Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation
A review

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Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are two conditions with an increased incidence and prevalence. Numerous studies highlight the pathophysiological links between HFpEF and AF and the common risk factors. Patients with HFpEF have a high incidence of AF. It is difficult to determine which of the pathologies appears first: HFpEF or AF. In HFpEF, left atrium suffers a structural and functional remodelling process, which contributes to the occurrence of AF. Also, AF determines dyastolic dysfunction, the main mechanism for HFpEF development. The diagnosis of HFpEF in the presence of AF is more difficult, because the symptoms of HF resemble those of AF. Also, the presence of AF makes more difficult the correct echocardiographic evaluation of patients with HF. More research is needed in order to develop new therapies that can improve the prognosis of patients with HFpEF and AF.

Keywords: heart failure, atrial fibrillation, diastolic dysfunction, left atrial enlargerment

Heart failure (HF) represents the final stage of evolution of a large number of cardiovascular diseases, having an increasing incidence and prevalence. The diagnosis of HF is based on symptoms, such as fatigue or breathlessness, and signs, such as pulmonary crackles, peripheral oedema and elevated jugular venous pressure, caused by cardiac structural or functional abnormalities, with elevated intracardiac pressures or reduced cardiac output. Depending on the ejection fraction of the left ventricle (LVEF), HF is classified in heart failure with reduced ejection fraction (HFrEF), with an LVEF <40%, HF with preserved ejection fraction (HFpEF), characterised by an LVEF >50% and HF with mid-range ejection fraction (HFmEF), with a LVEF in the range of 40-49% [1].

Heart failure with preserved ejection fraction (HFpEF) is a type of congestive heart failure in which LVEF is > 50%. Patients with HFpEF have no dilated left ventricle, but have thicker left ventricular wall, with increased filling pressures. Most patients have additional evidence of alteration of left ventricular filling, also classified as diastolic dysfunction, which is generally accepted as the likely cause of heart failure in these patients [1]. The patients diagnosed with HFpEF often associate comorbidities [2], such as atrial fibrillation (AF), that may influence their treatment and prognosis. It is difficult to determine which of the pathologies appears first: HFpEF or AF. In HFpEF, left atrium suffers a structural and functional remodelling process, which contributes to the occurrence of AF. Also, AF determines dyastolic dysfunction, the main mechanism for HFpEF development.

Epidemiology

HFpEF and AF are common pathologies, with an increasing prevalence, being associated with high morbidity and mortality. AF is the most common rhythm disorder in patients with HFpEF, with a prevalence between 20 and 40% at the time of admission [2]. Also, AF has a higher incidence in women compared with men (35 events/1000 person-year vs 21.2 events/1000 person-year) [3]. Two-thirds of patients with HFpEF will be diagnosed with AF during the course of the disease [4]. Studies on this comorbid association have not clearly demonstrated which of the two is installed first: HFpEF or AF? Surveys, registries and trials suggest that HFpEF has a higher incidence in patients with a longer duration of AF [5]. Also, HFpEF has an incidence rate of 4.90 per 1000 persons diagnosed previously with AF and 0.85 for those without AF [6].

The Framingham Heart Study has found that AF is a risk factor for the new onset HFpEF [7]. Studies like AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management), REALISE-AF (Real-life global survey evaluating patients with atrial fibrillation) and RACE-II (Rate Control Efficacy in Permanent Atrial Fibrillation) sustain that AF predicts HFpEF [8-10]. AFFIRM study was initiated in 2002 and enrolled 4.060 subjects hospitalised for persistent AF. The study has found that HFpEF was diagnosed in 8% of 4060 patients with paroxysmal/ persistent atrial fibrillation [10]. The REALISE-AF registry has enrolled patients from 26 countries worldwide, with the aim to determine the therapeutic control of AF. This registry showed that 18% of hospitalised patients with permanent AF developed HFpEF in the course of the disease [9]. Also, the EORP-AF Pilot registry (EURO bservational Research Programme on Atrial Fibrillation), based on 3119 subjects with AF, noticed that HFpEF was diagnosed in 17% of elderly patients, diagnosed previously with persistent/permanent AF [11]. RACE II is a study which showed that lenient rate control is as effective as a strict rate control in AF. This study showed that 24% of 614 patients

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diagnosed with permanent AF developed HFpEF in the course of the disease [8].

