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REVIEW ARTICLE

Phenotype mapping of heart failure with preserved ejection fraction

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Abstract

Heart failure with preserved ejection fraction (HFPEF) has become the main phenotypic model of heart failure (HF) in community and referral patients in Brazil and in the world. Despite advances in the development of new drugs for HF treatment, there has been no significant improvement in mortality of this condition.

According to many studies, this can be explained by the heterogeneous nature of HF physiopathology, whose basic mechanisms may result in different clinical presentations, culminating in the emerging of different phenogroups in this syndrome. In this context, phenotype mapping of HFPEF has emerged as a possible solution, since it enables the development of clinical trials that establish specific therapeutic strategies for each phenotypic profile.

New technologies in the field of artificial intelligence have enabled the assessment of a large volume of data and infer intrinsic patterns and different outcomes. Thereby, it is possible to obtain mutually exclusive categories of HFPEF, with a phenotype mapping of the syndrome and grouping of patients according to their phenotypic features. Besides, other diseases can have the same clinical phenotype but different pathophysiological basis, the so called "phenocopies".

These tools enable the analysis and categorization of the wide spectrum of heart failure, contributing to solve the dilemmas of the treatment of this syndrome.

Introduction

Heart failure with preserved ejection fraction (HFPEF) has become the main phenotypic model of heart failure (HF) in community and referral patients in Brazil and in the world.[1,2]

Only two forms of clinical presentations of HFPEF used to be recognized – first, in the outpatient setting, elderly women patients, intolerant to exercise, usually with no clinical evidence of congestion;[3,4] and second, patients admitted to emergency departments with hypertensive crisis, acute atrial fibrillation and acute pulmonary edema.[5]

Clinical profiles of HFPEF have been gradually identified. For example, HFPEF has been associated with pulmonary arterial hypertension and valve diseases – aortic stenosis, mitral stenosis – and deposition diseases, such as senile amyloidosis.[6,7]

In the last decades, progresses have been made in the understanding of pathophysiological mechanisms involved in HFPEF and the influence of comorbidities in the development and progression of the disease. In addition to diastolic dysfunction, abnormal chronotropic response, left atrial dysfunction, and altered physiology of coronary endothelium and systemic and pulmonary microcirculation have been reported. Molecular changes related to oxidative stress and a proinflammatory state have been also described, and seem to be associated with aging, hypertension, obesity and other cardiovascular and non-cardiovascular diseases.[8,9]

Despite advances in the study of HFPEF pathophysiology and development of new drugs, there has been no significant improvement in mortality or clinical outcome of this condition.[10]

A new discipline – phenomics – involving bioinformatics and artificial intelligence (machine learning) has been increasingly used for the study of phenotypes, including many areas of clinical medicine. More recently, it has been applied in cardiology for the study of HFPEF. Application of objective methods for identification of phenotypes goes in line with precision

Keywords

Heart Failure / physiopathology; Stroke Volume; Phenotype; Machine Learning; Artificial Intelligence.

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medicine, a new paradigm that has been successfully used in oncology. This approach considers genetic variability, environment, and lifestyle of each patient, allowing an individualized approach for the treatment and prevention of diseases.[11-13]

The aim of the present study was to present a narrative review of the literature to describe the clinical phenotypes of HFPEF and its potential impact on the management of patients and on clinical research.

Methods

Bibliographic review

We conducted a narrative review, from a clinical perspective, of studies published in MEDLINE using the PubMed search engine. The following MeSH (Medical Subject Heading) terms were used - (heart failure with preserved ejection fraction [tiab] OR diastolic heart failure [tiab] OR hfnef [tiab] OR hfpef [tiab]) AND (phenoc* [tiab] OR phenotype* [tiab]).

The search was carried out in February 2017, and 136 articles published in the period from 1990 and 2017 were identified. Thirty articles were independently selected by four investigators for detailed analysis. Additional articles were selected from the reference lists of the retrieved articles.

Pathophysiology of HFPEF

Heart failure (HF) is a complex clinical syndrome characterized by symptoms and signs caused by abnormal cardiac function and/or structure that leads to decreased cardiac output and/or increased intracardiac pressures.

