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Heart failure with mid-range left ventricular ejection fraction: New entity?

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Acronyms
AHF: acute heart failure
BNP: brain natriuretic peptide
HF: heart failure
HFmrEF HF with mid-range left ventricular ejection fraction
HFpEF: HF with preserved left ventricular ejection fraction
HFrEF: HF with reduced left ventricular ejection fraction
HBP: high blood pressure
LVEF: left ventricular ejection fraction

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ABSTRACT

Currently, a new classification of patients with heart failure (HF) according to the left ventricular ejection fraction (LVEF), the HF with mid-range LVEF (HFmrEF) between 40 and 49% is described. This is included in the previous classification of HF with LVEF greater than 50% or preserved LVEF (HFpEF) and HF with reduced LVEF (HFrEF), less than 40%. This new group of patients represents between 16-20% of patients with HF, thus, since its publication, there have been several studies interested in discovering the characteristics of these. After reviewing the studies that we currently have, we can draw some conclusions regarding those with HFmrEF, which share clinical, epidemiological and etiological characteristics with the other two patterns (HFpEF and HFrEF); therefore, it is possible that the HFmrEF represents more a transitional state between HFrEF and HFpEF than an independent entity in itself. Patients with HFpEF do not show differences in mortality compared to the other two groups, except in those with ischemic heart disease in whom mortality is similar to that in patients with HFrEF. It is recommended to treat those who have HFmrEF in a similar way to those with HFpEF, although it has been observed that the former benefit from a treatment similar to those with HFrEF.

Keywords: Heart Failure, Left ventricular ejection fraction, Classification, Therapeutics

Insuficiencia cardíaca con fracción de eyección intermedia: ¿Nueva entidad?

RESUMEN

En la actualidad se describe una nueva clasificación de pacientes con insuficiencia cardíaca (IC) según la fracción de eyección del ventrículo izquierdo (FEVI), la IC con FEVI intermedia (ICFEi) entre 40 y 49%. Esta se incluye en la anterior clasificación en IC con FEVI mayor del 50% o FEVI preservada (ICFEp) y la IC con FEVI reducida (ICFEr), menor del 40 %. Este nuevo grupo de pacientes representa entre el 16-20% de los pacientes con IC, por lo que desde su publicación han habido varios estudios interesados en descubrir las características de estos. Tras revisar los estudios de los que disponemos actualmente se pueden extraer algunas conclusiones respecto a los que presentan ICFEi, que comparten características clínicas, epidemiológicas y etiológicas con los otros dos patrones (ICFEp e ICFEr); por lo que cabe la posibilidad de que la ICFEi represente más un estado transicional en-

tre ICFEr y ICFEp que una entidad independiente en sí misma. Los pacientes con ICFEi no presentan diferencias en la mortalidad frente a los otros 2 grupos, excepto en aquellos con cardiopatía isquemia en los cuales la mortalidad es simi-lar a la de pacientes con ICFEr. Se recomienda tratar a los que tienen ICFEi de forma similar a aquellos con ICFEp, aunque se ha observado que los primeros se benefician de un tratamiento similar a los que padecen ICFEr.
Palabras clave: Insuficiencia cardíaca, Fracción de eyección del ventrículo izquierdo, Clasificación, Terapéutica

INTRODUCTION

The heart failure (HF) is a disease with a high prevalence (2%) in adulthood, that can reach up to 8% in patients older than 65 years. It is one of the main causes of hospitalization, being responsible for 2.5% of health expenditure[1-3]. For this reason, all facts about the disease are important and, therefore, the constant research for a better understanding of the HF's mechanism and how to improve its treatment.

The most important terminology for describing HF is based on the classification according to the left ventricular ejection fraction (LVEF)[4], which, historically, has been defined in two groups: the HF with LVEF less than 40%, or the HF with reduced LVEF (HFrEF), and with LVEF greater than 50%, or HF with preserved LVEF (HFpEF). Until then, patients with LVEF between 40-49% represented a blurred area[5]. In 2013, the guidelines of the American Heart Association defined for the first time the term "mid-range left ventricular ejection fraction (HFmrEF)" that includes these patients with LVEF between 40 and 49%[6]. Later, in the 2016, the European Society of Cardiology (ESC) defined the HFmrEF in patients with ejection fraction between 40 and 49%[7].

