 86 studied animals

	CTR (n=8)	D-8 (n=20)	D-12 (n=30)	D-16 (n=28)
Weight (g)	251.5±18.3	248.1±17.1	246.1±15.5	253.3±8.9
LVEDD (mm)	6.0±0.7	5.8±0.4	5.6±0.6	5.9±0.7
LVESD (mm)	3.1±0.8	2.8±0.5	2.7±0.4	3.0±1.1
SW thickness (mm)	1.5±0.2	1.6±0.2	1.6±0.1	1.4±0.2
PW thickness (mm)	1.5±0.2	1.6±0.3	1.6±0.2	1.5±0.2
LV mass (g)	1.1±0.1	1.0±0.1	1.0±0.1	1.1±0.1
2D LVEF (%)	72.2±9.9	72.7±4.9	73.5±7.5	72.2±6.5
Heart rate (bpm)	289±18.8	317±48.9	316±26.3	295±34.7

CTR: control group; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; PW thickness: posterior wall thickness at maximum diastole; SW thickness: septal wall thickness at maximum diastole; 2D LVEF: ejection fraction determined by the method of LV fractional shortening. ANOVA followed by the Tukey-Kramer multiple comparisons test.

LVEF results obtained by the two-dimensional method revealed that groups D-12 and D-16 exhibited a significant reduction of LV systolic function compared to their respective controls: 68.3±5% vs 58.4±9%, $p < 0.01$, for groups CTR-12 vs D-12; 66.0±6% vs 47.6±15%, $p < 0.01$, for group CTR-16 vs D-16. Thus, there was a 14.5% reduction in LVEF in group D-12 and a 27.9% reduction in group D-16. No decrease in LVEF was detected in group D-8, $p > 0.05$ (Figure 2).

The heart rate observed during echocardiography was significantly lower among D-16 animals (227±30 bpm) than among their controls (272±18 bpm), $p < 0.01$. There was no difference in this parameter for the remaining experimental groups.

Table 2 – Mortality, weight, and echocardiographic parameters of the 58 surviving animals according to experimental group

	CTR-8 (n=8)	D-8 (n=16)	CTR-12 (n=8)	D-12 (n=21)	CTR-16 (n=8)	D-16 (n=13)
Mortality	0%	20%	0%	30%	0%	67.9% *
Weight (g)	444±19	368±32 *	505±23	366±30 *	534±29	331±21*
LVEDD (mm)	7.1±0.9	6.7±0.7	8.1±0.8	7.6±0.7 †	8.1±0.4	7.7±0.8 †
LVESD (mm)	3.5±0.8	3.6±0.5	4.2±1.1	4.5±0.7 †	4.3±0.5	5.1±0.8 *†‡
SW thickness (mm)	1.5±0.2	1.5±0.1	1.7±0.2	1.6±0.2	1.6±0.1	1.5±0.1
PW thickness (mm)	1.5±0.2	1.6±0.3	1.6±0.3	1.5±0.1	1.5±0.1	1.4±0.2 †
LV mass (g)	1.2±0.2	1.2±0.3	1.5±0.2	1.3±0.2 *	1.3±0.1	1.2±0.1
2D LVEF (%)	70±8	66.7±5	68.3±5	58.4±9 *†	66.0±6	47.6±15 †‡*
Heart rate (bpm)	278±22	258±40	271±21	251±27	272±18	227±30 †‡*

*CTR: control group; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; PW thickness: posterior wall thickness at maximum diastole; SW thickness: septal wall thickness at maximum diastole; 2D LVEF: ejection fraction determined by the method of LV fractional shortening. *p<0.05 compared to the control group according to age (unpaired t-test); †p<0.05 compared to group D-8 (ANOVA and Tukey post-test); ‡p < 0.05 compared to group D-12 (ANOVA and Tukey post-test).*

The LV mass estimated by echocardiography was significantly reduced in D-12 and D-16 animals compared to their controls, $p < 0.05$. No differences in estimated LV mass were observed between D-8 animals and their controls.

Comparative analysis of different groups that received DOXO

A comparative analysis of the groups receiving different DOXO doses revealed a progressive decrease in LVEF (2D LVEF) between D-8 and D-12 ($p < 0.05$), D-8 and D-16 ($p < 0.001$), and D-12 and D-16 ($p < 0.05$) (Table 2).

Quantitative analysis of histological changes by light microscopy

A histopathological analysis of the heart of control animals stained with H&E did not reveal any pathological changes, whereas the hearts of animals infused with DOXO showed myocyte injury with reduction and degeneration of myocardial fibers, a significant decrease of myofibrils with loss of myofibrillar organization, and periarteriolar fibrosis in the myocardium and interstices, associated with collagen deposition (Figure 3). The changes detected in group D-8 were less pronounced than in groups D-12 and D-16.

Quantification of fibrosis

For a quantitative analysis of fibrosis, samples were stained with picrosirius red. A higher percentage of fibrosis was observed in groups D-8 (6.0±2.3%), D-12 (10.6±3.3%), and D-16 (9.8±2.3%) compared to the control (2.3±1.0%), $p < 0.001$. Additionally, groups D-12

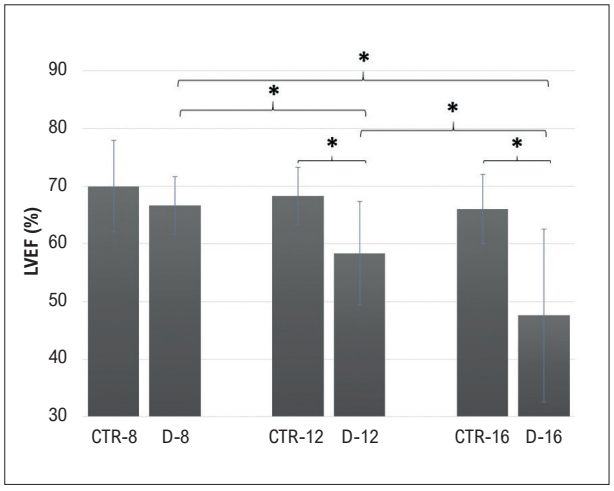

Figure 2 – *Mean left ventricular ejection fraction (LVEF) values obtained in each of the study groups. * p < 0.05 compared to the control group according to age (unpaired t-test) and compared between groups (ANOVA and Tukey post-test).*

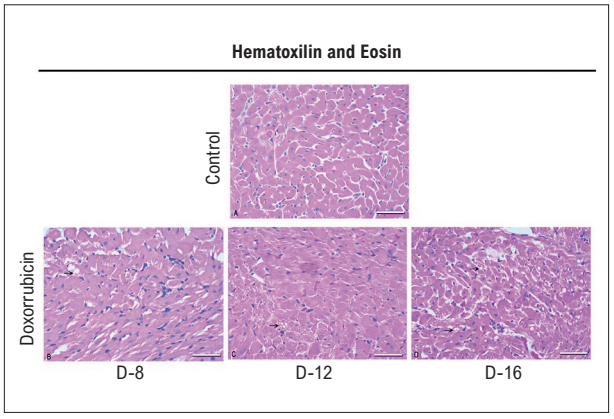

Figure 3 – *Representative histological sections stained with hematoxylin and eosin (H&E) from the control (CTR) and doxorubicin (DOXO) groups (D-8, D-12, and D-16). Myocardial fiber loss and degeneration are observed in animals after DOXO infusion (panels B, C, and D), with a significant reduction in myofibrils, edema, and vacuolar degeneration (marked by arrows). These changes are more pronounced with the increment of DOXO cumulative doses.*

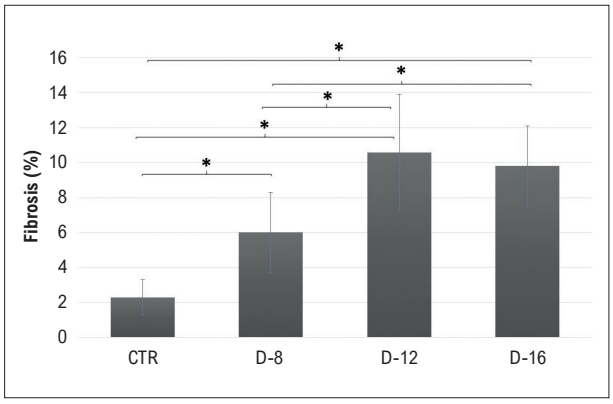

Figure 4 – *Mean fibrosis values obtained in the study groups. * p < 0.05 (ANOVA and Tukey post-test).*

and D-16 showed a larger area of fibrosis than group D-8, p < 0.001, but did not differ from one another (Figure 4).

Discussion

In the present study, we investigated the effectiveness of different cumulative doses of DOXO in inducing functional and cardiac changes, balancing these results with mortality rates intrinsically associated with higher cumulative doses in order to define the dose of DOXO with the best efficacy. The main results showed a significant reduction of LV systolic function starting with a cumulative dose of 12 mg/kg of DOXO, with greater dysfunction occurring with the cumulative dose of 16 mg/kg and no significant decrease in LVEF with the 8 mg/kg dose. Additionally, we observed a significant increase in myocardial fibrosis compared to control in all 3 studied cumulative doses; the highest degree of fibrosis was observed in groups receiving 12 mg/kg and 16 mg/kg, which exhibited similar degrees of fibrosis. A progressive increase in mortality was associated with higher doses, with an excessive rate at the cumulative dose of 16 mg/kg (67.9%). Taken together, these results suggest that the dose of DOXO with the best efficacy for the induction of dilated cardiomyopathy in rats was 12 mg/kg.

Mortality rates

The high mortality rate observed in the present study agrees with values reported in previous studies, ranging from 36 to 82%.[15,18,24,25] Previous studies have shown that variations in mortality rates are related to three main reasons: total dose administered, duration of the period of infusion, and time of observation. Mortality increases with higher doses, shorter periods of administration, and longer periods of observation.[15,24,26]

In addition to myocardial injury, high cumulative doses of DOXO produce renal, bone marrow, and gastrointestinal toxicity that may contribute to increased mortality rates due to the induction of hyperkalemia, hypervolemia, anemia, diarrhea, and malnutrition.[24,27] In addition to losing weight and muscle mass, the animals become weak and unable to feed properly, with a consequent progressive and generalized muscle weakness that may contribute to increased mortality. In the present study, animals in D-12 and D-16 showed significant differences in general aspect and weight compared to their respective controls, indirectly supporting the presence of these debilitating mechanisms. These changes have also been described by other authors.[15,22,24,27]

In vivo structural and functional cardiac changes

In general, studies using DOXO were designed for investigating histopathological lesions[28] and studying the drug's cardiotoxicity,[29] mainly focusing on metabolic changes and oxidative stress[15,30-32] instead of assessing the degree of in vivo ventricular dysfunction or mortality. Thus, their objective was not to characterize a model of HF or dilated cardiomyopathy, and we found a wide variety of protocols in the literature. Our study intended to describe a protocol that would be adequate, effective, and of better yield, reproducing an experimental model of non-ischemic dilated cardiomyopathy based on in vivo structural and functional changes but with acceptable mortality rates.

We highlight that in this study, we chose the intravenous infusion of DOXO at increasing cumulative doses. In a previous study with rats, O'Connel et al.[33] compared 2 protocols of DOXO infusion, a short one and a prolonged one, in the induction of dilated cardiomyopathy. In this study, we observed that both protocols generated similar histological injuries, although only the prolonged infusion was associated with structural and functional changes similar to those detected in clinical dilated cardiomyopathy. These findings support the idea that a prolonged infusion time is more effective than a short infusion when the main outcome is the induction of structural and functional changes.[33]

In the present study, we observed a clear correlation between the cumulative dose of DOXO and the degree of ventricular dysfunction that occurs progressively from the cumulative dose of 12 mg/kg. Our results show that the animals receiving a cumulative dose of 16 mg/kg presented more marked functional and structural cardiac changes assessed in vivo by 2D echocardiography when compared to their respective control groups. These changes were mainly characterized by an increase in LVESD, a decrease in LVEF, and a reduction of estimated LV mass. However, the mortality rates for this group were excessive, since more than two-thirds of the animals did not survive up to two weeks after the induction of cardiomyopathy.

Conversely, the cumulative dose of 12 mg/kg was assciated with structural changes that were not as marked as those observed with the 16 mg/kg dose, but it enough to cause a significant reduction in LV ejection fraction and an increase in myocardial fibrosis. In addition, the mortality rate for this group (30%) was acceptable, leading us to conclude that this protocol might be adequate for the induction of ventricular dysfunction with DOXO in rats.

Our results corroborate the findings of previous studies suggesting that cumulative doses above 12 mg/kg are associated with increased mortality.[18,22,34] The results obtained by Spivak et al.[34] using a shorter DOXO dosing

time suggested that cumulative doses above 12 mg/kg are associated with a mortality rate of more than 40%, thus being inappropriate for in vivo research on HF.[34] Indeed, the study by Schwarz et al.[22] demonstrated that higher doses (such as 25 mg/kg over a period of 10 weeks) are associated with a higher degree of ventricular dysfunction but also with high mortality rates, reaching 52%.[22]

Histopathological changes

In the present study, we observed clear morphological differences between groups. The injuries were typical from reports of DOXO-induced dilated cardiomyopathy in humans[35] and in other animal models,[36-38] ie, predominantly involving damage to the myocytes with loss and degeneration of myocardial fibers, a significant reduction in myofibrils, fibrosis and collagen deposition, in addition to edema and cardiomyocyte vacuolization, intracellular edema, and myofibril disorganization. The collagen deposition observed in our study was similar to that reported in previous studies using this experimental model.[23,39] The cumulative dose of DOXO associated with significant histological damage in our study was in agreement with reports that suggested a dose of 15 mg/kg as the most effective in inducing histopathological injury.[40]

It should be noted that even though ventricular dysfunction was more marked at the 16 mg/kg dose, the degree of tissue injury represented by fibrosis was similar in groups D-12 and D-16, suggesting a possible dissociation between these two parameters in this range of cumulative DOXO doses. These results support previous evidence obtained by our research group showing a relative dissociation between the degree of tissue injury and the intensity of left ventricular dysfunction with the use of different regimens of DOXO infusion.[33]

Our results show that the induction model using a total cumulative dose of DOXO of 16 mg/kg with 8 weekly injections of 2 mg/kg is the one that best leads to morphological and functional changes in the animals, but it involves high, ethically unacceptable mortality, which discourages the use of this protocol. In addition, the difficulty in maintaining a highly aggressive model of ventricular dysfunction for the minimum period of time required for evaluating a given therapeutic intervention is a relevant factor in the choice of the most efficient protocol.

Conclusions

Our results indicate that the model with 6 weekly injections of 2 mg/kg of DOXO, with a cumulative dose of 12 mg/kg, presents the best efficacy for inducing dilated cardiomyopathy, resulting in significant left ventricular remodeling, systolic function impairment, and tissue injury associated with acceptable mortality rates.

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Author Contributions

Conception and design of the research: Tanaka DM, O'Connell JL, Schmidt A, Simões MV; Acquisition of data: O'Connell JL, Fabricio CG, Romano MMD, Campos EC, Oliveira LFL, Carvalho EEV; Analysis and interpretation of the data: Tanaka DM, O'Connell JL, Fabricio CG, Romano MMD, Campos EC, Oliveira LFL, Schmidt A, Carvalho EEV, Simões MV; Statistical analysis: Tanaka DM, Simões MV; Obtaining financing: Simões MV; Writing of the manuscript: Tanaka DM, Campos EC; Critical revision of the manuscript for important intellectual content: Tanaka DM, O'Connell JL, Fabricio CG, Romano MMD, Oliveira LFL, Schmidt A, Carvalho EEV, Simões MV.

Potential Conflict of Interest

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

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Study Association

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Myocarditis: Whole Heart Involvement Revealed by Cardiac Magnetic Resonance Mapping. A Case-control Study

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Abstract

Background: **Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) only demonstrates regional abnormalities in myocarditis and does not adequately assess diffuse myocardial involvement.**

Objectives: **To evaluate possible differences in T1 and T2 mapping between ventricular wall segments with and without LGE in patients with myocarditis, compared to control subjects.**

Methods: **In a case-control design, 22 patients with CMR evidence of myocarditis and 18 controls with normal CMR were assessed. The study included: (1) T1 mapping (shortened modified Look-Locker Inversion recovery); (2) LGE; (3) T2 mapping (steady-state free precession); and (4) the T2 signal intensity of the myocardium divided by that of skeletal muscle (T2 ratio). T1 and T2 mapping of affected (LGE+) and unaffected (LGE−) ventricular segments of cases were compared, as were those of controls versus cases. The level of significance was set at a two-sided alpha level of 0.05.**

Results: **Comparing only patients with myocarditis, ventricular segments with evidence of late enhancement (LGE+) showed a mean T1 value significantly different from that of unaffected (LGE−) ventricular walls (1057 ± 30 versus 1028 ± 48; p = 0.0001). Comparing myocarditis versus controls, the mean T1 value of negative LGE segments in cases (myocarditis +) was significantly different from the mean of the corresponding walls in controls (1028 ± 48 versus 996 ± 10; p < 0.0001). The mean T2 maps of negative LGE walls in cases were not statistically different from those of controls (49 ± 4 versus 49 ± 1; p = 0.9229).**

Conclusions: **This case-control study suggests that T1 mapping demonstrates significant involvement of the myocardium of patients with myocarditis, even in the absence of LGE. Specifically, T1 mapping could reveal diffuse myocardial involvement not evidenced by LGE imaging. T2 mapping was noncontributory.**

Keywords: **Myocarditis, Contrast Media, Magnetic Resonance Imaging.**

Introduction

The current incidence of myocarditis is unknown.[1] The epidemiology of this condition is poorly documented, due to the heterogeneity of clinical presentation and challenging diagnosis.

According to the Dallas criteria, myocarditis is defined histologically by the presence of an inflammatory infiltrate in the myocardium, alongside degenerative and/or necrotic changes in adjacent cardiomyocytes, which differ from the ischemic damage associated with myocardial infarction.[2] Etiologically, it may be secondary to infectious or noninfectious processes. In developed nations, the leading cause of myocarditis is viral infection, while in developing countries the main causes are rheumatic carditis, Chagas disease, and HIV-related.[3]

Among several methods available for diagnosis, cardiac magnetic resonance (CMR) is the noninvasive modality best able to characterize the inflamed myocardium, demonstrating edema, necrosis, and fibrosis. The Lake Louise Criteria (LLC) for diagnosis of myocarditis on CMR are based on techniques such as T2-weighted imaging, early gadolinium enhancement, and late gadolinium enhancement (LGE).[4] However, these CMR sequences have some limitations, such as an inability to identify diffuse fibrosis and the need for paramagnetic contrast. Another

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CMR method, the T2 ratio, defined as the T2 signal intensity (SI) of the myocardium divided by that of skeletal muscle, has also been losing ground to newer and more objective imaging techniques. These include T1 mapping, contrast-enhanced T1-weighted imaging, characterization of the extracellular volume (ECV) fraction, and T2 mapping, all of which have demonstrated superior diagnostic accuracy compared to the LLC.[5] Furthermore, T1 and T2 mapping do not require gadolinium contrast,[6] while contrast-enhanced T1-weighted imaging and ECV mapping do.

Considering advances in imaging modalities and confirming the need for change in diagnostic criteria, a proposed update to the LLC was published in December 2018.[5]

In view of the limitations of the current criteria for CMR diagnosis of myocarditis and given uncertainties surrounding the putative diagnostic superiority of T1 and T2 mapping, as well as the advantage of not requiring gadolinium contrast, we designed this study to test the hypothesis that T1 and T2 map values would be altered both within the myocardial wall segments affected by late gadolinium enhancement (LGE+) and in seemingly unaffected regions (LGE−). Within this context, the objective of the present case-control study was to compare T1 mapping, T2 mapping, and T2 ratio between affected (LGE+) and non-affected (LGE−) wall segments in patients with myocarditis and controls without myocarditis.

Methods

Study population profile

This retrospective case-control study included 22 cases with acute myocarditis (age 34 ± 16 years; 13% female) and 18 controls (age 42 ± 12 years; 16% female). Study participants underwent CMR at Hospital Moinhos de Vento, located in Porto Alegre, Rio Grande do Sul, Brazil, between January 2017 and June 2019. Analysis of CMR reports was performed consecutively, based on the date of the scans.

The criteria for inclusion of cases were presence of mesocardial and/or subepicardial LGE, which is currently the gold standard method, in addition to European Society of Cardiology criteria for clinically suspected myocarditis.[7] All cases had (a) symptoms of chest and/or abdominal pain, dyspnea, or palpitations; (b) elevation of cardiac troponin I or T levels > 160 pg/mL; and (c) presence of LGE in the expected anatomical region on CMR.

The criteria for inclusion of controls were (a) symptoms of chest pain, dyspnea, or palpitations; (b) normal/unavailable troponin I or troponin T values; and (c) no evidence of edema, necrosis, fibrosis, or ischemia on CMR.

The ratio of controls to cases was 1:1, and they were matched by age and sex. Exclusion criteria were: CMR demonstrating LGE pattern suggestive of other conditions, such as ischemic cardiomyopathy, hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, amyloidosis, aortic stenosis, or pulmonary hypertension; and contraindications to CMR.

In all patients, the workup included LGE (132 case wall segments and 108 control wall segments), T1 mapping (132 case wall segments and 108 control wall segments), T2 mapping (130 case wall segments and 108 control wall segments), and T2 ratio ≥ 2:1 (20 affected case wall segments and 21 unaffected case wall segments).

Other variables of interest were: reason for CMR; left ventricular ejection fraction; left ventricular dimensions (atrial, diastolic, and systolic) and volumes (end-diastolic volume, end-systolic volume, and stroke volume); anatomic region of fibrosis (subepicardial or mesocardial; walls: anterior, inferior, inferolateral, anterolateral, or septal; and segments: basal, medial, and apical); comorbidities (ischemic heart disease, stroke, diabetes mellitus, hypertension, ventricular/supraventricular arrhythmia, smoking, renal failure, heart failure, neoplasia); presence of symptoms (dyspnea, chest pain/discomfort, palpitations, abdominal pain); troponin levels; and the endomyocardial biopsy.

Ventricular walls were analyzed according to the presence or absence of LGE. The T1 and T2 maps of the affected (LGE+) walls of cases were compared with the T1 and T2 maps of the contralateral unaffected (LGE−) walls of the same patients. In addition, the T1 and T2 maps of the LGE− walls of cases (patients with myocarditis) were compared with the T1 and T2 maps of the same walls in non-myocarditis controls. The mean T1 and T2 values of the LGE+ walls, the mean T1 and T2 values of the LGE− walls of the patients with myocarditis, and the mean T1 and T2 values of controls were compared. Figure 1 shows image analysis among myocardial walls.

For analysis of T1 and T2 maps, the average values obtained in controls were considered the reference range for normality.

Ethical approval was granted for all study procedures. As the study was purely observational, there were no physical or biological risks. There was also no personal contact or contact via telephone or social media with the participants. Data analysis was confidential, and the participants' names, addresses, and other contact information were not disclosed. In view of the foregoing and of the impossibility of accessing the participants' contact information in medical records, pursuant to National Health Council Resolution 466/2012, the institutional Research Ethics Committee waived the usual informed consent requirement. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were used as a guide for case-control studies.

Cardiovascular magnetic resonance

CMR imaging was performed at 1.5 Tesla in a Siemens Healthcare AERA 45 mT scanner, using an 18-channel coil. Briefly, cine images were obtained in three long-axis sections (four-chamber, three-chamber, two-chamber) and in the short-axis plane, from the base to the apex of the heart. Tissue characterization was performed in a mid-ventricular short-axis view of the left ventricle, with T1 and T2 mapping, turbo spin-echo (TSE) T2-weighted, and short tau inversion recovery (STIR) sequences. LGE images were acquired by sectioning the whole heart, in a manner similar to the cine acquisition along the same axis. For T1 mapping, the shortened modified Look-Locker Inversion recovery (ShMOLLI) acquisition method was used before administration of the contrast agent. LGE images

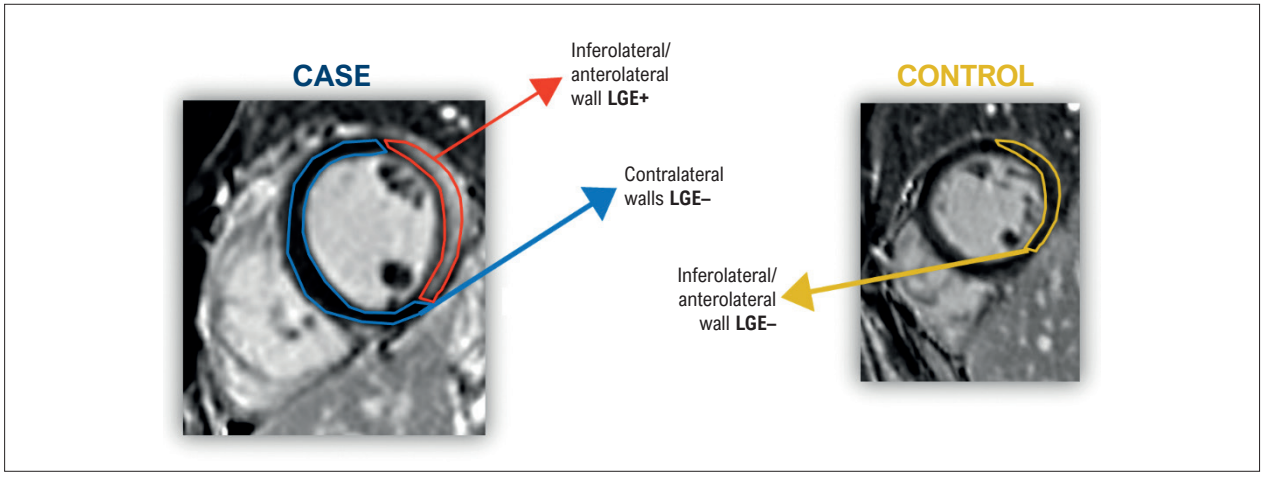

Figure 1 – *Image analysis among groups of walls of cases and controls. Designed in MS PowerPoint. LGE: late gadolinium enhancement.*

were acquired in the long- and short-axis planes, using a T1-weighted phase-sensitive inversion recovery (PSIR) sequence, 10 minutes after intravenous administration of gadobutrol (Gadovist - Bayer, total 0.20 mmol/kg).

Image analysis

Left ventricular volumes and ejection fraction were analyzed on cine images using Argus software (Siemens Medical Solutions). Short-axis T1 and T2 mapping images, T2 ratio, and LGE were subsequently analyzed. On T2-weighted dark blood images, edema is diagnosed when the T2 ratio is ≥ 2:1. The ratio was obtained as the T2 SI of the myocardial region of interest (with LGE) divided by the SI of skeletal muscle. T1 and T2 values were obtained from quantitative analysis of all T1 and T2 maps, rather than on visualization of color mapping. When delimiting the endo- and epicardial contours, care was taken to avoid contamination by the ventricular cavity and extra-myocardial structures to minimize the partial volume effect on T1/T2 values of the myocardium. In acute myocarditis, identification of remote myocardium can be challenging, because the inflammatory process is often global; thus, a myocardial region without LGE was chosen to represent the myocardium least affected by the disease process, with care also taken to avoid regions of abnormally low SI. Acute myocardial inflammation was considered when the mean T1 value was > 996 ms and the mean T2 value was > 49 ms. Focal areas of LGE were defined as those with a standard deviation of SI ≥ 2.0 above the mean SI of the remote myocardium. To calculate the extent of myocardial injury detected by tissue characterization techniques, the percentage of abnormal myocardium, as defined above, was determined for each segment and then averaged for that patient.

Assessment of CMR image quality

Each myocardial segment of the left ventricle was rigorously assessed for image quality before inclusion in the final analyses. Only segments with minimal or no artifacts were included. Three controls were rejected due to artifacts. Four controls were excluded due to unavailability of map data.

Statistical analysis

Data were expressed as mean ± standard deviation or median (confidence interval). A paired Student's t test for continuous distribution with normal distribution was used to compare the walls. For categorical variables, the chi-square or Fisher's exact tests were used. The significance level was set at 5%. Analyses were carried out in the SPSS 21.0 (SPSS, Chicago, IL) and MedCalc 2020 software environments. Due to the unclear prevalence of myocarditis, sample size calculation was not performed. The initial sampling plan provided for 20 cases of myocarditis; 22 cases were found and ultimately included. This number is consistent with the existing literature.[8]

Results

The most common symptom reported as the reason for suspicion of myocarditis and performance of CMR was chest pain (91%). The included patients had few comorbidities. Almost 70% of cases underwent CMR as hospital inpatients, while 95% of controls were scanned in an outpatient setting. Clinical and anatomic profile of myocarditis cases and controls are expressed in Table 1.

T2 ratio

For analysis of the T2 ratio, values ≥ 2:1 were considered abnormal.

The mean T2 ratio for LGE+ regions in cases were 2.75 ± 1, which is indicative of myocardial wall edema.

The mean T2 ratio for LGE− regions in patients with myocarditis was 1.50 ± 0.2, which represents a normal value for these walls.

Accordingly, comparison of the T2 ratio in affected versus unaffected walls showed a statistically significant difference (2.75 ± 1 versus 1.50 ± 0.2; $p < 0.0001$).

Table 1 – Clinical and anatomic profile of myocarditis cases and controls

Characteristic	Myocarditis (n=22)	Controls (n=18)
Mean age – years (SD)	34 (16)	42 (12)
Female sex – n (%)	3 (13)	3 (16)
Race - White – n (%)	22 (100)	18 (100)
Reason to perform CMR – n (%)		
Suspected myocarditis	13 (59)	4 (22)
Normal catheterization	6 (27)	3 (17)
Chest pain	1 (5)	11 (61)
Abnormal troponin	2 (9)	0 (0)
Status at the time of CMR – n (%)		
Inpatient	15 (68)	1 (5)
Outpatient	7 (32)	17 (95)
Comorbidities – n (%)		
Hypertension	4 (18)	2 (11)
Diabetes mellitus	0 (0)	0 (0)
Coronary artery disease	0 (0)	0 (0)
Stroke	0 (0)	0 (0)
Heart failure	0 (0)	0 (0)
Smoker	1 (5)	0 (0)
Other medical history – n (%)		
Arrhythmia	0 (0)	0 (0)
Chronic renal disease	0 (0)	0 (0)
Malignancy	0 (0)	1 (5)
Symptoms – n (%)		
Chest pain	20 (91)	15 (83)
Dyspnea	1 (5)	1 (5)
Palpitation	1 (5)	3 (17)
Abdominal pain	3 (14)	0 (0)
Biopsy – n (%)	1 (5)	0 (0)
hsTroponin, pg/ml,* median (IQR)		
First	820 (369 - 76510)	NA
Second	2800 (431 - 14960)	NA
Third	1306 (399 - 40440)	NA
Fourth	2190 (716 - 9140)	NA
LGE topography – n (%)		
Subepicardium	17 (77)	NA
Mesocardium	19 (86)	NA
Anterior	7 (32)	NA
Inferolateral	21 (95)	NA
Anterolateral	15 (68)	NA
Inferior	7 (32)	NA
Inferoseptal	4 (18)	NA
Anteroseptal	4 (18)	NA
Heart dimensions – mean (SD)		
LVEF, %	51 (6)	65 (6)
Left atrium, mm	31 (8)	34 (10)
LVDD, mm	51 (6)	51 (3)
LVSD, mm	37 (6)	32 (4)
Septum, mm	6 (1)	6 (1)
Inferolateral wall, mm	6 (1)	6 (1)
End-diastolic volume, ml	165 (50)	154 (26)
End-systolic volume, ml	82 (32)	52 (14)
Stroke volume, ml	84 (21)	101 (19)
LVEF by group – n (%)		
< 40%	1 (5)	0 (0)
40-50%	5 (22)	0 (0)
> 50%	16 (73)	18 (100)

*hsTroponin: high-sensitivity troponin; LGE: late gadolinium enhancement; LVDD: left ventricular diastolic diameter; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; SD: standard deviation; CMR: cardiac magnetic resonance. *NR < 160 pg/mL.*

Late gadolinium enhancement

In patients with myocarditis, LGE+ images were often seen in more than one ventricular wall segment. The most affected region was the inferolateral wall (95%), followed by the lateral wall (68%), anterior wall (32%), inferior wall (32%), and septum (18%). Regarding myocardial injury pattern, mesocardial involvement was most common (86%), followed by the subepicardium (77%). The mean fibrosis mass by quantitative analysis was 12 g (9% of the myocardium). The number of segments affected by LGE was 58 of 132 in cases (44%) and 0 of 108 (0%) in controls.

T1 mapping

On analysis of T1 mapping, values ≥ 996 ms were considered abnormal. By this parameter, the number of affected segments was 111 of 132 (84%) in cases. The LGE+ segments of the cases (patients with myocarditis) showed a mean T1 value significantly different from the LGE− segments of the same patients. On between-group comparison, the mean T1 maps of LGE− ventricular walls in the patients with myocarditis were significantly different from the mean of the corresponding walls in controls. The mean T1 values in each group are given in Table 2.

Observing the most frequently abnormal region in our patient population, the inferolateral wall, the mean T1 value of the affected segment in cases was 1068 ± 47 ms, which is significantly different from all unaffected contralateral segments in these same cases. This change remained significant when we compared all unaffected segments of cases to those of controls. Figure 2 shows a representative image of the inferolateral wall.