HF patients can have different phenotypes according to morphofunctional characteristics of the disease, and receive different therapeutic approaches.[14,15] Based on this, patients are usually classified into patients with HF with reduced ejection fraction (HFrEF), marked by left ventricular ejection fraction (LVEF) lower than 40% - and HF with preserved ejection fraction (HFpEF), characterized by LVEF greater than 50%. Recently, the European Society of Cardiology has proposed a new phenotype – "HF with midrange ejection fraction" – with intermediate ejection fraction (LVEF between 40 and 49%) and a clinical profile different from HFeEF and HFpEF.[16]

The main diagnostic criteria of HFPEF – the focus of this study – are the clinical profile of LVEF equal to or greater than 50%, increased levels of brain natriuretic peptide (BNP) (greater than 35pg/mL or NT-proBNP greater than 125 pg/mL) and at least one of these two criteria – important structural cardiac disease (left ventricular hypertrophy and/or increased left atrium) and diastolic dysfunction.[16]

HFPEF is characterized by reduced end-diastolic volume, left ventricular hypertrophy, and increased left atrial volume and left ventricular filling pressure. These pathophysiological abnormalities are associated with increased left ventricular stiffness, decreased left ventricular relaxation, cardiomyocyte hypertrophy, myocardial interstitial fibrosis and reduced intramyocardial capillaries.[17-19] In addition, a proportion of patients with HFpEF present atrial fibrillation, which further aggravates cardiac function.[20]

The classical presentations - HFeEF and HFpEF – used to be distinguished only by the remodeling pattern of cardiac chambers and extension of myocardial dysfunction, culminating in different therapeutic responses. However, it is known today that morphofunctional changes are also based on molecular alterations, which are also different between these conditions.[10]

Left ventricular diastolic dysfunction, an important diagnostic criterion for HFPEF, may be explained by increased myocardial stiffness, resulting from changes in extracellular matrix and/or cardiomyocytes.[10] There are evidence that extracellular matrix stiffness results mainly from collagen metabolism. Excess deposition of type I collagen, the subtype with the highest stiffness property, is explained by increased synthesis and/or decreased degradation of this compound. Type I collagen synthesis can be measured by procollagen type I carboxy-terminal propeptide, which derives from type I procollagen and acts as a biomarker. Decreased degradation of type I collagen is caused by downregulation of matrix metalloproteinases (MMPs) and/or upregulation of tissue inhibitors of metalloproteinases (TIMPs). TIMP-1 plasma levels have also been suggested as promising biomarkers in HFPEF.[9,10]

Excess collagen is found in only one third of patients with HFPEF, even in the presence of ventricular stiffness, which usually results from an intrinsic cardiomyocyte condition, and may be related to the protein structure and/or to the disruption of the sarcomere structure.[9,10]

Cardiomyocyte structure depends directly on regulation of constituent proteins, and myocardial stiffness may indicate an unbalance in this process. One of the main proteins involved in this regulation is titin, an elastic constituent protein of cardiomyocytes, with two isoforms

- N2B (stiffer) and N2BA (more compliant). Changes in the ratio of one isoform to the other and phosphorylation of the fibers, as well as oxidative stress can have an impact on myocardial compliance, leading to stiffness.[9,18]

Disruption of sarcomere structure is the mechanical factor of ventricular relaxation. It is an energy-consuming reaction, and, for this reason, the lack of energy stores impairs a normal left ventricular relaxation. Recent studies have demonstrated a decreased phosphate creatinine/adenosine ratio in patients with HFPEF, which is consistent with a decline in myocardial energy store.[21-23]

In addition to interstitial (collagen-related changes) and structural (regulation of constituent proteins) changes, unbalanced levels of chemical mediators, especially of monophosphate cyclic guanine (cGMP), may also explain myocardial stiffness in HEPEF. Activation of protein kinase G (PKG) by cGMP results in phosphorylation cascade of proteins important for cardiomyocyte integrity – phosphorylation of titins inhibits cardiac hypertrophy and increases myocardial compliance, phosphorylation of potassium channels inhibits tissue ischemia, and phosphorylation of troponin I increases left ventricular relaxation. Also, PKG activation by cGMP increases calcium reuptake by sarcoplasmic reticulum.[9]