The differentiation of patients with HF according LVEF is important, as it relates to different underlying causes: demographic characteristics, comorbidities and response to treatments. Only in those with HFrEF, treatments have achieved the reduction of morbidity and mortality[8]. Thus, it is important to stimulate clinical and therapeutic research in the new group of patients with LVEF between 40 and 49%, and to describe whether there is a therapeutic behavior to improve the morbidity and mortality of these patients[9,10].

EPIDEMIOLOGY OF THE HFmrEF

The LVEF represents a major function in the classification of patients with HF. In previous studies, only patients with HFpEF and HFrEF were included, excluding those with LVEF between 40-49% or even including them in the group of patients with HFpEF. Recent studies have shown that the prevalence of HFmrEF is increasing, as it is estimated to represent 20% of the case s with HF, and it is expected that with the increasing age of the population this figure will grow in coming years[11-13]. It is, therefore, important to identify the HFmrEF as a separate group and to study the characteristics, pathophysiology and treatment of this group of patients, since there is currently evidence of which treatments improve mortality in those presenting HFrEF but not of the ones that have HFpEF or HFmrEF[8].

CLINICAL FEATURES

The clinical characteristics of patients with HFmrEF are heterogeneous. In recent years, multiple studies have been carried out to try to specify them. In 2007, in the OPTIMIZE-HF study, an analysis of 41267 patients that considered the hospitalized ones with HF according to the echocardiographic profile, including other variables, found that those with HFmrEF resembled more patients with HFpEF[14]. The same result was observed in the GWTG-HF registry, in which patients with HFmrEF were compared with those who presented HFpEF and HFrEF; in this registry was pointed out the fact that patients with HFmrEF shared a characteristic with those who had HFrEF, which was the ischemic heart disease[15]. A Swedish registry of HF, with 42987 patients, yielded that the rates of ischemic heart disease were 60% in patients with HFrEF, 61% with HFmrEF and 52% with HFpEF[16]; and a global registry of those who suffered from acute heart failure (AHF) in nine countries of Europe, Latin America and Australia, in which 4953 patients were included, the result was that those who had HFmrEF shared characteristics with those

of HFrEF and HFpEF. It was also observed that patients with HFmrEF presented higher prevalence of high blood pressure (HBP), and low prevalence of acute renal failure, they had more hospitalizations for acute coronary syndrome and they were given more intravenous vasodilator treatment. In this case, short-term mortality was lower than in those who had HFrEF and similar in patients with HFpEF[17].

The REDINSCOR II registry, where 1420 patients from 20 Spanish hospitals were included, yielded that those with HFmrEF were alike those who had HFpEF in characteristics such as age, HBP and atrial fibrillation. On the other hand, patients with HFrEF share the male predominance and a higher rate of ischemic heart disease. There were no differences in mortality between these groups[18].

The CHART-2, where 3480 patients were included, yielded that the clinical characteristics of those with HFmrEF are intermediate among those with HFpEF and HFrEF; that is why patients with HFmrEF seem to represent a transitional state between HFrEF and HFpEF rather than an independent entity[12]. A similar result was obtained in the Spanish registry RICA, where can perceived that the clinical characteristics of patients with HFmrEF are similar to those who suffer from HFpEF. In this registry, a better prognosis is observed in those who have HFmrEF with respect to those diagnosed with HFrEF[19]. In the same way, in a study conducted the Spanish registry EAHFE, where 6856 patients with AHF were analyzed, yielded that those with HFmrEF present intermediate characteristics between patients with HFpEF and HFrEF[20].

Regarding the treatment, nowadays beta-blockers have proved to enhance the prognosis in patients with HFrEF, and in recent studies the results suggest that this benefit also applies to those with HFmrEF[21].

PATHOPHYSIOLOGY OF THE HFmrEF

Studies suggest that the HFrEF and the HFpEF represent different pathophysiological syndromes[22]. The first is characterized by systolic dysfunction and the second diastolic. In the ESC guidelines is suggested that patients with HFmrEF present both: diastolic and systolic dysfunction; what makes us wonder if they have an entity in themselves, or simply –as mentioned– represent a transition between patients with HFpEF and HFrEF.