Table 2 – Between-group comparison by T1 mapping in affected (LGE+) walls of cases versus all other unaffected (LGE−) walls in these cases and the respective unaffected (LGE−) walls of controls

Affected wall (LGE+)	T1 mapping in cases' affected walls (mean ± SD)	p (a)	T1 mapping in all cases' unaffected walls (LGE−) (mean ± SD)	p (b)	T1 mapping of respective wall in controls (mean ± SD)	p (c)
Anterior (n)	1017 ± 41 (7)*	0.3201	1037 ± 44 (15)**	0.0013	981 ± 47 (18)*	0.0859
Inferolateral (n)	1068 ± 47 (21)*	0.0011	1027 ± 49 (71)**	0.0084	994 ± 38 (18)*	<0.0001
Anterolateral (n)	1075 ± 61 (15)*	0.0168	1032 ± 56 (43)**	0.0284	999 ± 40 (18)*	0.0002
Inferior (n)	1079 ± 31 (7)*	0.0037	1018 ± 45 (15)**	0.5783	1010 ± 36 (18)*	0.0002
Inferoseptal (n)	1059 ± 17 (4)*	0.6912	1074 ± 71 (8)**	0.0038	1001 ± 44 (18)*	0.0191
Anteroseptal (n)	1005 ± 69 (4)*	0.1450	1074 ± 71 (8)**	0.0023	993 ± 48 (18)*	0.6776
General Mean (n)	1057 ± 30 (58)**	0.0001	1028 ± 48 (74)**	<0.0001	996 ± 10 (108)**	<0.0001

a: analysis between T1 mapping in cases by affected wall and T1 mapping in all unaffected walls of the same patients; b: analysis between T1 mapping in all case's unaffected walls and T1 mapping of respective wall in controls; c: analysis between T1 mapping in cases by affected wall and T1 mapping of respective wall in controls. LGE+: presence of late gadolinium enhancement; LGE-: absence of late gadolinium enhancement; SD: standard deviation; n: number of patients; n** number of walls assessed.*

T2 mapping

On analysis of T2 mapping, values ≥ 49 ms were considered abnormal. By this parameter, the number of affected segments was 69 of 130 (53%) in cases. The LGE+ segments of the cases showed a mean T2 value significantly different from the LGE− segments of the same patients. The mean T2 values of LGE− segments among cases were not significantly different from the mean T2 values of controls. The mean T2 values in each group are given in Table 3.

Regarding the inferolateral wall, T2 values again showed a significant difference between abnormal myocardial segments and unaffected walls in the same patients. Figure 3 shows a representative image of the inferolateral wall, and Figure 4 shows the relationship between different imaging methods.

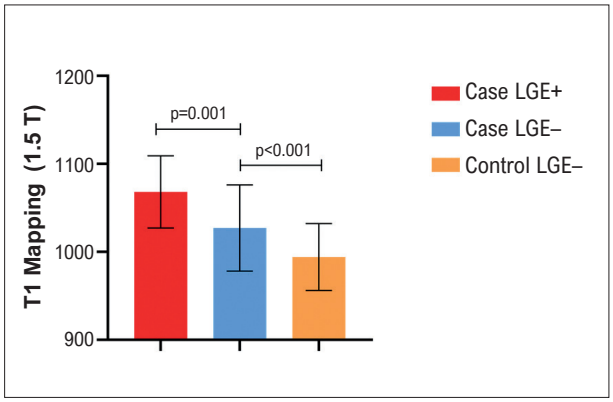

Figure 2 – *Inferolateral wall and the intermediate T1 map value of all unaffected walls of cases (blue bar: case LGE−). The T1 values of supposedly normal myocardium actually differed from that of the controls and from that of the affected walls of the same cases. * All p < 0.05. Values expressed as means. Designed in GraphPad Prism 9. LGE: late gadolinium enhancement.*

Discussion

The present case-control study demonstrates that T1 mapping allows a more comprehensive, in-depth assessment of supposedly normal myocardium in patients with CMR-proven myocarditis. Comparison of LGE+ versus LGE− segments in cases and of cases versus controls revealed not only a regional inflammatory process, but also diffuse myocardial involvement.

Although T1 mapping has been progressively used as an adjunctive tool in the diagnosis of myocarditis,[9] the present study was designed to investigate this method as a means of detecting myocardial involvement in areas of the heart that are considered unaffected by myocarditis when evaluated by LGE alone. Comparatively, we found that even seemingly normal myocardial segments in patients with myocarditis could be compromised by inflammation. A mean T1 value of 1028 ± 48 ms in the unaffected walls of the patients with myocarditis proved to be statistically different from that of controls, which confirms the hypothesis that supposedly unaffected segments were in fact not normal. On the other hand, myocardial edema, as assessed by T2 mapping, showed no difference between the LGE− segments of cases and those of controls. The findings of this study are consistent with the existing literature.[10]

The proportion of affected segments in cases was 44% when analyzed by LGE alone and 84% when assessed by

Table 3 – Between-group comparison by T2 mapping in affected (LGE+) walls of cases versus all other unaffected (LGE−) walls in these cases and the respective unaffected (LGE−) walls of controls

Wall	T2 mapping in cases' affected walls (LGE+) (mean ± SD)	p (a)	T2 mapping in all cases' unaffected walls (LGE−) (mean ± SD)	p (b)	T2 mapping of respective wall in controls (mean ± SD)	p (c)
Anterior (n)	53 ± 5 (7)*	0.2955	50 ± 5 (15)**	0.7851	49± 3 (18)*	0.0803
Inferolateral (n)	52± 5 (21)*	0.0062	49 ± 4 (71)**	0.6339	49 ± 4 (18)*	0.0760
Anterolateral (n)	51± 5 (15)*	0.2190	49 ± 5 (43)**	0.2245	48 ± 3 (18)*	0.0235
Inferior (n)	49 ± 5 (7)*	0.8068	48 ± 4 (15)**	0.8121	48 ± 4 (18)*	0.6734
Inferoseptal (n)	51± 5 (3†)*	0.3317	48 ± 3 (8)**	0.6868	48± 3 (18)*	0.1092
Anteroseptal (n)	49± 1 (3†)*	0.7519	48± 3 (8)**	0.6105	49 ± 3 (18)*	0.9868
General Mean (n)	51 ± 2 (56)**	0.0008	49 ± 4 (74)**	0.9229	49 ± 1 (108)**	<0.0001

a: analysis between T2 mapping in cases by affected wall and T2 mapping in all unaffected walls of the same patients; b: analysis between T2 mapping in all case's unaffected walls and T2 mapping of respective wall in controls; c: analysis between T2 mapping in cases by affected wall and T2 mapping of respective wall in controls. LGE+: presence of late gadolinium enhancement; LGE–: absence of late gadolinium enhancement; SD: standard deviation; n: number of patients; n** number of walls assessed; †: one wall lost due to image artifact.*

T1 mapping. This result was interpreted as demonstrating a significant diffuse involvement of the myocardium, to the extent that almost the entire heart could be considered impaired in our patients with myocarditis.

The contribution of this finding to our knowledge of myocarditis is twofold: a) by enhancing the diagnostic performance of CMR in patients with myocarditis, particularly in borderline or difficult-to-diagnose cases; and b) by introducing a novel concept in the diagnosis of myocarditis which allows objective, numerical, and quantifiable assessment of myocardial involvement, unlike current LGE-based criteria, in which the diagnosis is subjective and operator-dependent. In addition, it should be noted that T1 mapping could obviate the use of gadolinium-based contrast agents, which eliminates the risk of allergic reactions, allows use in patients with renal failure, and reduces cost.

A multicenter observational study showed that T1 and ECV values were strong predictors of poor prognosis in non-ischemic dilated cardiomyopathy.[11] Nevertheless, it remains unknown whether this altered myocardium is in itself a predictor of cardiovascular events in myocarditis and other cardiovascular diseases, due to a lack of studies with sufficient follow-up.

The diffuse T1 abnormalities in seemingly unaffected myocardial segments described in our study may have a major prognostic impact in the long term. Taylor et al note that diffuse fibrosis has been identified as an etiological factor in diastolic dysfunction, heart failure, and sudden death.[12]

Regarding T2 mapping, some studies have shown that this method might be able to locate areas involved in myocarditis with better sensitivity than conventional T2-weighted images alone. In 1.5-Tesla CMR, a cutoff value of > 59 ms demonstrated 94% sensitivity and 97% specificity for identification of affected myocardium.[13] Using a mean of > 49 ms, our study confirmed a statistically significant difference between cases with affected LGE+ walls and controls (Table 3).

The mean T2 ratio in LGE+ segments was 2.75 ± 1, which is an abnormal value, whereas, in segments without late gadolinium enhancement (LGE−), this ratio was normal. While T1 mapping was able to demonstrate

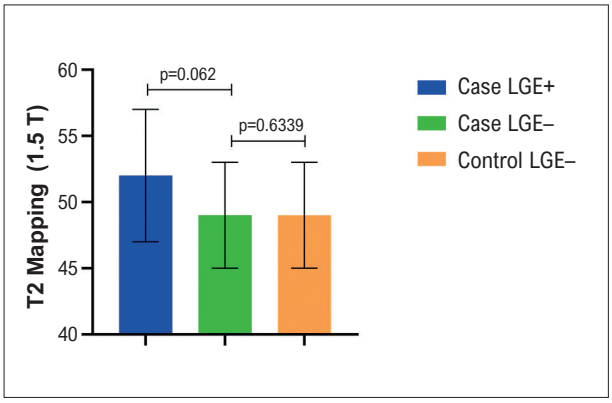

Figure 3 – *Analysis of the inferolateral wall by T2 mapping showed significant difference between LGE+ walls of cases (blue bar) and LGE− walls of the same cases (green bar). No significant difference was found compared to LGE− walls of controls (yellow bar). Values expressed as means. Designed in GraphPad Prism 9. LGE: late gadolinium enhancement.*

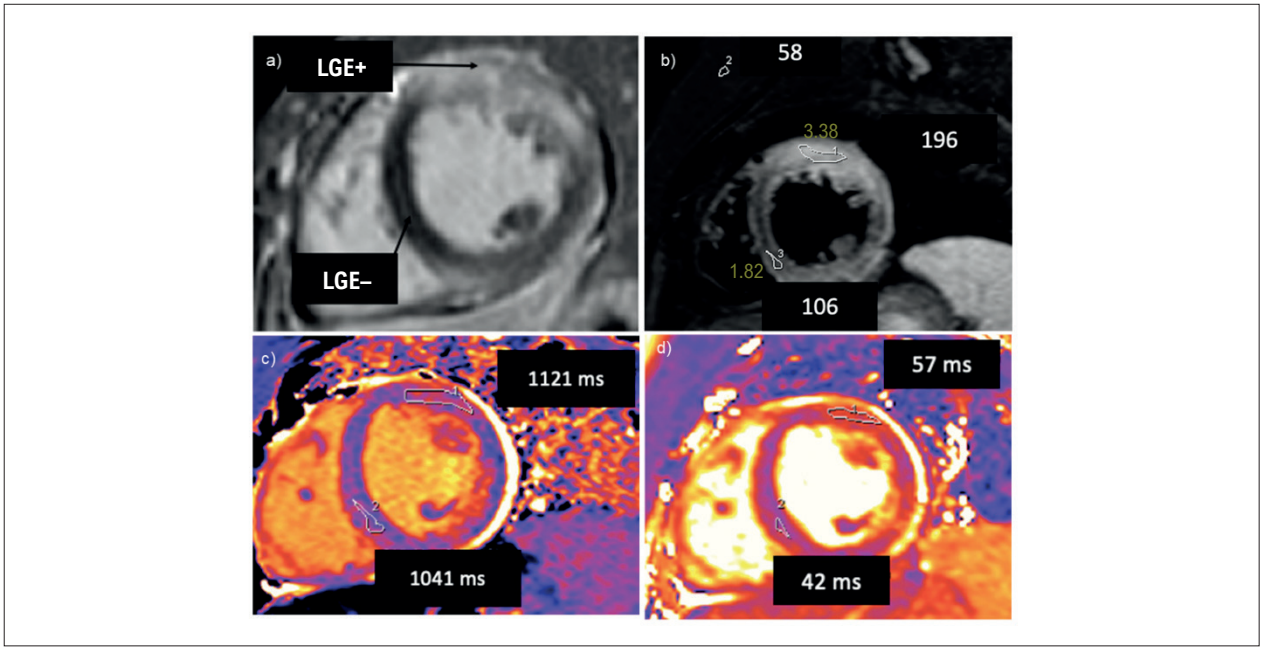

Figure 4 – *Relationship between different imaging methods: a) LGE+ in anterolateral wall and LGE– in septum; b) T2 ratio (3.38) shows edema in anterolateral wall and normal value (1.82) in septum; c) Affected T1 map in anterolateral wall (1121 ms) and in the septum (1041 ms); d) Affected T2 map in anterolateral wall (57 ms) and normal in the septum (42 ms). Designed in MS PowerPoint. LGE: late gadolinium enhancement.*

that, in addition to a regional inflammatory process, myocarditis is characterized by widespread, diffuse myocardial involvement, the T2 ratio was consistent with the presence or absence of LGE and did not reflect this diffuse inflammation. T2 ratio failed to detect the alterations suggestive of diffuse involvement detected by T1 mapping.

A systematic review assessed the prevalence of abnormal CMR findings in recovered COVID-19 patients. Almost 47% of recovered patients exhibited one or more abnormal CMR findings, which included elevated native T1 or T2 values.[14] Another review that assessed data of 199 patients with the same profile showed that the most common imaging findings were abnormalities in T1 (73%) and T2 mapping (63%) and edema on T2/STIR sequences (51%). LGE was observed in only 43% of cases. Similar to our previous pandemic data with non-COVID-19 patients, this study revealed that new quantitative mapping techniques are essential to detect diffuse myocardial inflammation also associated with COVID-19.[15]

Therefore, T1 mapping was the only CMR technique capable of identifying diffuse changes in myocardial tissue, demonstrating abnormalities even in apparently normal ventricular walls.

Considering that the reference values of maps are determined by the value of the controls, and these are related to the characteristics of the patients at the study center and the magnetic resonance imaging device used, we believe that the work has internal validity.

Study limitations

Patients included in this study were selected at the time of CMR and not necessarily at the time of diagnosis with myocarditis. This may have slightly reduced the diagnostic accuracy of CMR, considering that the diffuse changes in the myocardial tissue could be in a healing curve after a few days, and T1 map values may be lower than in the acute phase. However, as our main objective was to compare myocardial segments in the same patients, this limitation may actually have enhanced, rather than jeopardized our analysis.

Although a T1 map has its own normality value according to the center in which it is evaluated, by way of comparison, our mean T1 map was slightly higher than reported in previous studies.[8,16] This may have reduced the odds of finding significant differences between cases and controls. However, even considering this unexpected finding, we were able to detect a significant difference between the T1 values of controls and the LGE– segments of cases. We thus believe this was a conservative bias. This limitation may also have decreased the statistical significance of the analysis of T2 map values between groups.

Other limitations include the small sample size, the retrospective design, and the absence of endomyocardial biopsy to confirm the imaging findings.

Conclusion

This study suggests that, in patients with myocarditis, even ventricular wall segments with no LGE are abnormal on T1 mapping. The abnormal T1 map values found in

LGE− were intermediate between those of LGE+ walls in cases and those of LGE− walls in controls. Specifically, T1 mapping revealed a diffuse myocardial involvement not evidenced by LGE imaging. This method should be used to demonstrate whole heart involvement in the diagnosis of myocarditis.

Author Contributions

Conception and design of the research and Writing of the manuscript: Pereira TB, Schvartzman PR, Beck-da-Silva L; Acquisition of data: Pereira TB, Balk M, Pereira GB, Ramos SR, Giordani L, Schvartzman PR; Analysis and interpretation of the data: Pereira TB, Balk M, Pereira GB, Ramos SR, Giordani L, Schvartzman PR, Beck-da-Silva L; Statistical analysis: Pereira TB, Beck-da-Silva L; Critical revision of the manuscript for important intellectual content: Schvartzman PR, Beck-da-Silva L.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Tiago Bartzen Pereira, from Universidade Federal do Rio Grande do Sul.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Moinhos de Vento under the protocol number 3.796.462. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Review Article

Left Atrial Cardiomyopathy as a Generator of Heart Failure with Preserved Ejection Fraction

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Abstract

The left atrium is an anatomical structure relevant to the maintenance of the physiological hemodynamics of the cardiovascular system. Atrial cardiomyopathy (aCMP), defined as any change in the structure, architecture, contractility or electrophysiology of the atria, is associated with adverse clinical implications, and responsible for atrial fibrillation and stroke. Heart failure with preserved ejection fraction (HFpEF) with a predominance of atrial fibrillation (AF) is a unique clinical phenotype, characterized by mechanical dysfunction of the left atrium, congestive symptoms and poor prognosis. aCMP is a common condition among patients with HFpEF and AF. Due to the strong association between aCMP and HFpEF, the diagnosis of aCMP has clinical relevance in patients with HFpEF. The objective of this review is to help identify aCMP as a risk factor for the development of HFpEF.

Introduction

The left atrium is an anatomical structure with great importance for the maintenance of the physiological hemodynamics of the cardiovascular system, serving as a reservoir, conduit and pump, functions that contribute to the left ventricular (LV) filling. Consequently, left atrial (LA) dysfunction is associated with adverse clinical implications, highlighting the importance and applicability of its diagnosis. This is particularly true and known in the setting of mitral stenosis, aortic stenosis, atrial fibrillation (AF) and has recently gained attention in the context of heart failure (HF) syndrome with preserved ejection fraction (HFpEF).[1]

HFpEF is a syndrome of high prevalence and high morbidity and mortality. The pathophysiology of the HFpEF phenotype is partially known, still with pivotal doubts, which surely led to the delay in the establishment of a disease-modifying treatment that only began to advance in recent years.[2] HFpEF is a prevalent syndrome, particularly in elderly female and hypertensive patients, and one of the mechanisms observed in this group of patients is atrial cardiomyopathy (aCMP).[3] Both aCMP and HFpEF are associated with increased left atrium, which is a recognized marker of LV diastolic dysfunction and is independently associated with increased risk of morbidity and mortality. The role of all three phases of LA function in patients with HFpEF is less well understood, especially in those patients with no history of AF and with normal left atrium.[4]

The objective of this review is to help identify aCMP as a risk factor for the development of HFpEF.

To structure this review article, two databases were searched, Medline and Scielo, for the following keywords in English "heart failure with preserved ejection fraction; atrial fibrillation; atrial myocardiopathy". The survey took place in June 2022. Prospective and retrospective studies were included and clinical cases and abstracts presented at scientific meetings were excluded. The eligibility of each study was independently assessed by two investigators. The divergent opinions regarding the relevance of the articles were resolved by consensus among the authors.

Atrial cardiomyopathy and HFpEF

The atria

The atria have a very complex structure differing from that of the ventricles and provide an important contribution to cardiac physiology. This structural complexity has important implications for the atrial mechanical function that are identified today as markers of aCMP.[5] The atria have an impact on ventricular filling and serve as a reservoir but are also important elements of the cardiac conduction system, as they protect the sinus node and the atrioventricular node. The atria also secrete atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), which are important regulators of homeostasis.[6,7]

Each atrium has a characteristic morphology of atrial body and appendage (Figure 1). In the body, there is a venous component with the orifices of the systemic and pulmonary veins and a vestibular component that surrounds the atrial outlet.[8] The interatrial septum separates the atrial bodies. The venous component of the left atrium is located posterosuperiorly and receives the pulmonary veins at the four corners, forming a prominent atrial dome.[8]

The appendix of the left atrium is smaller and narrower than the appendix of the right atrium, with different

Keywords

Atrial Function, Left; Atrial Fibrillation; Heart Failure, Diastolic

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shapes and a distinct opening to the atrial body covering the left circumflex coronary artery. There are different morphologies of the LA appendage described in the literature and it seems that the appendix morphology is correlated with the risk of developing thrombogenesis.[9] However, despite the apparent inconvenience of the existence of the LA appendix, this structure is attributed a role in volume regulation. Animal studies have shown that the elimination of the LA appendix can inhibit the manifestation of thirst because of hypovolemia.[10]

Atrial cardiomyocytes are geometrically complex cylinders and the only clear microscopic morphological difference between atrial and ventricular cardiomyocytes is in their size. The transverse diameter of the atrial cardiomyocyte is 12μm while the diameter of the ventricular cardiomyocyte is around 22μm.[11,12]

The atria have a series of electrophysiological characteristics that make them different from the ventricles, and susceptible to the development of arrhythmias.[7] Atrial cardiomyocytes have action potential properties that are different from ventricular ones, mainly due to the distribution of distinct ion channels.[13] Atrial potassium current is lower than the ventricular potassium current, resulting in a less negative resting potential and a more gradual slope of phase 3 repolarization (Figure 2). These cellular electrophysiological features have implications for the mechanism of action of antiarrhythmic drugs and may also alter responses to cardiac arrhythmias.[14]

LA pump function represents the increase in LV filling due to active atrial contraction and is estimated by measurements of cardiac output with and without effective atrial systole. The relative importance of the LA contribution to LV filling and cardiac output remains controversial.[7]

The conduit function performed by the left atrium occurs mainly during ventricular diastole and represents the transport of blood volume that cannot be attributed to reservoir or pump functions, corresponding to approximately one third of atrial flow.[15] There is a reciprocal relationship between the conduction and the reservoir functions of the LA; a redistribution between these functions is an important compensatory mechanism that facilitates LV filling in the presence of myocardial ischemia, hypertensive heart disease and mitral stenosis. Conduit function is estimated by early diastolic transmitral flow, pulmonary vein flow in diastole, and LA strain during early diastole.[7]

Definition of aCMP

aCMP can be defined as any change in the structure, architecture, contractility or electrophysiology that affects the atria with the potential to produce clinically relevant manifestations, mainly arrhythmogenic.[7]

Diseases and syndromes such as systemic arterial hypertension, HFpEF HF with reduced ejection fraction (HFrEF), diabetes mellitus, and myocarditis, or conditions such as aging and endocrine abnormalities are known to induce or contribute to aCMP. However, the changes are not necessarily disease-specific and pathological features often share many similarities.[16,17] The extent of pathological changes can vary over time and location in the atrium, causing substantial intra- and inter-individual differences. Pro-inflammatory conditions such as chronic obstructive pulmonary disease, possibly mediated by interleukin-6 and tumor necrosis factor-α, are associated with atrial arrhythmias.[18] Furthermore, while some pathological processes can affect the atria very selectively, such as AF-induced remodeling, most cardiomyopathies that affect the atria also involve the ventricles to a greater or lesser extent.[7]

The EHRA/HRS/APHRS/SOLAECE Consensus[7] proposed a pathophysiological classification for atrial cardiomyopathies, with definition of four classes (EHRAS), namely: (I) main alterations of cardiomyocytes; (II) mainly fibrotic changes; (III) cardiomyocyte-pathology/fibrosis combination; (IV) mainly non-collagenous infiltration (with or without cardiomyocyte alterations) (Table 1). This simple classification can help convey the primary underlying pathology in various clinical conditions. However, the class may change over time and differ in atrial sites in some patients. Thus, this classification is purely descriptive

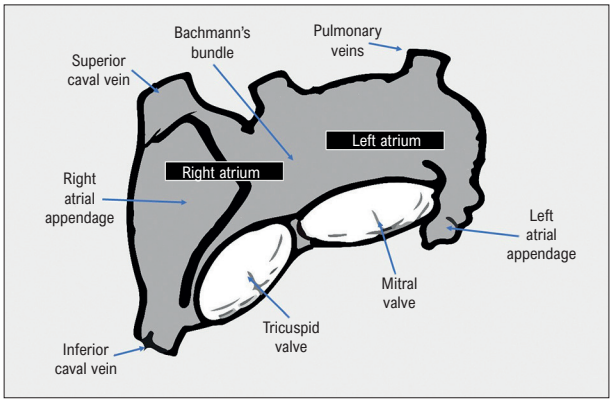

Figure 1 – *Representation of the upper and lower left and right atria; the Bachmann's bundle is part of the conduction system of the atria.*[7]

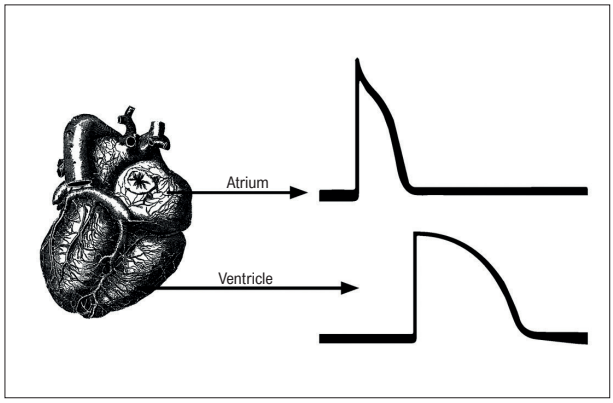

Figure 2 – *Action potential of atrial and ventricular myocytes.*[7]

Table 1 – Classification of Atrial Cardiomyopathy

Class	Histological Characterization
I	Morphological or molecular changes that "mainly" affect cardiomyocytes in terms of cellular hypertrophy and myocytolysis; no significant pathological tissue fibrosis or other interstitial changes
II	Predominantly fibrotic alterations; cardiomyocytes appear normal
III	Combination of cardiomyocyte changes (e.g., cellular hypertrophy, myocytolysis) and fibrotic changes
IV	Alteration of the interstitial matrix without accumulation of collagen fibers
IVa	amyloid accumulation
IVf	fatty infiltration
IVi	inflammatory cells
IVo	Other interstitial changes

EHRA/HRS/APHRS/SOLAECE Expert Consensus[7]

and, unlike other classifications such as NYHA, there is no progression in severity from EHRAS class I to class IV. This classification can be useful to describe pathological changes in biopsies and to correlate results obtained from imaging tests with diaseases.[7]

Atrial fibrillation

AF is the most common arrhythmia in patients with heart disease, affecting an estimated 33 million people worldwide.[19] It is important to emphasize that aCMP can be induced or exacerbated by AF, which has unique epidemiological, pathophysiological and clinical characteristics. AF-mediated aCMP is defined as having AF as the sole cause of ventricular dysfunction in patients with existing cardiomyopathy or HF.[20] Similar to cardiomyopathy caused by other arrhythmias, AF-induced cardiomyopathy can be at least partially reversed by restoration of sinus rhythm, thus creating a crucial opportunity for clinical intervention.[19]

Experimental and clinical studies have clarified the pathophysiological mechanisms of arrhythmia, especially on a molecular basis. Electrical, contractile and structural remodeling, calcium handling abnormalities, autonomic imbalance, and genetic factors appear to play a crucial role in the initiation and maintenance of AF. However, the exact pathophysiological mechanisms of AF are still not fully understood, and it is not known whether AF is an unclassified cardiomyopathy or a distinct disease.[21]

According to Coumel's triangle of arrhythmogenesis, three pillars are needed at the onset of clinical AF: (a) the triggering factor; (b) the arrhythmogenic substrate; and (c) the modulating factors. The interaction between these three elements determines the clinical picture of AF[21] (Figure 3).

Several modulating factors contribute to the onset and perpetuation of AF, with aging as a significant risk factor for the development of AF. Seminal studies by Spach and Dolber described microscopic evidence of fibrosis in association with an electrical uncoupling of connections in the aged human atrium. These structural changes were associated with conduction anisotropy, providing the necessary substrate for the reentry phenomenon.[22]

The role of inflammation in the onset of AF was supported by the fact that inflammatory states such as myocarditis, pericarditis and cardiac surgery are often associated with arrhythmia. Histological findings of atrial myocarditis were identified in patients with isolated AF.[23] Several prospective epidemiological studies have confirmed that inflammation may confer an increased risk of AF. The epidemiological relationship between the incidence of cancer and AF also supports the thesis that inflammation would be the common trigger between the two clinical conditions.[24]

Obesity is associated with an increased incidence of AF. There is a 3% to 8% greater risk of new onset AF with each unit increase in body mass index (BMI),[25,26] regardless of other cardiovascular risk factors such as dyslipidemia, hypertension, and diabetes. The mechanisms by which obesity can lead to AF are currently unknown. The increase in LA size correlates with BMI and is a possible explanation for the onset of AF in these patients. Diastolic dysfunction may be a result of myocardial thickening, increased plasma volume and increased neurohormonal activation.[27-30] An additional interpretation points out to the inflammatory action of extracellular vesicles of pericardial fat and its influence on cell apoptosis, fibrosis and proarrhythmic effect in the development of aCMP.[30]

Obstructive sleep apnea (OSA) is a strong predictor of AF incidence. OSA induces intermittent hypoxemia and hypercapnia, sympathetic activation, and changes in blood pressure. Elevated intrathoracic pressure caused by inspiration against an obstructed airway leads to an increase in the transmural pressure gradient, which in turn can lead to atrial stretch. In addition, OSA is associated with diastolic dysfunction.[31] These pathophysiological mechanisms can lead to greater vulnerability to AF. Patients with OSA have been shown to have a higher rate of recurrence of AF after successful cardioversion than patients without OSA, and treatment with continuous positive airway pressure reduces the occurrence of AF.[32]

Atrial cardiomyopathy, FA and HFpEF

The atrial myocardium is affected by many cardiac and non-cardiac conditions and is, in some respects, more sensitive than the ventricular myocardium.[33,34] There are three important mechanisms in the development of aCMP: fibrosis, electrical dysfunction, and mechanical dysfunction. Atrial inflammation is a key factor in the formation of atrial fibrosis and the increased risk of AF.[35] Progressive fibrosis can lead to conduction abnormalities as well as structural changes in the atrium. The loss of viable myocytes and the increase in wall tissue stiffness

due to excessive fibrosis ultimately reduce atrial function[36] (Figure 4).