Low BNP, microvascular inflammation and oxidative stress, which are common in several conditions, such as obesity and insulin resistance, suppresses GMPc synthesis pathways. This, in turn, inhibits PKG phosphorylation cascade and culminates in myocardial stiffness, characteristic of HFPEF.[8,9]

Although HFPEF is commonly referred as diastolic HF, the disease is not limited to ventricular relaxation problems. A study[24] demonstrated that myocardial contractility may be decreased in HFPEF, even if the end-systolic elastance (ESE) – used to measure myocardial contractility – is increased.[24] This apparent contradiction may be explained by the influence of cardiac chamber geometry on ESE. Concentric hypertrophy, characteristic of HFPEF, independently increases ESE, even with reduced left ventricular contractility.[21]

In HFPEF, vascular stiffness is generalized, resulting in elevated pressure, which aggravates ventricular stiffness and attenuates vascular dilation in exercise, thereby decreasing blood supply to musculoskeletal system. Increased vessel stiffness, associated with elevated left heart pressure, increases pulmonary pressure and consequently the mortality of these patients.[21]

Defects in diastolic, systolic, vascular and chronothropic functions elucidate the heterogeneous nature and complexity of HFPEF. Its multiple pathophysiological factors indicate the need of phenotyping of these patients, and identification of specific causes of the worsening of each phenotype. This strategy has become increasingly possible with biomolecular advances in medicine and will possibly guide therapeutic decisions based on specific pathophysiological changes.

Modulation of HFPEF phenotypes by epigenetics – a new frontier

Epigenetics is an emerging science involving the study of changes in the regulation of genes and their expression, regardless of their sequences. Environmental factors can affect intracellular signaling pathways in a way that can affect chromatin structure, resulting in the passage of altered gene expression patterns to the offspring by epigenetic memory, affecting the phenotypes of the diseases.[25,26]

New evidence suggests the involvement of epigenetic regulation in target cells related to cardiovascular pathogenesis, including HF and its different phenotypes.[27] Cardiomyocytes, for example, can adapt to environmental stress by epigenetic regulation. This dysregulation in genetic expression provides information about the pathogenesis of cardiac and vascular remodeling, dysfunction of progenitor cells and endogenous repair system, inflammation, fibrosis and cardiac dysfunction.[28,29]

Four epigenetic mechanisms in cardiovascular diseases have been identified – DNA methylation, chromatin remodeling by adenosine triphosphate (ATP)-dependent enzymes, histone modification and microRNA-dependent mechanisms.[30-32] Recent findings have associated these mechanisms with HFPEF-related diseases; however, evidence on the role of epigenetics in changes in cardiac function and structure, and clinical trials corroborating theories involving both epigenetics and cardiovascular disease are still lacking. Advances in studies on this field should contribute to HF prevention and provide enough evidence for the stratification of HF phenotypes.

Clinical phenotypes and phenotypic mapping

Current phenotyping tools combined with advances in genetics and systems biology have the potential to improve the classification of complex, heterogeneous systems, such as HFPEF. Analysis of patients' data aiming to establish a pattern of these variables may be performed

by machine learning algorithms. Machine learning is a field of artificial intelligence, in which a computer is programmed to learn the relationship between the objects of study by data processing and accumulate experience with previous problem-solving approaches. Machine learning algorithms are classified into supervised and unsupervised. While supervised learning is focused on outcome prevention, unsupervised learning aims to infer intrinsic structures of the data.

Therefore, in this approach, a large volume of data can be analyzed and mutually exclusive categories of HFPEF can be obtained by phenotype mapping of the syndrome and grouping of patients in subgroups according to phenotypic characteristics. Phenotypic classification of patients with HFPEF would be helpful to the development of clinical trials on therapeutic strategies specific to each phenotypic profile.[12]

A recent study was the first to identify phenogroups of a heart disease, and the first to use the machine learning technique as an approach to solve the heterogeneity of a cardiovascular syndrome by phenotype analysis.[33]

The data analyzed for patients' classification using the machine learning approach included clinical variables, physical features, laboratory data and electrocardiogram and echocardiogram parameters.

Although the patients shared many clinical characteristics, they were classified in three subgroups with distinct characteristics and prognosis:[33]

• Group 1, composed of younger patients, with moderate diastolic function and relatively normal BNP levels. These patients have the mildest myocardial remodeling, electrical dysfunction and hemodynamic change, although 65% of them had moderate diastolic dysfunction and elevated pulmonary capillary pressure (PCP) and pulmonary artery systolic pressure.

