REVIEW

Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction: Pathophysiology and the Role of Catheter Ablation

Sokratis Pastromas, MD, Deputy Director, First Cardiology Department, Henry Dunant Hospital Center, Athens, Greece

* Email: spastromas@yahoo.gr

Abstract

Atrial fibrillation (AF) and heart failure (HF) often coexist, and the prognosis of patients who have both these conditions is worse than those with either condition alone. Heart failure with preserved ejection fraction (HFpEF) is a clinical condition that was initially characterized as diastolic dysfunction HF, then as HF with normal ejection fraction, and more recently as HFpEF. About one-third of patients with HFpEF suffer from AF. Although, both clinical entities share common pathophysiologic mechanisms, current knowledge of the relationship between AF and HFpEF is limited. Catheter ablation, although data from randomized trials in this category of patients are limited, seems to have beneficial effects regarding maintenance of sinus rhythm and re-hospitalization rates. ***Rhythmos 2020;15(2):29-32.***

Keywords*:* atrial fibrillation; heart failure; heart failure with preserved ejection fraction; tachycardia-induced cardiomyopathy; catheter ablation

Abbreviations: AF = atrial fibrillation; AV = atrioventricular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction; TICM = tachycardia-induced cardiomyopathy

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a common clinical syndrome, associated with high morbidity and mortality rates and currently represents approximately 50 % of HF cases.[1] HFpEF is mainly a clinical diagnosis, consisting of typical HF symptoms in patients with left ventricular ejection fraction (LVEF) ≥50%.[2] The diagnostic criteria include both elevated levels of natriuretic peptides and echocardiographic evidence of left ventricle diastolic dysfunction or structural heart disease.[2] Epidemiological data from large clinical trials, such as the Framingham Heart Study, have shown that patients with HFpEF are usually older overweight women with a high prevalence of comorbidities including atrial fibrillation (AF).[3] Nowadays, about 30 and 25 million patients suffer from AF and HF, respectively.[4,5] Both AF and HF have high prevalence but also, they share common pathophysiological mechanisms. The combination of these conditions is associated with worse clinical outcomes and higher rates of hospitalization. Most of the data are derived from clinical trials of patients with heart failure with reduced ejection fraction (HFrEF). However, HFpEF accounts for up to 50% of prevalent HF, and is thought to be more closely related to AF than HFrEF.[1,] Thus, in the Framingham Heart Study, the presence of AF was more strongly linked to incident HFpEF than HFrEF.[3] Overall, 62% of patients with HFpEF had AF at any time, which was significantly higher than the HFrEF cohort in the Framingham cohort. Moreover, the presence of AF may be a marker of more advanced HFpEF and worse exercise tolerance.[6] Atrial fibrillation is mostly presented as asymptomatic paroxysmal AF, so the diagnosis can be easily missed.[7] Additionally, patients with AF could exhibit symptoms, such as dyspnea and impaired exercise tolerance, which could overlap with HFpEF, making difficult the diagnosis.

Pathophysiology

Risk factors that predispose to HFpEF and AF

Many of patients with HFpEF who experience AF during the course of their disease, share common risk factors and pathophysiological mechanisms. Comorbidities and risk factors include diabetes mellitus, obesity, coronary artery disease, obstructive sleep apnea, smoking and hypertension.[8] It is known that systemic inflammation plays an important role in the pathophysiology process in both HF and AF (**Fig**. 1). Additionally, we know that the incidence of AF increases in older patients and the age-related left ventricular diastolic dysfunction contributes to the occurrence of AF.[9]

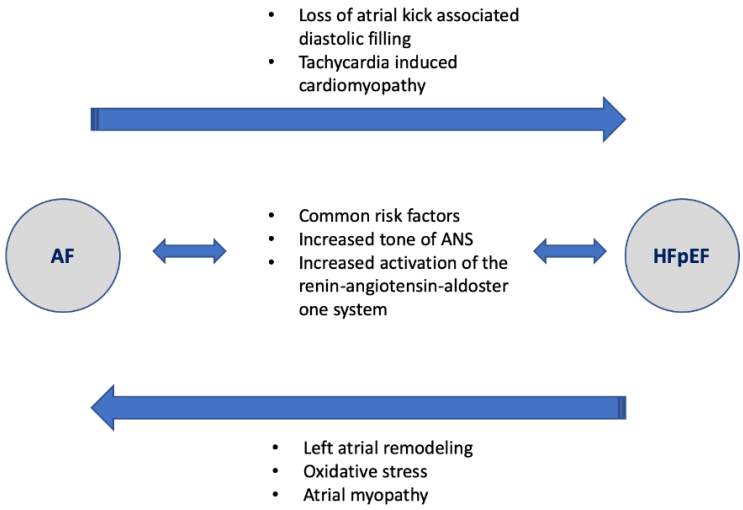

Figure 1. Common risk factors and pathophysiologic mechanisms between atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). ANS = autonomic nervous system

AF as the cause of HFpEF

Atrial fibrillation itself could directly lead to HFpEF via left atrium dilatation and loss of atrial systole, which impairs the diastolic left ventricular (LV) function and subsequently the cardiac output. In sinus rhythm atrial contraction is estimated to contribute up to 20% of the cardiac output. It is noteworthy that atrial systole in adults > 50 years old is responsible for up to 70% of ventricular filling.[10] During AF the contractile coordination between atria and ventricles (atrioventricular-AV dyssynchrony) worsens the diastolic LV function causing HF symptoms. Furthermore, atrioventricular annular remodeling with progressive mitral and tricuspid regurgitation may be another mechanism by which AF causes HFpEF.[11] Additionally, AF with rapid ventricular response causes shortening of diastolic intervals without significant worsening in systolic function.[12]