The atria are activated, in addition to the three specialized internodal tracts, through functional cardiomyocytes,[37] so that any change in the atrial myocardium can cause significant electrophysiological disturbances. Furthermore, atrial cells, both cardiomyocytes and non-cardiomyocyte elements such as fibroblasts and endothelial cells, react rapidly and extensively to pathological stimuli and are influenced by many predisposing genetic factors. Responses include hypertrophy and contractile dysfunction of atrial cardiomyocytes, arrhythmogenic changes in the cardiomyocyte ion channel, proliferation of atrial fibroblasts, hyperinnervation, and thrombogenic changes.[38] Thus, atrial diseases have a substantial impact on cardiac performance, occurrence of arrhythmia, especially AF, and increased risk of stroke.[39,40]

HF is a common cause of AF[33] and atrial phenotype induced the disease is complex. A particularly important component is atrial fibrosis, which in experimental models occurs earlier in the course of HF, and to a much greater extent than in the ventricles, at least in part due to phenotype differences of atrioventricular fibroblasts.[34] In HF, fibrosis is slow and the AF-promoting substrate predominantly accompanies fibrosis rather than other components of atrial remodeling, such as ionic current or connexin changes. In HF, increased ventricular pressure or volume is a strong trigger for atrial enlargement and remodeling. In chronic conditions, LA volume and tension correlate with LV end-diastolic pressures, regardless of ejection fraction. Mechanical stress induces stretching and stiffening of the atria. Atrial fibrosis is perpetuated by atrial distention and is related to activation of profibrotic signaling cascades and apoptosis/necrosis of cells, as well as activation of a fetal genetic program.[7]

Unlike AF-induced remodeling, changes in atrial ionic current in HF do not shorten the action potential duration or cause general slowing of conduction and therefore do not directly contribute to the formation of arrhythmias.[41]

AF-predominant HFpEF is a unique clinical phenotype, characterized by LA mechanical dysfunction, congestive symptoms, and poor prognosis. ACMP is a common condition among patients with HFpEF and AF, and is associated with worse pulmonary vascular resistance and right ventricular function, and higher oxygen consumption. In addition, these patients may have abnormalities in right atrial function that lead to increased venous congestion. Patients with HFpEF with predominance of AF may have marked LA remodeling without substantial changes in LV performance. While loss of LA contractile function due to AF undoubtedly contributes to the clinical manifestations of aPMC, reduced LA compliance adversely compromises hemodynamics.[38]

Recently, a new element has been identified as a contributing factor to the pathophysiology of HFpEF. Dilatation of the mitral and tricuspid valve rings contributes to valve regurgitation by worsening atrial remodeling and can lead to an overload in a small, rigid ventricle, thereby causing an increase in filling pressures.[42] In addition, mitral annulus dilatation results in functional mitral regurgitation, further contributing to LA dysfunction. These findings suggest that aPMC may occur disproportionately to LV dysfunction in HFpEF with a predominance of AF.[1]

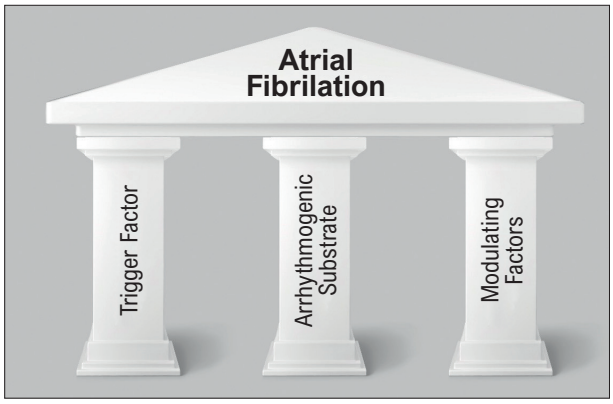

Figure 3 – *According to Coumel's triangle of arrhythmogenesis, three pillars are needed at the onset of clinical arrhythmia: the triggering factor, the arrhythmogenic substrate, and the modulating factors.*[21]

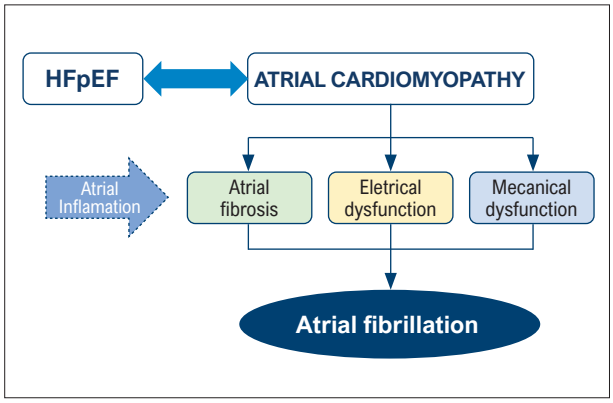

Figure 4 – *Atrial cardiomyopathy is composed of atrial fibrosis, mechanical dysfunction, and electrical dysfunction. The evaluation of these three components is done through different methods; HFpEF: heart failure with preserved ejection fraction.*[35]

HFpEF and AF share common pathophysiological features including a relative nitric oxide deficiency[34] and symptoms like dyspnea and exercise intolerance. Such nonspecific symptoms in isolated AF are commonly thought to be secondary to the arrhythmia. However, these patients likely have substantial aCMP, and restoration of sinus rhythm may not completely relieve symptoms. These patients should be considered as having HFpEF with a predominance of AF. Indeed, in a cohort of patients with AF and unexplained dyspnea, the probability of undiagnosed HFpEF was greater than 50%.[43] Recently, a risk score for HFpEF, the H2FpEF score, identified AF as the most important clinical variable to predict HFpEF among patients with dyspnea. Thus, aCMP secondary to AF is one of the main contributors to the pathogenesis of HFpEF.[43]

The left atrium stretches in HFpEF due to the chronic elevation of LV filling pressure and LA pressure, resulting in LA remodeling. Therefore, atrial size is often increased in HFpEF, which has not only become a diagnostic criterion, but is also useful as a prognostic factor.[44] Although LV diastolic dysfunction is the fundamental pathophysiological change in HFpEF, this condition is difficult to be determined solely by the occurrence of diastolic dysfunction. In fact, LA dilation (LA volume >32mL/m^2) was recommended to be included as an additional structural abnormality for the diagnosis of HFpEF in the European Society of Cardiology[45] guideline and the Brazilian Heart Failure Guideline.[46] Previous studies have shown that patients with HFpEF had a larger LA size than hypertensive patients with LV hypertrophy. Indeed, LV hypertrophy is also a common precursor of HFpEF and an indicator of elevated left atrial pressure leading to atrial remodeling.[47,48]

A population-based cohort study[3] showed that more than two-thirds of patients with HFpEF had AF before (risk factor), concomitantly or after the diagnosis of HFpEF (comorbidity), highlighting the interaction of these two conditions. At the diagnosis of HFpEF, patients with AF (previous or concomitant) were older and had larger atria, worse diastolic dysfunction, and higher BNP levels than those in sinus rhythm, consistent with more advanced HF. The development of incident AF was associated with advanced age, systemic arterial hypertension, renal dysfunction, LA dilatation and diastolic dysfunction in the diagnosis of HF. Importantly, both prevalent AF and incident AF were associated with worse survival in HFpEF even after adjusting for potential confounding factors. These data suggest that AF may be a risk factor and potentially a comorbidity of increased mortality in HFpEF, independently of other known risk factors.[3]

HFpEF increases the risk of aCMP and AF

The most commonly recognized mechanism by which HFpEF gives rise to AF is the structural and functional remodeling of the left atrium, which is substrate for aCMP. In patients with HFpEF, LA volumes are 68% greater compared to age-matched controls and 40% greater than in patients with hypertensive heart disease without HF.[49] LE enlargement in HFpEF is a well-established proarrhythmic substrate associated with atrial fibrosis,[49] and the abnormal distribution of gap junctions and loss of cell-to-cell coupling in areas of fibrosis contribute to electrical remodeling, increased atrial refractoriness and development of AF.[50,51]

In aCMP, there is also the important role of gap junctions in atrial remodeling, involving atrial connexin proteins[52] and the consequent heterogeneity of impulse propagation, establishing reentry circuits that predispose to AF.[52] In this case, studies have not been able to define the underlying disorder, whether HFpEF or aCMP. Therefore, it remains a diagnostic dilemma to discriminate HFpEF from aCMP/AF due to converging symptoms like shortness of breath and exercise intolerance. However, accurately distinguishing one condition from another is important as their treatments may differ, in part because of the potentially different pathophysiology.[42] Therefore, the overlap of AF with HFpEF makes the interpretation of the definitive causal mechanism based on clinical features complex.[52]

Mechanisms by which aCMP and AF give rise to HFpEF

As aCMP leads to LA dilation, alters atrial function and causes atrial fibrosis, it can be a direct cause of HFpEF. Indeed, successful cardioversion of AF is associated with restoration of atrial booster pump function and improved ventricular filling, with the atrial contribution to ventricular filling increasing from 30% to 47% one month after return to sinus rhythm.[53] AF is also associated with LV myocardial fibrosis, which in turn contributes to diastolic dysfunction and HFpEF. In addition, atrioventricular annulus remodeling with progressive mitral and tricuspid regurgitation may be another mechanism by which aCMP causes HFpEF. ANP depletion, which occurs in permanent AF, can lead to further vasoconstriction and congestion and thus set the stage for incident HFpEF.[54]

HFpEF and aCMP share common pathophysiological mechanisms, as a substantial proportion of patients with HFpEF experience AF. Also, these conditions probably share pathophysiological mechanisms, such as systemic inflammation, neurohumoral activation, increased activity of the renin-angiotensin-aldosterone system, endothelial dysfunction, reduced ANP release, mitral and tricuspid annular remodeling, chronotropic incompetence and tachycardiomyopathy.[52]

In aCMP, it has been often proposed that HF develops due to tachycardia or cardiomyopathy induced by hemodynamic changes, cellular effects, and neurohormonal activation. The hemodynamic changes that lead to aCMP are: shortened diastasis, reduced cardiac output, structural effects such as eccentric LV remodeling, subendocardial fibrosis and impaired myocardial perfusion. The main cellular alterations related to aCMP include changes in the cytoskeleton, disruption of the mitochondrial matrix and abnormal manipulation of calcium. Finally, neurohormonal activation, such as the upregulation of the renin-angiotensin-aldosterone system and natriuretic peptides would also be involved in the development of aCMP.[55,56]

Diagnosis of aCMP

The correct diagnosis of aCMP is of clinical importance and includes electrocardiography (ECG), echocardiography, cardiac magnetic resonance (CMR) imaging, and biomarkers, which can identify and quantify structural, mechanical, and electrical dysfunction in the atria (Figure 5).

An abnormal electrocardiogram (ECG) can provide information about conduction disorders and electrical remodeling. Studies analyzing ECG parameters have reported heterogenous definitions of aCMP[57] (Figure 6).

Analysis of fibrillatory waves (f waves) may be suitable for detecting both electrophysiological and structural changes in the atria. Coarse-wave AF, defined as f-wave amplitude in

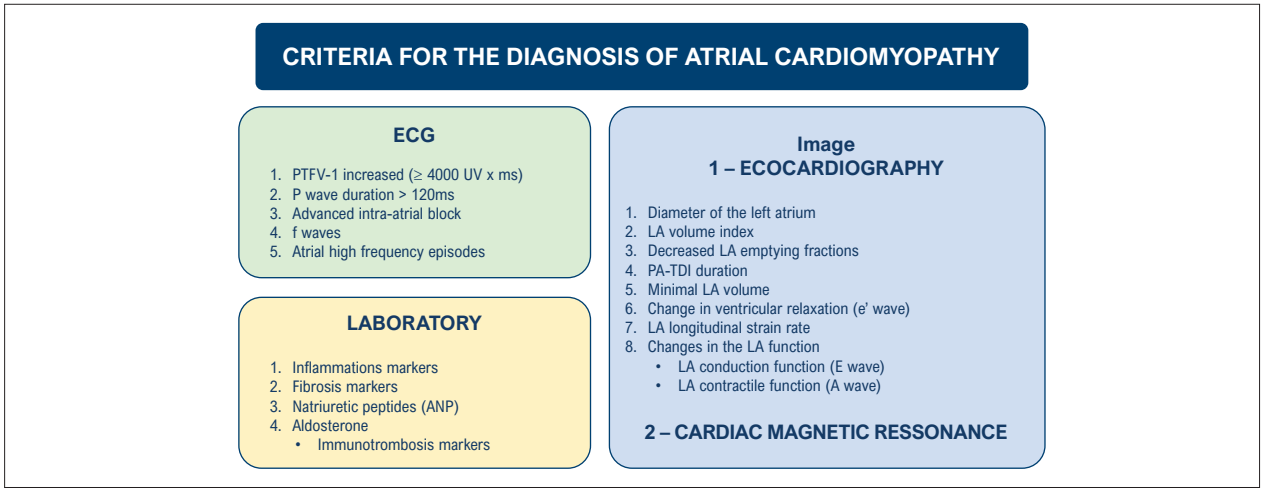

Figure 5 – *Main laboratory criteria, electrocardiogram and echocardiogram for the diagnosis of atrial cardiomyopathy;[57] PTFV-1: power terminal force on lead V1; PA-TDI: total atrial conduction time assessed by tissue Doppler; LA: left atrial.*

lead V1 ≥1mm, is associated with decreased LA appendage ejection fraction and decreased maximum atrial emptying velocity.[57] F-wave amplitude strongly correlates with LA volume measured by echocardiography.[58]

The P wave represents atrial depolarization and is associated with atrial electrical remodeling. P wave parameters include its duration, dispersion, axis, voltage, area, atrial block and terminal force in lead V1 (PTFV1).[59] P-wave parameters are predictive of ischemic stroke, regardless of AF, suggesting that they may reflect atrial remodeling independent of arrhythmogenesis.[59]

PTFV1 is an electrocardiographic marker for atrial remodeling. The P wave in lead V1 is usually biphasic, where the second negative portion of the P wave represents the propagation of excitation in the left atrium. PTFV1 is determined by multiplying the amplitude of the second portion of the P wave by its width. A PTFV1 ≥ −4,000μV × ms is considered pathological.[57]

An ECG analysis using artificial intelligence was performed to detect CMPa in 613 patients with HFpEF.[60] This method is based on a computer-aided algorithm that analyzes data of resting 12-lead ECG and includes a statement (criteria) about the probability of AF. Structural heart disease was more severe in patients with a higher probability of AF assessed by artificial intelligence, with LV hypertrophy, higher LA volumes, and decreased LA reservoir on echocardiography. Each 10% increase in the likelihood of AF by artificial intelligence resulted in a 31% higher risk of developing new-onset AF among patients with sinus rhythm and without prior AF. In the total population, every 10% increase in the likelihood of AF by artificial intelligence led to a 12% greater risk of death.

Echocardiography is the imaging technique of choice for screening and monitoring patients with abnormal LA morphology and function due to its widespread, non-invasive, and cost-effective use. Thus, echocardiography may be useful in detecting aCMP. In studies that investigated the usefulness of echocardiography, aCMP was defined by demonstrating an association of abnormal LA size with primarily clinical outcomes such as AF and AF recurrence after ablation and ischemic stroke.[57]

The LA volume (LAV) index is more accurate to estimate atrial size than LA diameter.[57] Increased LAV index has been described as a potential early marker of aCMP and is often present in patients with AF.[61]

In addition to LAV abnormalities that represent structural remodeling, assessment of atrial function can provide other important indicators for the presence of aCMP. Both increased LA and decreased LA void fraction are common phenomena

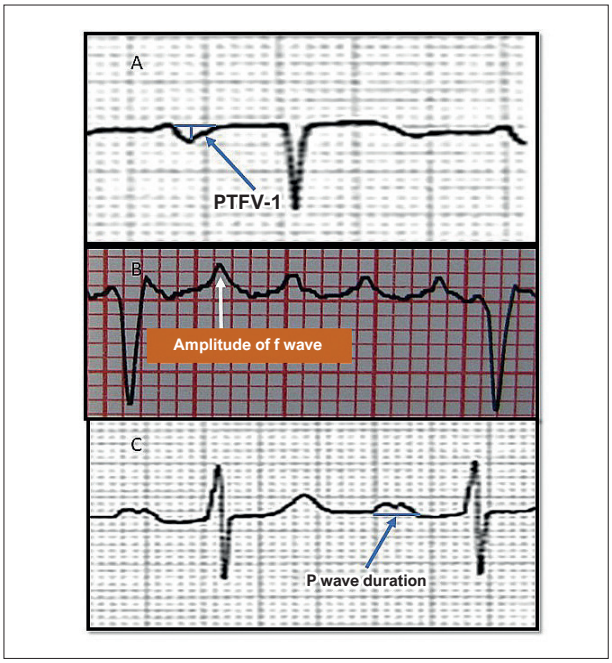

Figure 6 – *Examples of electrocardiogram changes that may indicate atrial cardiomyopathy.[57] PTFV-1: power terminal force on lead V1.*

in patients with AF, with a negative correlation between LA size and void fraction.[61]

The assessment of LA function is also possible by Doppler echocardiographic measurements, and altered LA function may be indicative of aCMP. While LA conduction function, represented by transmitral E wave velocity, increases with greater incidence of AF, there is an opposite effect on LA contractile function, represented by transmitral A wave velocity and the mitral annular tissue Doppler velocity.[61]

Another important marker of aCMP would be LA deformity (atrial strain), a cyclic process analyzed in three phases: reservoir phase, conduit phase and contraction phase. Traces of LA strain obtained by speckle-tracking echocardiography are largely a mirror image of strain in the left ventricle, since the LA and left ventricle share the mitral annulus.[62] The superiority of atrial strain over left atrial volume index, a variable already well established in the evaluation of patients with HFpEF, has been discussed.[63]

CMR imaging is considered the gold standard for assessing structural and functional changes in the heart. Gadolinium-enhanced CMR shows good performance in the assessment of atrial fibrosis, helping to identify eligible patients for AF ablation and to predict the course of sinoatrial node dysfunction, AF progression, and stroke risk in AF patients.[7]

Several circulating biomarkers, including inflammatory and fibrosis biomarkers and atrial peptides, have been proposed to estimate atrial remodeling and aCMP. However, there are conflicting results, as biomarkers related to inflammation and fibrosis are not specific to these conditions. In view of this, the clinical value of biomarkers in the assessment of aCMP is unclear and their use in routine screening is questionable.[57]

Treatment of aCMP

The treatment of aCMP should involve the control of underlying risk factors, anticoagulation, and the use of medical therapy established in the guidelines.[19] Controlling heart rate is a reasonable first step in controlling clinical symptoms and restoring cardiac function. Heart rate control with short-term cardioversion can also be attempted in the initial phase. For long-term treatment, existing evidence supports the use of AF ablation as a preferred strategy for patients who are good candidates for the method. Long-term heart rate control can be used as an alternative for patients who are not good candidates for AF ablation or who prefer a conservative management strategy even knowig it may be inferior to ablation in long-term clinical outcomes. With close monitoring, antiarrhythmic drugs can be used in a group of patients independently or as an adjunct to AF ablation to aid in rhythm control. When this control is not possible and pharmacological rate control is inadequate, atrioventricular nodal ablation with physiological stimulation may be considered.

Numerous randomized controlled trials and multicenter observational registries have demonstrated the superiority of AF ablation over drug therapy for maintaining sinus rhythm. However, late recurrences are common and associated with more advanced atrial substrate and structural heart disease.[19]

Conclusion

aCMP has been associated with HFpEF and has a significant impact on atrial function and the development of arrhythmias, especially AF. AF occurs in more than half of individuals with HFpEF, and HFpEF occurs in more than a third of individuals with AF. Although HFpEF and aCMP frequently coexist, there are numerous unanswered questions about the pathophysiology, symptomatology, diagnosis, and prognosis of both conditions. When together, aCMP and HFpEF offer a poor prognosis to patients.

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Conception and design of the research and Acquisition of data: Jorge AJL; Writing of the manuscript: Jorge AJL, Martins WA, Mesquita ET, Carvalho MRM; Critical revision of the manuscript for important intellectual content: Jorge AJL, Martins WA, Mesquita ET.

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Review Article

Echocardiography in Heart Failure with Preserved Ejection Fraction: From Primary Care to Tertiary Hospitals

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Introduction

Heart failure (HF) is a highly prevalent and incident clinical syndrome that mostly affects older adults. It is one of the main causes of hospital admission, which is a strong prognostic marker, considering that approximately 50% of hospitalized patients will be readmitted within 6 months.[1]

HF with preserved ejection fraction (HFpEF) is hemodynamically defined as an inability of the heart to meet adequate metabolic demands under normal filling pressures. This concept is fundamental, given that patients with normal left ventricular (LV) ejection fraction (EF) (> 50%) usually have normal cardiac output, but are only able to maintain this output at the expense of increased filling pressures. Some patients are known to show signs of congestion at rest, but the vast majority only presents clinical symptoms during effort.[2]

Echocardiography (ECHO) is the main tool used in this population. It is highly available, noninvasive, and easily applicable. However, EF assessment alone may not be sufficient to support the presence of HFpEF.

Concepts in the diagnosis of heart failure with preserved ejection fraction

HFpEF is currently defined as a clinical syndrome of HF with LVEF > 50% in the absence of a previously reduced EF. Patients' symptoms fundamentally result from increases in LV filling pressures at rest or during effort. Documenting this increase in pressure using practical and reproducible means is one of the major challenges in the diagnostic process. Guidelines define HFpEF according to:[3]

1. Presence of signs and symptoms of HF
2. LVEF ≥ 50%
3. Absence of syndromes "simulating" HFpEF
4. Evidence of increased filling pressures or correlated noninvasive markers (elevated E/e' ratio, increased left atrial volume, and increased levels of natriuretic peptides)

Keywords

Heart Failure; Prognosis; Diagnosis.

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Clinical syndromes that mimic heart failure with preserved ejection fraction

Patients with HFpEF are typically older, obese, and female and have predisposing comorbidities such as hypertension, metabolic syndrome, lung disease, and renal failure. Differentiating a cardiac origin from noncardiac conditions is very difficult for the physician when faced with patients with nonspecific symptoms suggestive of HF, such as fatigue, reduced effort capacity, dyspnea on exercise, and lower limb edema. This is a very common problem in clinical practice.

Diagnostic scores

Two diagnostic algorithms – the H_2FPEF score and the HFA-PEFF algorithm of the European Society of Cardiology[4,5] – assess pre-test probability in order to distinguish HFpEF from dyspnea of noncardiac origin. The combination of clinical and laboratory data, including electrocardiogram and ECHO analysis, will estimate whether the probability of HFpEF is low, intermediate, or high. The Emerging Topics Update of the Brazilian Heart Failure Guideline[6] has objectively summarized this line of reasoning (Tables 1 and 2). Figure 1 shows how to apply these scores.

Echocardiography

We will now describe the main objective of our review, which consists of extracting the greatest number of data from this great diagnostic tool. Notice the amount of information obtained from ECHO when creating the HFA-PEFF score for HFpEF diagnosis (Table 2). In addition to ventricular diameters and LVEF calculation, an estimate of the pulmonary artery systolic pressure (PASP), the E/e' ratio by tissue Doppler, the indexed left atrial volume (LAV), the indexed LV mass, the relative wall thickness (RWT) and, if possible, the study of myocardial deformation (global longitudinal strain) will be obtained. The accuracy of the variables provided by the ECHO will be analyzed, as well as how to use them.

Ejection fraction

LVEF should be obtained from a biplanar study, classically using Simpson's method.[7] The limitations of using EF assessment alone in decision making have been previously described.[8] However, in the setting of HF, a LVEF > 50% is considered significant, thus starting the clinical reasoning within the HFpEF model.

Estimation of mean left atrial pressure in patients with normal ejection fraction

Careful quantification of cavity dimensions and volumes is extremely important before estimating filling pressures. The presence of structural changes, such as LV hypertrophy and/or left atrial (LA) dilatation, indicates a more marked cavity remodeling. The correct assessment of diastolic function will allow an adequate extraction of volume data. Diastolic dysfunction is a combination of abnormal ventricular relaxation, myocyte deformation, and LA function, culminating in elevated filling pressures.

The first step consists of analyzing the mitral flow pattern, known as the E/A ratio. In many cases, this pattern alone may be sufficient. Patients with an E/A ratio ≤ 0.8 and an E wave velocity ≤ 50 cm/s have a normal mean LA pressure, whereas those with an E/A ratio ≥ 2 have an elevated LA pressure. In intermediate cases, other variables will be used, such as the E/e' ratio, indexed LAV, and peak tricuspid regurgitation velocity (TRV)[9] (Figures 2 and 3).

The relationship between flow velocity in early diastole (E wave, measured by pulsed Doppler) and mitral annular velocity (e' wave, which represents mean septal and lateral annular velocities, measured by tissue Doppler) reflects the mean capillary pressure (CP). An E/e' ratio ≥ 15 at rest has good diagnostic sensitivity in identifying an elevated CP, reinforcing the likelihood of HFpEF as the etiology of symptoms. However, an E/e' ratio in the intermediate range (9-14) is much less sensitive and should not be used as an isolated echocardiographic parameter; the entire diagnostic algorithm should be used instead.[10]

This algorithm showed good accuracy (84%) in identifying patients with HFpEF when applied to those with normal LVEF and complaints of fatigue during effort. Clinical evaluation, which included chest radiography and N-terminal B-type natriuretic peptide levels, was only 64% accurate. The use of these echocardiographic variables was also evaluated with regard to the prediction of hospital readmission in 30 days. When the E/e' ratio was added to the clinical score, there was a 29% increase in the prediction of readmission risk.[11]

Patterns of diastolic dysfunction are also prognostic markers, as they show changes in left atrial compliance, with atrial dilatation, mitral regurgitation, and atrial fibrillation (AF), the so-called progressive atrial remodeling (Figure 4). The indexed LAV represents a marker of chronic remodeling and is much more accurate than the diameter measure. In patients in sinus rhythm without valve disease, an indexed LAV > 34 mL/m² was an independent predictor of death, HF, and stroke.[12,13] Different cut-off values are recommended for the indexed LAV in patients in sinus rhythm and patients with AF. Table 2 shows major and minor criteria according to the indexed LAV.

The PASP is calculated by peak TRV, using the modified Bernoulli equation (PASP = 4 x TRV squared, added to the estimated right atrial pressure). Elevated PASP, especially if associated with right ventricular (RV) dysfunction, is an important variable of poor prognostic in HFpEF.[14] A peak TRV > 2.8 m/s indicates elevated PASP and represents an indirect marker of diastolic dysfunction.[15]

Table 1 – H_2FPEF score for the diagnosis of heart failure with preserved ejection fraction

	CLINICAL VARIABLE	CHARACTERISTICS	POINTS
H_2	Heavy Hypertension	BMI > 30 2 or more anti-hypertensive drugs	2 1
F	Atrial fibrillation	Paroxysmal or persistent	3
P	Pulmonary hypertension	PASP > 35 mm Hg (echocardiogram)	1
E	Older patients	Age > 60 years	1
F	Filling pressures	E/e' > 9	1

Source: Marcondes Braga et al[6]. BMI: body mass index; PASP: pulmonary artery systolic pressure.

Structural changes

Initial studies suggested that patients with HFpEF have concentric LV hypertrophy, which leads to reduced

Table 2 – HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction

Criteria	Major (2 points)	Minor (1 point)
Functional	Septal e' < 7 Lateral e' < 10 or E/e' > 15 or TRV > 2.8 m/s (PASP > 35 mm Hg)	E/e' 9-14 or GLS < 16%
Morphological	Indexed LAV > 34 mL/m² or LV mass 149/122 g/m² (M/W) and RWT > 0.42	Indexed LAV 29-34 mL/m² or LV mass > 115/95 g/m² (M/W) or IVS or PW ≥ 12 mm
Biomarker (sinus rhythm)	NT-proBNP > 220 pg/mL or BNP > 80 pg/mL	NT-proBNP 125-220 pg/mL or BNP 35-80 pg/mL
Biomarker (atrial fibrillation)	NT-proBNP > 660 pg/mL or BNP > 240 pg/mL	NT-proBNP 365-660 pg/mL or BNP 105-240 pg/mL

GLS: global longitudinal strain; IVS: intraventricular septum; LAV: left atrial volume; M: men; NT-proBNP: N-terminal pro–B-type natriuretic peptide; PASP: pulmonary artery systolic pressure; PW: posterior wall; RWT: relative wall thickness; TRV: tricuspid regurgitation velocity; W: women. Source: Marcondes Braga et al.[6]

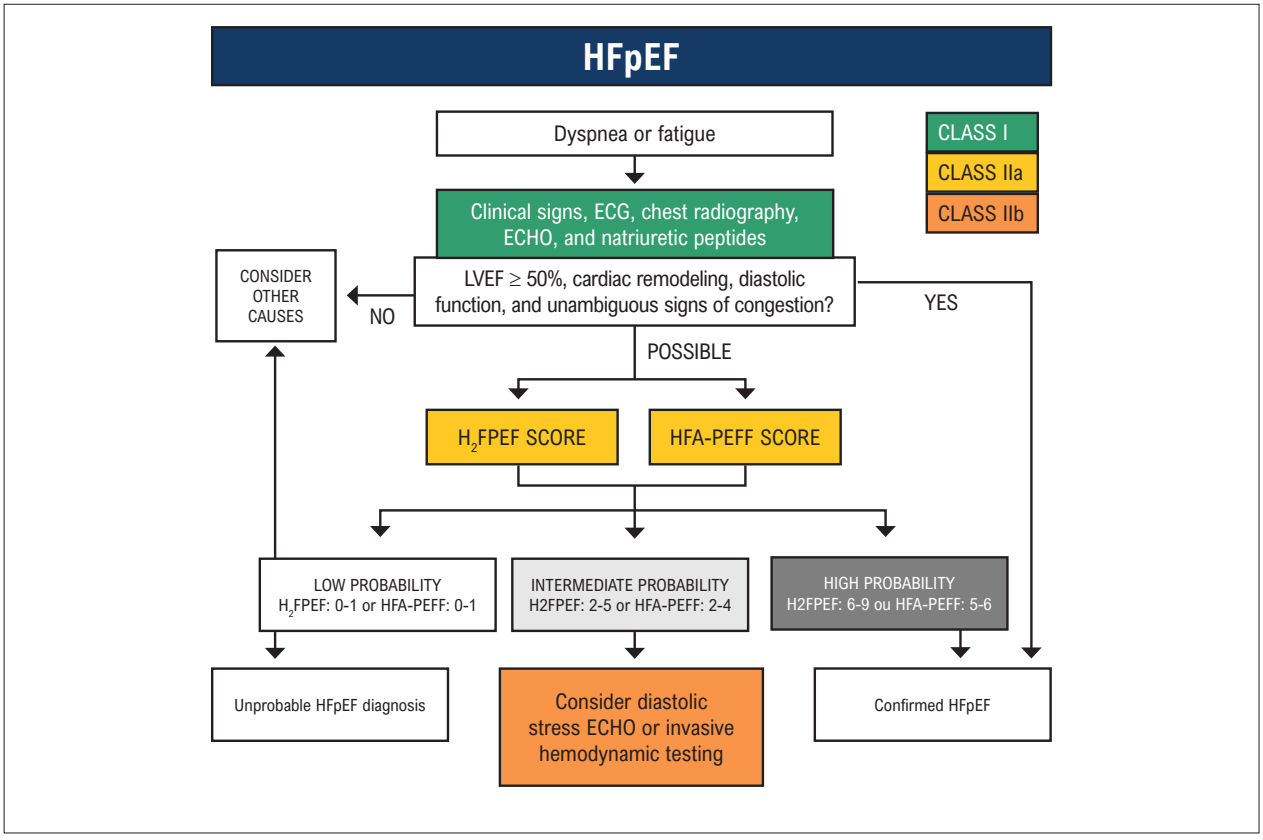
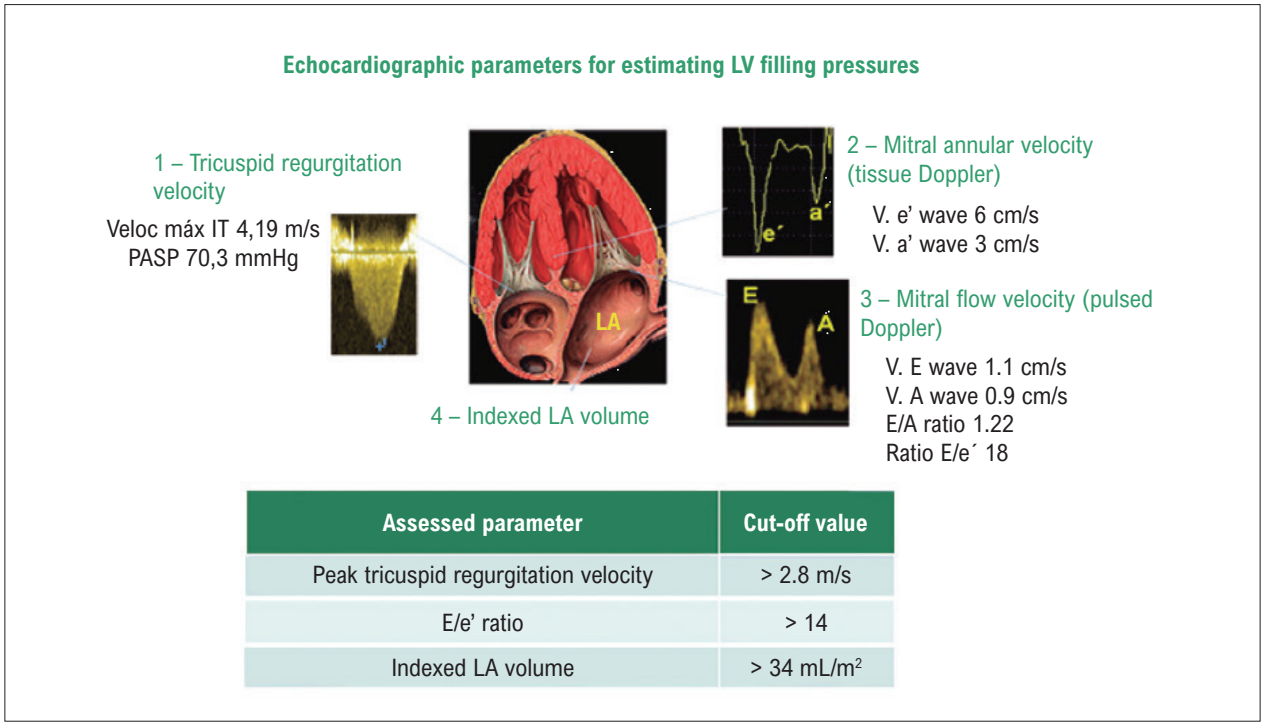


Figure 1 – *Diagnostic flowchart of heart failure with preserved ejection fraction (HFpEF). ECG: electrocardiogram; ECHO: echocardiography; LVEF: left ventricular ejection fraction. Source: Marcondes Braga et al.[6]*



Assessed parameter	Cut-off value
Peak tricuspid regurgitation velocity	> 2.8 m/s
E/e' ratio	> 14
Indexed LA volume	> 34 mL/m²

Figure 2 – *Diastole and volume estimation in heart failure. LA: left atrial; LV: left ventricular; PASP: pulmonary artery systolic pressure. Source: adapted from Nagueh SF.[9]*

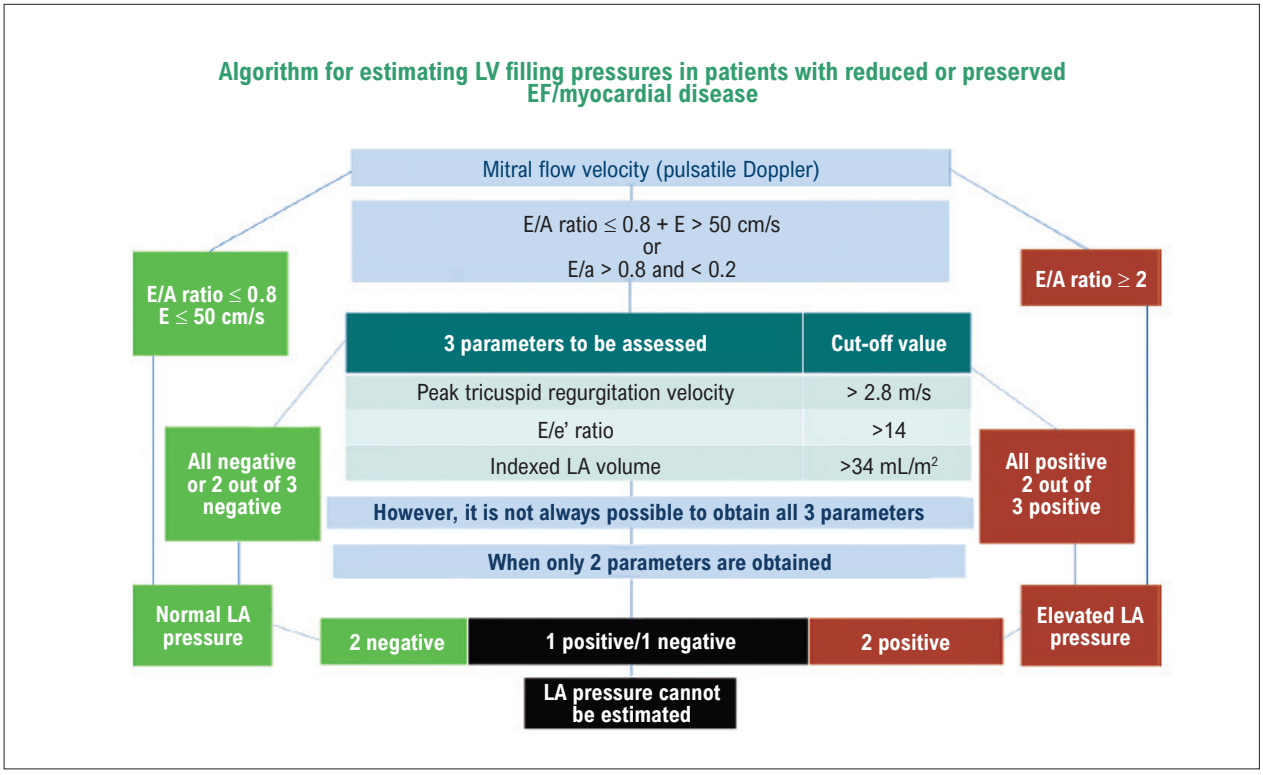


Figure 3 – *Diagnostic algorithm based on echocardiographic data. EF: ejection fraction; LA: left atrial; LV: left ventricular. Source: adapted from Nagueh SF.*[9]

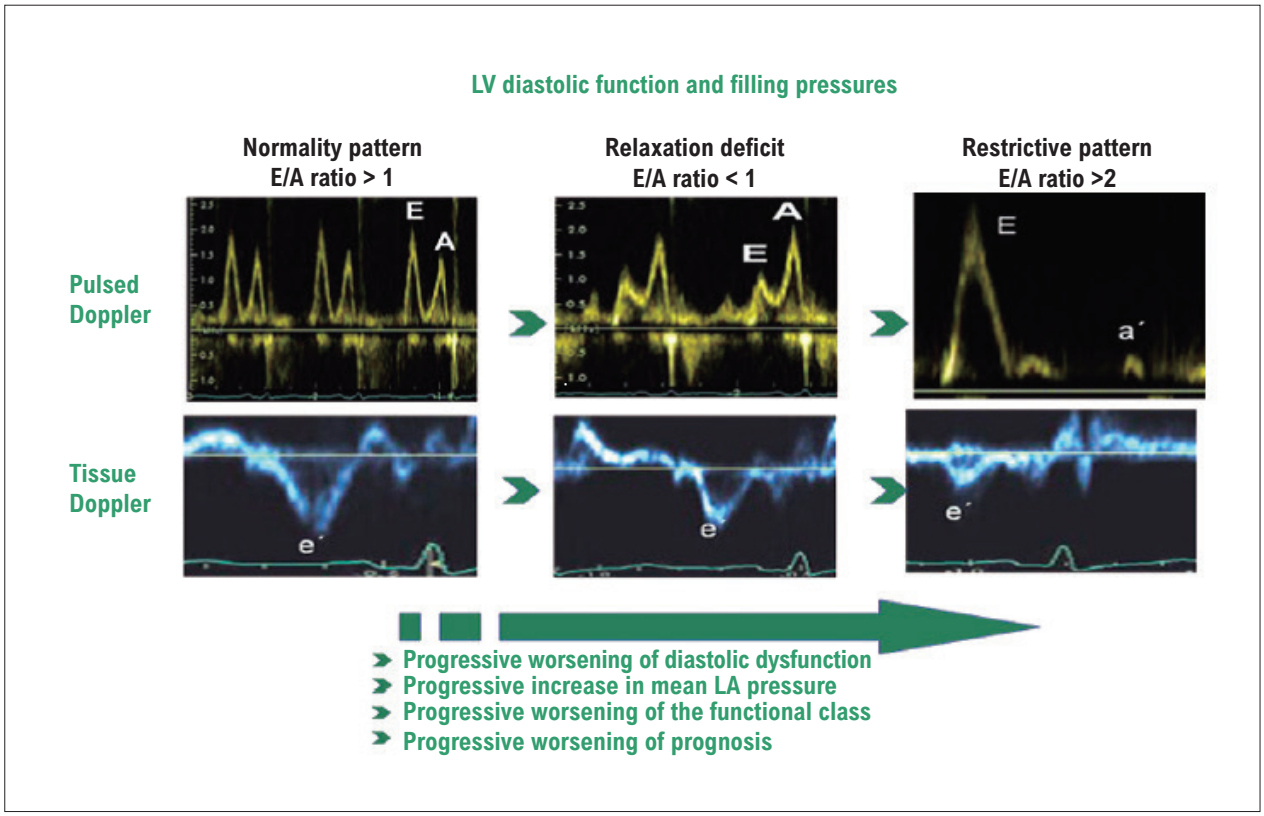


Figure 4 – *Patterns of diastolic dysfunction. LA: left atrial; LV: left ventricular. Source: personal archive.*

distensibility and, consequently, elevated filling pressures.[16] In addition, indexed LV mass has also shown a modest relationship with invasive measurement of filling pressures (r = 0.41-0.48).[17,18] However, several studies have shown that many patients with HFpEF exhibit concentric remodeling in the absence of hypertrophy or normal ventricular geometry.[19-21] Corroborating this affirmation, LV hypertrophy was recently shown to be highly specific (88%) but not very sensitive (26%) in the diagnosis of HFpEF, meaning that the absence of LV hypertrophy does not rule out HFpEF.[3] LV geometry is often classified using RWT, which consists of multiplying the LV posterior wall thickness (PWT) by 2 and dividing it by its end-diastolic diameter (EDD) (RWT = 2xEPP/PWT). There are four different patterns, described in Figure 5.