• Group 2 involved obese, diabetic patients, with a high prevalence of sleep apnea and impaired left ventricular relaxation. This group showed the highest PCP and highest pulmonary vascular resistance.

• Group 3 was composed of older patients, with significant chronic kidney disease and pulmonary hypertension. In this phenogroup, a more severe myocardial remodeling and electric dysfunction was observed, with a longer QRS-T interval, higher relative thickness of cardiac walls, higher left ventricular mass index, higher E/e' ratio and worse right ventricular function.[33]

In addition, different phenogroups had different clinical course and outcomes, and distinct risk stratification. Prognosis was divided into the following categories: death, hospitalization for non-cardiac causes, hospitalization for cardiac causes, and hospitalization for HF. In group 1, the most frequent prognostic factors were hospitalization for cardiovascular and hospitalization for non-cardiovascular diseases; in group 2, hospitalization for non-cardiovascular causes and HF, and in group 3, the most prevalent outcome was death, followed by hospitalization for HF.[33]

However, although ideally the subgroups should be mutually excluding, some patients had overlapping clinical features, especially in the analysis of group 1 patients (Figure 1). Even so, this was a pioneer study in the phenotyping of complex cardiovascular syndromes.[33]

In light of the above, one may infer that the use of the machine learning tool in international centers would provide new, essential information on HFPEF epidemiology.

Considering that this study was conducted in a North American setting,[33] it is expected that results observed in the subgroups are different from those in South America. Therefore, application of the technique in Latin American prevalence studies is paramount for future phenotype mapping of HFPEF in Brazil.

Treatment

Classical therapeutic approach of HFPEF has not reduced mortality and morbidity rates of these patients. Thus, considerable differences between the phenogroups indicate the importance of a specific therapeutic approach, since advances in therapies have been so far hampered by such phenotypic complexity. To deal with that, new therapies that have a direct effect on signaling cascades involved in the pathophysiology of the HFPEF have been proposed.[34,35] Today, these therapies varied from signaling pathways of systemic inflammation to myocardial elasticity, and additional therapies to different comorbidities associated with the same pattern of phenotypic predisposition to the disease.

Aging, obesity, systemic hypertension, type 2 diabetes mellitus, kidney failure, and sleep apnea can trigger a chronic systemic inflammation that affects the myocardium and other organs. The patient may have pulmonary hypertension, sodium retention and impaired oxygen extraction by skeletal muscles.

For patients with pulmonary congestion or metabolic risk, it is recommended the use of diuretics, statins, organic nitrites /nitrates, energy-intake restriction, stimulants of PKG pathway, and extracellular matrix-stimulating agents, like spironolactone.

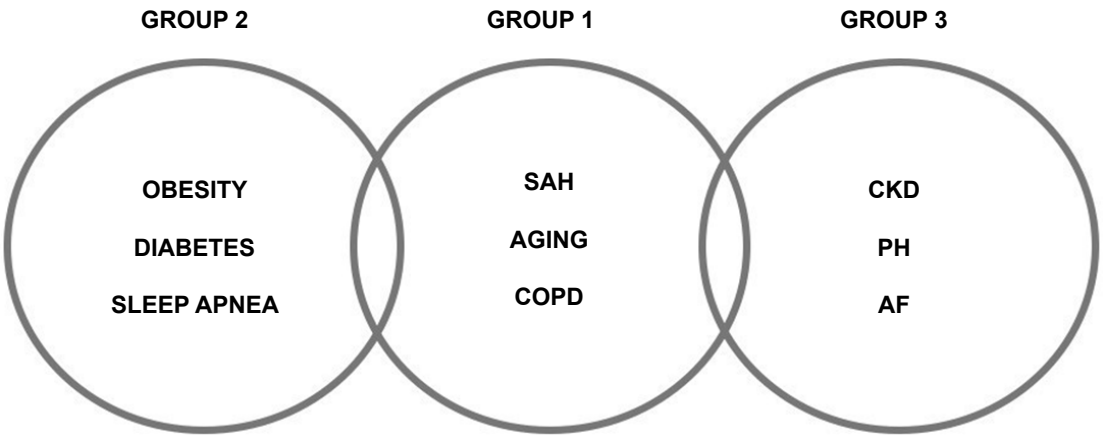

Figure 1 - Phenogroups of heart failure with preserved ejection fraction. SAH: systemic arterial hypertension; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; PH: pulmonary hypertension; AF: atrial fibrillation.