On the other hand, other studies noticed that HFpEF is a major risk factor for developing AF. A report from Framingham Heart Study established a 6-fold increase in the risk for paroxysmal AF in patients diagnosed previously with HF [12]. The prevalence of AF increases with the severity of HF, in HFpEF the prevalence of AF being between 15 and 41% [11]. In the Olmsted County population cohort, newly AF was diagnosed in 939 subjects with HFpEF, two-thirds of them developing AF during the course of HFpEF [13]. OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) is a program established in 2004, designed to improve the medical care in patients hospitalized for HF. The program noticed that persistent AF was diagnosed frequently in patients hospitalised for HFpEF [14]. ADHERE (Acute Decompensated Heart Failure National Registry) is a registry designated to improve care in patients with HF. This registry was established in 2001 and enrolled 65.180 patients with decompensated heart failure from 263 hospitals from the United States. The registry noticed that paroxysmal AF was diagnosed in 33% of 65.180 patients hospitalised for advanced HFpEF, especially in elderly women [10]. I-PRESERVED trial (Irbesartan in Heart Failure with Preserved Ejection Fraction) enrolled 4128 patients with the LVEF >45%, in order to study the effects of irbesartan in patients with HF. This trial showed also that the main causes for hospitalization in patients with HF were arrhythmia, stroke and myocardial infarction. This trial, developed in 2008, showed that paroxysmal AF was diagnosed in 29% from 4128 hospitalised patients with advanced HFpEF, especially women [15]. CHARM-Preserved (Candesartan in Heart Failure: Assesment of Reduction in Mortality and Morbidity) investigated the effect of addition of an angiotensin-receptor blocker (candesartan) to current treatment in patients with HF. This trial included 3023 patients between 1999 and 2000, and diagnosed paroxysmal AF in 29% of 3023 hospitalized patients with advanced forms of HFpEF [16].

Risk factors and pathophysiological links

An important proportion of patients diagnosed with HFpEF develop AF at some point in the evolution of the disease. HFpEF and AF share common risk factors, predisposing to both pathologies simultaneously. Common risk factors, such as hypertension, aging, obesity and obstructive sleep apnea syndrome, are associated with a major risk of developing concomitant HFpEF and AF [17].

An important risk factor for HFpEF and AF is aging. The incidence of new-onset AF in HFpEF increases with age, via ventricular stiffening and age-related ventricular diastolic dysfunction [18-20]. Obesity is another risk factor which can lead to HFpEF and AF, being a comorbidity associated with systemic inflammation, endothelial dysfunction, oxidative stress, microvascular inflammation and diastolic dysfunction, predisposing to HFpEF [21]. Hypertension causes left ventricular hypertrophy with annular remodeling and mitral valve regurgitation, and left atrial enlargement, a direct cause for AF. Also, hypertension leads to fibrosis and diastolic dysfunction, with reduced ventricular filling. In hypertension, up-regulation of renin-angiotensin-aldosterone system contributes to the proarrhythmic effects, because angiotensin II causes atrial fibrosis and disorders in the electrical impulse propagation [22].

In HFpEF, the left atrium presents structural and functional remodeling, which is the major mechanism for AF development. Enlargement of the left atrium is the proarrhythmic substrate in patients with HFpEF. Atrial fibrosis and loss of cell-to-cell junctions predispose to arrhythmia, with increased atrial refractoriness and a non-homogeneity of the electrical impulse propagation, with re-entry circuits [23]. Electrical remodeling has an important role, changes in ionic channels leading to arrythmia by delayed after-depolarizations and triggered activity. In HFpEF, calcium overload leads to after-depolarizations, predisposing to arrythmia [24].

Neurohormonal systems are important in HFpEF. Atrial natriuretic peptide (ANP) is an atrial hormone produced as a response to stretch, which increases diuresis and vasodilation. In patients with diastolic dysfunction, reduction in the amount of ANP leads to decreased diuresis and congestion, with structural and mechanical atrial remodeling, this being another mechanism by which HFpEF gives rise to AF [25]. Numerous studies observed that in permanent AF, reduction in the amount of ANP leads to volume overload, with development of HFpEF [25,26].

HFpEF promotes AF by atrial dilatation, the main mechanism in AF, with fibrosis and structural remodeling. Also, AF leads to diastolic dysfunction, the main cause for HFpEF [26]. AF contributes to the remodeling of the atrio-ventricular valves, with mitral and tricuspid regurgitation [27]. AF is characterized by loss of atrial systole, which decreases cardiac output by 25%, especially in patients with diastolic dysfunction [26].