According to Table 2, assigned points differ according to mass and RWT values. Table 3 summarizes the accuracy of the main markers used.

When evaluating LV morphology, pathologies that mimic HFpEF should be excluded. Whenever significant hypertrophy is identified, the diagnosis of amyloidosis should be considered, especially in the presence of pericardial effusion or apical sparing pattern (the LV apex is "spared" from involvement) by global longitudinal strain.[22] In a series of patients with thicknesses > 12 mm, amyloidosis accounted for 13% of hospitalized patients with "HFpEF".[23] Figure 6 shows an example of amyloidosis.

Diastolic stress echocardiography – assessment of patients with dyspnea, normal left ventricular ejection fraction, and normal left atrial pressure at rest

Much of the difficulty in diagnosing HFpEF is associated with the fact that filling pressures are often normal at rest and only become elevated during exercise testing. Thus, invasive cardiopulmonary exercise testing has emerged as the gold standard to confirm or exclude the diagnosis of HFpEF as a cause of dyspnea.[24,25] Recent studies have evaluated whether similar data can be obtained noninvasively using diastolic stress ECHO.[26] Information acquisition during effort can unmask systolic and diastolic dysfunction. The most frequently studied parameters are the E/e' ratio and peak TRV, which indicate increases in CP and PASP, respectively. The European Association of Cardiovascular Imaging and the American Society of Echocardiography recommend a staged protocol, preferably on a semi-supine bicycle, until the patient reaches the predicted

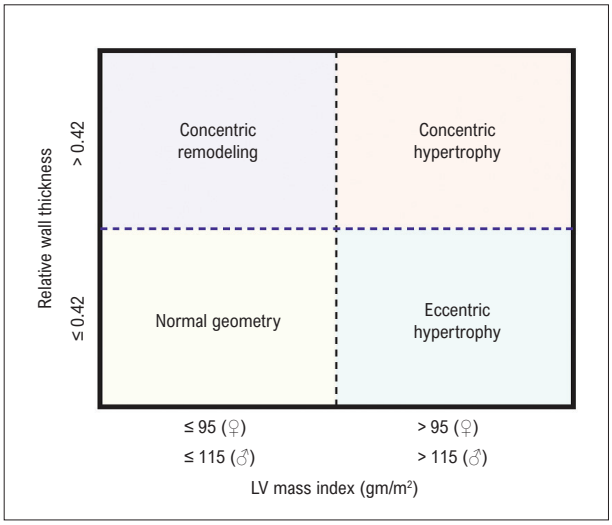


Figure 5 – *Patterns of ventricular geometry. Source: adapted from Lang RM.[7]*

Table 3 – Objective evidence of structural and functional cardiac abnormalities consistent with the presence of diastolic dysfunction/elevated left ventricular filling pressures

Parameter	Cut-off values	Observations
Indexed LV mass	> 115/95 g/m² (M/W)	Although the presence of concentric remodeling or hypertrophy is a marker of HFpEF, the absence of hypertrophy does not exclude the diagnosis of HFpEF
Relative wall thickness	> 0.42	
Indexed LA volume	> 34 mL/m² (sinus rhythm)	In the absence of valve disease, LA dilation reflects chronically elevated LV filling pressures (in AF, the threshold is > 40 mL/m²)
E/e' ratio at rest	> 9	Sensitivity of 78% and specificity of 59% for the presence of HFpEF confirmed by invasive exercise testing. If a higher cut-off value (> 13) is used, the sensitivity is reduced to 46%, but with greater specificity (86%)
Peak tricuspid regurgitation velocity at rest	> 2.8 m/s	Sensitivity of 54% and specificity of 85% for the presence of HFpEF confirmed by invasive stress test

LA: left atrium; AF: atrial fibrillation; HFpEF: heart failure with preserved ejection fraction; LV: left ventricle. Source: adapted from McDonagh.[3]

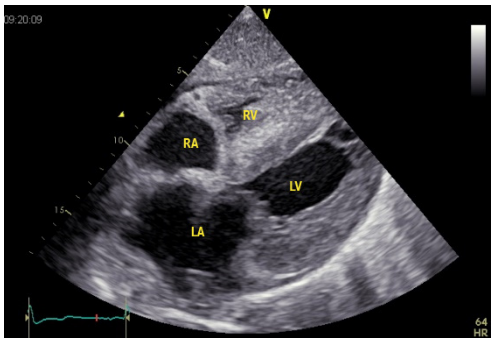


Figure 6 – *Cardiac amyloidosis with extensive myocardial infiltration, valves, and interatrial septum. RV: right ventricle; RA: right atrium; LV: left ventricle; LA: left atrium. Source: personal archive.*

maximum heart rate or develops limiting symptoms. The test is considered abnormal if the E/e' ratio at peak stress is ≥ 15, with or without TRV > 3.4 m/s. It should be noted that increased TRV alone should not be used for the diagnosis of HFpEF, as it may simply represent a normal hyperdynamic response to effort, caused by increased pulmonary flow, even in the absence of diastolic dysfunction.[27-29]

In the presence of inconclusive results, one should consider performing an invasive stress test, measuring CP at rest and during effort (algorithm described in Figure 1).

Special cases

In patients with AF, the determination of the diastolic function pattern is compromised, given the absence of the A wave. However, filling pressures may be estimated using the E/e' ratio or other variables. In cases of high filling pressures, the E-wave deceleration time and the isovolumetric relaxation time (IVRT) will be reduced.

In patients with pulmonary hypertension who develop RV overload, ventricular interdependence is usually altered, with a paradoxical septal movement. In these cases, only the lateral mitral annular velocity should be used, as the septal annular velocity will be reduced.

Another common situation, especially among older adults, is mitral annular calcification, which considerably reduces e' wave velocity, overestimating the E/e' ratio. In these cases, the E/A pattern on pulsed Doppler and the IVRT should be used instead of the E/e ratio.[30,31]

Conclusions

Diagnosing HFpEF is not simple, and the interaction between the clinician and the echocardiographer plays a key role in this process. The examiner has great responsibility and may even screen some patients in the outpatient setting, identifying higher risk phenotypes. Identifying specific imaging features can reduce the time until diagnosis; however, in most cases, clinical suspicion will be raised in a detailed report. There are controversies about the best indexes for obtaining LV filling pressures noninvasively, which are often tested in different settings and with different objectives. The adequate use of each discussed marker, respecting their limitations, will be of great value for the clinician in their etiological search.

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Critical revision of the manuscript for important intellectual content: Garcia MI

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

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Review Article

Diagnostic Scores in Heart Failure with Preserved Ejection Fraction

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Abstract

The diagnosis of heart failure with preserved ejection fraction (HFpEF) can be challenging and diagnostic scores have been proposed to help in the diagnostic process. This article reviews these scores to provide insights on their role and interpretation in clinical practice. To date, two scores have been validated for the diagnosis of HFpEF. The H2FPEF includes clinical – obesity, hypertension, atrial fibrillation, age – and echocardiographic data – pulmonary hypertension and E/e' ratio. The HFA-PEFF uses multiple echocardiographic parameters on structural and functional cardiac abnormalities and includes natriuretic peptide blood levels. The accuracy of the H2FPEF score appear to be superior to the HFA-PEFF score in identifying patients with elevated pulmonary capillary wedge pressure at rest or during exercise, but the gold-standard definition of HFpEF is still a matter of debate. A high rating in either of the two scores has a high positive predictive value, and the scores are most useful when HFpEF is clinically suspected, but the diagnosis is uncertain.

Introduction

The diagnosis of heart failure with preserved ejection fraction (HFpEF) can be challenging. In the universal definition of heart failure (HF), HF is a syndrome with signs/symptoms caused by cardiac structural/functional abnormalities, corroborated by either elevated natriuretic peptides or objective evidence of systemic/pulmonary congestion by imaging method or hemodynamic measurement.[1] In a patient with overt congestion and left ventricular ejection fraction (LVEF) ≥ 50%, it is usually easy to diagnose HFpEF. Nevertheless, the diagnosis becomes difficult when signs/symptoms are not typical, such as in outpatients with exertional dyspnea, particularly in the presence of comorbidities. In the last years, two approaches have been proposed and validated for the diagnosis of HFpEF, which may help the clinician to make decisions in equivocal cases. This article reviews these approaches to provide insights on their role and interpretation in clinical practice.

Keywords

Diastolic Heart Failure; Diagnosis; Patients.

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The H2FPEF score

The H2FPEF score was developed by Reddy at al.[2] at the Mayo Clinic, Rochester, USA. The authors used data from 414 consecutive patients undergoing a supine cycle ergometry exercise test with hemodynamic catheterization to investigate dyspnea of unknown origin.[2] They defined HFpEF as elevated pulmonary capillary wedge pressure (PCWP) at rest (≥15 mm Hg) or during exercise (≥25 mmHg). Patients without evidence of cardiac cause for dyspnea after exhaustive clinical evaluation and with normal pressures at rest and during exercise were classified as having non-cardiac dyspnea.

From the results, they built a score using six parameters: obesity, hypertension, atrial fibrillation, age, pulmonary hypertension and elevated filling pressures – the last two measured by echocardiogram (Table 1).[2] Each parameter is given a score according to the presence of the respective criteria. The final H2FPEF score is calculated by the sum of points, indicating low probability (< 2 points), intermediate probability (2-5 points) or high probability (> 5 points) of HFpEF.

The HFA-PEFF score

A consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology proposed a four-step diagnostic algorithm for HFpEF: step 1 (P) – pre-test assessment; step 2 (E) – echocardiographic and natriuretic peptide HFpEF score; Step 3 (F1) – Functional testing; and Step 4 (F2) – Final etiology. On Step 2 (E), the authors proposed the HFA-PEFF score, which was based on

Table 1 – H2FPEF score items[2]

	Parameter	Characteristic	Points
H_2	**H**eavy	BMI > 30 kg/m²	2
	Hypertension	≥ 2 antihypertensive medications	1
F	Atrial **F**ibrillation	Persistent or paroxysmal	3
P	**P**ulmonary hypertension	PASP > 35 mmHg*	1
E	**E**lderly	Age > 60 years	1
F	**F**illing Pressures	E/e'>9*	1
H2FPEF score			Sum (0-9)
Interpretation		0-1: Low probability (unlikely HFpEF) 2-5: Intermediate probability 6-9: High probability (likely HFpEF)	

*BMI: body mass index; PASP: pulmonary artery systolic pressure; HFpEF: heart failure with preserved ejection fraction. *Measured by echocardiogram.*

echocardiographic and natriuretic peptide measurements. The echocardiographic criteria reflect consensus recommendations for the diagnosis of left ventricular diastolic dysfunction with specific cutoff points.[3,4] The HFA-PEFF score has three domains: functional, morphological and biomarker (Table 2). For each domain, a maximum of two points can be scored – two points if any major criterium is met; one point if one minor criterium and no major criterium is met; and no point if no criteria (major or minor) are met. The HFA-PEFF score results from the sum of the points in each domain, which guides the next step in the algorithm. A score less than 2 points indicates that HFpEF is unlikely, and an alternative diagnosis should be considered, while a score above four points is considered diagnostic for HFpEF. Patients with intermediate score (2-4 points) need further evaluation, and a diastolic stress test is proposed as a next step (step 3, functional testing).[3]

Performance of H2FPEF and HFA-PEFF scores for the diagnosis of HFpEF

The performance of diagnostic tests can be evaluated by their sensitivity, specificity, positive and negative predictive values, along with their discrimination and calibration performances. Model discrimination is related to its ability to distinguish between individuals with and without the disease and is measured by the area under the ROC curve (AUC). Model calibration reflects how closely the predicted probabilities agree with the actual outcomes. To estimate the performance of a diagnostic score in clinical practice, they should be externally validated – *i.e.* discrimination and calibration should be measured in a sample that was not used to build the score.

Both H2FPEF and HFA-PEFF scores have been externally validated in different populations, such as patients with unexplained dyspnea or those recently hospitalized for HF. Overall, they showed good discrimination with an AUC consistently estimated as above 0.80 (Table 3). They also showed good model calibration, with predicted probabilities that were similar to observed ones (Hosmer-Lemeshow goodness-of-fit test p values above 0.05).

Comparison between the H2FPEF and HFA-PEFF scores

The HFA-PEFF score requires the measurement of natriuretic peptides and a large number of echocardiographic parameters compared with the H2FPEF score (Table 4). This narrows the use of the HFA-PEFF score to settings where the resources needed to calculate it are available.

Also, these scores disagree with each other in clinical practice, which can further complicate their use. Almost two fifths (28 to 41%) of patients have discordant estimates of the probability of HFPEF from H2FPEF and HFA-PEFF scores.[5-7] Studies have compared the accuracy of the two scores, with divergent findings. While two studies showed superior discriminating power with the H2FPEF score, other two showed they were similar, and one study showed superior AUC with the HFA-PEFF score (Table 3). These discrepancies likely result from methodological differences, sample size, lack of appropriate control group and criteria for defining HFpEF as "gold standard" (see below).

When the hemodynamic definition of HFPEF was used – *i.e.* increased PCWP at rest or during exercise, the H2FPEF seemed to perform better, while the HFA-PEFF had higher false negative rates. For instance, 25% of patients with low H2FPEF scores (0-1 points), but 56% of those with low HFA-PEFF scores had HFpEF by the hemodynamic definition.[6] On the other hand, when both scores were high, 94% had HFpEF.

Table 2 – HFA-PEFF score items[3]

Domain	Major criteria (2 points)	Minor criteria (1 point)	Score (Max 2 points per domain)
Functional	Septal e' < 7 Lateral e' < 10 Average E/e' ratio ≥ 15 TR velocity > 2.8 m/s (PASP > 35 mmHg)	Average E/e'ratio 9-14 GLS < 16%	
Morphological	LAVI > 34 mL/m² ou LVMI > 149/122 g/m² (m/w) and RWT > 0.42	LAVI 29 - 34 mL/m² LVMI > 115/95 g/m² (m/w) RWT > 0,42 LVWT ≥ 12 mm	
Biomarker (Sinus Rhythm)	NT-proBNP > 220 pg/mL BNP > 80 pg/mL	NT-proBNP 125 - 220 pg/mL BNP 35 - 80 pg/mL	
Biomarker (Atrial fibrillation)	NT-proBNP > 660 pg/mL BNP > 240 pg/mL	NT-proBNP 365 - 660 pg/mL BNP 105 - 240 pg/mL	
HFA-PEFF score			Sum (0-6)
Interpretation		0-1: Low probability (unlikely HFpEF) 2-4: Intermediate probability 5-6: High probability (HFpEF diagnosis)	

TR: tricuspid regurgitation; PASP: pulmonar artery systolic pressure; LAVI: left atrial volume index; LVMI: left ventricular mass index; m: men; w: women; RWT: relative wall thickness; LVWT: left ventricular wall thickness; GLS: global longitudinal strain; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal B-type natriuretic peptide; HFpEF: heart failure with preserved ejection fraction.

Table 3 – Diagnostic scores for heart failure and preserved ejection fraction

Author, year of publication	Country	Population	N	Accuracy (AUC [95% Confidence Interval])	Definitive "Gold Standard" HFpEF diagnosis
Reddy et al. 2018[2]*	United States	Patients with unexplained dyspnea	100	H2FPEF: 0.886 [0.789-0.941]	Elevated PCWP at rest (≥ 15 mmHg) or during exercise (≥ 25 mmHg)
Sepehrvand et al. 2019[8]	Canada	Patients at-risk for HF with LVEF ≥ 50%, known HFpEF and age- and sex-matched healthy controls	424	H2FPEF: 0.80 (0.75–0.84)	Clinical consensus from two HF specialists.
Aizpurua et al. 2020[9]	Netherlands and United States	Outpatients with suspected HFpEF	270	HFA-PEFF: 0.90 (0.84–0.96)	Clinical consensus from two HF specialists.
Ouwerkerk et al. 2020[10]	Singapore	Asian adults with clinical diagnosis of HFpEF vs hypertensive controls§	506	H2FPEF: 0.822 [0.788-0.857] HFA-PEFF: 0.821 [0.784-0.821]	Clinical HF diagnosis from a HF specialist.
Wijk et al., 2020[5]	Netherlands	Outpatients with suspected HFpEF	363	H2FPEF: 0.77 [0.71-0.83] HFA-PEFF: 0.88 [0.82-0.93] ‡	Clinical consensus from two HF specialists.
Tada et al., 2021[11]	Japan	Patients recently hospitalized for HFPEF vs non-HFPEF patients referred to echo for dyspnea	372	H2FPEF: 0.89 [0.86-0.93] HFA-PEFF: 0.82 [0.78-0.86]‡	Clinical diagnosis of acute HF according to Framingham criteria by two experienced cardiologists.
Parcha et al., 2021[12]	Multiple countries	HFpEF patients included in the TOPCAT and RELAX trials vs age-sex-race matched participants with unexplained dyspnea from ARIC cohort	934	H2FPEF: 0.838 HFA-PEFF: 0.800	Inclusion in HFPEF trials.
Churchill et al., 2021[13]	United States	Patients with unexplained dyspnea	156	H2FPEF: 0.74 [0.66-0.81] HFA-PEFF: 0.73 [0.65-0.81]	Elevated PCWP at rest (≥ 15 mmHg) or during exercise (≥ 25 mmHg) coupled with a PCWP/cardiac output slope > 2.0 mmHg. $L^{-1}.min^{-1}$
Reddy et al., 2022[6]	United States, the Netherlands, Denmark, and Australia	Patients with unexplained dyspnea	485	H2FPEF: 0.845 [0.810-0.875] HFA-PEFF: 0.710 [0.659-0.756]†	Elevated PCWP at rest (≥ 15 mmHg) or during exercise (≥ 25 mmHg)

*PCWP: pulmonary capillary wedge pressure; ARIC: Atherosclerosis Risk in Communities; LVEF: left ventricular ejection fraction; HFpEF: heart failure with preserved ejection fraction; HF: heart failure. *From the testing data subset for external validation in the original publication. † p for AUC comparison between the two scores < 0.001. ‡ p for AUC comparison between the two scores < 0.01. § The study reported validation for two cohorts, but only one is being reported here*

Table 4 – Characteristics of the H2FPEF and HFA-PEFF scores

Characteristic	H2FPEF score	HFA-PEFF score
Gold standard HF definition in the score derivation	Invasive hemodynamic test	Expert consensus recommendation
Number of parameters	6	13
Echocardiographic variables	2	9
Inclusion of natriuretic peptides	No	Yes

HF: heart failure.

Lack of gold standard definition for the diagnosis of HFpEF

The main issue on validating the diagnostic scores is the lack of a "gold standard" for the diagnosis of HFpEF. Because HF is a syndrome, the diagnosis relies on a combination of signs, symptoms and multiple complementary exams. While this argues for an expert consensus to define HFpEF, this is also subject to subjectivity and high inter-observer variability, particularly in equivocal cases where scores are expected to be used. On the other hand, defining HFpEF by increased filling pressures at rest or during the exercise is more appealing, since invasive measurements are highly reproducible, and it is strongly related to mechanisms underlying the pathophysiology of HFpEF.[6] In this regard, the hemodynamic exercise testing has been proposed as the gold standard method for the diagnosis of HFPEF, although it has not been widely accepted.

H2FPEF and HFA-PEFF scores in the prognosis of HFpEF

Although the H2FPEF and HFA-PEFF scores have been developed for the diagnosis of HFpEF, they are also associated with HF-related events. The ability to predict HF hospitalization, which is supposedly pathognomonic of HF (due to overt congestion), could indicate whether the score is detecting cases that will progress to an unequivocal diagnosis of HF. In the Atherosclerosis Risk in Communities cohort, both scores were directly associated with increased risk of HF hospitalization or mortality in individuals with unexplained dyspnea.[7] Noteworthy, the event rates in those with elevated H2FPEF and/or HFA-PEFF were similar to those with previously diagnosed HFpEF. This suggests that these scores helped to identify patients with either undiagnosed HFpEF or at higher risk of developing clinical HF.

In patients with stablished HFpEF, both scores were also related to the prognosis, with patients with high scores having increased risk of HF-related events (Table 5).

Final comments and how the scores should be used

The main indication for the use of diagnostic scores in HFpEF is the uncertainty in the diagnosis. The scores have been well validated for patients with unexplained dyspnea and suspected HF. Therefore, they should not be applied to asymptomatic patients, with symptoms clearly due to an alternative cause or when the diagnosis of HF is unequivocal.

In practice, we can interpret a high score of either instrument (H2FPEF > 5 or HFA-PEFF > 4) as highly suggestive of HFPEF, while a low score in both instruments (H2FPEF and HFA-PEFF > 2) virtually rule out HFpEF. Nevertheless, the low scoring in one algorithm only is more likely to be a false negative result, particularly for the HFA-PEFF. For instance, a patient with low HFA-PEFF score and high clinical suspicious of HFpEF would warrant further investigation.

Table 5 – Association between scores for HFPEF and prognosis

Author, year of publication	Design	Sample	N	Score criteria (vs comparator)	Results*
Myhre et al. 2019[14]	Cohort (from a clinical trial)	HFpEF patients in the TOPCAT trial	362	H2FPEF per 1-point increase	HR: 1.12 (1.02–1.23) for the composite of CV mortality, HF hospitalization or aborted cardiac arrest
Selvaraj et al., 2020[7]	Cohort	Unexplained dyspnea	641	H2FPEF ≥ 5 (vs asymptomatic individuals) HFA-PEFF ≥ 4 (vs asymptomatic individuals)	HR: 2.38 (1.80–3.16); HR: 2.67 (2.11–3.38) for the composite of all-cause mortality and HF hospitalization
Sotomi et al. 2021[15]	Cohort	Hospitalized HFpEF patients	804	HFA-PEFF 6 (vs 2 to 5) at discharge	Adj HR: 1.45 (1.10 – 1.90) for HF re-hospitalization and all-cause death
Verbrugge et al. 2021[16]	Cohort	Hospitalized HFpEF patients	443	HFA-PEFF - every 1-point increase HF2FPEF – every 10%-probability-increase	Adj HR: 1.19 (1.04 – 1.38) and 1.17 (1.05 – 1.33) for HF re-hospitalization and all-cause death
Sun et al. 2021[17]	Cohort	Hospitalized HFpEF patients	358	HFA-PEFF ≥ 5 (vs ≤ 2)	Adj HR: 5.29 (1.24–22.59) for all-cause death
Sun et al., 2021[18]	Retrospective cohort	Hospitalized HFpEF patients	476	H2FPEF ≥ 6 (vs <2)	Adj HR: 6.35 (1.48–27.22) for all-cause mortality Adj HR: 2.06 (1.35–3.14) for re-hospitalization
Hwang et al., 2021[19]	Retrospective cohort	Hospitalized HFpEF patients	1105	H2FPEF ≥ 6 (vs <2)	Adj HR: 1.29 (1.06–1.59) for the composite of all-cause mortality and HF re-hospitalization
Suzuki et al. 2010[20]	Cohort	Patients with at least one cardiovascular risk factor	356	H2FPEF per 1-point increase	Adj HR: 1.91 (1.46–2.50) for the composite of cardiovascular mortality and HF hospitalization
Seoudy et al. 2022[21]	Cohort	Post-TAVI with preserved EF	570	H2FPEF ≥ 6 (vs <5)	Adj HR: 2.70 (1.70–4.28) for the composite of all-cause mortality and HF hospitalization
Egashira et al. 2022[22]	Cohort	Hospitalized HFpEF patients	502	HFA-PEF ≥ 5 (vs 2 to 4)	Adj HR: 1.66 (1.11 – 2.50) for HF re-hospitalization

** Data presented as hazard ratio (95% confidence interval). HR: Hazard ratio; HFPEF: heart failure with preserved ejection fraction; TAVI: transcatheter aortic valve implantation; EF: ejection fraction; HF: heart failure.*

Compared with the HFA-PEFF score, the H2FPEF score uses a simpler approach and seems to be more accurate in detecting HFpEF defined by the hemodynamic criteria. Although this might suggest a preference for the H2FPEF score, the diagnosis of HFPEF lacks a gold standard to validate against. The definition of HFPEF has evolved and results of recent positive clinical trials in this population may guide the development of more definitive diagnostic criteria that will help finding patients who will benefit from interventions that change their prognosis.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Fernandes-Silva MM.

Potential Conflict of Interest

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

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Review Article

The Role of Biomarkers in Heart Failure with Preserved Ejection Fraction

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Introduction

A large proportion of patients with heart failure (HF) have preserved left ventricle (LV) ejection fraction (HFpEF)[1] or slightly reduced systolic function. Although specific cutoff recommendations are constantly evolving, the European Society of Cardiology (ESC) has recently proposed the term HF with mildly reduced ejection fraction (HFmrEF) for values between 40–49% and HFpEF for ejection fraction ≥ 50%.[2] In the past, different cutoffs were used in studies of HFpEF, ranging from 40% to 55%. Additionally, there is significant overlap between HFpEF and HFmrEF. For these reasons, in this chapter we consider them as a whole.

HFpEF is associated with many comorbidities and has a high rate of morbidity and mortality, both in ambulatory and in-hospital cohorts.[3-5] HFpEF is a heterogeneous syndrome with diverse etiologies and phenotypes and different pathophysiological pathways, which are not fully understood.[6,7] Circulating biomarkers may represent important tools to aid in the diagnosis and prognosis of this condition.[8,9]

In this review, we discuss the role of biomarkers that reflect different pathological pathways in HFpEF, with most attention given to myocardial stretch and injury biomarkers such as natriuretic peptides (NP) and troponin. We also provide an overview of biomarkers of inflammation, oxidative stress, fibrosis, and vascular dysfunction.

Natriuretic peptides

NP are endogenous hormones with a variety of hemodynamic, renal, and neurohormonal effects. They are considered the gold standard biomarkers in HF and are secreted almost exclusively by the heart. Although the role of NP has been more extensively demonstrated in patients with reduced ejection fraction (HFrEF), their clinical value has been shown across the whole spectrum of ejection fraction.[10-12] However, the mean concentrations are lower in patients with HFpEF than in those with HFrEF.[13,14] Nevertheless, a specific cutoff does not exist to differentiate HFpEF from HFrEF due to significant overlapping.[14]

NP are mainly released in response to myocardial wall stress, leading to an elevation of LV filling pressures (Figure 1). The NP of most clinical importance are B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP). Other NP such as atrial natriuretic peptide (ANP), N-terminal proANP, and C-type NP (CNP), although of importance in terms of pathophysiology, have not been used in clinical practice due to the complex logistics required for their measurement.

Diagnosis of HFpEF

The role of NP in the diagnosis of HF, including HFpEF, has been examined in several reports, both in acute and chronic settings.[1,13,15-21] Villacorta et al.[13] and Maisel et al.[15] (in initial studies in the acute setting with BNP)[13,15] and Januzzi et al. (with NT-proBNP)[16] demonstrated good accuracy for the diagnosis of HF in the entire spectrum of ejection fraction. More recently, Januzzi et al. have confirmed the findings for NT-proBNP in the ICON-RELOADED study.[17] In this study, 41.3% of patients with a diagnosis of acute HF had an LV ejection fraction ≥ 50%. The negative predictive value for NT-proBNP was excellent, close to 98%. In the non-acute setting, Tschöpe et al., in a study with 68 patients with diastolic dysfunction, found that NT-proBNP levels were significantly elevated as compared to those of healthy controls and correlated well with invasive measurements of LV filling pressures.[19] Jorge et al., in a population-based study, found that BNP < 42 pg/mL had a sensitivity of 92% and a negative predictive value of 99% for the diagnosis of HF, regardless of

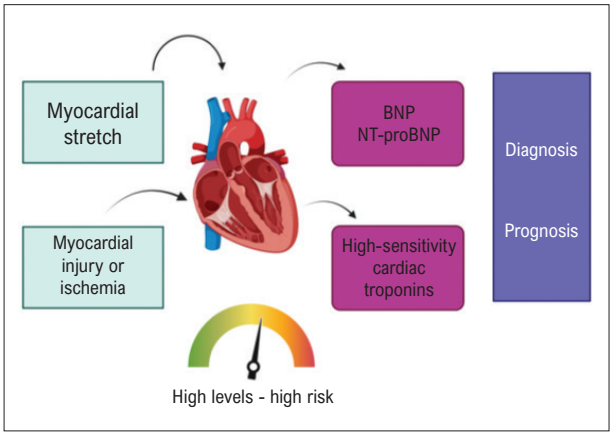

Figure 1 – *Standard cardiac biomarkers in HFpEF: NT-proBNP and hs-cTn. NT-proBNP: N-terminal pro-B-type natriuretic peptide.*

Keywords

Heart failure; Preserved Ejection Fraction; Biomarkers.

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the ejection fraction. In this study, 59% of the population with HF had HFpEF. A recent meta-analysis of 51 studies found that NP have reasonable diagnostic performance in the detection of HFpEF in the non-acute setting, with an area under the curve (AUC) of 80%.[21] The best utility of these markers was for ruling out diastolic dysfunction or HFpEF, with a negative predictive value of 85%. The specificity and positive predictive value, however, were poor (65% and 60%, respectively).

In all studies mentioned above, patients with HFpEF had lower values of NP than patients with HFrEF. A possible explanation for this could be a stronger association of NP with end-diastolic wall stress, which is lower in HFpEF than in HFrEF.[22]

Although NP have been proved to be a good tool for the diagnosis of HFpEF, there are some caveats. NP are influenced by many cardiac and non-cardiac disorders that seem to be even more important in HFpEF. Increased levels of NP are expected in atrial fibrillation, older adults, and those with renal dysfunction. A fivefold increase in NT-proBNP has been reported in patients with HFpEF and atrial fibrillation compared to those in sinus rhythm.[23] In contrast, lower values are observed in obese patients.[12]

All of these characteristics are common in patients with HFpEF, which could explain the unexpected results observed in some studies. For example, Arjan et al. found that 29% of symptomatic outpatients with HFpEF and elevated pulmonary wedge pressures had "normal" BNP values (< 100 pg/mL), suggesting that a normal BNP level may not exclude the diagnosis of HFpEF.[24] More recently, Verbrugge et al. observed similar results.[25] Using invasive hemodynamics, they retrospectively compared patients with HFpEF and high NT-proBNP values (≥ 125 pg/mL), HFpEF and normal NT-proBNP values (< 125 pg/mL), and a third group of controls with normal hemodynamics. Patients with HFpEF and normal NP (37% of the population with HF) were younger than those in the high NP group, had a higher rate of obesity, and had less structural heart diseases as assessed by echocardiography. The highest event rate was observed in the group with high NP values, but patients with normal NT-proBNP still had a 2.7-fold higher risk for mortality or HF readmission compared with controls. The limitations of the study were its retrospective nature and the fact that it was performed with patients referred to a tertiary center for invasive hemodynamic tests, possibly causing a referral bias.