For hypertension phenotype, anti-hypertensive are the most recommended treatment, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers and calcium channel blockers, highlighting the importance of this treatment to HF prevention, to vascular conditions not related to HF (such as stroke and myocardial infarction) and to improve the quality of life of HFPEF patients. The CHARM-Preserved, PEP-CHF and TOPCAT studies demonstrated a reduction in hospitalization rates of patients with HFPEF by blockage of the renin-angiotensin-aldosterone system. These studies used, respectively, an angiotensin II receptor blocker, ACE inhibitors and an aldosterone antagonist (spironolactone).[36-38] Inhibition of the renin-angiotensin-aldosterone system would be of benefit to the patients due to the association of neurohormonal activation with hypertension and volume retention.[39,40]

Control of heart rate is mediated by activation of the sympathetic system, which has a direct effect on adverse outcomes in patients with HFPEF. A study derived from the I-Preserve study showed an association between increased heart rate and higher incidence of death for cardiovascular causes and hospitalizations in patients in sinus rhythm.[41] Therefore, heart rate control would be an effective treatment target.

In patients with pulmonary hypertension, the use of dobutamine improved pulmonary vascular function, and studies on new pulmonary vasodilators targeting GMPc, endothelin and nitric oxide (NO)[32] have also been developed (Table 1). In patients with kidney dysfunction, sildenafil had no significant effects in the RELAX clinical trial.[42] Due to the high prevalence of patients with HFPEF and pulmonary hypertension, and its intrinsic relationship with morbidity and mortality, pulmonary vasodilation is paramount in the treatment of these patients.[43]

Based on the studies reviewed, we conclude that phenotype mapping in HFPEF has enabled the development of a new generation of clinical trials aimed at new therapeutic approaches (Figure 2).

HFPEF accounts for nearly half of HF patients on treatment and its prevalence has increased. Cardiovascular disease phenotypes are complex, with many influencing factors. Systemic inflammatory reaction and microvascular endothelial dysfunction lead to ventricular remodeling and dysfunction. Specific therapeutic interventions should be multifaceted and focused on stages of these signaling cascades. New therapeutic approaches should encompass metabolic control, modulation of inflammatory response, control of pulmonary hypertension, prevention of muscle weakness, and reduction of sodium and water retention. Due to the wide range of interventions, phenotype mapping becomes an essential tool for future investigations and clinical trials (to confirm the results). Possibly, there will be more significant changes as new genetic, cellular, molecular and immunologic biomarkers are incorporated and used to discriminate treatment groups in a clear and objective manner.

Cardiac diseases that simulate HFPEF – Phenocopies

The term "phenocopies" was first used in the study of hypertrophic cardiomyopathies, in which a subgroup of

Table 1 - Example of therapeutic strategies for different phenotypes of heart failure with preserved ejection fraction

	Lung congestion	+ Chronotropic incompetence	+ Pulmonary hypertension	+ Skeletal muscle weakness	+ Atrial fibrillation
Overweight/ Obesity/ Metabolic syndrome/ Type 2 DM	. Diuretics (loop diuretics in DM) . Caloric restriction . Statin . Nitrate/Inorganic nitrite . Sacubitril . Spironolactone	+ Atrial pacemaker + Avoid betablockers and cardioselective calcium channel blockers	+ Pulmonary vasodilator + Anticoagulation (in PTE)	+ Exercise program	+ Cardioversion + Control of HR + Anticoagulation
+ SAH	+ ACEI/ARB + Calcium channel antagonist	+ ACEI/ARB + Atrial pacemaker	+ ACEI/ARB + Pulmonary vasodilator	+ ACEI/ARB + Exercise program	+ ACEI/ARB + Cardioversion + Control of HR + Anticoagulation
+ Kidney dysfunction	+ Ultrafiltration if necessary + nephroprotective drugs (ACEI/ARB)	+ Ultrafiltration if necessary + Atrial pacemaker	+ Ultrafiltration if necessary + Pulmonary vasodilator	+ Ultrafiltration if necessary + Exercise program	+ Ultrafiltration if necessary + Cardioversion + Control of HR + Anticoagulation
+ CAD	+ ACEI + Myocardial revascularization	+ ACEI + Revascularization + Atrial pacemaker	+ ACEI + Revascularization + Pulmonary vasodilator	+ ACEI + Revascularization + Exercise program	+ ACEI + Revascularization + Cardioversion + Control of HR + Anticoagulation