The ischemic heart disease may be the pathophysiological basis of these patients. Like the Swedish registry[23], other studies such as Chioncel *et al.*[24] or Rickenbacker *et al.*[25] showed higher percentages of underlying ischemic heart disease in patients with HFpEF. The REDINSCOR II[18] registry also obtained that the most frequent cause was myocardial ischemia, with 39.1%, and AF with 39.4%. In the ESC HF Long Term[24] registry was observed that the similarities between HFmrEF and HFrEF suggest that the first represents the recovery of patients with HFrEF or an early stage of it.

PROGNOSIS

The prognosis of patients with HFmrEF is alike those with HFpEF, except for those with ischemic heart disease, in which mortality is similar to patients with HFrEF[23].

In the OPTIME HF[14] registry, a mortality of 3.9% was perceived in patients with HFrEF, in HFmrEF of 3% and in HFpEF of 2.9%. In the GWTG-HF the recorded mortality, at 30 days and a year, in patients with HFmrEF was of 8.2% and 35.1%, respectively; in the HFpEF of 8.5% and 35.6%; and in the HFrEF of 9.5% and 37.5%[13].

In the REDINCOR II, no significant differences were found in hospital mortality among the three groups; the most frequent cause of death was refractory HF and death from non-cardiovascular causes[18].

Another study of the EAHFE registry, with 3958 patients with AHF, yielded that after adjusting the hazards ratios (HR) for the discordant variables among the groups, no significant differences in mortality were found after an episode of worsening, for the group HFmrEF with respect to the HFpEF and HFrEF groups[20].

The recent study of Hamatani *et al.*[26], based on two Japanese registries (Wet-HF and NaDEF), which analyzes the prognosis role of the brain natriuretic peptide (BNP) in patients with HF according to their LVEF, yielded that the prognostic value of the BNP in those with HFmrEF has intermediate characteristics between patients with HFpEF and HFrEF[26]. The BNP is a hormonal peptide released predominantly by the ventricular myocardium, in response to myocardial stress, hence, in patients with HFpEF, lower levels of BNP are observed than in those who have HFrEF. It seems that the cases with HFmrEF have intermediate characteristics between these two groups.

Concerning to what is the most appropriate destination for patients with HFmrEF, in the EAHFE registry was appreciated that AHF patients with HFmrEF entering the Cardiology Department have less reconsultations at 30 days that the ones admitted at the Internal Medicine Department, or those discharged directly from the Emergency Department[27].

THERAPEUTIC STRATEGIES

The definition of HFmrEF is still very recent, therefore, we have not enough information to state what should be the treatment of these patients. The ESC guidelines suggest that until more information is available, they should be treated in a similar way of those with HFrEF[7].

Within these guidelines can be found some clinical studies in phase II and III in patients who suffer from HF with LVEF, regarding the benefit of certain drugs against placebo. In the CHARM-Preserved[28], a study was carried out with candesartan versus placebo in patients with LVEF greater than 40%, stage II-IV of the NYHA and history of hospitalization for cardiac causes with a follow-up of 3 years, in which a trend towards reduction of 11% was observed in the combined endpoint of cardiovascular mortality and hospitalization due to HF (22% vs. 24%; p=0.12 unadjusted, p=0.051 adjusted).

In the SENIORS[29], a study of nevibolol versus placebo was performed in patients with confirmed HF as admission for HF in the last 12 months or LVEF less than or equal to 35%, or both; in the last 6 months, age greater than or equal to 70 years and with a follow-up of 1.8 years; in which a reduction of 14% was observed in the combined variable of all-cause mortality or cardiovascular hospitalization (31% vs. 35%; p=0.04).

In the PARAMOUNT[30], a study of sacubitril/valsartan versus valsartan was performed in patients with HF with LVEF greater than or equal to 45%, stage II-III of the NYHA, NT-proBNP greater than 400pg/ml and with a follow-up of 12 weeks; in which a reduction of change NT-proBNP-ratio with sacubitril/valsartan was observed, 0.77 (HF95%; 0.64-0.92: p=0.005).

In the rest of the studies carried out, no significant differences in mortality were found: PEP-CH[31], where perindopril was studied against placebo; I-PRESERVE[32], ibesartan versus placebo; ALDO-DHF[33] and TOPCAT[34], spironolactone versus placebo; DIG-PEF[35], digoxin versus placebo; and RELAX[36], sildenafil versus placebo.

Although in the ESC guidelines is recommended to treat patients with HFmrEF similar to those with HFpEF, it has been proven that those with HFmrEF benefit from a similar treatment to those suffering from HFrEF.

