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Atrial Fibrillation In Heart Failure With Preserved Ejection Fraction

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Abstract

Background: Heart failure with preserved ejection (HFpEF) represents nearly half of all patients with heart failure (HF). The objective of this study was to examine the characteristics of patients with atrial fibrillation (AF) and HFpEF to determine factors that might explain the adverse prognosis.

Methods and Results: Data were collected on 196 patients with HFpEF in a non-hospitalized setting. Clinical and laboratory variables were collected. Patients with AF were compared to those with sinus rhythm. AF was present in 25% of the study population. Individuals with AF had a significant ($p<0.05$) and three-fold greater B-type natriuretic peptide level than individuals without AF. Individuals with AF had significantly ($p<0.05$) larger left atrial volumes. AF was associated with evidence of significantly ($p<0.05$) worse diastolic function and was also significantly greater prevalence of moderate mitral or tricuspid regurgitation. In multivariate analysis, considering age, left atrial volume index, E/A ratio, E/e' and left ventricular internal diameter (LVID), only age and left atrial volume index were significant ($p<0.05$) independent factors related to the presence of atrial fibrillation in HFpEF.

Conclusions: AF in patients with HFpEF is an indication of more severe or advanced heart failure. Several explanations are possible as unifying cellular pathways that links atrial fibrillation and HFpEF specifically processes leading to increases in atrial and ventricular inflammation and/or fibrosis.

Introduction

Atrial fibrillation (AF) is a well-recognized indicator of increased morbidity and mortality [1,2]. A number of factors such as age, heart failure, diabetes mellitus, previous stroke and hypertension identify individuals at higher risk for an adverse outcome which often is thromboembolism, justifying the need for anticoagulation [3,4]. There are, however, challenges with the definition of some of those factors [5]. The reason for the adverse interaction of heart failure and atrial fibrillation is not completely understood. The type of heart failure in patients with AF is more likely to be heart failure with preserved ejection (HFpEF) rather than heart failure with reduced ejection fraction [6]. HFpEF, which affects nearly half of all patients with heart failure, carries a 50% mortality over 5 years [7–9].

Key Words

Atrial Fibrillation; Heart Failure With Preserved Ejection Fraction, Left Atrial Volume

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We and others have demonstrated the importance of the coexistence of AF with HFpEF because the combination is associated with a poor outcome [10]. In 1,744 patients with HFpEF referred for cardiopulmonary stress testing at the Cleveland Clinic, AF was associated with impaired contractile reserve, less peak exercise performance and increased mortality [11]. In the Candesartan in Heart failure-Assessment of moRtality and Morbidity (CHARM) study, AF was associated with greater relative risk of the major outcomes in patients with HFpEF than in patients with HFrEF [12]. In an outcomes registry of patients treated for AF, HFpEF was associated with poor long-term outcomes [6]. In a retrospective study of 8,931 patients, AF was associated with a poorer 5-year survival in those with HFpEF than those with HFrEF and it was independent of age [13]. In 1,765 patients enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, Atrial fibrillation at enrollment was associated with increased risk for cardiovascular events and atrial fibrillation that occurred after randomization was associated with an increased risk of morbidity and mortality, that was not influenced by spironolactone [14].

The objective of this study was to examine the characteristics of patients with AF and HFpEF to determine factors that might explain the adverse prognosis.

Methods

The study population has been previously described [10]. Briefly, it is a retrospective study of 196, consecutive, patients with HFpEF who presented in an ambulatory cardiology clinic setting. The study was approved by our Institutional ethics committee. Each patient chart was carefully reviewed by one data collector. The inclusion criteria were (i) adults over the age of 18, and (ii) HFpEF confirmed on a transthoracic echocardiogram (TTE). HFpEF was defined based on the 2016 European Society of Cardiology criteria that included a left ventricular ejection fraction (LVEF) ≥50% [15]. The exclusion criteria were indeterminate diastolic dysfunction on TTE, previous cardiac surgery or severe valvular heart disease. Patients with valvular heart disease graded as mild or moderate were included.