Adapted from: Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation. 2016;134(1):73-90. DM: diabetes mellitus; SAH: systemic arterial hypertension; CAD: chronic artery disease; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; PTE: pulmonary thromboembolism; HR: heart rate

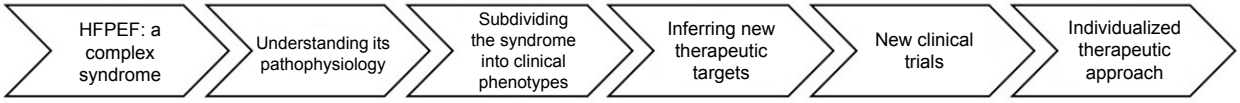

Figure 2 - The process towards effective therapies of heart failure with preserved ejection fraction: HFPEF: heart failure with preserved ejection fraction.

diseases was found to mimic their phenotypic features. We found that this concept may be extended to HFPEF. Due to the heterogeneity nature of HFPEF, other diseases may have the same clinical phenotype and thereby be considered their "phenocopies". Although both therapeutic intervention and prognosis of the diseases are different, their similar clinical presentation hampers the differential diagnosis. One pertinent example of a disease that mimics the clinical pattern of HFPEF is cardiac amyloidosis.[44,45]

Cardiac amyloidosis is a restrictive cardiomyopathy, regardless of its type, characterized by progressive diastolic dysfunction followed by systolic dysfunction and arrhythmia. It may be first identified as exercise intolerance or HF. The diagnosis of cardiac amyloidosis is usually established in the late stages of the disease, since the disease affects the same elderly population affected by HFPEF. However, the exact contribution of amyloidosis to HFPEF has not been elucidated. Protein accumulation leads to asymptomatic left ventricular

hypertrophy, with late diagnosis due to its gradual progression. Nevertheless, it is worth pointing out that individuals with HFPEF usually have other comorbidities that independently contribute to diastolic dysfunction.[46-48]

In addition to cardiac amyloidosis, "phenocopies" include other diseases such as hypertrophic cardiomyopathy, cirrhotic cardiomyopathy,[49] low-flow, low-gradient aortic stenosis, cardiac sarcoidosis and hemochromatosis (Figure 3).

The identification of "phenocopies" in HFPEF may enable an individualized approach to molecular targets and functional abnormalities, such as the use of certain drugs in senile amyloidosis, and betablockers and/or calcium channel antagonists in hypertrophic cardiomyopathy. Besides, the chance of diagnostic errors may decrease and that of early diagnosis of other diseases may increase when the presence of diseases that mimic HFPEF is considered.

The use of the machine learning technique for patients' grouping by phenotypes allows the analysis of a wide variety of variables and relationship between them, and to classify them in mutually exclusive phenogroups. In addition to allowing a phenotype categorization and to contribute to a therapeutic revolution, the identification of possible "phenocopies" is crucial for the differential diagnosis of a HFPEF model (Figure 4).

Conclusions

HFPEF is a common syndrome, whose prevalence will increase in the community. However, classification of phenogroups and results of therapeutic approaches are still incipient.

Today, the concept of adopting a phenotype network to explain HFPEF disrupts the Cartesian model in suggesting a complex approach of these patients, who may have many morphofunctional patterns. These distinct patterns may be related to abnormal signaling processes in the myocardium and associated with systemic inflammation, which is increased in patients with HFPEF and comorbidities.

Phenotype mapping of heterogeneous clinical syndromes, such as HFPEF, enables the categorization of patients, and can serve as a basis for the development of clinical trials and identification of new therapeutic approaches.