Another mechanism by which AF gives rise to HFpEF is the irregular and rapid ventricular conduction, with left ventricular dysfunction and tachycardia-induced cardiomyopathy [28]. Cardioversion, with sinus rhythm restoration, increases the left ventricular volume, with hemodynamic improvement [29]. Also, AF is associated with chronotropic incompetence, with changes like reduced cardiac output, structural remodeling like subendocardial fibrosis, affected myocardial perfusion and cellular changes with electrical alteration [30-32].

Diagnostic challenges

The diagnosis of HFpEF in the presence of AF may be difficult, because symptoms of HF resemble those of AF. Also, parameters of diastolic dysfunction measured at echocardiography may be harder to obtain in patients with atrial fibrillation. Natriuretic peptide levels are increased in AF, whether or not accompanied by HF. Symptoms of HFpEF, such as breathlessness and fatigue, are present in both pathologies separately, but are more accentuated when HFpEF coexists with AF. Other symptoms, such as orthopnea and nocturnal dyspnea, may be present in HFpEF [33]. The physical examination of patients with HFpEF may detect signs like increased venous pressure, pulmonary crackles and auscultation of the third heart sound.

Circulating natriuretic peptides, like N-terminal pro-B-type natriuretic peptide (NT-proBNP), are increased in HFpEF and are used to confirm the diagnosis. However, AF is associated with increased levels of NT-proBNP, even if is associated or not with HFpEF, making the diagnosis more difficult [34, 35]. The clinical trials proposed different cut-off values for the left atrial volume index and for NT-proBNP in HFpEF associated with AF [36]. These levels are not uniformly. In the SOCRATES study (Soluble Guanylate Cyclase Stimulator in Heart Failure Studies-Preserved), the cut-off for NT-proBNP was >600 pg/mL and in PARAGON-HF trial (Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejection fraction), the cut-off for NT-proBNP with AF was >900 pg/mL.

Transthoracic echocardiography in HFpEF shows preserved left ventricle ejection fraction (>50%) and

diastolic dysfunction, with left atrium enlargement. The left atrial enlargement and atrial dysfunction are diagnostic criteria for HFpEF in sinus rhythm, but dilated left atrium exists also in AF, with or without HFpEF. Numerous studies have demonstrated that the filling pressures are increased in patients with AF [37]. Isovolumic relaxation time, mitral deceleration time, diastolic flow progression and pulmonary venous flow assessment are also utilized for the diagnosis of HFpEF and AF. The ratio of mitral peak E to tissue Doppler e' >15 septal and >13 lateral may predict severe outcomes in AF patients, being associated with mortality, decreased exercise capacity, low quality of life and risk of ischemic stroke [38].

Prognosis of patients with HFpEF and AF

HFpEF with AF is associated with increased mortality [39]. In patients with AF, the presence of HFpEF worsens the prognosis. A meta-analysis of 10 studies showed that mortality was higher in patients with AF and HFrEF than in those with AF and HFpEF, but hospitalization for HF and the risk for stroke were similar in both cases [38]. In the I-PRESERVE trial, the risk of stroke was higher in patients with HFpEF associated with AF, with a poor prognosis especially for women [40]. Numerous observational studies noticed that symptoms are less severe in patients in sinus rhythm with HFpEF, compared with patients in sinus rhythm and HFrEF [41].

Treatment of patients with HFpEF and AF

Treatment of patients with HFpEF and AF represents a challenge, because there are no clear recommendations for treatment of patients with HFpEF and AF in the current international guidelines. There are particular therapeutic aspects from patient to patient. The objectives of the treatment in patients with HFpEF and concomitant AF are the management of cardiovascular and non-cardiovascular comorbidities, anticoagulation in order to prevent stroke and thromboembolism, normalization of the fluid balance, heart rate and rhythm control, and restoration of the sinus rhythm with antiarrhythmic drugs, cardioversion or catheter ablation.

Comorbidities, such as diabetes, obesity, renal dysfunction, pulmonary disease and anaemia should be diagnosed and appropriately managed [42-45]. Specific programs to maintain body weight should be implemented. Sleep apnea syndrome needs to be identified and treated. Also, other cardiovascular diseases, such as hypertension and myocardial ischemia, should be controlled and treated with antihypertensive, respectively with anti-ischemic drugs.