Due to the reduced performance of biomarkers in some subgroups of patients (the ones mentioned above), some authors have used machine learning techniques, combining clinical variables with biomarkers as a continuous variable in an effort to improve diagnostic accuracy. This strategy has been successfully used for the diagnosis of acute myocardial infarction using high-sensitivity troponins[26] and for the diagnosis of pulmonary embolism using D-dimer.[27] Recently, Lee et al. developed a model named CoDE-HF, which used machine learning techniques to overcome the barriers observed in some subgroups due to the influence of clinical variables on the diagnostic performance of NT-proBNP.[28] They combined the biomarker with ten clinical variables. This tool ruled in and ruled out acute heart failure more accurately than did any approach using NT-proBNP thresholds alone and performed consistently across all subgroups.

HFpEF is a complex disease whose pathophysiology is poorly understood, and its diagnosis is difficult to establish. To simplify the diagnostic approach for the clinician, clinical scores were created. The two most used are the H_2FPEF score,[29] developed by the Mayo Clinic, and the HFA-PEFF score, created by the ESC.[30] An important difference between these two scores is that the H_2FPEF score does not include biomarkers. In contrast, the HFA-PEFF score incorporates NP. Both scores are recommended by the main HF guidelines, with no preference of one over the other.[2,31,32] In the external validation of H_2FPEF,[33] the score had a poor performance in patients presenting with dyspnea. On the contrary, HFA-PEFF demonstrated good accuracy in the validation cohort.[34] Of note, the biomarker domain performed almost as well as the whole score (AUC 89% vs 90%, respectively). However, 3 out of 11 patients classified in the low-probability category still had HFpEF, underscoring the relatively low sensitivity of the score. A prospective head-to-head comparison between the two scores is lacking. In this regard, only one case-control study has been carried out.[35] In this investigation, both scores discriminated patients with HFpEF from controls, but the H_2FPEF score had a greater AUC (84% vs 71%). Specificity was robust for both scores, but sensitivity was poorer for HFA-PEFF (false-negative rate of 55% for low-probability scores compared with 25% for H_2FPEF). However, these results should be interpreted with caution due to the retrospective nature of the study.

Prognosis of HFpEF

The usefulness of NP goes beyond their diagnostic role. The higher the values, the higher the event rates. In the acute setting, NT-proBNP is considered a strong independent predictor of all-cause mortality, as described in the study by Lopuszynski et al. performed in a cohort hospitalized with HFpEF.[36] Admission and discharge levels and relative changes during hospitalization confer the same relative risk information for HFpEF as in HFrEF.[37]

In chronic HF, several studies have shown that NP provide strong and independent prognostic information.[38-41] In the I-PRESERVE Study, NT-proBNP emerged as one of the strongest predictors of all-cause mortality or cardiovascular hospitalization.[39] There was a continuous linear increase in the incidence of the primary endpoint from the lowest to the highest quartiles of NT-proBNP.[40] A recent unsupervised cluster analysis based on a wide range of biomarkers found that higher levels of NT-proBNP identify a subgroup of HFpEF patients (who also have higher levels of cardiac troponins) who are at the highest risk of death or HF hospitalization.[41]

Guiding Therapy in HFpEF

Although there is a suggestion that NP may be helpful in guiding therapy in patients with HFrEF, few studies have examined this issue in patients with HFpEF. Maeder et al.[42] studied 123 patients with HFpEF (ejection fraction > 45%) who were randomized to standard medical therapy, titrated to reduce symptoms to NYHA class ≤ II or also to reduce NT-proBNP below the inclusion threshold (400 or 800 pg/mL, depending on age). Differently from

patients with HFrEF, patients with HFpEF did not benefit from this strategy. In fact, NP-guided therapy tended to worsen 18-month outcomes in patients with HFpEF. This finding was later confirmed in a meta-analysis performed by Brunner-La Roca et al.[43] In contrast, patients with the so-called "mid-range" ejection fraction, now referred to as mildly reduced ejection fraction, seemed to have the same benefits with NP-guided therapy as patients with HFrEF. Rickenbach et al.,[44] using data from the TIME-CHF trial, demonstrated a benefit of NT-proBNP-guided therapy regarding survival free of HF hospitalization in HFrEF and HFmrEF, but not in HFpEF.

High-sensitivity cardiac troponins

Traditionally used in the diagnosis of acute myocardial infarction, cardiac troponins are now being increasingly detected in HF due to improvements in assay sensitivity. This is referred to as myocardial injury (acute or chronic).[11] Values of cardiac troponins in HF may be elevated in the whole spectrum of ejection fraction but are higher in HFrEF compared to HFpEF.[45] Elevated high-sensitivity cardiac troponin (hs-cTn) discriminates a subgroup of patients with HFpEF who have ongoing myocardial damage, higher wall stress, or impaired microcirculation, as evidenced in a mechanistic study performed by Obokata et al.[46]. They compared 38 patients with HFpEF with 20 control patients. Those with HFpEF had higher troponin levels at rest, which correlated with higher pulmonary capillary wedge pressure and worse systolic and diastolic tissue Doppler velocities. Additionally, troponins correlated with a greater degree of oxygen supply-demand mismatch.

Baseline hs-cTn has been shown to predict HFpEF in older adults, especially in those without LV hypertrophy at baseline.[47] There was a 2.4-fold increase in the incidence of HFpEF in patients in the third tertile of troponin compared with patients in the first tertile. In the acute setting, several studies have shown a prognostic role of hs-cTn measured at admission or discharge in patients hospitalized with decompensated HFpEF.[48-50]

Both hs-cTn T and I are elevated in chronic HFpEF and are independently associated with poorer outcomes.[11,12,51] In the study by Gohar et al.[51], the hs-cTn T assay provided the greatest additional prognostic value in HFpEF in comparison with hs-cTn I and NT-proBNP. However, hs-cTn I was more strongly associated with composite events in men with HFpEF.

Serial measurements of hs-cTn in patients with HFpEF have also been studied. In a substudy of the PARAGON-HF trial, investigators demonstrated that hs-cTn T was reduced by sacubitril/valsartan therapy compared to valsartan and that patients with a decrease in hs-cTn T (from randomization to 16 weeks to a value at or below the median value of 17 ng/L) subsequently had a lower risk of the composite outcome than those who had persistently elevated hs-cTn T values.[52] Thus, both baseline and serial measurements of hs-cTn seem to be useful to predict events in patients with HFpEF. Figure 1 illustrates the stimulus for hs-cTn release and its role in clinical practice in HFpEF.

Other biomarkers

NP and hs-cTn are standard and established cardiac biomarkers. Their accuracy in the diagnosis and prognosis of cardiovascular conditions in great part results from the fact that they are secreted almost exclusively by the heart. However, heart diseases have systemic repercussions and are influenced by systemic conditions as well. In this regard, there is a potential role for systemic biomarkers in HFpEF, which are driven by different pathways (Figure 2). These markers are not useful for diagnosis, since they are not specific for the heart, but are important prognostic markers.

GDF-15

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-β cytokine superfamily associated with inflammation and oxidative stress.[53] It has emerged as a useful marker in many cardiovascular conditions, such as coronary artery disease, atrial fibrillation, and HF, and also in non-cardiac disorders such as obesity and COVID-19.[53] GDF-15 is elevated in patients with HFpEF and provides additional prognostic information over clinical variables and traditional biomarkers.[54,55] Izumiya et al.[54] demonstrated a positive association of GDF-15 with NYHA class and BNP, and GDF-15 strongly predicted cardiovascular events. Interesting findings were also observed by Santhanakrishnan et al.[55]. They compared different biomarkers in HFrEF vs HFpEF and their relation to each other. GDF-15 strongly differentiated HFpEF cases from healthy controls and the NT-proBNP/GDF-15 ratio distinguished between HFrEF and HFpEF. This finding is consistent with the important role of inflammation in HFpEF.

Many patients with HFpEF have atrial fibrillation and an important role of GDF-15 in this scenario has been

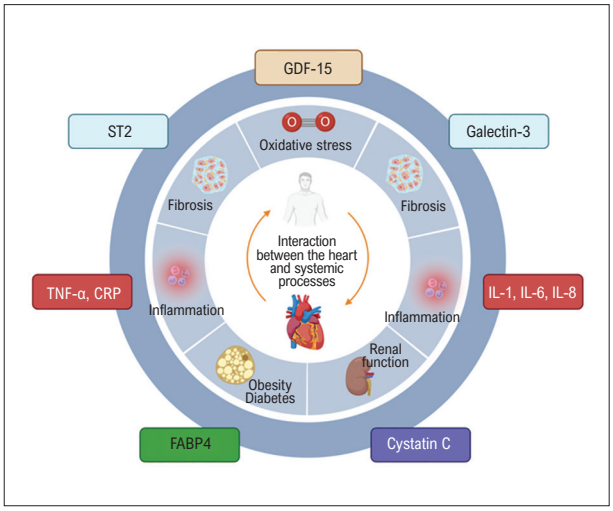

Figure 2 – *Systemic biomarkers involved in HFpEF, addressing the relationship of systemic processes and the heart. CRP: C-reactive protein; FABP4: fatty acid-binding protein 4; GDF-15: growth differentiation factor 15; IL: interleukin; ST2: suppression of tumorigenicity 2; TNF: tumor necrosis factor.*

demonstrated.[56-58] GDF-15 is the strongest predictor of bleeding in patients with atrial fibrillation taking anticoagulants.[56] The ABC (age, biomarker, clinical history) score is a biomarker-based risk score developed for the prediction of stroke and bleeding in patients with atrial fibrillation. The ABC bleeding score[56] incorporates GDF-15 and hs-cTn, and the ABC stroke score[57] incorporates NP and hs-cTn. Both ABC scores outperformed the traditional risk scores in atrial fibrillation (ABC bleeding and HAS-BLED, AUC 0.69 vs 0.62, respectively; ABC stroke and CHADSVASC, AUC 0.67 vs 0.59, respectively).[58]

Thus, GDF-15 is a promising biomarker in HFpEF. In addition to the prognostic role, it may contribute to elucidating the pathophysiology of HFpEF and identifying specific target therapies.

ST2

ST2 is a member of the interleukin 1 receptor family, also known as interleukin 1 receptor-like 1 (IL1RL-1).[59] ST2 stands for "suppression of tumorigenicity 2". ST2 is the receptor for interleukin-33 (IL-33), which exerts its effects by binding to the transmembrane receptor ST2L isoform, anchored in the myocyte membrane. The interaction of IL-33 and ST2L has been proven to be cardioprotective in experimental models, reducing myocardial fibrosis, cardiomyocyte hypertrophy, and apoptosis and improving myocardial function. However, the soluble ST2 receptor (sST2) works as a decoy receptor, which inhibits ST2L binding to IL-33. For this reason, sST2 has been proposed as a marker of cardiac hypertrophy, fibrosis, and remodeling.[59]

In HFpEF, ST2 release may be related to myocardial stress and an elevated LV filling pressure, as demonstrated by the direct correlation of ST2 levels with the diastolic load measured on the basis of the LV end diastolic pressure.[60,61] The TIME-CHF study measured circulating levels of different biomarkers and sST2 levels were higher in patients with HFpEF compared to those with HfrEF.[45] In patients presenting with acute dyspnea and normal LV systolic function, ST2 was the only biomarker predicting mortality.[62] These results were also observed in the study by Manzano-Fernandes et al. in acutely decompensated HF, where the prognostic value of ST2 in HFpEF was comparable to that in HFrEF.[63] These findings suggest that ST2 may be a useful prognostic marker in HFpEF, especially in the acute setting.

Galectin-3

Galectin-3 (Gal-3) has also been mechanistically involved in cardiovascular inflammation and fibrosis.[11] In the PARAMOUNT trial, Gal-3 correlated with disease severity as evidenced by the positive correlation with NT-proBNP and the E/E' ratio in patients with HFpEF.[64] In a study with 592 patients, Gal-3 was a stronger predictor of mortality in patients with HFpEF compared to those with HFrEF.[65] In addition, serial measurements of GAL-3 seem to be valuable. In the ALDO-DHF trial, increases in Gal-3 over time were associated with all-cause mortality.[66] Finally, Gal-3 can predict the development of HFpEF in patients with comorbidities (de Boer 2013).[67]

Inflammatory markers

Elevated levels of inflammatory cytokines such as TNF-α, IL1, IL6, IL8, and CRP are often observed in patients with HFpEF.[10] Circulating levels of TNF-α receptors (TNFR1 and TNFR2) are associated with the severity of diastolic dysfunction and symptoms.[10] Nevertheless, scarce evidence on their prognostic role is currently available.

Fatty acid-binding protein 4

Fatty acid-binding proteins (FABPs) are intracellular lipid chaperones.[12] FABP4—also known as adipocyte FABP or aP2—plays an important role in the development of obesity, insulin resistance, diabetes, and atherosclerosis and has been associated with cardiac remodeling and left and right ventricular dysfunction.[68,69] In a substudy of the TOPCAT trial, FAPB4 was associated with the risk of death or HF admission in HFpEF, independently of the MAGGIC risk score.[70] Recently, Harada et al. reported that event-free survival was significantly decreased in patients with HFpEF and FABP4 ≥ 43.5 ng/mL.[69]

Cystatin C

Cystatin C is secreted by nucleated cells at a constant rate, filtered and reabsorbed by the glomeruli, and then completely decomposed by intact renal tubules; it provides a more accurate method for estimated glomerular filtration rate (eGFR) measurement.[12] Excess cystatin C may promote myocardial fibrosis and ventricular hypertrophy and increase atrial volume.[12] It is a strong risk factor for new-onset HFpEF[71] and is associated with worse NYHA classification, even after adjustments for eGFR.[72] Furthermore, it is an independent predictor of unfavorable outcome in patients admitted with HFpEF.[73] In chronic HFpEF, data are less compelling. In one study, there was a trend for predicting death or HF admission, but without significance in multivariate analysis.[12] Table 1 provides a summary on the role of important biomarkers in HFpEF.

Future Biomarkers

Circulating microRNAs (miRNAs)

They offer attractive potential as epigenetic disease biomarkers due to their biological stability and ready accessibility in liquid biopsies.[12] Numerous clinical cohort studies have revealed unique miRNA profiles in different disease settings, suggesting their utility as markers with diagnostic and prognostic applications. In one study, a panel of eight HFpEF-related miRNAs was reported as valuable in identifying HFpEF.[74] However, there is no consensus on which specific miRNA might better serve as a HFpEF biomarker. Further research is needed to understand their role in HFpEF (Figure 3).

Metabolomics

Patients with HFpEF have a specific metabolic profile as compared to those with HFrEF. In an exploratory study,[75]

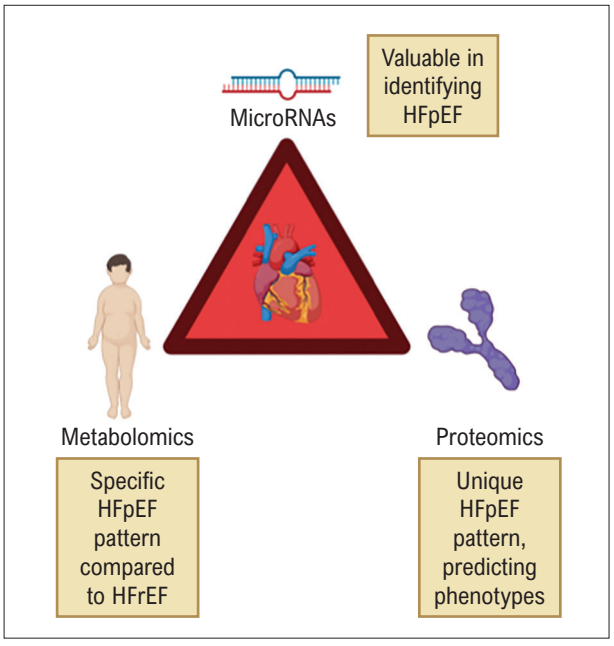

Figure 3 – *Novel biomarkers in HFpEF. The role of these new biomarkers in clinical practice still needs to be validated, but they may be useful in phenotyping HFpEF in the future. HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction.*

patients with new-onset HFpEF had a diverging metabolite pattern compared to that of patients with HFrEF, reflecting potential differences in pathophysiological mechanisms. Patients with HFpEF displayed elevated hydroxyproline, reflecting fibrosis; elevated symmetrical dimethylarginine, indicating oxidative stress; and elevated alanine, cystine, and kynurenine, reflecting a state of increased inflammation compared with patients with HFrEF. Patients with HFpEF also had lower levels of cGMP and cyclic adenosine monophosphate, suggesting impaired cell signaling. Finally, serine and arginine were lower in patients with HFpEF than in those with HFrEF, reflecting endothelial dysfunction.

Proteomics

An analysis of 92 proteins from the Olink Cardiovascular II Panel and their association with obese HFpEF has been recently reported in the LIFE-Heart study.[12] Obese patients with HFpEF exhibited higher circulating biomarkers of volume expansion (adrenomedullin), myocardial fibrosis (thrombospondin-2), and systemic inflammation (galectin-9, CD4) compared to obese non-HFpEF or lean HFpEF patients.

In the setting of HFpEF and diabetes, Hanff et al., using SomaScan assays and proteomic analyses of plasma from participants in the TOPCAT trial and the Penn Heart Failure Study, identified 10 proteins with differential expression in patients with HFpEF and diabetes. These proteins included fatty acid-binding protein, alpha-1-microglobulin/bikunin precursor, trafficking protein particle complex subunit 3, pigment epithelium-derived factor, tumor necrosis factor ligand superfamily member 15, ubiquitin-conjugating enzyme E2 G2, reticulon-4 receptor, insulin, cartilage intermediate layer protein 2, and apolipoprotein M. Of these, apolipoprotein M was found to mediate 72% of the association between diabetes and risk of cardiovascular death, aborted cardiac arrest, and HF hospitalization.[76] In addition, the use of SomaScan technology has shown that HFrEF, HFmrEF and HFpEF have unique patterns of circulating proteins.[77] Thus, it may be possible to use proteomic assays to more accurately predict the phenotype

Table 1 – Summary of the pathophysiology and potential role of different biomarkers in HFpEF

Biomarker	Mechanism of action	Role in HFpEF
Natriuretic peptides	Myocardial stretch; marker of hemodynamic load	Diagnosis and prognosis
hs-cTn	Released by cardiac ischemia or myocardial stress or injury	Predictor of mortality and incidence of HFpEF; adds prognostic value to NP
GDF-15	Inflammation, oxidative stress; secreted by cytokines	HF phenotyping; predictor of mortality; NT-proBNP/GDF-15 ratio differentiates HFpEF from HFrEF
ST2	High levels block the favorable effects of IL-33 by limiting activation of the cascade triggered by the IL-33/ST2L interaction	High levels associated with cardiac fibrosis and remodeling and worse outcomes
Galectin-3	Marker of inflammation, deposits type-1 collagen leading to fibrosis, inflammation, and cardiac remodeling	HFpEF phenotyping and risk stratification; predicts the development of HFpEF in patients with comorbidities
Inflammatory markers (TNF-α, IL1, IL6, IL8, and CRP)	Inflammation	Levels of TNF-α receptors are associated with the severity of diastolic dysfunction and symptoms;
FABP4	Development of obesity, insulin resistance, diabetes, and atherosclerosis	Predictor of death or heart failure admission
Cystatin C	Renal function marker; excess cystatin promotes myocardial fibrosis and hypertrophy	Strong risk factor for new-onset HFpEF; predicts outcomes, especially in acute HFpEF

CRP: C-reactive protein; FABP4: fatty-acid-binding protein 4; GDF-15: growth differentiation factor 15; HFpEF: heart failure with preserved ejection fraction; hs-cTn high-sensitivity cardiac troponin; IL: interleukin; NP: natriuretic peptides; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ST2: suppression of tumorigenicity 2; TNF: tumor necrosis factor.

of patients with HF. Further research is needed to validate and translate proteomic data into clinical practice.

Conclusions

HFpEF is a complex disease whose pathophysiology is not completely understood. Biomarkers are useful tools in the management of HFpEF. NP are the gold standard biomarker for the diagnosis of HF in the whole spectrum of ejection fraction. However, their diagnostic performance in HFpEF is inferior to that observed in HFrEF, especially in obese patients.

For prognostic purposes, it seems reasonable that the use of multiple markers reflecting the activation of different pathophysiological pathways may more accurately identify high-risk individuals. NP and hs-cTn are useful cardiac prognostic markers and many non-cardiac biomarkers reflecting inflammation, fibrosis, and oxidative stress, among other pathways, may provide additional information.

The pathophysiological basis for identifying and classifying HFpEF based on a multimarker strategy seems logical and deserves further research. The information on non-cardiac components of HFpEF may increase our understanding of the disease and may be useful in determining HFpEF phenotypes that may guide therapy and clinical trials.

Author Contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Villacorta H; Analysis and interpretation of the data: Villacorta H, Maisel AS; Critical revision of the manuscript for important intellectual content: Maisel AS.

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Dr. Humberto Villacorta - Speaker honoraria from Roche Diagnostics

Dr. Alan S Maisel - Consulting from Abbott

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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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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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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 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]

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

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.

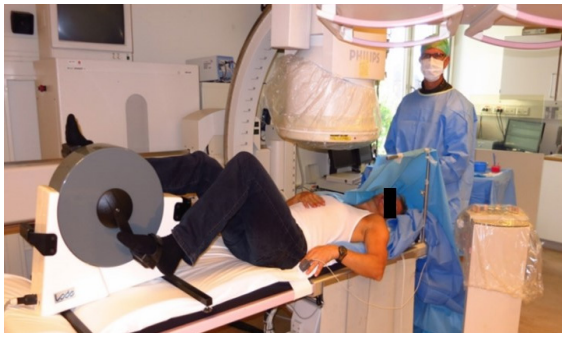

Figure 1 – *Simulation of patient positioning for invasive hemodynamic monitoring in the diagnosis of heart failure with preserved ejection fraction.*

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.

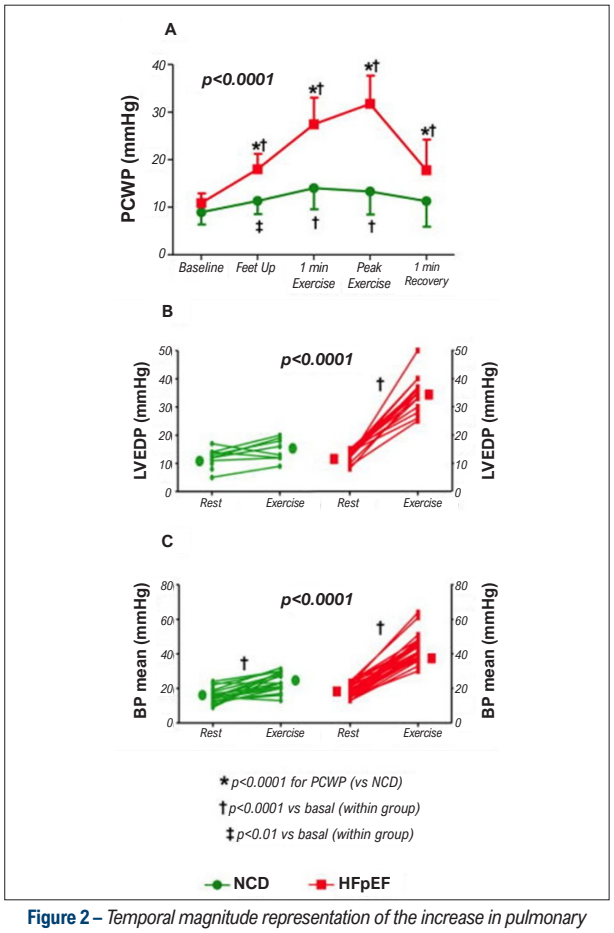

Figure 2 – *Temporal magnitude representation of the increase in pulmonary capillary pressure and left ventricular end diastolic pressure during exercise in patients with heart failure with preserved ejection fraction (Obokata et al. Circulation 2017; 135:825-38, authorized by the author). LVEDP: left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

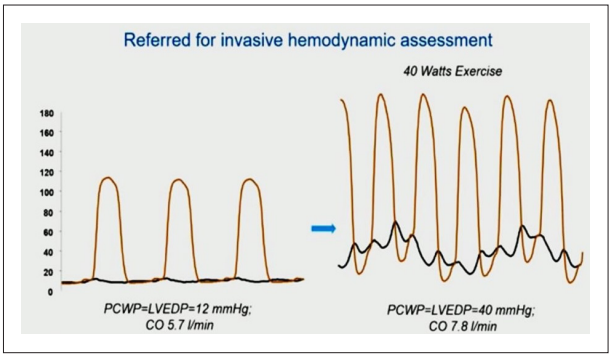

Figure 3 – *Representation of pulmonary capillary pressure (PCWP) and left ventricular end diastolic pressure (LVEDP) curves at rest and at maximum effort of a patient with heart failure with preserved ejection fraction; adapted from Barry et al.*[25]

Potential Conflict of Interest

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Review Article

Pathophysiological Bases of Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction and Implications for Management

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Pulmonary hypertension (PH) associated with left heart disease is classified as group 2, and it encompasses both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).[1] In both diseases, the development of PH is associated with an unfavorable clinical course in the natural history of the disease, and knowledge about its pathophysiology is still uncertain, which may have practical implications from the diagnosis to the treatment of heart failure.[2,3]

Prevalence, definition, and diagnosis

The prevalence of PH in patients with HFpEF is widely heterogeneous, with frequencies ranging from 36% to 81%,[4] and this is due to the diagnostic means used, to the time of progression of the underlying disease,[3] and to the different ejection fraction cut-off points used to define HFpEF. For example, in a subanalysis of the PARAGON study, the prevalence of PH in patients with HFpEF was 31%.[5] Moreover, the different phenotypes of HFpEF may present with a lower or higher degree of PH, depending on the increase in pulmonary vascular resistance, the increase in right atrial pressure, and associated concomitant chronic kidney disease.[6]

Group 2 PH is defined as mean pulmonary artery pressure > 20 mmHg and pulmonary capillary pressure > 15 mmHg. Right heart catheterization is considered the gold standard for accurate measurement of pulmonary pressures, and it is valuable in evaluation of the hemodynamic response to physical exertion, providing important information for differentiating between group 2 PH and other etiologies.[1]

However, in clinical practice, the most useful test for diagnosis of PH, regardless of ejection fraction, is Doppler echocardiogram. Although it is examiner-dependent and sensitive to variations in posture and blood volume, estimation of pulmonary artery systolic pressure on Doppler echocardiogram serves both as a diagnostic parameter of HFpEF and as a prognostic parameter in estimating the degree of PH.

Left ventricular dysfunction

The first pathophysiological change observed in HFpEF is impairment of left ventricular relaxation and filling with a consequent increase in left atrial pressure and backward transmission of this elevation to the pulmonary system, initially characterizing pulmonary venocapillary hypertension.[7]

Hypertrophy and diastolic dysfunction, which are common in hypertension and obesity, play a role in altering left ventricular relaxation. However, the multiple comorbidities that are common in patients with HFpEF also have negative effects on the myocardium, stimulating oxidative stress and hypertrophic pathways.[8]

Paulus and Tschope[9] have proposed a unifying hypothesis to centralize the role of pro-inflammatory pathways in increased proliferation of collagen in myocytes and in the impact on elasticity. In this hypothesis, the high rigidity of the myocardial wall would be sustained by increased titin protein phosphorylation, overexpression of growth factor-β signaling, reduced expression of elastase, high mitochondrial oxidative stress, and epigenetic alterations that definitively impair cellular homeostasis.

Left atrial remodeling and dysfunction

The change in left ventricular relaxation is followed by volume and pressure overload in the left atrium. The left atrium, in turn, is very sensitive to these elevations, and it initiates a process of remodeling and dysfunction, which play a determining role in the elevation of pulmonary pressures.[7,10]

The left atrium becomes more rigid early and dilates slowly, and this is a peculiar substrate in the induction of atrial fibrillation. Furthermore, the coexistence of other comorbidities and the inflammatory pathways described corroborate atrial remodeling and dysfunction and also contribute to the induction of atrial fibrillation. This phenotype is associated with mitral regurgitation and greater elevation of pulmonary vascular resistance in patients with HFpEF.[10,11]

Any increase in left atrial pressure directly influences pulmonary hemodynamics and exacerbates symptoms.[7] Although studies on pulmonary circulation in humans are scarce, some data have revealed that the chronic effects of increased left atrial pressure on the pulmonary vasculature may represent different phenotypes according to the level of left atrial pressure elevation.

Keywords

Pulmonary Hypertension; Heart Failure; HFpEF

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Pulmonary artery and venocapillary remodeling

The sustained increase in left atrial pressure is transmitted back to the pulmonary veins, which undergo a remodeling process consisting of luminal narrowing due to increased neointimal thickening and medial hypertrophy.[11] Some studies have shown a direct correlation between pulmonary artery systolic pressure and neointimal thickening, but the necessary trigger for this endothelial dysfunction is not yet known; or be it, we do not know what stage or degree of left atrial pressure elevation would be the necessary trigger for vascular alterations.[12]

The maintenance of high pressure on the pulmonary venocapillary system causes insufficiency of pulmonary capillaries and arterioles, with barotrauma that ruptures the endothelial layer and promotes swelling of fluids and proteins in the interstitium. This edema triggers a cascade of molecular and inflammatory markers that inhibit nitric oxide activity and increase endothelin expression, leading to luminal occlusion and alveolar septal thickening. The progression of this cascade leads to remodeling of the pulmonary arteriolar system and to reduced gas diffusion through the alveolar membrane, which, in the second stage, composes the arterial pattern of PH associated with HFpEF.[7,12,13]

The impairment of right ventricular function in HFpEF occurs in two ways: 1 – the sustained elevation of pulmonary pressures promotes hypertrophy, dilation, functional tricuspid insufficiency, and right ventricular dysfunction; 2 – right ventricular diastolic dysfunction and increased stiffness occur before systolic dysfunction, with slower progression to dilation and functional deterioration.

Treatment

There is no specific treatment for group 2 PH, and the use of pulmonary vasodilators is contraindicated. Some experiments have tried, unsuccessfully, to test appropriate therapies for pulmonary arterial hypertension in patients with left ventricular diseases, but they may have run into phenotypic differences in patients with HFpEF.

It is believed that the variability of hemodynamic phenotypes in HFpEF (isolated pre-capillary hypertension or combined pre- and post-capillary hypertension) may interfere with the negative results with respect to the use of vasodilators for group 2 PH.

Conclusion

PH in HFpEF has similar pathophysiological mechanisms, which are also different from PH in HFrEF. In both situations, the patients' prognosis and the natural course of the disease are compromised, and there is no specific treatment for this comorbidity, beyond the already widely known standard treatment for the underlying disease, heart failure.

Author Contributions

Conception and design of the research e Acquisition of data: Freitas Jr. AF, Frota DCR, Rassi S; Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Freitas Jr. AF.

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

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Review Article

Flowchart for Treatment of Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) manifests as a heterogeneous syndrome, with pathophysiological variety, often associated with other comorbidities. Furthermore, the therapy performed in these patients is related to the treatment of correlated comorbidities. In this context, the specific pharmacological treatment of HFpEF is a challenge, given the lack of evidence from studies that would prove a significant reduction in mortality outcomes. In this article, we will analyze the management for the control of arterial hypertension and atrial fibrillation as well as evidence from studies on the use of the main classes of medications recommended for the treatment of patients with HFpEF, such as sodium-glucose cotransporter 2 inhibitors, renin-angiotensin system inhibitors, neprilysin inhibitors, and nitrates.

Introduction

Heart failure with preserved ejection fraction (HFpEF), which is defined as left ventricular ejection fraction (LVEF) ≥ 50%, accounts for at least 50% of all patients with heart failure (HF). In addition to the fact that its prevalence is increasing, it is associated with significant morbidity and mortality.[1]

HFpEF is a heterogeneous disorder with contribution from comorbidities such as hypertension, diabetes, obesity, coronary artery disease (CAD), chronic kidney disease, and specific causes such as cardiac amyloidosis.[2-4] Patients with HFpEF are older, and they are more frequently women. Furthermore, it is more common to observe non-cardiovascular comorbidities, chronic kidney disease, and atrial fibrillation (AF) in these patients. [5]

Clinical trials have used varying definitions of HFpEF (for example, LVEF ≥ 40%, 45%, or 50%). In any case, diagnosis should include the following: (1) signs and symptoms of HF; (2) LVEF ≥ 50%; (3) objective evidence of structural and/or functional cardiac abnormalities consistent with the presence of left ventricular diastolic dysfunction/increased left ventricular filling pressures, including increased natriuretic peptides. [6,7]

To date, no specific drug therapy has demonstrated a reduction in cardiovascular mortality in trials on HFpEF. Therefore, the recommended management is the same as that for HF in general, with the use of diuretics, especially loop diuretics, to reduce congestion. Additionally, weight loss and physical exercise can improve symptoms and functional capacity; therefore, they should be considered in appropriate patients.[8,9] It is necessary to identify symptoms and treat specific causes, such as amyloidosis, in addition to management of contributing comorbidities, such as hypertension, CAD, and AF.