The study of Cleland *et al.*[21] yielded that the use of beta-blockers in patients with HF, in sinus rhythm, had a benefit on morbidity and mortality more evident in those who had HFrEF, but also in those with HFmrEF.

If we observe the medication used in patients with ventricular dysfunction in the HF registries according to their LVEF, it can be confirmed that those who suffer from HFmrEF present a significantly different therapeutic strategy compare to those with HFrEF and HFpEF, what reflects the absence of specific recommendations on the conduct to be followed in patients with HFmrEF.

In the RENDINSCOR II[18] registry was observed that the use of angiotensin-II receptor antagonists (ARA-II) in patients with HFrEF was 78.8%, in HFmrEF of 72 .4% and in HFpEF of 63.1%. The use of beta-blockers in the HFrEF was 86.2%, HFmrEF 71.8% and HFpEF 59.5%. The antialdosterone in HFrEF, 65.8%, HFmrEF, 45%, and HFpEF, 28.5%; and diuretics in HFrEF 89.4%, HFmrEF 82.6% and HFpEF 84.6%.

In the Heart Failure Long-Term Registry[24], using beta-blockers and ARA-II was of 90% in patients with HFrEF and HFmrEF, and in patients with HFpEF was 75%. The use of mineralocorticoid receptors' antagonists was 70% in patients with HFrEF, 55% in HFmrEF and 35% in HFpEF. Regarding the use of ivabradine, it was 10% in patients with HFrEF and HFmrEF and 5% in patients with HFpEF.

As for the acute therapeutics in patients with HF, the EAHFE registry yielded that there are no differences in the treatment provided at the emergency department compare to patients with HFpEF who are attended for an acute decompensation of HF, when compared with the other two groups[20]. With this, the role of in-hospital and out-hospital emergency departments with respect to the prognosis of patients with AHF, regardless of their LVEF, remains uncertain[37-41].

TREATMENT OF COMORBIDITIES

As we have described, the pathophysiology of the

HFmrEF is, until today, unknown; and according to the ESC guidelines[7] it has similarities with the HFpEF, where can be found conditions associated with different phenotypes, including cardiovascular diseases (atrial fibrillation, HBP, pulmonary hypertension, peripheral arterial disease) and non-cardiovascular diseases (diabetes mellitus, chronic kidney disease, anemia, iron deficiency, chronic obstructive pulmonary disease and obesity). If the mortality of patients with HFpEF and HFmrEF are compared with those who have HFrEF, there can be observed that the first ones usually take place due to non-cardiovascular causes.

Until now, it has not been shown that any treatment reduces the morbidity and mortality in patients with HFmrEF, but it seems important to carry out interventions to improve symptoms, quality of life and evolution, without exacerbating the HF[7,42].

In CHART-2[12] was observed that patients who initially have HFmrEF and pass to HFrEF show worse prognosis than those who remain in HFmrEF or improved its preserved ejection fraction. In this study was found that in the first year, 44% of patients with HFmrEF pass to HFpEF and 16% to HFrEF; and at 3 years, 45% and 21%, respectively. There were observed as predictive values of changes in the LVEF: the ischemic heart disease as a negative factor and female sex as a positive. No significant changes were confirmed in the association of the use of certain drugs and changes in the LVEF; beta-blockers and diuretics did not show improvement in the LVEF of patients with HFrEF.

THE FUTURE ABOUT THE HFmrEF

The term of HFmrEF is relatively recent, although in previous ESC guidelines[7], the existence of a blurred area between the HFrEF and the HFpEF was mentioned. It is likely that identifying HFmrEF as a separate group will stimulate research on the characteristics, pathophysiology and treatment of this group of patients. It is believed that patients with probable HFmrEF have a slight diastolic dysfunction but with characteristics of systolic dysfunction.

There is still ignorance concerning patients with HFmrEF; therefore, it is important to carry out future studies where patients with HFmrEF can be included and to learn more about the pathophysiology of these patients, their etiology, the phenotype, how to treat comorbidities, what treatment is beneficial to improve morbidity and mortality, and the convenience of their inclusion in the risk scales for ambulatory patients or with AHF[43-45]. It is believed that these studies are feasible since those that have HFmrEF represent a quarter of patients with HF, thus, we have tools to develop prospective studies and learn more about their characteristics.

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