Author contributions

Conception and design of the research: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR. Acquisition of data: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR. Analysis and

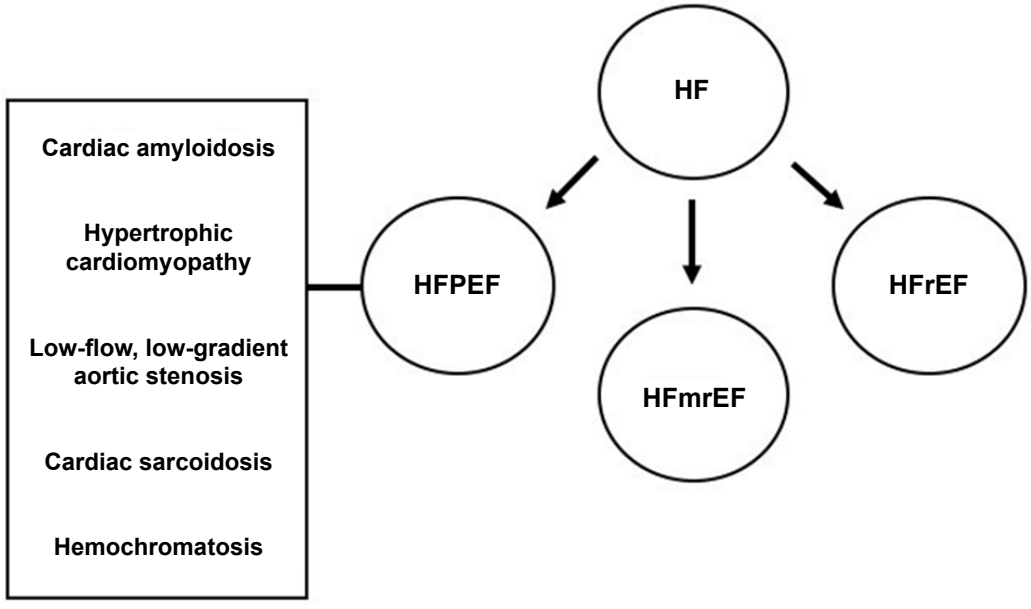

Figure 3 - Phenocopies of heart failure with preserved ejection fraction. HF: heart failure; HFPEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction.

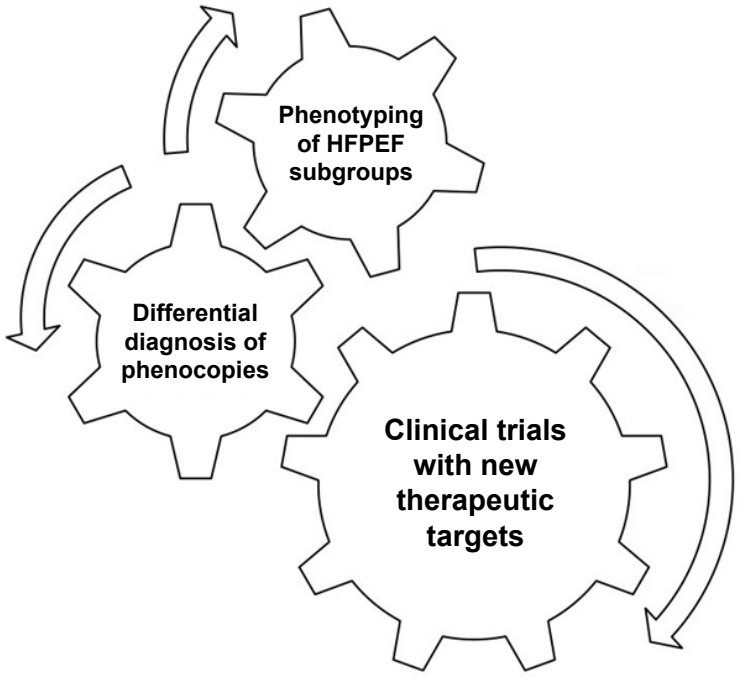

Figure 4 - Future management of heart failure with preserved ejection fraction. HFPEF: heart failure with preserved ejection fraction.

interpretation of the data: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR. Writing of the manuscript: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR. Critical revision of the manuscript for intellectual content: Mesquita ET, Grion DC, Kubrusly MC, Silva BBFF, Santos EAR.

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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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