Control of arterial hypertension

The role of blood pressure control is well established in preventing HF, as well as in reducing other cardiovascular events and mortality from HF in patients without baseline HF.[10-16]

The SPRINT (Systolic Blood Pressure Intervention Trial) and meta-analyses have established that patients at high cardiovascular risk benefit from more intense blood pressure control, as this significantly reduces HF and other cardiovascular outcomes.[11,12,17] That said, recent guidelines on the clinical management of hypertension have established blood pressure targets in HFpEF that extrapolate those for the treatment of patients in general.[18]

However, optimal targets for blood pressure and antihypertensive regimens are not known for patients with HFpEF. Renin-angiotensin-aldosterone system (RAAS) antagonists, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone antagonists, and possibly neprilysin receptor antagonists, may be first-line agents, given the experience with their use in trials on HFpEF.[3,19-23] For adults with HFpEF who have persistent hypertension after treatment of volume congestion with diuretics, ACEIs or ARBs and titrated beta blockers should be prescribed to achieve systolic blood pressure below 130 mmHg.[18]

Beta blockers can be used to treat hypertension in patients with a history of acute myocardial infarction,[22] symptomatic CAD, or AF with rapid ventricular response. This medication interferes with chronotropism and, therefore, needs to have its effects balanced, with possible exercise intolerance in some patients.[24]

Keywords

Heart Failure; Diastolic Heart Failure; Medication Therapy Management

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Sodium-glucose Cotransporter 2 Inhibitors

The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) demonstrated a significant benefit of the sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin in patients with symptomatic HF with LVEF > 40% and elevated natriuretic peptides.[25]

Empaglifozin led to a 21% lower relative risk of the composite outcome of cardiovascular death or hospitalization for HF, which was mainly related to a 29% lower risk of hospitalization for HF with the use of the medication; lower cardiovascular death was not significant (hazard ratio, 0.91; 95% confidence interval, 0.76 to 1.0), with no benefit in all-cause mortality. The effects were observed consistently across all pre-specified subgroups, including patients with or without diabetes.[26]

Although the benefit in the primary outcome did not have a significant difference between the pre-specified LVEF subgroups (< 50%, 50% to 60%, and > 60%),[25] in another study with subgroup analysis by ejection fraction, there was less benefit in the reduction of total hospitalizations (first and recurrent) due to HF heart failure with higher LVEF > 60%.[26]

Empagliflozin, in addition to resulting in a decrease in total hospitalizations for HF, promoted a reduction in the estimated glomerular filtration rate (eGFR) and a modest improvement in quality of life at 52 weeks.[25]

Management of atrial fibrillation

Large randomized clinical trial data are not available to guide a specific therapy in patients with AF and HFpEF. Currently, the comprehensive care of AF in this context is extrapolated from guidelines on clinical practice for AF, but with individualization strategies to control rhythm or frequency in these patients.

Although beta blockers and non-dihydropyridine calcium channel blockers are often considered first-line agents for heart rate control in patients with HFpEF, recently, a smaller, open-label study, RATE-AF,[27] was conducted in elderly patients with AF and symptoms of HF (the majority with preserved LVEF). This study compared the use of the beta blocker bisoprolol to digoxin, and the primary quality of life outcome was similar between both groups at the end of 6 months. In both groups, there was a similar decrease in heart rate, but adverse events such as dizziness, lethargy, and hypotension occurred more with the beta blocker than with digoxin. Moreover, several secondary endpoints of quality of life, functional capacity, and reduced NT-proBNP at the end of 12 months also favored digoxin.

Mineralocorticoid receptor antagonists

The TOPCAT study investigated the effects of spironolactone in patients with HFpEF. In this study, a small reduction (hazard ratio, 0.89) was observed in the analysis of the composite outcome involving death, aborted cardiac death, and hospitalization for HF. However, this reduction was not statistically significant, although hospitalization for HF was reduced (hazard ratio, 0.83). Furthermore, the group that received the treatment had more adverse effects, such as hyperkalemia and increased creatinine levels.[28] Regarding the effects of breast pain and related gynecomastia that led to treatment discontinuation, they were equal between the different regions of the study.[29]

Careful monitoring of potassium, renal function, and diuretic dosing at baseline and follow-up are fundamental to minimizing the risks of hyperkalemia and worsening renal function.

A post hoc analysis[29] showed efficacy in the Americas (hazard ratio, 0.83), but not in Russia-Georgia (hazard ratio, 1.10). In the Americas, linked to efficacy, more frequent occurrence of hyperkalemia and renal involvement was also observed. In Russia-Georgia, the same benefits were not observed, as was the case with the adverse effects.[29] In the latter population, a sample in the active treatment arm showed no detectable levels of a spironolactone metabolite.

Post hoc analyses have limitations, but they do suggest a possible benefit in appropriately selected patients with symptomatic HFpEF (LVEF ≥ 45%, elevated BNP level, or admission for HF at 1 year, eGFR > 30 mL/min/1.73 m^2, creatinine < 2.5 mg/dL, and potassium < 5.0 mEq/L).

Furthermore, another post hoc analysis suggested that the potential efficacy of spironolactone was greater at the lower end of the LVEF spectrum.[30]

Renin-angiotensin-aldosterone system inhibitors

Although RAAS inhibition strategies have been successful in the treatment of heart failure with reduced ejection fraction, and RAAS activation is suggested in HFpEF, clinical trials with RAAS inhibition have not shown great benefits in patients with HFpEF. For example, in a meta-analysis of 7,694 patients with HFpEF, comprising 4 studies evaluating ARB, there was no sign of benefit regarding hospitalization for HF (hazard ratio, 0.92; 95% confidence interval, 0.83 to 1.02) or in cardiovascular or all-cause mortality (hazard ratio, 1.02).[31,32]

The CHARM-Preserved trial (Candesartan in patients with chronic HF and preserved left-ventricular ejection fraction) evaluated patients with LVEF > 40%, who were randomized to an ARB, candesartan, or placebo.[19]

The primary outcome (cardiovascular death or hospitalization for HF) was not significantly different between the 2 groups (hazard ratio, 0.89; 95% confidence interval, 0.77 to 1.03, p = 0.118; hazard ratio adjusted for covariates, 0.86; p = 0.051).

Cardiovascular mortality was identical in both groups, whereas hospitalizations for HF were lower in the candesartan arm. However, this result was observed only in the covariate-adjusted analysis, and it was still borderline in relation to statistical significance (hazard ratio, 0.84; 95% confidence interval, 0.70 to 1.00; p = 0.047; unadjusted p = 0.072).

With respect to individuals hospitalized for HF (reported by the investigator), the results obtained with the candesartan group were better than with placebo

(230 versus 279; p = 0.017). Furthermore, another improvement observed in the CHARM studies was identified through a post hoc analysis, in which these results with candesartan were found to be better at the lower end of the LVEF spectrum.[33]

Angiotensin receptor blockers and neprilysin inhibitors

The PARAMOUNT-HF (Prospective Comparison of ARNi with ARB on Management of Heart Failure with Preserved Ejection Fraction) study, a phase II randomized clinical trial in patients with HFpEF (LVEF ≥ 45%), compared sacubitril-valsartan with the ARB valsartan. They observed a lower level of NT-proBNP after 12 weeks of treatment with the neprilysin and angiotensin receptor inhibitor.[34]

The PARAGON-HF study (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Global Outcomes in Heart Failure and Preserved Left Ventricular Ejection Fraction) was carried out with 4,822 patients with HFpEF (LVEF ≥ 45%, admission for HF at 9 months or elevated natriuretic peptides and eGFR ≥ 30 mL/min/m^2). In this study, the comparison between sacubitril-valsartan and valsartan did not achieve a significant reduction in the primary composite outcome of cardiovascular or total death or in first and recurrent hospitalizations for HF (rate ratio, 0.87; 95% confidence interval, 0.75 to 1.01; p = 0.06).[20]

In the sacubitril-valsartan group, 15% of patients had an improvement in New York Heart Association class at 8 months; 76.3% had no change, and 8.7% had a worsening of New York Heart Association class, in comparison with 12.6%, 77.8%, and 9.6%, respectively, in the valsartan group (odds ratio for improvement, 1.45; 95% confidence interval, 1.13 to 1.86).

Given that the primary outcome was not met, further analyses are exploratory. That said, there was no benefit of sacubitril-valsartan regarding cardiovascular death (hazard ratio, 0.95) or total mortality (hazard ratio, 0.97), but there was a sign of a benefit with the angiotensin receptor-neprilysin inhibitor for hospitalizations due to HF (rate ratio, 0 .85; 95% confidence interval, 0.72 to 1.00; P = 0.056). The use of sacubitril-valsartan was less associated with hyperkalemia and increased serum creatinine, but a higher incidence of hypotension and angioedema was observed in this group.[20]

In pre-specified subgroup analyses, a differential effect was observed for LVEF and sex. The benefits of sacubitril-valsartan compared to valsartan were seen in patients with LVEF below the median (45% to 57%; rate ratio, 0.78; 95% confidence interval, 0.64 to 0.95) and in women (rate ratio, 0.73; 95% confidence interval, 0.59 to 0.90).[20,35,36]

Nitrates

Nitrate therapy may reduce pulmonary congestion and improve exercise tolerance in patients with heart failure with reduced ejection fraction. With respect to HFpEF, data from previous studies indicate that 15% to 50% of patients are treated with nitrates.[19,21,37,39]

Nonetheless, the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction) study[39] randomized 110 patients with LVEF ≥ 50% on stable HF therapy for comparison between isosorbide mononitrate and placebo. This analysis included patients who did not use nitrate and who had activities limited by dyspnea, fatigue, or chest pain. In the results of this study, no beneficial effects were observed regarding activity levels, quality of life, exercise tolerance, or NT-proBNP levels. In fact, daily activities showed a dose-dependent reduction effect among patients who received isosorbide mononitrate.[39]

Although routine use of nitrates in patients with HFpEF does not appear to be beneficial, patients with HFpEF and symptomatic CAD can still receive symptomatic relief with nitrates.

With respect to phosphodiesterase-5 inhibition, it increases the nitric oxide system, positively regulating cyclic guanosine monophosphate activity. The RELAX study (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction)[40] randomized 216 patients with LVEF ≥ 50% on stable HF therapy with reduced exercise tolerance (peak oxygen consumption < 60% predicted) for the use of sildenafil or placebo. However, this study observed a lack of improvement in oxygen consumption and exercise tolerance.

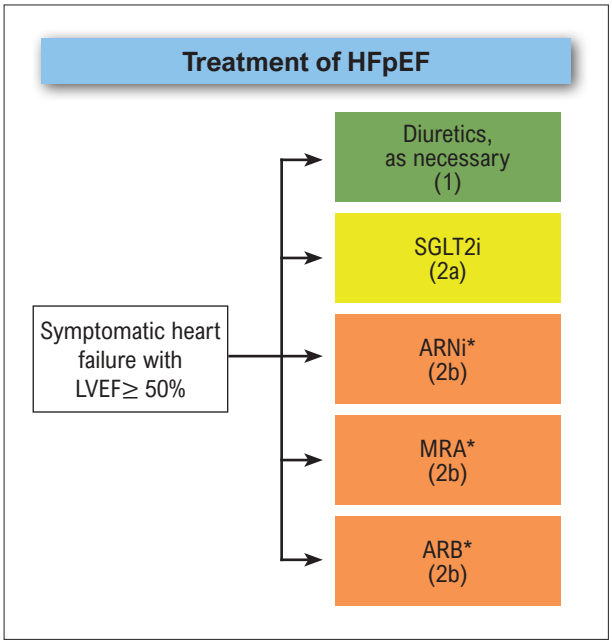

Figure 1 – *Recommendations for patients with LVEF (≥ 50%). Adapted from Heidenreich, P. A. et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines* Circulation. *2022;145:e895–e1032.*
Medication recommendations for HFpEF are exhibited. ARB: angiotensin receptor blocker; ARNi: angiotensin receptor-neprilysin inhibitor; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium-glucose cotransporter 2 inhibitor.
**Greater benefit in patients with LVEF closer to 50%.*

Conclusion

Studies related to approaches to treatment of HFpEF have shown advances. In this context, SGLT2i have showed a favorable result in terms of reducing cardiovascular death or hospitalization. For the first time, there is a medication that has demonstrated significant benefits in patients with preserved ejection fraction (Figure 1). This evolution in the study of HFpEF provides an opportunity to choose a therapy with a better cardiovascular outcome for patients.

Author Contributions

Analysis and interpretation of the data and Critical revision of the manuscript for important intellectual content: Figueiredo Neto JA; Writing of the manuscript: Figueiredo Neto JA, Santos JVS, Figueiredo VMS, Galvão NG.

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

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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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Review Article

Heart Failure with Improved Ejection Fraction

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Abstract

Cardiac remodeling is generally an adverse sign linked to the progression of heart failure (HF). However, in remodeled hearts, reverse remodeling is an important sign of cardiac recovery associated with a better prognosis. Ejection fraction may improve spontaneously following resolution of the processes that promote cardiac dilatation. In HF with reduced ejection fraction, treatment with neurohormonal blockade is an important strategy to promote improvements in ejection fraction. Improved ejection fraction can identify recovered patients with a better prognosis. In patients with HF with reduced or mildly reduced ejection fraction undergoing treatment, we should always investigate the ejection fraction development and optimize treatment by targeting an improved ejection fraction.

HF with improved ejection fraction is a current topic with several new publications, and given its importance, it has been highlighted in the main HF guidelines.

Update of the guidelines for the diagnosis and treatment of HF

In view of a better outcome for patients with improved ejection fraction, the European and Brazilian HF Societies have updated concepts and underscored the value of reverse remodeling. Therefore, in 2021, the guidelines presented a revised patient classification based on ejection fraction and provided better defined groups (without an overlap of ejection fractions), classifying patients into 4 groups that further highlight and better define improved fraction ejection (Table 1).[1-3]

Valuing improved ejection fraction was important as it is a clinical finding that can identify patients with a better prognosis. It should be systematically investigated in patients with reduced or mildly reduced ejection fraction, as the improvement in ejection fraction indicates better control of HF and myocardial injury, whereas the lack of improvement with treatment may indicate more severe disease, although it more often indicates that treatment could be implemented.

Keywords

Keywords: Heart Failure; Prognosis; Patients

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Ventricular remodeling

Ventricular remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors.[4] Remodeling may be physiological and adaptive during normal growth or pathological due to myocardial infarction, cardiomyopathy, hypertension, or valvular disease. Myocardial remodeling can be defined as molecular, cellular, and interstitial changes in the myocardium leading to changes in the size, mass, geometry, and function of the heart as a result of myocardial injury.[4] In response to these changes, there is cardiac function reduction and cardiac dilatation associated with circulatory congestion, which characterize HF as a clinical syndrome.[4] Cardiac remodeling is generally an adverse sign linked to HF progression. However, in remodeled hearts, reverse remodeling is an important sign of cardiac recovery associated with a better prognosis.

The pathophysiological importance of cardiac remodeling has been well demonstrated in the studies conducted by the Pfeffers. Initially, Marc and Janice Pfeffer, in experimental studies using a rat model of myocardial infarction, showed that the death of rats was strongly associated with the degree of cardiac dilatation and reduction of ejection fraction.[5,6] The demonstration of the pathophysiological and prognostic importance of cardiac remodeling in HF was expanded with the results of studies using angiotensin-converting enzyme (ACE) inhibitors in the treatment of these infarcted rats, which showed that ACE inhibitors prevented cardiac remodeling and, in some cases, promoted reverse remodeling.[6] The rats treated with ACE inhibitors that showed attenuated ventricular dilatation or reverse remodeling had better outcomes than those that did not.[5,6]

Subsequently, Marc Pfeffer coordinated the Survival and Ventricular Enlargement (SAVE) trial, whose results showed that this remodeling concept could also be applied to humans and that treatment with ACE inhibitors modified the natural history of myocardial infarction and infarction-related HF.[7] Patients with myocardial infarction and ejection fraction of < 40% treated with captopril had a reduction in cardiovascular events of approximately 40%.[7]

Since then, the role of cardiac remodeling has been investigated in HF studies and in HF registries, confirming these findings.[8-17]

Table 1 – HF classification according to ejection fraction[1-3]

Heart failure reduced ejection fraction (HFrEF) – EF < 40%
Heart failure mildly reduced ejection fraction (HFmrEF) – EF 41%-49%
Heart failure preserved ejection fraction (HFpEF) – EF > 50%
Heart failure improved or recovered ejection fraction (HFimpEF). For those with an EF of < 40% who had a 10-point increase and remained with an EF of > 40%.

Reverse ventricular remodeling

Cardiac dilatation is therefore identified as an important and definite marker of poor prognosis. Conversely, its reversal is associated with improved outcomes.

Spontaneous reversal occurs in situations in which the cause of ventricular dysfunction has been corrected, such as in heart rate control in tachycardiomyopathy, in cases of treated hypothyroidism and hyperthyroidism, in hypertensive patients after hypertension control has been achieved, in myocarditis that has reversed the inflammatory condition, and when a cardiotoxic agent is discontinued, such as cessation of drinking in cases of alcoholism or of a prescribed chemotherapeutic agent.[12]

Reverse remodeling also occurs as a result of the treatment of ventricular dysfunction, and several studies have shown that drugs or procedures that modify ventricular remodeling, either by preventing or delaying cardiac dilatation or by improving ejection fraction, are associated with better patient outcomes.[17,18] Not all drugs used in the treatment of HF influence cardiac remodeling.[18] Post-infarction animal studies showed that beta-blockers, aldosterone antagonists, and renin-angiotensin system (RAS) inhibitors prevented cardiac dilatation, whereas hydralazine and digitalis did not.[18]

Therefore, clinical and experimental evidence suggests that the renin-angiotensin-aldosterone system and the sympathetic system play an important role in the process. Sacubitril/valsartan and, to a lesser extent, sodium-glucose cotransporter 2 (SGLT2) inhibitors also promote reverse remodeling, and this reversal plays a role in improving the prognosis of patients treated with these drugs.[19-21]

The Valsartan Heart Failure Trial (Val-HeFT) also confirmed the association between reverse remodeling and improved prognosis, but it went further and documented the importance of the magnitude of reversal in remodeling. In the Val-HeFT, where patients were divided into quartiles according to the magnitude of remodeling, treatment with angiotensin-receptor blocker proved to be effective in reducing mortality from quartiles 2 to 4 by promoting a reduction of 11%, 15%, and 20% in the risk of death in quartiles 2, 3, and 4, respectively.[18] The Vasodilator-Heart Failure Trial (V-HeFT) I and V-HeFT II also observed the role of the magnitude of reversal in remodeling and reported that a 5-point increase in ejection fraction was the strongest predictor of mortality among the study variables.[22] About 30% of patients had a > 5-point increase in ejection fraction and 50% had a > 10-point increase in ejection fraction.

The percentage of patients who show improved ejection fraction when treated is still a matter of debate. Reversal of cardiac dilatation has been described in 30% to 60% of patients treated with neurohormonal blockade. Cioffi et al, evaluating factors associated with improved ejection fraction in patients over 70 years of age, found improved ejection fraction in 36% of outpatients during a mean follow-up of 17 months. Predictors of this improvement included absence of diabetes, history of hypertension, and treatment with beta-blockers, the latter increasing by 3.4 times the chance of reversal.[23] Overall, studies have shown that patients with coronary artery disease experience less reverse remodeling, especially those with myocardial infarction, which has generally been observed in patients with complete left bundle branch block.

Improvement in cardiac remodeling has also been observed in registries of HF cases. In the IMPROVE-HF Registry, which analyzed 3994 patients hospitalized for compensated HF, ejection fraction improved by more than 10% in 28.6% of patients.[8]

In the Swedish HF Registry, analyzing 4942 cases, patients with improved ejection fraction had a lower risk of mortality than those without any improvement.[9] The worse outcome was observed in those with reduced ejection fraction[9] (Figure 1). This registry showed that the lowest mortality occurred in patients with mildly reduced or reduced ejection fraction who had some increase in ejection fraction; increases in ejection fraction were observed in 25% of patients with mildly reduced ejection fraction and in 26% with reduced ejection fraction, of whom 10% achieved an ejection fraction of > 50% and 16% remained at mildly reduced ejection fraction levels[9] (Figure 1). The data from the registry and previously mentioned data underscore the importance of improved ejection fraction, which promotes an improvement in prognosis even when not achieving the levels proposed as improved ejection fraction in current guidelines.

When analyzing cardiac remodeling, increased adrenergic activity appears to play a major role in ventricular remodeling, since beta-blockers have shown greater reversal of cardiac dilatation than ACE inhibitors (Figure 2). While ACE inhibitors attenuate ventricular dilatation and slightly increase ejection fraction, beta-blockers are associated with a marked reduction in ventricular diameters and improvements in ejection fraction.[24]

There is a growing number of studies documenting the importance of reverse ventricular remodeling in

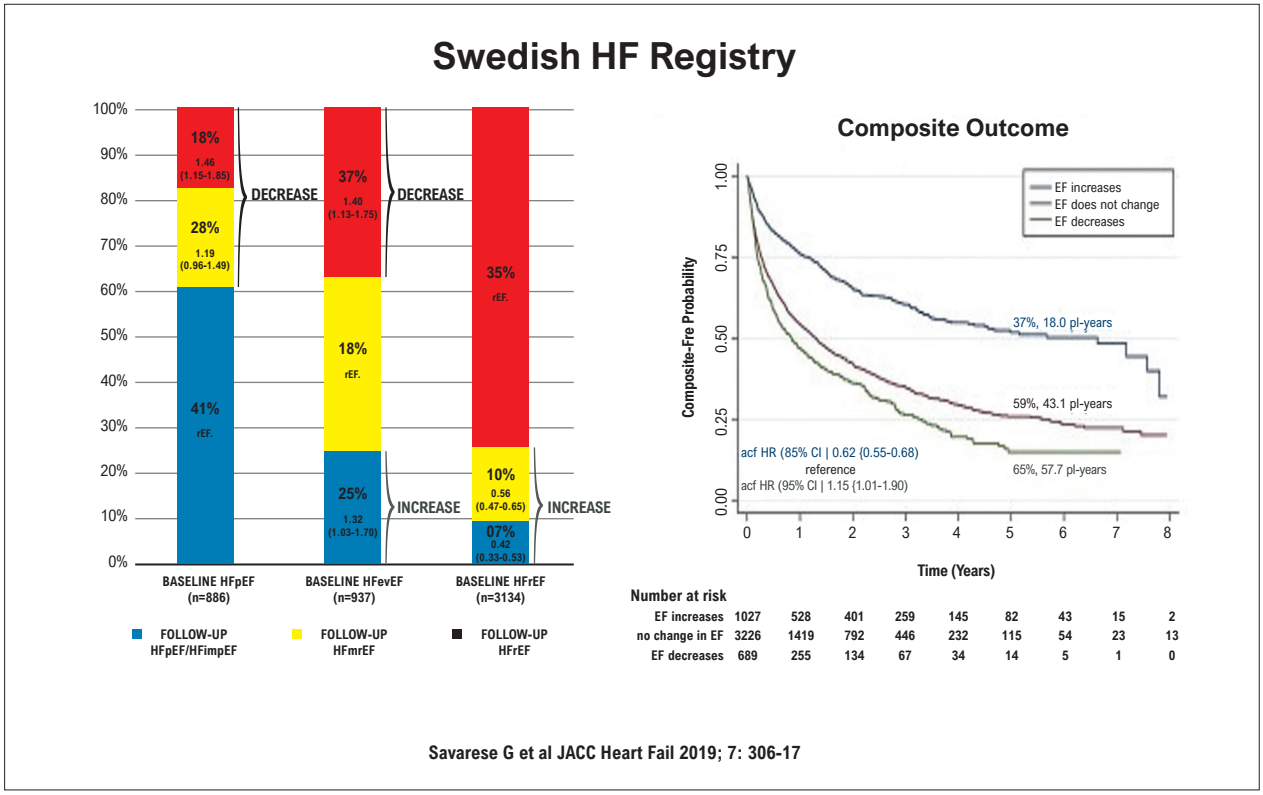

Figure 1 – *Reverse cardiac remodeling with improved ejection fraction was accompanied by a significant reduction in mortality. HFpEF: heart failure preserved ejection fraction; HFrEF: heart failure reduced ejection fraction; HFimpEF: heart failure improved or recovered ejection fraction; HFmrEF: heart failure mildly reduced ejection fraction.*

the prognosis of HF.[10-22] Patients who show regression of ventricular dilatation or improvement in ejection fraction with treatment have a better quality of life and lower morbidity/mortality than those with continued dilatation.[10-22]

In the study by Cioffi et al, follow-up results showed that patients with reverse remodeling had lower mortality (3%) than those without reverse remodeling (22%).[23] In the V-HeFT I and II, mortality at 1-year follow-up was 29%, 16%, and 6%, respectively, for patients with a > 6-point reduction in ejection fraction, those with values between -5 and +5, and those with a > 5-point increase in ejection fraction.[22]

Hoshikawa et al found an association of prognosis with reverse cardiac remodeling.[25] They divided patients into 3 groups: those with complete reverse remodeling, defined as left ventricular (LV) end-diastolic diameter < 55 mm and fractional shortening > 25%; those with partial reversal; and those without reversal. All patients without reversal of cardiac dilatation died within a mean follow-up of 5 years. All patients who had some reversal of cardiac dilatation survived. In this study, in which all patients were treated with neurohormonal blockade, 78% had reversal of cardiac dilatation, 57% of whom had complete reverse remodeling.

The same research group reanalyzed their patients, and Matsumura et al, evaluating the role of reverse remodeling in long-term outcomes, found that all patients with regression of cardiac dilatation survived, whereas those with increased cardiac dilatation either died or required a transplant at 12-year follow-up.[26] In this population of patients with dilated cardiomyopathy, 35.6% had some reversal of cardiac dilatation, 37% of whom had normalization of diameters and ejection fraction.[26] Overall, the authors reported that all patients who showed some reversal remained alive at the end of 12 years, indicating that even small improvements are indicative of a good response to treatment.[26]

In addition to clinical trials and small-sample studies, reverse cardiac remodeling was also the topic of a meta-analysis involving 69,766 patients from 30 randomized trials, which reported a strong association between improved ejection fraction and reduced mortality.[27] Overall, there was a significant 49% reduction in mortality in patients who had improved ejection fraction compared with those who did not.[27] Regression analysis showed that a 5% improvement in mean ejection fraction corresponded to a 14% relative reduction in mortality (odds ratio 0.86; 95% CI, 0.77-0.96; p=0.013). Overall, patients with reverse remodeling were 4.9 times more likely to survive than those without reverse remodeling, for each 5% absolute increase in ejection fraction.[27]

A much better outcome is observed in patients with reversal of cardiac dysfunction, even if only partial, so that we should consider it one of the primary goals of treatment. Patients without reversal of cardiac dysfunction should have their treatment regimen reassessed and, in the absence of reversal, be followed up more closely and carefully, as these are the patients

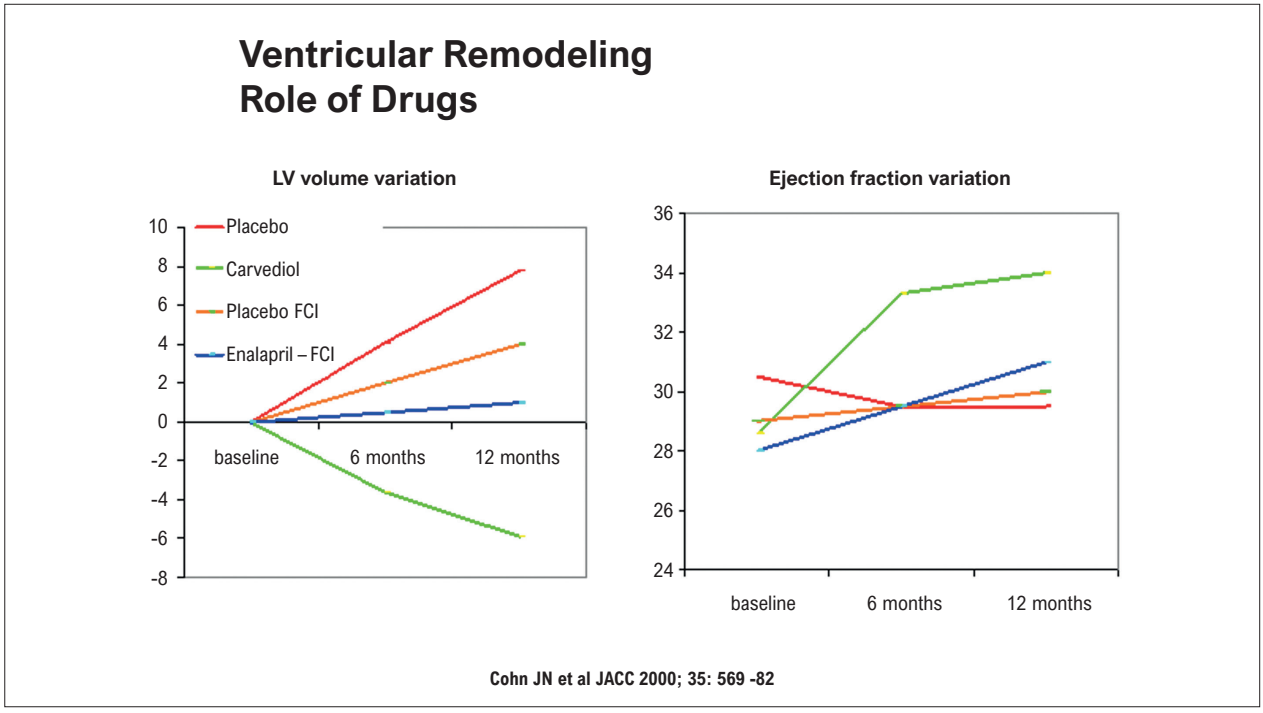

Figure 2 – *Role of drugs in reverse ventricular remodeling. Beta-blockers were more effective in reversing cardiac remodeling. LV: left ventricular; FCI: Function Class I.*

at risk of complicated outcomes. An effective treatment should lead to reverse cardiac remodeling. It is worth mentioning that reversal is more frequent when drugs that have been proven to modify the evolution of patients with HF are used, a blocker of the renin-angiotensin system, a beta-blocker, spironolactone and an inhibitor of SLGT2, which has been called the four fantastic., as they reduce mortality, hospitalizations, and procedures such as cardiac resynchronization, also promote reverse remodeling.[12-22] No reversal may indicate that the prescribed doses are insufficient or the disease is so severe that the patient will not respond as desired to the proposed regimen.

In the treatment of HF, the prescribed dose is extremely important. Reverse remodeling is often not observed because the drugs have been prescribed at low doses. The importance of the prescribed dose was highlighted in the FAST-Carvedilol study conducted at our institution.[28] In this study, half of the patients were discharged with a carvedilol dose of 3.125 mg or 6.25 mg twice daily and the other half had their dose increased rapidly during hospitalization and were discharged with the maximum tolerated dose. In the outpatient clinic, the carvedilol dose was not increased by their physicians for various reasons, mostly for borderline blood pressure, so that the mean dose of carvedilol was 6.99 mg/day in the control group and 16.19 mg/day in the intervention group. During follow-up, the intervention group showed reversal of cardiac dilatation, which was observed in the first 3 months of treatment (Figure 3), whereas the low-dose group showed no reversal.[28] The 1-year survival was 43.5% in the control group vs 65.2% in the intervention group. Our data draw attention to the critical role of dose in both reversing cardiac dilatation and reducing mortality (which are probably interconnected).[28]

More accurate drug titration has been implemented in specialized HF clinics. In a study conducted in the Netherlands, in which treatment optimization was led by nurses, a higher rate of patients achieved the effective doses (target doses) after nurse-led up-titration.[15] Of 345 patients with HF with reduced ejection fraction at 9-month follow-up, 69% achieved ≥ 50% of the recommended dose of RAS inhibitors and 73% achieved ≥ 50% of the recommended dose of beta-blockers. The main reasons for not achieving the target doses were hypotension (RAS inhibitors and beta-blockers), bradycardia (beta-blockers), and renal dysfunction (mineralocorticoid receptor antagonists).[15] LV ejection fraction improved from a mean of 27.6% at baseline to 38.8% at 9-month follow-up. Each 5% increase in LV ejection fraction was associated with a reduction in mortality of 16% (hazard ratio 0.84 [0.75–0.94], p=0.002) and 15% (hazard ratio 0.85 [0.78–0.94], p=0.001) for the composite endpoint of death and/or hospitalization after a mean of 3.3 years of follow-up. The authors concluded that optimized up-titration in a specialized nurse-led HF clinic promoted an improvement in LV ejection fraction and a reduction in morbidity/mortality in patients with new-onset HF.[15]

We have used this approach of assessing ejection fraction improvement as a guide to treatment. In patients who do not experience reverse remodeling, we have increased the dose of medication, especially of beta-blockers, thus achieving reversal of cardiac dilatation, which had not been achieved with the usual dose. In patients who have a persistent heart rate of > 70 bpm with optimal treatment, the use of ivabradine has been effective in reversing cardiac dilatation.[24]

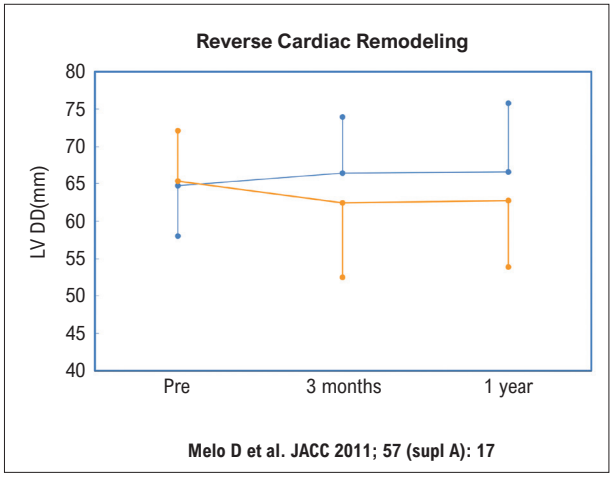

Figure 3 – *The importance of carvedilol dose in reverse ventricular remodeling. Patients receiving a dose of 3.125 mg or 6.25 mg twice daily showed no reduction in ventricular diameters (blue line), but this reduction was observed in those receiving a dose of 12.5 mg or 25 mg twice daily (orange line).*

At the University of São Paulo Heart Institute-InCor, we have attempted to determine the role of improved ejection fraction in HF prognosis by investigating patients from the different teams of InCor, Brazilian Unified Health System (SUS), health plans, private patients, patients with cardiomyopathy, valvular disease, or coronary artery disease, and geriatric patients.[24] We investigated all patients who were treated at InCor in 2017 with a diagnosis of HF (13,121 patients). Of these, 3670 had reduced ejection fraction and two follow-up echocardiograms. In this group with two echocardiograms, 64.5% showed some improvement in ejection fraction, and in 31.3% this improvement allowed us to classify them in the improved ejection fraction group according to the new guidelines; 30% showed no improvement in ejection fraction. At 1000-day follow-up, mortality was 16.3% for patients with improved ejection fraction vs 30.3% for those with no improvement in ejection fraction. Any improvement in ejection fraction was associated with a mortality rate lower than that observed in patients with no improvement (22.4% vs 30.3%), supporting evidence that any reversal of cardiac remodeling is associated with an improvement in the prognosis of patients with HF.[24]

A crucial point to consider in the presence of improved ejection fraction is that, in most cases, the patient is not cured. The patient experiences reverse remodeling and shows improved ejection fraction due to adequate response to treatment, but treatment withdrawal or even dose reduction, in general, can promote cardiac re-remodeling with reduced ejection fraction. This reduction was well documented in the TRED-HF trial, designed to monitor ejection fraction after treatment withdrawal, reporting a relapse of the dilated cardiomyopathy in approximately 40% of cases.[29] After reinstating treatment, not all patients returned to their pre-withdrawal ejection fraction levels. Therefore, the take-home message is that the treatment should not be withdrawn because the patient has improved ejection fraction.