A meta-analysis has found that renin-angiotensin-aldosterone antagonism is needed in patients with HFpEF and AF, using angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers and mineralocorticoid receptor antagonists [46]. However, some clinical trials showed that ACEI have no influence on mortality. The CHARM study showed that angiotensin-converting enzyme inhibitors prevent HF hospitalization [47]. There are some therapeutic differences between HFpEF and HFrEF. There are studies suggesting that ACEI do not have the same effect in HFpEF with AF as in HFrEF, but data are limited. Mineralocorticoid-receptor antagonists reduce fibrosis in patients with heart failure, being currently investigated for their efectiveness in HFpEF with AF [48]. Also, PARAMOUNT phase II trial (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion) noticed that neprilysin inhibitors restore ANP levels and the angiotensin receptor-neprilysn inhibitor LCZ696 reduces left atrial volume in HFpEF [49].

Anticoagulation and antioxidants therapy is essential in patients with HFpEF and AF, as AF is associated with high risk of stroke and thromboembolism. The risk of stroke is similar in AF with HF, regardless of the ejection fraction. The clinical trials noticed that anticoagulants have the same efficacy in AF, with or without HF [50-52]. Clinicians can choose between direct oral anticoagulants or non-antivitamin K (for patients >65 years or with other risk factors).

The loop and thiazide diuretics are used to reduce congestion and volume overload, normalizing the fluid balance, thus improving the symptoms and controlling hypertension.

Symptoms of AF in patients with HFpEF are improved with heart rate control therapy. Rate control therapy is recommended especially in elderly patients with HFpEF and AF, to reduce symptoms related to rapid heart rate and, also, to improve the ventricular filling time. Heart rate control in HFpEF and AF should target an initial heart rate of <110 bpm, using beta-blockers as the first-line choice for the long-term control of heart rate [53]. Digoxin can be used in HFpEF with AF for heart rate control, but is mostly preferred in HFrEF [54]. Studies noticed that the combination beta-blocker/digoxin is associated with an improvement in left ventricular ejection fraction, compared with placebo [55]. Also, calcium channel blockers (non-dihydropyridine calcium channel blockers - verapamil or diltiazem) are used for heart rate control in patients with AF and HFpEF. This class is not recommended in patients with HFrEF and AF. If patients with HFpEF and AF are refractory to rate control therapy and symptoms persist, rhythm control therapy with antiarrhythmic drugs, cardioversion (if haemodynamic compromise) or catheter ablation can be used. Antiarrhythmic drugs, such as dofetilide (which is not approved in Europe) and amiodarone are used for rhythm control in patients with persistent symptoms under rate control therapy.

Catheter ablation is recommended in patients who have failed to antiarrhythmic drugs. Data suggests that ablation in AF with HFpEF is associated with an improvement of left ventricle ejection fraction [56]. Also, studies have found that catheter ablation for AF with HFpEF is associated with improved diastolic function [57]. Advanced AF ablation techniques, which are currently under investigation, promise a better prognosis, even in patients with HFpEF and atrial remodeling.

Clinical studies did not demonstrate the superiority of rate or rhythm control strategy in patients with AF [58]. In AF-CHF trial, there were not differences between rate or rhythm control regarding the cardiovascular death in patients with HF and AF [59]. Rhythm control strategy for AF in patients with HFpEF can fail in some cases, either because the intervention was delayed, either when the adverse effects of AF were already irreversible. Studies on catheter ablation in AF show that restoration of sinus rhythm is associated with improvement of left ventricular ejection fraction [60]. Guidelines recommend rhythm control therapy for patients with persistent symptoms of AF and HF, despite the correct treatment for rate control [61].

Resynchronization, implantable defibrillator and mechanical support are part of the management of patients with AF and HFpEF. The trials suggest that patients with HFpEF and AF are at risk to develop sustained ventricular tachyarrythmia and arrhythmic death, so implantable cardiac devices may be indicated to improve prognosis

[62]. It is not known if cardiac resynchronization therapy (CRT) has benefits in Hope, with or without AF. The real benefits of CRT in HFpEF will be explored in future trials, because dyssynchronysm in HFpEF differs from HFrEF.

Future studies are required for the optimal strategy regarding rate and rhythm control in patients with AF and HFpEF. Also, optimal methods for improving efficacy and safety are needed. Ablation is an encouraging alternative, but more information is needed regarding effectiveness, complications and benefits in patients with HFpEF and AF. Also, the best treatment strategy needs to be established. There are upcoming trials, such as CASTLE-AF, that studies the effects of catheter ablation for AF in patients with HF, IMPRESS-AF (that studies the effects of spironolactone in AF with HFpEF), expected to report their results.

Conclusions

HFpEF frequently coexist with AF, but unanswered questions remain about the pathophysiology, symptomatology, diagnosis, treatment and prognosis of these two conditions. More research is needed to develop new therapies that can improve clinical outcomes and quality of life in patients with HFpEF and concomitant AF.

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