Left ventricular fibrosis is found in many patients with HFpEF and despite LV hypertrophy due to hypertension, AF plays a primary role in the pathophysiologic process.[8] The presence of persistent AF has been reported as an independent predictor of LV fibrosis, regardless of ejection fraction.[8] In the same study paroxysmal AF did not predict LV fibrosis at the same degree as permanent AF.[8] The AF-induced ventricular fibrosis has been related primarily to the tachycardia induced cardiomyopathy (TICM).[13] TICM is a reversible systolic dysfunction associated with some types of tachyarrhythmias (commonly AF) or high burden of premature ventricular beats. The exact mechanisms underlying TICM are not fully defined, but include subclinical ischemia, abnormalities in energy metabolism, redox stress and calcium overload and most data are derived from patients with HFrEF.[14] Underlying histologic changes are characterized by cardiomyocyte lengthening and hyperplasia, extracellular matrix changes, myocardial fibrosis, myofibril misalignment, loss of sarcomere register, and apoptosis.[15] Beyond the high heart rate during AF, the asynchronous myocardial contraction can lead to LV dysfunction.[15]

HFpEF as the cause of AF

Echocardiographic data from patients with HFpEF show, in most of the cases, structural and electrical remodeling of the left atrium (LA) which is related with high incidence of AF and atrial fibrosis. Compared to age-matched control subjects in the general population, patients with HFpEF have 68% larger LA volumes.[16] Increased left atrium stretch leads to anisotropy with increased dispersion of refractoriness leading to an increased vulnerability to AF.[17,18] Underlying histologic changes include abnormal electrical coupling between cardiomyocytes through gap junctions involving atrial connexin proteins and loss of cell-to-cell coupling in areas of fibrosis.[19] All these processes lead to electrical remodeling and increased atrial refractoriness and development of re-entry circuits predisposing to AF.[20,21]

Inflammatory cytokines in addition to the upregulation of the autonomic sympathetic system and the renin-angiotensin-aldosterone system contribute to the development of structural remodeling of the left atrium.[22] High adrenergic activity seems to play an important role not only on the initiation but on the maintenance of AF, as well.[23] Elevated natriuretic peptide levels and increased sarcoplasmic reticulum calcium content, increases afterdepolarizations originating from the pulmonary veins which have been recognized as the triggers for AF.[24,25]

Prognosis of patients with HFpEF and AF

It is known that the presence of AF in patients with HF increases the mortality rates compared to HF patients without AF (HR: 1.30 and 2.45, respectively).[26] The type of HF seems to have a different impact on outcomes. Data from a meta-analysis have shown that all-cause mortality was significantly higher in patients with HFrEF and AF than in those with HFpEF and AF (RR: 1.24; 95% CI: 1.12 to 1.36; $p < 0.001$). However, the hospitalization and stroke rates were similar between the two groups.[27] Women with HFpEF and AF had worse prognosis compared to men, as noted in the I-PRESERVE study.[28] From the same study, data have shown that stroke rates in HFpEF patients were doubled in those with a history of AF, regardless of whether they were in AF at the time of assessment.[29]

Role of catheter ablation in patients with AF and HFpEF

Catheter ablation, compared with amiodarone therapy, significantly reduces recurrent AF in patients with HFrEF. In general, patients with HF have a high recurrence of AF and more frequently require repeat ablation procedures. CASTLE-AF showed the efficacy of rhythm control by AF ablation in patients with HFrEF.[30] Machino-Ohtsuka et al. first demonstrated the safety and efficacy of AF ablation in patients with coexisting AF and HFpEF, showing a success rate of 73% with one or two procedures and pharmacotherapy, and improved diastolic function associated with sinus rhythm.[31] In another retrospective analysis, Black-Maier et al concluded that procedure

success rate and functional improvement after AF ablation were similar in HFrEF and HFpEF.[32] Moreover, Machino-Ohtsuka et al showed that rhythm control in AF-HFpEF via either ablation or medication led to a significantly reduced composite of cardiovascular death and HF hospitalization compared with rate control.[31]

Recently, Fukui et al presented the results of a single-center, retrospective analysis of 85 consecutive AF-HFpEF patients who received either catheter ablation or antiarrhythmic drugs and/or beta-blockers. AF ablation was performed with pulmonary vein antrum isolation (PVAI) plus focal ablation, superior vena cava ablation, and cavotricuspid isthmus linear ablation.[33] The primary endpoint was re-hospitalization due to HF. During a mean follow-up of 792 days, more patients in the ablation group were free from HF hospitalization (P = 0.039) and in the multivariate analysis, catheter ablation was the only factor that reduced the re-hospitalizations due to HF (OR = 0.15; P < 0.001). As regards the sinus rhythm maintenance, no significant difference was seen between the two groups (P=0.119). According to the National Heart, Lung, and Blood Institute report, AF ablation in HFpEF is one of the major unmet research needs in this field.[33] Currently, only one study on this field, Treatment of Atrial Fibrillation In Preserved Cardiac Function Heart Failure (TAP-CHF, NCT04160000), is currently active and is scheduled to be completed by 2024.

Conclusion

AF-HFpEF is a complex clinical entity and the global burden of both diseases is going to increase as the population ages, and the prevalence of comorbidities like hypertension, diabetes mellitus, obesity, and coronary artery disease is increasing. Currently, stroke and systemic embolism prophylaxis is the only therapy known to reduce mortality among patients with AF-HFpEF. Catheter ablation seems to have beneficial effects in these patients regarding the hospitalization rates. However, randomized clinical trials are warranted to confirm the hypothesis that achieving long-term sinus rhythm by ablation, will have impact on the reduction of hard end points, such as the mortality and the stroke rates.

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