In conclusion, we should always optimize the treatment of HF by prescribing drugs at the doses recommended in Guidelines and in clinical trials.[1-3] To confirm the effectiveness of treatment, an echocardiogram can be obtained to determine whether the treatment has promoted an improvement in ejection fraction. If an improvement has been achieved, the treatment can be considered effective and there is no need to review the doses or the treatment regimen.[12-22] If no reversal of cardiac dilatation has been documented, this finding is indicative of treatment ineffectiveness and treatment should therefore be improved by up-titrating drug doses, by prescribing new drugs, or even by recommending an intervention.[1,2]

Patients with improved ejection fraction have a better prognosis, better quality of life, and lower morbidity/mortality than those with an ejection fraction that does not improve or that deteriorates after treatment.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Barretto ACP.

Potential Conflict of Interest

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Physical Training in Heart Failure with Preserved Ejection Fraction

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Heart failure (HF) is a clinical syndrome caused by functional and/or structural cardiac abnormalities in association with elevated natriuretic peptides or other objective evidence of pulmonary and/or systemic congestion.[1] These abnormalities result in increased intracardiac pressures and/or inadequate cardiac output at rest and/or during exertion.[2]

HF with preserved ejection fraction (HFpEF), although it is included in this definition, is a pathology with a more challenging and complex approach, and it is more common in older patients, predominantly in the female sex, as well as in patients who have multiple comorbidities such as atrial fibrillation, chronic kidney disease, and other non-cardiovascular pathologies, which sometimes overlap with the patients' clinical condition.[2] According to more recent data, 50% of patients with HF have preserved ejection fraction, and its prevalence in relation to HF with reduced ejection fraction (HFrEF) continues to ascend at an annual rate of approximately 1%.[3]

Diagnosis is still considered a challenge, and it involves the evaluation of various clinical, echocardiographic, and functional factors. The use of scores, such as the H2FPEF and the HFA-PEFF, is recommended to improve the accuracy of the process, and invasive hemodynamic measures may even be used in cases specific.[2,4]

Few randomized clinical trials have shown positive outcomes, analyzing combined or secondary outcomes, mainly the reduction of hospitalizations due to HF, or they have shown benefits in subgroup analyses.[5-8] This characteristic reinforces the current concept of the presence of different phenotypes within the syndrome, which could then benefit from individualized approaches and therapies.[3]

Consequently, in this scenario, non-pharmacological treatment has become an essential first-line approach to strengthen therapy in order to promote improved survival and quality of life.

Evidence has shown that cardiopulmonary rehabilitation in HFpEF, based on aerobic exercise, promotes cardiovascular protection with multisystem benefits, such as inhibition of cardiomyocyte hypertrophy; reduced inflammation, fibrosis, and microvascular dysfunction; and improvement in mitochondrial metabolism and endothelial function. Randomized controlled studies have found varying results regarding the effects of exercise in this population, whereas other studies have shown an increase in cardiorespiratory fitness, exercise tolerance, and quality of life, as well as improved diastolic function.[9] The objective of this review is to understand the rationale for the beneficial mechanisms of exercise in HFpEF, review the main scientific data that support this measure as part of the non-pharmacological treatment of this pathology, and describe how and why we should encourage our patients to adopt the practice of physical exercises in their daily lives.

Pathophysiological rationale for the benefits of physical training in HFpEF

When we compare patients with HFpEF to a control group of patients with hypertension or other comorbidities, we see that the former's peak oxygen consumption (VO_2) is 30% to 70% lower than that of the other groups, as shown in Figure 1.[10]

Reduced VO_2 is a parameter of reduced aerobic functional capacity, which is currently considered a new vital sign, as well as a marker of independence for daily activities, which increases the chance of functional dependence.[11] Several mechanisms seem to explain this fact in patients with HFpEF. An initial study by Kitzman et al hypothesized that the following 3 mechanisms are involved in this reduction in functional capacity: a reduction in cardiac output on exertion, a rapid increase in pulmonary capillary pressure, and a smaller difference in the arterial-venous oxygen gradient,[12,13] with several subsequent studies diverging as to which pathophysiological mechanism would be predominant in HFpEF. It is especially interesting that the reduction in the arterial-venous oxygen gradient possibly occurs due to hypoperfusion of peripheral skeletal muscles[14] or to a decrease in skeletal muscle oxidative metabolism.[15] Both mechanisms reinforce the hypothesis of "peripheral hearts", which will be subsequently discussed. Another mechanism that seems to explain exercise intolerance in this group of patients is chronotropic incompetence,[16] which is particularly important in patients with specific etiologies of HFpEF, such as cardiac amyloidosis.

Keywords

Physical training; Heart Failure; Preserved Ejection Fraction; Cardiac Rehabilitation

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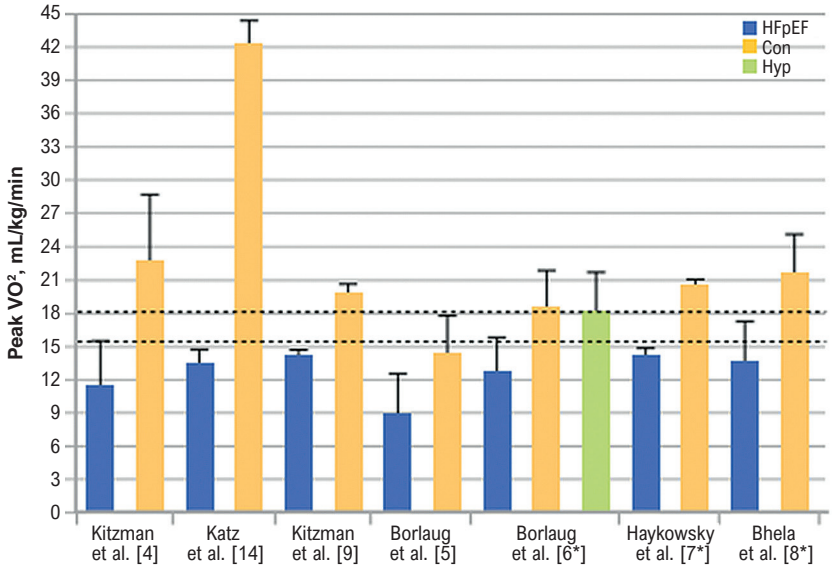

Figure 1 – *Comparison of aerobic capacity between patients with heart failure with preserved ejection fraction; patients from a control group matched by age, sex, and other comorbidities without heart failure; and patients with hypertension without heart failure. Adapted from Haykowsky, M et al.[10] HFpEF: heart failure with preserved ejection fraction; Hyp: hypertension; VO²: oxygen consumption.*

Clinical studies involving exercise or cardiovascular rehabilitation and HFpEF

In spite of similar prevalence between HFpEF and HFrEF, there are considerably fewer data on the role of physical training in HFpEF. Nonetheless, 7 controlled trials (5 randomized, 1 multicenter) on exercise training in patients with HFpEF have demonstrated that physical training is a safe and effective intervention to improve symptoms, increase aerobic capacity and endurance, and improve self-reported quality of life.[17-24] We will describe some of these studies in the following paragraphs.

In HFrEF, it is known that physical training improves exercise capacity and reduces morbidity.[25] As suggested by previous meta-analyses, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) showed that an exercise training program prescribed in patients with chronic symptomatic HFrEF was safe, with a modest reduction in clinical events when added to optimal medical therapy.[26,27]

In 2007, a prospective, multicenter study on physical training in HFpEF was conducted to investigate whether exercise training would improve exercise performance, diastolic function, and quality of life in patients with HFpEF over 3 months. The results showed that the mean increase in peak VO_2 was 2.6 ml/min/kg in the physical training group compared to a slight decrease of 0.7 ml/min/kg in the control group. The net benefit of training was 3.3 ml/min/kg (95% confidence interval: 1.8 to 4.8, p = 0.001), translating to a number needed to treat of 3.5 (95% confidence interval: 2.0 to 12.0, p = 0.006) to achieve an increase of at least 3 ml/min/kg at the individual level. Diastolic function in exercise with an increase in peak VO_2 was correlated with improved E/e' ratio (r = −0.37, p = 0.002), thus improving diastolic function and quality of life in patients with HFpEF.[21]

Another 2:1 randomized, prospective study, carried out in Israel, selected patients with HF with preserved, mildly reduced, and reduced ejections fractions to practice guided physical activity, with the control group receiving only routine treatment without guidance regarding physical exercise. Their results showed an improvement in ejection fraction (p = 0.02), and there was an improvement in exercise tolerance in the group of patients with HFpEF.[22]

A systematic review of exercise-based rehabilitation among patients with HF regardless of ejection fraction evaluated outcomes such as all-cause mortality, all-cause hospitalizations, and quality of life. The study suggests that there is a reduction in mortality only after 12 months of follow-up (RR 0.88, 95% confidence interval 0.75 to 1.2), in addition to a reduction in all-cause hospitalizations (RR 0.70, interval of 95% confidence interval 0.60 to 0.83) and hospitalizations due to HF in fewer than 12 months (RR 0.59, 95% confidence interval 0.42 to 0.84). It also suggests improved quality of life according to the Minnesota Living with Heart Failure Questionnaire (mean difference −7.11, 95% confidence interval −10.49 to −3.73). Unfortunately, this publication did not analyze HFrEF and HFpEF populations separately.[28]

Another publication of a Portuguese cross-sectional study, which was specific to the population with HFpEF, provided evidence of a direct relationship between quality of life and physical fitness, which was evaluated according to the following 3 parameters: cardiorespiratory fitness, dynamic balance, and mobility and muscular fitness. The parameter

of dynamic balance and mobility was shown to be the only predictor independently associated with the quality of life score according to the Minnesota Living with Heart Failure Questionnaire in the physical (beta 0.570, p = 0.04) and emotional (beta 0.611 p = 0.002) dimensions, making it possible to infer the importance of including this group of exercises in these patients' rehabilitation.[29]

Notwithstanding proof of positive outcomes in patients with HF, an Italian study showed that a rehabilitation program with moderate intensity exercises for patients with HF, regardless of ejection fraction, during the first 4 months, did not show a significant change in ejection fraction (HFpEF: 54.61% ± 3.31% versus 54.21% ± 2.32% and HFrEF: 36.56% ± 2.31% versus 39.59% ± 2.95%; p group = 0.0001, p time = 0.57, p interaction = 0.46), left ventricular systolic diameter (HFpEF: 36.22 ± 1.57 versus 40.93 ± 4.15 and HFrEF: 51.67 ± 2.84 versus 51.90 ± 3.19 mm; p group = 0.004, p time = 0.19, p interaction = 0.24), left ventricular systolic diameter (HFpEF: 55.00 ± 1.58 versus 50.78 ± 1.93 and HFrEF: 65.33 ± 2.80 versus 65.49 ± 3.44 mm; p group = 0.002, p time = 0.12, p interaction = 0.10), or global longitudinal strain analysis (HFpEF: −13.73 % ± 1.23% versus −12.74% ± 0.95% and HFrEF: −9.59% ± 0.94% versus −9.77% ± 0.98%; p group = 0.0001, p time = 0.57, p interaction = 0.46).[30]

A very interesting subanalysis of physical activity in patients with HFpEF came from the TOPCAT trial. Some interesting points are raised in this article. First, only 11% of the 1751 patients followed the physical activity recommendations given by the guidelines at the time, which shows the poor adherence (by patients or by physicians themselves) to physical activity in this group of patients. Second, when comparing patients with a worse degree of physical activity with those with levels close to ideal, there was an increase in hospitalization due to HF and mortality in the first group. Finally, there was a dose-response relationship, where only physical activity levels above those recommended by the guidelines were related to a lower risk of hospitalization and mortality (Figure 2).[31]

When evaluating the types of physical training in HFpEF, there is evidence showing that intervals of high-intensity exercises seem to present better peak VO_2 and improved diastolic ventricular diameter compared to moderate-intensity training,[30] making it possible to infer that there is an exercise profile with better results in this population.

How to practice or prescribe physical exercise in HFpEF?

In the mid-1980s, Weber demonstrated the clinical applicability of the cardiopulmonary exercise test (CPET) through the use of peak VO_2 in classification of HF.[32] In 1991, Mancini stratified the risk of cardiovascular death using peak VO_2 values in patients with advanced HF.[33] Since these 2 studies, but mainly after the 2000s, with the discovery and use of new variables, the method has been gaining ground in therapeutic and prognostic evaluation and in the prescription of exercise for patients with HFrEF.[34] Over the past 10 years, with the advance of pathophysiological knowledge of HFpEF, the method has also been used in the evaluation of exercise intolerance and in the prescription of physical rehabilitation in patients with preserved systolic function.[16]

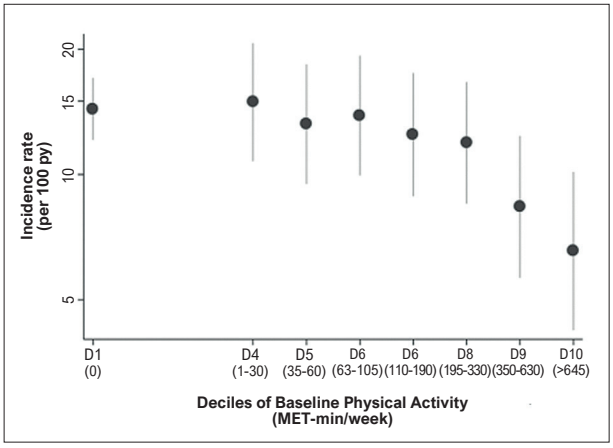

Figure 2 – *Incidence rates of the primary endpoint (cardiovascular death, resuscitated cardiac arrest, or hospitalization due to heart failure) in patients from the TOPCAT trial, according to baseline physical activity level. Adapted from Hegde et al.[31]*

The CPET allows for objective and quantitative evaluation of functional capacity through the measurement of VO_2 at peak effort. In the context of exercise prescription, the intensity of aerobic training can be calculated using the heart rate (HR) reserve, or preferably, the HR corresponding to determined percentages of peak VO_2.[35,36] In patients with HFpEF, continuous aerobic exercise is recommended for 45 to 60 minutes, 3 to 5 times a week, at moderate to high intensity. During the first few weeks of exercise, training HR should correspond to 40% to 50% of peak VO_2. During the following weeks, training HR should be gradually increased to 70% to 80% of peak VO_2. Alternatively, a percentage of HR reserve can be used as a measure of training intensity. HR reserve is the value of the difference between the peak HR obtained on the conventional exercise stress test and the baseline resting HR (peak HR − resting HR), and it corresponds to the increase in HR obtained at the maximum effort achieved. For exercise prescription, the HR range for beginning training is calculated as follows: 40% to 70% (peak HR − Resting HR) + resting HR.[36] For instance, if a patient has a resting HR of 70 bpm and they reached a peak HR of 160 bpm, they have a HR reserve of 90 bpm. Thus:

Training HR lower limit:
$0.4 \times 90 + 70 = 36 + 70 = 106$ bpm

Training HR upper limit:
$0.7 \times 90 + 70 = 63 + 70 = 133$ bpm

Training range (initial): from 106 to 133 bpm

Progressively, the training range should be increased during the rehabilitation process.

Several studies have demonstrated the efficacy and safety of high-intensity interval training (HIIT) in patients with HFpEF.

This type of training appears to improve cardiac autonomic function, through baroreflex modulation, reduced arterial stiffness, and mediation of vagal control resulting from reduced circulating angiotensin II. HIIT is based on the repetition of short to long activities of high-intensity exercises interspersed with periods of active or passive recovery (15 to 60 seconds of exercise at HR at 80% to 100% of peak VO_2, followed by 15 to 60 seconds of exercise at 40% to 60% of VO_2 peak, for example). Patients with HFpEF should start training at short intervals and gradually increase the exercise time.[37] The Borg scale of perceived exertion can also be used to guide the progression of training, regardless of whether the modality is continuous or interval. A brief period (3 to 5 minutes) of warm-up and cool-down should be recommended before and after each training session.[16]

Physical training programs should involve not only aerobic exercises, but also stretching, strength, and breathing exercises. In 1984, Rigatto et al, in a study on cardiovascular physiology, defended the idea of "peripheral hearts" affirming that the circulatory pump function was not exclusive to the heart and that other organs also act as sources for the transportation of blood and uptake of oxygen by the body. Strengthening the "pulmonary heart" by training the intercostal and diaphragmatic muscles improves respiratory mechanics, increases blood flow, and relieves the sensation of dyspnea.[38] Strength exercises should be prescribed 2 to 3 times a week with a load defined by percentages of "maximum resistance" (MR). MR corresponds to the greatest absolute weight that a patient can support when exercising a certain muscle group. This training should be prescribed at low intensity with higher number of repetitions (30% to 40% of RM, 10 to 15 repetitions) or at higher intensity with lower number of repetitions (40% to 60% of RM, 8 to 12 repetitions). For instance, a patient who has a MR of 3 kg for biceps flexion should start strength training with a load of 1.2 kg (40% of 3 kg). Progressively, the load and the number of repetitions should be increased under the supervision of a physical therapy or physical education professional. With the increase in muscle mass, there is an increase in peripheral oxygen uptake (with an increase in the arterial-venous oxygen gradient) and a consequent increase in the peak VO_2 value, as reflected by the improvement in functional capacity.[16]

Conclusion

HFpEF is a clinical syndrome, which, like HFrEF, leads to an accentuated exercise limitation. Therapeutic approaches are still limited, and they remain unsatisfactory, to the extent that they do not modify the natural course of the disease. As a non-pharmacological intervention, physical training has emerged as a potential strategy to be included in the therapeutic arsenal of HFpEF.

Cardiac rehabilitation causes exercise capacity to increase and clinical symptoms to improve.[39] Physical training is a fundamental component of these programs, in conjunction with dietary guidelines, encouraging adherence to medication, preventive measures such as vaccination, abstinence from alcohol and tobacco, and medical consultations. Prescriptions should ideally be individualized, taking into consideration the combination of moderate- and/or high-intensity aerobic training, localized muscular resistance exercises, and respiratory muscle training (ventilatory training).

Unfortunately, the data related to hard outcomes, such as mortality, are still not conclusive enough for us to be able to affirm that cardiovascular rehabilitation has any impact on them. Nevertheless, the improvement in these patients' peak VO_2, functional capacity, and independence for activities of daily living, in addition to the fact that it assists in controlling the multiple comorbidities that normally accompany these patients with HFpEF, lead us to conclude that physical training plays an important part in their treatment.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for important intellectual content: Montenegro CEL; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Aguiar MIR, Tavares DCF, Nogueira FF, Lyra ACAS, Gomes TQM, Montenegro CEL.

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

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Diagnosis of Heart Failure with Preserved Heart Failure in the Office Setting: How to Assemble this Puzzle?

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Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure (HF) in patients older than 65 years of age, accounting for more than 50% of all cases of HF.[1] However, despite more than 30 years of research on this intriguing and challenging heart disease, there is a lack of consensus on the diagnostic approach and a wide variation in guidelines' criteria.[2,3] This lack of uniformity in the definition and the difficult diagnosis are partly due to an incomplete understanding of the complexity of HFpEF – its pathophysiology, phenotypic heterogeneity and natural history. The 2022 AHA/ACC guideline highlights that evidence supporting increased filling pressures at rest or during exercise is important for the diagnosis of this disease.[3]

Therefore, the diagnosis of HFpEF remains a challenge in clinical practice. When assessing a patient with signs and symptoms of HFpEF, several "pieces" must be considered, as shown in detail in Table 1. It is important to examine the patient, evaluate the comorbidities and risk factors for HFpEF, and to design an accurate approach, not necessarily an invasive or complex one, to establish the correct diagnosis and the best therapeutic approach.

A common situation is that of patients coming to the office with dyspnea and/or exercise intolerance, whose clinical examination and natriuretic peptide levels give rise to diagnostic doubts. The most important step here is the application of the H2FPEF and the HFA-PEFF scores.[5-7] The H2FPEF score is a simple risk score, easy to use in the office setting. The score was first calculated based on the identification of clinical and imaging variables that were independently associated with the invasive diagnosis of HFpEF in a population cohort (Table 2).[6] The odds of HFpEF doubles for each one-unit H2FPEF score increase, with a c-statistic of 0.841.[3] In light of the possibility of HFpEF, the H2FPEF score can be used to either exclude HFpEF among patients with a low score (0-1) or to confirm the diagnosis

Table 1 – Diagnostic tools in heart failure with preserved ejection fraction[4]

Diagnostic tools in HFpEF	Criteria	Remarks
History	Dyspnea / Fatigue/ Orthopnea exertion intolerance Risk factors and comorbidities	Cardinal symptoms Highlights:[5] Exertional dyspnea in more than 90% of patients Fatigue in nearly 60%
Physical examination	- Jugular venous distension - Rales - Edema - Third heart sound	Low sensitivity to clinical signs[5] Edema in approximately 40% of patients Presence of other signs in less than 20%
Natriuretic peptides (NT-proBnp or BNP)	ESC major criteria: NT-proBNP >220 or BNP> 80 (sinus rhythm) NTproBNP >660 or BNP > 240 (AF); ESC minor criteria: NTproBNP >125 or BNP> 35 (sinus rhythm); and NTproBNP > 365 or BNP > 105 (FA)	Nearly 20% of patients with HFpEF by invasive methods have normal NT-proBNP (<125) Sensitivity: 77% Specificity: 53%
Echocardiogram	Diastolic dysfunction Lateral, mitral and septal tissue doppler; e' and E/e' ratio	ESC criteria: Septal e' <7 or lateral e' <10 (<75 years old); Septal e'<5 or lateral e'<7 (≥75 years old); E/e' ratio: ≥15 (major), 9–14(minor)
	Increased left atrial volume (mL/m2)	ESC criteria: **Major:** left atrial volume index >34 (sinus rhythm), >40 (AF); **Minor:** left atrial volume index = 29–34 (sinus rhythm), 34–40 (AF)
Cardiopulmonary test	Markers of functional impairment: peak VO2 and Ve/VCO2 slope	Useful in discriminating HFpEF from non-cardiac dyspnea Sensitivity: 91% Specificity: 51%

HFpEF: heart failure with preserved ejection fraction; ESC: European Society of Cardiology; BNP: B-type natriuretic peptide; NT-pro BNP: N-terminal (NT)-pro hormone BNP; AF: atrial fibrillation. Adapted[4]

Keywords

Heart Failure; Diastolic Heart Failure; Diagnosis.

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Table 2 – Description of the H2FPEF diagnostic algorithm

Clinical variable	Characteristics	Points
H2 - Heavy (obesity) - Hypertension	BMI > 30Kg/m2 2 or more antihypertensive medicines	2 1
F - Atrial fibrillation	Paroxysmal or persistent	3
P - Pulmonary hypertension	PASP>35mmhg (echocardiogram)	1
E - Elder	Age > 60 years	1
F - Filling pressures	E/e'> 9	1

BMI: body mass index; PASP: pulmonary artery systolic pressure. Adapted[6]

of the disease, with reasonable reliability, among patients with higher scores (6-9). However, there remain patients with intermediate scores (in any of the scores), who require further tests.[6]

It is worth pointing out that the therapeutic approach in the office setting has improved with the implementation of scores and tools available. However, clinical examination – symptoms, comorbidities, risk factors and cardinal signs – assessment of natriuretic peptides, echocardiogram and diagnostic scores may not be sufficient to confirm or exclude the diagnosis of HFpEF.

When the basic approach is not sufficient, it is necessary to go beyond. The flowchart presented in the Brazilian guidelines on heart failure (Figure 1) indicates the pathways in this scenario of intermediate probability.[8,9] One more piece needs to be added here. Patient referral for exercise stress echocardiogram, invasive hemodynamic monitoring at rest and during exercise is an indispensable step. Also, it is important to evaluate the etiology of secondary HFpEF, with special attention to the "red flags", in which additional diagnostic tests and specific therapies for infiltrative cardiomyopathies would be needed, as in suspected cardiac amyloidosis.[10]

Conclusion

During the last years, HFpEF has been increasingly recognized as a highly complex syndrome, with different phenotypes, in which the heart is definitely not the only organ affected. Identifying the limitations in assessing these patients was a big step. Current diagnostic approach, putting the pieces together, has certainly enhanced our capacity to diagnose this increasingly prevalent disease. However, not all pieces of this amazing puzzle – the HFpEF – have been identified, and we do not always get to a definite diagnosis in the office; yet, there is still a way to go. In situations where uncertainty remains high after the careful use of available tools, we must go on, with complementary tests (exercise stress and/or diastolic stress test) and referral to specialized centers, and do not stop until all the pieces are put together.

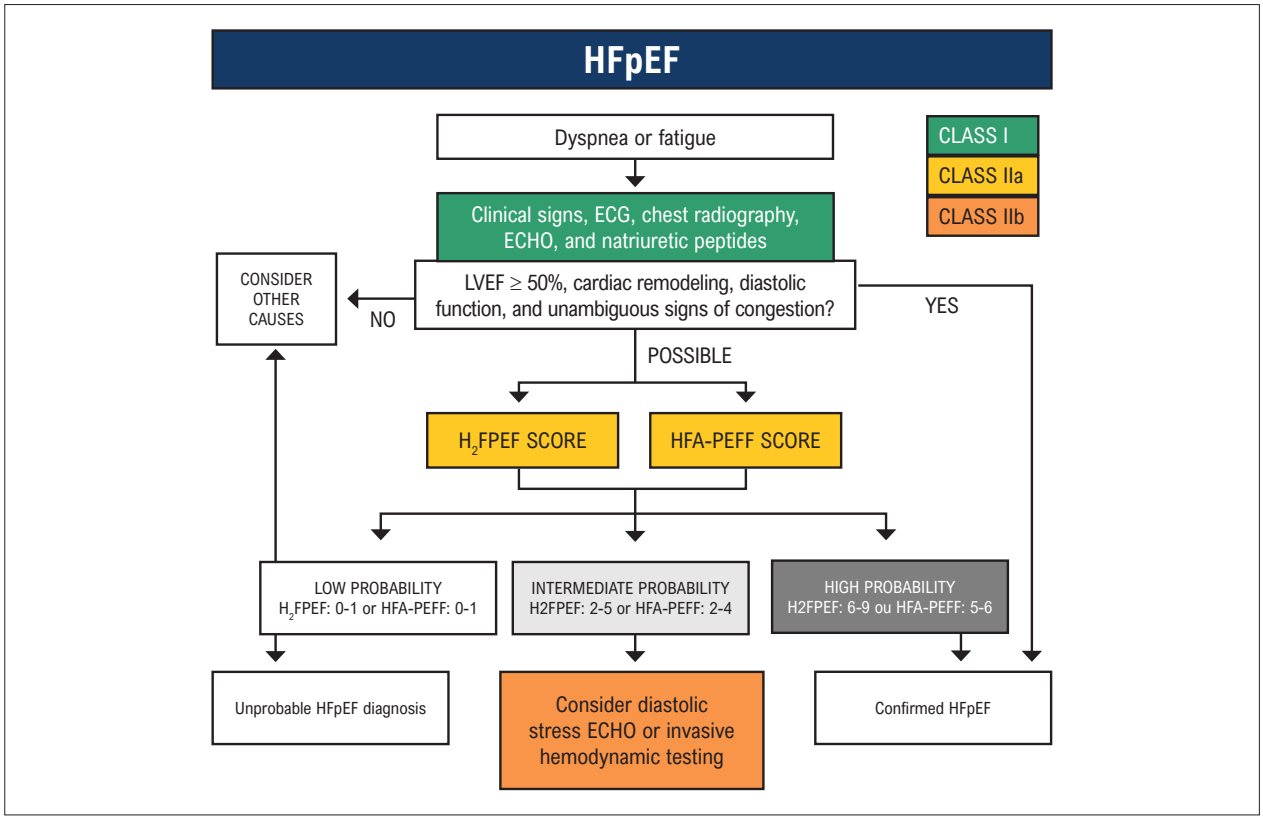

Figure 1 – *Brazilian Society of Cardiology guidelines for the diagnosis of heart failure with preserved ejection fraction (HFpEF).*[9]

Author Contributions

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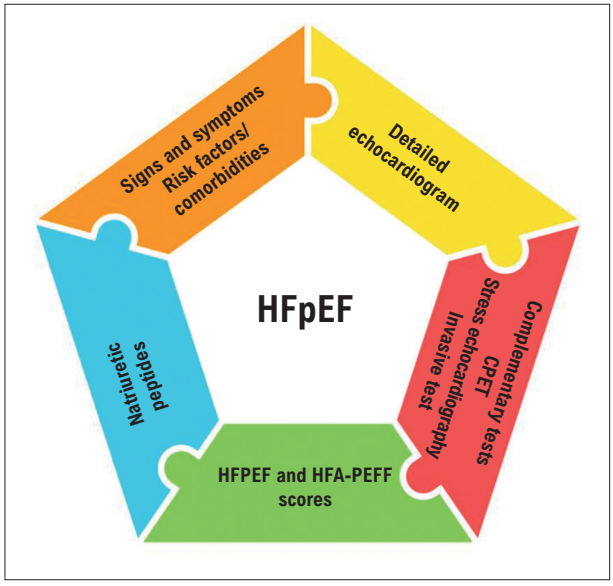

Figure 2 – *Simplified diagnosis of heart failure with preserved ejection fraction (HFpEF) in the office setting – assembling the puzzle; CPET: cardiopulmonary exercise testing.*

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When to Suspect Infiltrative or Storage Cardiomyopathy in Patients with HFpEF?

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Heart failure with preserved ejection fraction (HFpEF) is a frequent clinical syndrome, and it has accounted for 40% to 50% of heart failure hospitalizations in several reports published in the literature.[1,2] It is a distinctly heterogeneous syndrome, and, with this diversity of scenarios, patients with a restrictive cardiomyopathy phenotype have been increasingly identified, especially elderly patients with cardiac amyloidosis.

Restrictive cardiomyopathies are diseases of the heart muscle that can arise due to various etiologies, including genetic abnormalities, infiltrative diseases, and storage diseases. From a pathophysiological point of view, they have in common the fact that they cause an increase in ventricular rigidity. Their real prevalence is unknown, but they are considered the least common form of cardiomyopathies.[3] The infiltrative and storage diseases that can cause HFpEF include diseases with very different characteristics and evolution, such as amyloidosis, sarcoidosis, hemochromatosis, lysosomal disorders, and glycogen storage disorders.[4]

Reaching an etiologic diagnosis is a challenge, but the following clues should be followed during initial assessment:[5] (1) Age – The restrictive forms in young adults (< 30 years of age) are largely due to genetic abnormalities that lead to increased fibrosis and abnormal deposition of iron, proteins, or glycogen. When it occurs in the elderly (> 65 years), cardiac amyloidosis predominates. (2) Family history – Autosomal dominant inheritance pattern suggests hereditary transthyretin amyloidosis or sarcomeric mutations, whereas X-linked inheritance indicates Fabry disease. (3) Clinical evaluation – Neuropathy may be found, and it suggests amyloidosis, whereas the presence of lymphadenopathy may accompany sarcoidosis. Fabry disease, on the other hand, may lead to cutaneous, neurological, and renal manifestations; (4) Electrocardiogram – low voltage, pseudoinfarction pattern, bundle branch blocks, and atrioventricular block suggest amyloidosis or sarcoidosis.

Keywords

Cardiomyopathies; Diagnosis; Heart Failure, Diastolic

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Over time, the assessment of cardiomyopathy with non-invasive methods has been improving and contributing to the diagnosis of these diseases.[6] Figure 1 exhibits a proposal for a flowchart to be followed in patients with HFpEF and restrictive disease with the aim of facilitating the identification of patients with infiltrative and storage cardiomyopathy in this phenotype.

Transthoracic echocardiography represents the initial step in the diagnosis of HFpEF. In clinical scenarios where HFpEF presents with a restrictive pattern and increased left ventricular thickness, hypertensive heart disease and hypertrophic cardiomyopathy should be ruled out. In this scenario, infiltrative diseases grow in importance. Other findings in these patients include high filling pressures, normal left ventricular diameter, and highly dilated atria. Progressive atrial enlargement can lead to atrial arrhythmias and the development of secondary ventricular-atrial regurgitation. As a complement to echocardiography, cardiac magnetic resonance imaging stands out, with substantial added value for these diseases. Its image resolution more reliably defines the phenotype. Late enhancement obtained by means of gadolinium-based contrast can indicate alterations that are more suggestive of certain restrictive etiologies, differentiating them from constrictive pericarditis. Special sequences may even indicate the presence of myocardial edema and iron overload.[5,7] More recently, T1 mapping has made it possible to quantify diffuse interstitial fibrosis, in a manner that differentiates etiologies of infiltrative and storage cardiomyopathy (amyloidosis and Fabry disease, for example).[8,9]

The data obtained from imaging methods guide more specific tests, as follows: (1) pyrophosphate scintigraphy and/or biopsy studies for amyloidosis, (2) genetic tests for storage diseases, (3) positron emission tomography and biopsies for sarcoidosis, and (4) ferritin measurement and genetic testing for hemochromatosis.

Of all these diseases that can lead to myocardial restriction and, consequently, to HFpEF, cardiac amyloidosis is the one that stands out the most, and it warrants special attention. In 95% of cases, it is associated with deposition of transthyretin (ATTR) or light chains (AL). Currently, it is recognized that the ATTR form accounts for about 13% of HFpEF cases.[10] A similar prevalence has been found in patients with severe aortic stenosis.[11] It is believed that the presence of amyloidosis, which is often undiagnosed, is one of the factors responsible for continued failures in trials on the treatment of HFpEF.[12] The diagnosis of cardiac amyloidosis, like the other diseases mentioned, requires a high degree of suspicion. Left ventricular wall thickness > 14 mm in conjunction

with fatigue, dyspnea, or edema, especially in the context of discordance between left ventricular thickness on the imaging method and QRS voltage on the electrocardiogram, in addition to compromised left ventricular longitudinal strain with apical preservation on echocardiography are findings that strongly suggest the presence of this disease.[13] Magnetic resonance imaging has made it possible to increase diagnostic capacity by detecting the expansion of the myocardial interstitium, leading to the classic pattern of diffuse delayed enhancement of gadolinium.[5]

An approach to definitive diagnosis capable of differentiating between the two main types of cardiac amyloidosis (AL and ATTR) has recently been published in the position statement proposed by the Department of Heart Failure (DEIC, acronym in Portuguese) of the Brazilian Society of Cardiology (Figure 2).[14]

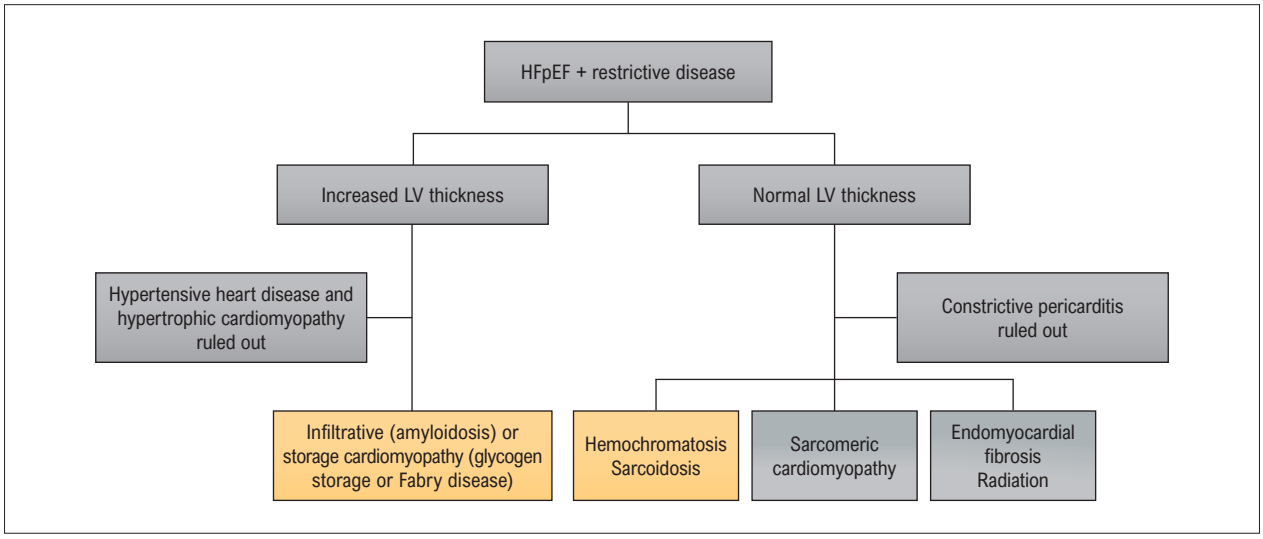

Figure 1 – *Flowchart for investigation of heart failure with preserved ejection fraction and restrictive disease. HFpEF: heart failure with preserved ejection fraction; LV: left ventricle. Adapted from reference.[6]*

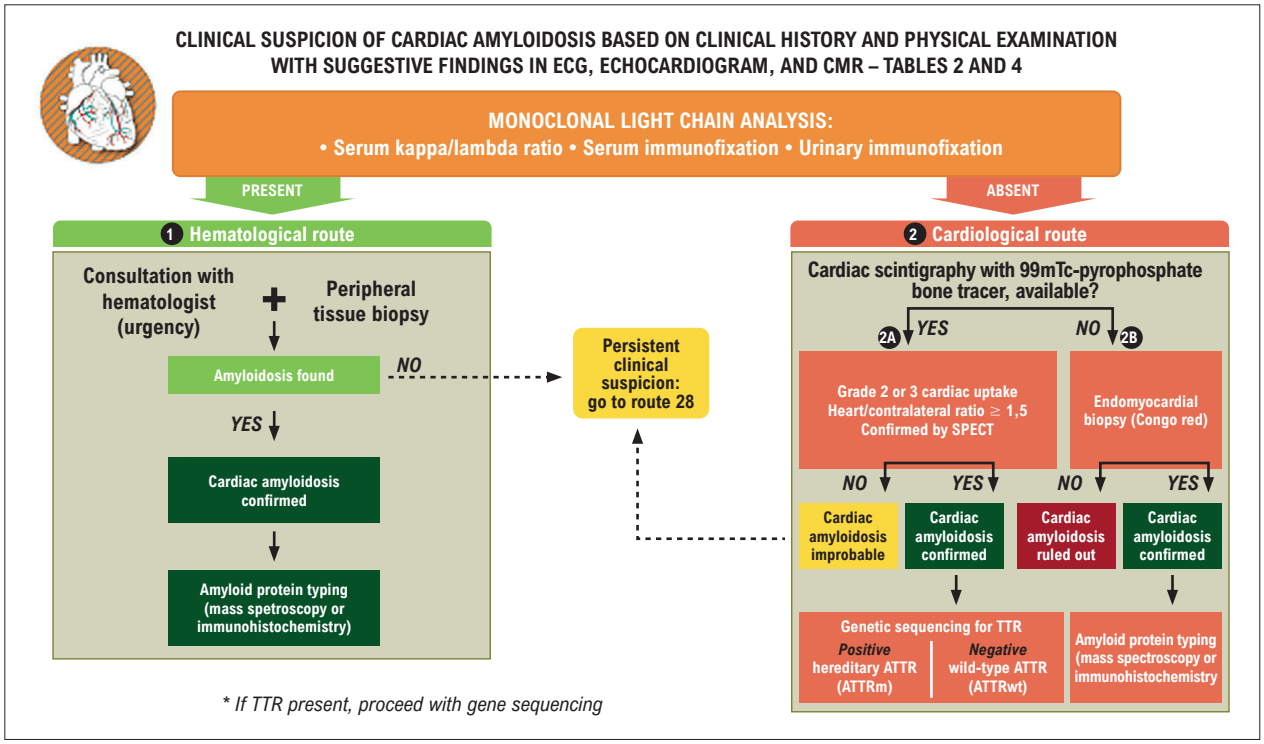

Figure 2 – *Flowchart for investigation of cardiac amyloidosis.[12]*

In conclusion, it is important to emphasize the investigation of specific phenotypes in patients with HFpEF, including infiltrative and storage diseases. Although some of these diseases are rare (Fabry, for example), others have established epidemiological relevance (such as amyloidosis), and it is fundamental to underscore that specific treatment alters the natural history of these patients.

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The Importance of Controlling Comorbidities in HFpEF and How They Influence Disease Evolution

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Heart failure (HF) is a disease with high morbidity and mortality in Brazil and in the world, and HF with preserved ejection fraction (HFpEF) accounts for more than half of cases. Effective pharmacological treatment options for HFpEF are scarce, with poor outcomes and an annual mortality of 10 to 30%. Mortality from noncardiovascular causes is high, which is to be expected given the high number of comorbidities[1] (Figure 1). The syndromic diagnosis is composed of several etiologies and diseases, each one with a specific treatment but with common aspects regarding clinical presentation.

An approach based on the different phenotypes of the disease was proposed, which comprises multiple situations experienced by the group of patients with HFpEF. Each phenotype is dependent on the different presentations of comorbidity severity, which constitutes a challenge for the definitive clinical diagnosis of HFpEF by a clinical cardiologist. Diagnostic scores with probabilistic models were developed to facilitate HFpEF diagnosis, using clinical, echocardiographic, and biomarker variables, such as B-type natriuretic peptide (BNP) and N-terminal portion of BNP. A more detailed description of the diagnosis is beyond the scope of this article.

The main comorbidities in HFpEF include systemic arterial hypertension (SAH), obesity, diabetes, atrial fibrillation (AF), chronic kidney disease (CKD), anemia, macro and microvascular coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and obstructive sleep apnea (OSA), among others. This population is composed of older patients with an elevated frailty index. Although comorbidities are similar between older patients with and without HFpEF, those with the disease have more symptoms, such as reduced cardiorespiratory fitness and higher rates of obesity. One of the most common symptoms of HFpEF is dyspnea during effort. However, symptoms of poor exercise tolerance are common among older patients and may reflect normal physiological changes related to aging or may be correlated with noncardiac etiologies. Patients with HFpEF commonly have poor quality of life, increased frequency of hospitalizations, and increased mortality, mostly from cardiovascular causes. Regarding drug treatment, the priority is to try to treat current comorbidities with effective therapies, such as renin-angiotensin-aldosterone system (RAAS) inhibitors, calcium channel blockers, aldosterone inhibitors, diuretics to reduce congestion, and, more recently, sodium glucose cotransporter 2 (SGLT2) inhibitors. Despite the available treatments, hospital readmission rates can reach 20% in 30 days and up to 50% in 1 year.

When treating specific comorbidities, the way they interact with HFpEF and with the treatment should be taken into consideration. SAH is one of the most common comorbidities in HFpEF and is closely involved in HFpEF development and progression. Changes in the ventricular wall, passive stiffness, ventricular-arterial coupling, systolic reserve, and chronotropic response occur.[2] SAH treatment is a cornerstone of HFpEF treatment and is associated with regression of left ventricular hypertrophy and improvement of diastolic function. Unfortunately, none of the therapies used to lower blood pressure resulted in reduced mortality in HFpEF.

Patients with HFpEF are 4.5 times more likely to develop COPD than age-matched controls. Patients with COPD have worse symptoms and a greater number of fatal and nonfatal outcomes independently.[3] Approximately 20% of patients with HF also have COPD and vice-versa. Importantly, the adequate treatment of one disease reduces the morbidity and mortality of the other.

Myocardial ischemia causes systolic and diastolic dysfunction and is part of the pathophysiology of HFpEF. A study with patients with HFpEF identified that most of them had chronic epicardial coronary disease, whereas more than 80% of the remaining patients had microcirculatory dysfunction, highlighting the high burden of unrecognized CAD in HFpEF. Results from the Prevalence of Microvascular Dysfunction in Heart Failure with Preserved Ejection Fraction (PROMIS-HFpEF) study showed a high prevalence of microvascular dysfunction in patients with HFpEF.[4] Myocardial ischemia without obstructive CAD in women increases the risk of major cardiovascular events.[5] Observational studies with patients with microvascular dysfunction have shown that long-term outcomes are marked by hospitalizations due to HFpEF.

In older people, the main clinical manifestation of HFpEF is exercise intolerance, usually of multifactorial cause, in which several comorbidities act together to trigger the clinical condition.[6]

Keywords

Comorbidity; Heart Failure; Hypertension

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Pulmonary hypertension is a very prevalent condition in HFpEF that remains without adequate treatment. Pulmonary vascular remodeling in advanced HFpEF was found to be very similar to vascular remodeling in pulmonary arterial hypertension.[7] Both diseases seem to arise at the peripheral level at the systemic and pulmonary vascular beds. At the vascular bed, remodeling is induced by reduced nitric oxide availability, whereas at the pulmonary level, the increased pressure results in vasoconstriction and reduced compliance, mediated by cyclic guanosine monophosphate reduction.[8]

Anemia occurs in approximately 50% of patients with HF, and lower hemoglobin levels are independently associated with decreased physical capacity, with consequent worsening of quality of life and increased adverse outcomes. In the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial, patients with anemia and HFpEF had higher levels of biomarkers (NT-proBNP), increased oxidative stress, and increased markers of necrosis. Iron deficiency and low ferritin values were associated with more severe left ventricular systolic dysfunction.[9]

Hypoxia-induced OSA stimulates the sympathetic nervous system and the RAAS as a result of alteration and oxidative stress, maintaining a systemic inflammatory state.[10] The final process pathway consists of alterations in collagen and cardiac titin, with the development of myocardial fibrosis and stiffening, leading to HFpEF progression. OSA treatment improved some surrogate outcomes, but there were no improvements in hard outcomes.[11]

Approximately 65% of patients with HFpEF have AF, and both conditions share similar risk factors. The worsening of left ventricular dysfunction is followed by remodeling and fibrosis of the left atrium, increasing the arrhythmogenic substrate.[12] Interestingly, the risk factors for HFpEF are identical to triggers of arrhythmia substrate. Atrial fibrillation increases the risk of readmission due to HFpEF.[13]

Obesity is very prevalent among patients with HFpEF. In the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) study, approximately 83% of patients were overweight or had obesity. The mechanisms proposed for patients with obesity include systemic inflammation, sodium retention, neurohormonal changes, and pulmonary hypertension. Proper diagnosis of HFpEF in euvolemic patients with obesity and unexplained dyspnea is difficult, especially because natriuretic peptides levels may be low and the echocardiographic window may be of poor technical quality in this group.

The paradox of obesity leading to a reduced risk of adverse events is debatable[14] and could be better assessed if waist circumference, which is a more direct marker of central adiposity, was used instead of body mass index in HFpEF with obesity.

Diabetes is a highly prevalent comorbidity, affecting 45% of patients with HFpEF. This group of patients often has more congestion and worse renal function, with an inadequate response to diuretics, elevated inflammatory markers, and an increased readmission rate within 30 days. New studies of diabetes and HFpEF have shown important results in hard outcomes, especially with the use of SGLT2 inhibitors.[15]

Renal dysfunction may trigger HFpEF. Approximately 50% of patients with HFpEF have CKD. Patients with CKD have impaired levels of diastolic function compared with those without CKD. A meta-analysis of more than 1 million patients with established HF reported higher rates of mortality among patients with HFpEF and CKD than among patients with HF with reduced ejection fraction and CKD. The opposite is also true: increased filling pressures and reduced cardiac output increase central venous pressure, leading to reduced renal flow and consequent worsening of renal function.[16] The good outcomes of SGLT2 studies, with improvement of renal function and HF, promote the possibility of a joint treatment for these conditions for the populations in question.

The lack of a HFpEF diagnosis is related to poor knowledge, uncertainty about pathophysiology and treatment, and more specific diagnostic criteria. Understanding the actual pathophysiological aspects of the disease, with a focus on optimizing the treatment of comorbidities, should significantly improve disease outcomes.

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Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Hoffmann Filho CR, Duraes AR, Erzinger GS.

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Ethics approval and consent to participate

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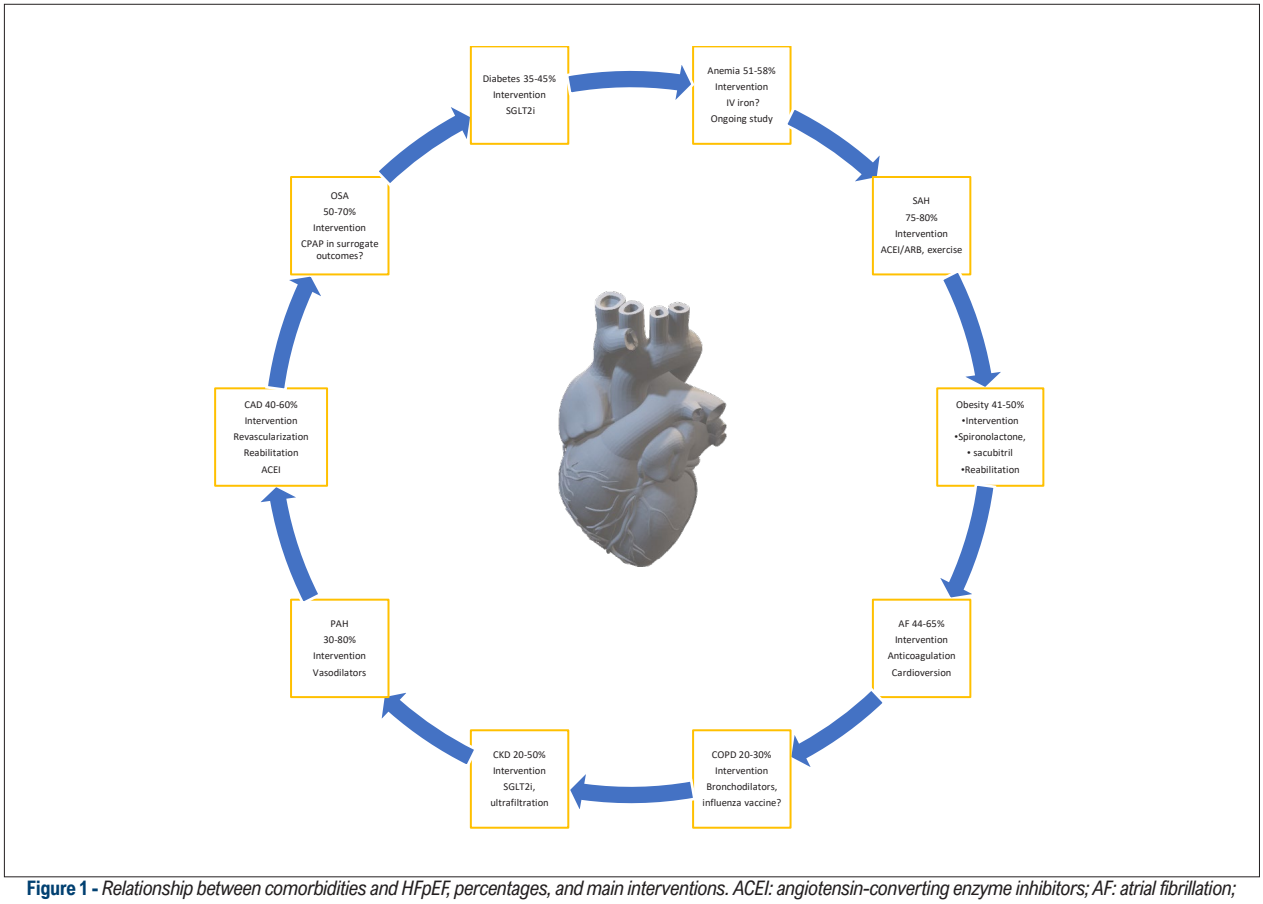

Figure 1 - *Relationship between comorbidities and HFpEF, percentages, and main interventions. ACEI: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARB: angiotensin receptor blockers; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea; PAH: pulmonary arterial hypertension; SAH: systemic arterial hypertension; SGLT2i: sodium-glucose cotransporter 2 inhibitors.*

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HFpEF: Evidence from Recent Clinical Trials and New Perspectives

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Heart failure (HF) is a highly prevalent clinical syndrome affecting more than 10% of the population older than 70 years of age, with a great impact on morbidity and mortality.[1,2] HF is traditionally divided into three categories based on the left ventricular ejection fraction (EF): HF with reduced EF (EF<40%; HFpEF), HF with intermediate EF (EF between 40% and 49%; HFiEF) and HF with preserved EF (EF>50%; HFpEF).[3]

HFpEF represents nearly half of HF cases in developed countries; its pathophysiology is complex and still little understood.[4] The great variety of HFpEF phenotypes, makes its diagnosis and treatment challenging. Unlike HFrEF, before the emergence of SGLT-2 inhibitors, no treatment had been shown effective in reducing the hard outcomes in HFpEF.[5] Also, the wide variability in diagnostic criteria of HFpEF adopted in different clinical trials may have contributed to the difficulty in showing therapeutic effectiveness in reducing mortality.

HFpEF accounts for more than 50% of all cases of HF and is associated with considerable mortality and morbidity.[6] The prognosis of HFpEF patients is dismal, with a one-year mortality rate of 10-30%.[7] The diagnosis is more difficult as compared with HFrEF, since several mechanisms have been implicated in its pathophysiology. Patients with HFpEF, when compared with HFrEF patients, are usually older, of female sex, and have comorbidities such as arterial hypertension, atrial fibrillation, pulmonary hypertension, diabetes mellitus, chronic renal disease, among others. The European Society of Cardiology guidelines recommended three criteria for the diagnosis of HFpEF – signs and symptoms of HF, LVEF ≥ 50%, increased natriuretic peptides and relevant structural heart disease and/or evidence of diastolic dysfunction.[3] However, despite these recommendations, due to the lack of pathognomonic criteria, there are still many uncertainties in the diagnosis of HFpEF.[8]

Several clinical trials have examined the use of proven-effective drugs in HFrEF. However, before the first results of studies on SGLT-2 inhibitors, all clinical trials had failed to demonstrate the benefits of pharmacological treatments in mortality and morbidity. The CHARM-Preserved trial showed that candesartan had an impact in preventing admissions for chronic HF but had no impact in reducing cardiovascular death compared with placebo.[9] Similarly, the PEP-CHF evaluated the effect of perindopril in HFpEF patients and did not show any significant difference in mortality or hospitalization.[10] The study suggested, however, improvement in symptoms and exercise capacity and fewer hospitalizations for HF with perindopril. In the I-PRESERVE, irbesatan did not improve the outcomes of mortality, hospitalization or quality of life.[11] The TOPCAT trial demonstrated that spironolactone significantly reduced hospitalizations for HF. However, a post-hoc analysis revealed that this benefit was more pronounced in the Americas (the United States, Canada, Brazil, and Argentina), while no significant differences were observed in Russia or Georgia.[12] Given the divergence of results between populations, issues about the homogeneity of patients, and likely randomization of less severe patients in the east European countries were raised. Results of the PARAGON HF[13] trial revealed a trend, but not significant, of reduced risk of hospitalization for heart failure or death with the use of the angiotensin receptor–neprilysin inhibitor (ARNI). A subgroup analysis, however, suggested benefit in patients with an EF between 45 and 57% and in women.[13] An interesting subanalysis of this population showed that the presence of HF signs and symptoms, particularly orthopnea and rales, were correlated with a higher risk for adverse CV events in patients with HFpEF.[14] Another important finding was a better blood pressure control in HFpEF patients and resistant hypertension treated with sacubitril–valsartan.[15] This result is particularly important considering the high prevalence of hypertension HFpEF and a close relationship between these clinical conditions.

A meta-analysis of 14 studies with a total of 19,573 demonstrated that none of the drugs tested significantly reduced mortality. However, ARNI and angiotensin converting enzyme inhibitors (ACEIs) were associated with a lower risk of hospitalizations in HFpEF patients (hazard ratio [HR] 0.73, 95%CI 0.60–0.87 and HR 0.64, 95% CI 0.43–0.96, respectively), and ARNIs were superior to angiotensin receptor blockers (ARBs) in reducing admissions for HF (HR 0.80, 95% CI 0.71–0.91).[16] Another meta-analysis including five studies corroborated this hypothesis – the study evaluated different renin-angiotensin-aldosterone system (RAAS) inhibitors and did not find statistically significant differences in cardiovascular mortality between the drugs. Also, ARNI was more effective in reducing hospitalizations compared with the other RAAS inhibitors.[17]

Despite the adoption of a LVEF ≥ 50% for the diagnosis of HFpEF, patients with a LVEF in the range of 40-49% have been included in these studies, which leads to a methodological

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Heart Failure; Stroke Volume; Mortality

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limitation. Different classifications have been proposed and several inclusion criteria have been used in the clinical trials over the years, contributing to a high heterogeneity of the studied populations.[1,5]

The discrepant results among the clinical trials could be explained by differences in the standardization of LVEF in randomized patients and in atrial natriuretic peptide (BNP) cut-offs used in the studies. These frustrating results call attention to the fact that the known effects of the RAAS blockade and beta-adrenergic blockers in reducing mortality and morbidity in HFeEF have not been demonstrated in HFpEF.

Nevertheless, the heterogeneity of clinical, morphometric and laboratory data of these studies, in addition to the lack of well-established diagnostic criteria of HFpEF stresses the need of establishing stricter inclusion criteria in HFpEF studies addressing not only clinical but also morphological and neuro-humoral aspects.

Throughout this long journey in search of pharmacological interventions, recent studies that tested sodium-glucose cotransporter-2 (SGLT2) inhibitors have generated great enthusiasm in the treatment of HF, as these medications reduced both cardiovascular death and hospitalization for HF in both HFrEF and HFpEF. The first clinical trial on this drug class was the EMPEROR Preserved, that included patients with EF > 40% and NT-proBNP ≥ 300 pg (≥ 900 pg in patients with atrial fibrillation) and showed the superiority of empagliflozin versus placebo. The primary outcome (cardiovascular death or hospitalization for HF) occurred in 415 (13.8%) of patients in the empagliflozin group vs 511 (17.1%) patients in the placebo group, *i.e.*, 6.9 vs. 8.7 events per 100 patient-years; (hazard ratio, 0.79; 95% CI, 0.69 – 0.90; p<0.001). The secondary outcome, hospitalization for HF, occurred in 8.6% in the empagliflozin group and in 11.8% in the placebo group (p<0.001).[18] Subgroup analyses showed that patients aged older than 70 years and NYHA functional class II seemed to respond better to therapy. Results of the DELIVER trial were recently published; the study compared the effects of dapagliflozin with placebo in 6263 patients with HF and mildly reduced LVEF (40-49%) or HF with LVEF < 40% (recovered HF), with median NT-proBNP of 1011pg/mL. Patients were randomly assigned to receive dapagliflozin (at a dose of 10 mg once daily) or placebo. The primary outcome was cardiovascular death or worsening HF (hospitalization for HF or an urgent visit for HF). After a median follow-up of 2.3 years, dapagliflozin reduced the primary outcome by 18%; it occurred in 16.4% in the dapagliflozin group and 19.5% in the placebo group; HR 0.82; 95%CI 0.73-0.92; p < 0.001). When the components of the primary outcome were analyzed individually, the benefit was mostly due to the reduction in worsening HF (HR 0,79; IC 95% 0,69-0,91), 0.88; 95% CI, 0.74 to 1.05). In addition, individuals treated with dapagliflozin showed an improvement in quality of life (Kansas City Cardiomyopathy Questionnaire). There was no increase in the incidence of adverse events (acute renal failure, hypoglycemia, or volume depletion) with dapagliflozin. The results of the primary outcome were consistent among the subgroups, including patients with and without diabetes, patients with EF greater or lower than 60%, and even in those with recovered EF.[19]

A recently published, pre-specified meta-analysis of the DELIVER and the EMPEROR-Preserved trials, with data of the 12251 participants of these studies, showed that SGLT2 inhibitors reduced the composite outcome of cardiovascular death or first hospitalization for HF in 20% (HR 0.80 [95%CI 0.73-0.87]), with a decrease in both components: cardiovascular death (0.88 [0.77–1.00]) first hospitalization for HF (0.74 [0.67–0.83]). These data reflect a change of paradigm in the treatment of HFpEF, in which, for the first time, significant reductions in mortality or hospitalization were observed in HFpEF.

Altogether, the studies evaluating the use of SGLT-2 inhibitors in HF, in a continuous spectrum of EF, have suggested a reduction in the risk of cardiovascular death and hospitalization for HF in a wide range of patients. Such benefit in the continuum of EF contributes to the understanding of common pathophysiological mechanisms in different phenotypic profiles.

In conclusion, SGLT-2 inhibitors have emerged as a new therapeutical option in HF, an alternative to the well-known, gold standard triple therapy. In addition to reducing hard outcomes, SGLT-2 inhibitors improved the quality of life of HF patients and become a mandatory therapeutic approach in this population.[20]

With the increasing understanding of the pathophysiology of HF and targeting several steps in the neurohumoral and inflammatory pathways, many molecules have been tested in robust clinical trials. These molecules include mineralocorticoid antagonists, single- and dual-acting glucagon-like peptide-1 (GLP-1), and inflammatory markers. It is hence expected that advances in the blockade of the complex mechanisms involved in HFpEF will reduce the morbidity and mortality of HFpEF and its increasing prevalence.

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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: Saraiva JFK, Moraes NR.

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Lessons from the EMPEROR Preserved

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In randomized clinical trials, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been shown effective in reducing the risk of cardiovascular (CV) death and hospitalization for chronic heart failure (CHF), as well as renal outcomes, regardless of the presence of diabetes. Despite these findings in patients with heart failure (HF) with reduced ejection fraction (EF) (HFrEF), retrospective subanalyses of patients with type 2 diabetes have suggested that many of preventable events have occurred in patients with a left ventricular (LV) EF (LVEF) greater than 40%.[1] In this regard, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) was carried out to evaluate the safety and efficacy of empagliflozin in patients with HFpEF. A total of 5988 patients with LVEF > 40% were randomized (Empagliflozin or placebo) and followed up for a median of 26.2 months; 45% of participants were women, symptomatic, with class II–IV heart failure, one hospitalization in the last year and N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels of more than 300 pg/mL if in sinus rhythm or > 900 pg/mL if in atrial fibrillation NT-PRO-BNP. The primary outcome – composite outcome of CV death or hospitalization for heart failure (HF) – occurred in 13.8% in the empagliflozin group and in 17.1% in the placebo group, with a hazard ratio of 0.79; 95% confidence interval (CI) of 0.69 to 0.90; p<0.001. No significant difference was found in CV death (HR 0.91, 95%CI 0.76-1.09), but a significant difference was observed in hospitalization for HF (HR 0.71, 95%CI 0.60-0.83), regardless of the presence of diabetes. However, this beneficial effect of empagliflozin was not detected in patients with EF>60% (HR 0.87, 95%CI 0.69-1.1) in a subgroup analysis and its limitations.[2]

When the outcomes were stratified by EF, 33% of patients had EF between 41 and 49% and the others an EF>50%. No difference in the effect of the medication was seen between patients with EF > 50% and patients with EF<60% or 41-49% (Table 1). Empagliflozin was superior to placebo in improving the combined outcome regardless of the presence of diabetes in patients with HFpEF. The effect was strengthened especially by the reduction in hospitalization for CHF rather than in CV mortality, which seems to be independent of baseline EF, even among patients with EF between 50% and 60%.[2] With these results, empagliflozin was approved for the treatment of patients with this profile, and generated enthusiasm in the scientific community. Previous medications such as candesartan, spironolactone and sacubitril-valsartan have shown no or modest beneficial effect, and predominantly in populations with lower EF.[3]

Although the mechanism of action of empagliflozin has not been elucidated, the marked reduction in hospitalizations for a condition with an increasing incidence in the world and high health care costs in public and private services seems quite relevant. Another issue to be discussed is the historical classification of CHF by EF cut-offs. Comparison of studies using different medications has shown that different ranges of EF are associated with distinguishable responses to the drugs; while in the lower strata (HFrEF) a reduction in mortality stands out, in the higher strata (HFpEF) a reduction in hospitalization is predominant.

When these data are put into perspective, despite potential differences between populations and outcomes, there are three main trials that evaluated the classes of drugs used in the treatment of HFpEF: the PARAGON[4] (neprilysin inhibitors), the EMPEROR-Preserved[2] (SGLT2i) and the TOPCAT[5] (mineralocorticoid receptor antagonists). In the PARAGON-HF[4] (patients with EF>45%), no benefit was found for the combined outcome, for hospitalization or for CV death. Analysis of subgroups raised the hypothesis, to be confirmed, that the composite outcome of hospitalization and CV death would be reduced by sacubitril–valsartan in the EF <57% stratum and in women. This hypothesis was also suggested by an exploratory analysis of the pool of patients of the PARAGON-HF and PARADIGM-HF trials. In the TOPCAT trial (patients with EF > 45%), spironolactone was shown to have a modest effect on hospitalization for HF, which was a component of the primary outcome, together with CV death and aborted cardiac arrest. There was a higher incidence of hyperkalemia and increased creatinine levels. A subgroup analysis (without an interaction test) suggested that patients with EF lower than the median (but not lower than 50%) would benefit the most from the drug.

Despite the differences for the outcome hospitalization for IC, exploratory and subgroup analyses that need confirmation, suggest the hypothesis that patients with EF between 40% and 60% would benefit from sacubitril-valsartan or spironolactone. However, so far, empagliflozin was the only medication that has been shown to reduce hospitalization for HF both in patients with EF ≤40%

Keywords

Heart Failure; Diastolic Heart Failure; Cardiovascular Diseases

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Table 1 – Results of empagliflozin by ejection fraction strata

Outcome	% of events with empagliflozin EF ≥50%	% of events with placebo EF ≥50%	p	% of events with empagliflozin EF 41-49%	% of events with placebo EF 41-49%	p	Interaction p-value
Combined	6.7%	8.0%	0.02	7.2%	10%	0.002	0.27
All cause-mortality	6.1%	6.1%	0.84	7.7%	8.0%	0.72	> 0.05
Total hospitalization rate	4.5%	5.7%	0.013	3.8%	6.5%	<0.001	0.06
Quality of life (KCCQ)	4.24	2.78	0.006	4.86	3.3	0.043	0.92

EF: ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire; data extracted from the Emperor-Preserved[2]

and in patients with EF >40%, as reported in the EMPEROR-REDUCED and EMPEROR-PRESERVED studies, respectively. These results give rise to discussion about patient classification based on EF cut-offs and creates an evidence gap for the subgroup of patients with EF>60%, in which the benefits obtained in the subgroup analysis are not maintained.[6,7]

In conclusion, although the mechanism of action of SGLT2i are not fully understood, these drugs reduce hospitalizations for HF regardless of the presence of diabetes and apparently of EF also. Among the therapeutic options available, this class of drugs seems to offer the greatest benefit. Nevertheless, unanswered questions remain, like how and when will medications that effectively affect CV and all-cause mortality in HFpEF patients be available, and why apparently none of these medications are effective in patients with EF>60%.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Lima IGC

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