Demographic data, medical history, cardiovascular risk factors, history of stroke, kidney disease, lung disease, other comorbidities, blood pressure, and laboratory test results were collected. The presence of atrial fibrillation was recorded based on a 12 lead ECG done at or before the most recent clinic visit. Records from the most recent clinic visit were used to obtain the information for each patient. Laboratory data included creatinine level, HbA1c, B-type natriuretic peptide (BNP), and lipid profile. The data on BNP were collected from the last hospital admission or during previous clinic visits when there was exacerbation of symptoms. Echocardiographic data included LVEF, valvular abnormalities, atrial and ventricular chamber sizes. The assessment of LVEF was determined by assessment of left ventricular cavity dimensions applying Simpson's method, in the majority of cases. In the other cases, a visual estimation was made. Visual estimation of LVEF by 2D echo by an experienced reader correlates well with EF determined by quantitative real-time three-dimensional echocardiography [16] The degree of diastolic dysfunction including diastolic parameters followed uniformly agreed upon recommendations [17]. Only patients whose diastolic function could be assessed during TTE were included in the tabular data.

Data analysis

Normally distributed continuous variables were described as mean and standard deviation, and others were expressed as medians and interquartile ranges. Tests of significance used analysis of variance (ANOVA) Kruskal-Wallis method for continuous traits and the Chi-squared test was used for categorical traits. A multivariate regression analysis was performed evaluating the presence or absence of atrial fibrillation using the variables: age, left atrial volume index, E/A ratio, E/e' and left ventricular internal diameter (LVID). All analyses were performed with RStudio version 1.2 (RStudio Inc., United States). A p-value of <0.05 was considered statistically significant.

Results

AF was present in 25% of the study population. Individuals with AF were significantly older that those in sinus rhythm (Table 1). Individuals with AF were less likely to have diabetes mellitus or coronary artery disease. Individuals with AF and those in sinus rhythm had identical left ventricular ejection fraction or identical systolic function. However, those with AF had a three-fold higher BNP level.

Individuals with AF had significantly (p<0.05) larger left atrial volumes. AF was associated with evidence of worse diastolic function as reflected by significantly (p<0.05) higher mitral E/A ratio, elevated left ventricular filling pressure and more moderate or severe diastolic dysfunction (Table 2). Although the type of atrial fibrillation was not collected, the high proportion with mitral E/A ratio data suggests the majority of cases had paroxysmal atrial fibrillation. AF was also significantly associated with a greater prevalence of moderate mitral or tricuspid regurgitation (severe valvular heart disease was an exclusion criterion). A multivariate analysis, performed to distinguish the presence atrial fibrillation, used the variables age, left atrial volume index, E/A ratio, E/e' and left ventricular internal diameter (LVID) and showed that this model was significantly (p=2.6663-05) related to the presence of atrial fibrillation. The multivariate analysis showed that of these variables only age (p=0.029) and left atrial volume index (p=0.00019) were significant independent factors related to the presence of atrial fibrillation.

Discussion

This study demonstrated that AF accompanying HFpEF is more often present in patients with more severe diastolic dysfunction, which was reflected by higher circulating levels of BNP, and echocardiographic evidence of a larger left atrium and moderate or severe diastolic dysfunction. While left atrial size (volume) was larger in patients with AF, it can be questioned whether the loss of coordinated atrial contraction in AF is responsible for the larger left atrial size. However, the presence of indices of elevated left ventricular filling pressure and higher prevalence of moderate and severe diastolic dysfunction suggest that the larger left atrial volume is an indicator of worse left ventricular diastolic dysfunction. In addition, there was a three-fold

Table 1: Study population demographics

	Atrial fibrillation (N=49)	Sinus rhythm (N=147)	p-value
Age (years)	83 (72.5, 87.5)	75 (67, 84)	0.003
Male (%)	33	48	0.043
Hypertension (%)	71	74	0.750
Diabetes (%)	10	29	0.001
Dyslipidemia (%)	41	55	0.066
Coronary artery disease (%)	24	41	0.006
Chronic kidney disease (%)	20	18	0.860
Stroke or transient ischemic attack (%)	12	7	0.340
Lung disease (%)	12	7	0.340
Obstructive sleep apnea (%)	8	7	0.990
Body mass index (kg/m2)	25.9 (22.9, 29.4)	25.6 (23.1, 31.3)	0.510
Systolic blood pressure (mmHg)	130 (120, 140)	135 (122, 145)	0.230
Low-density lipoprotein (mmol/L)	2.04 (1.5, 2.74)	2.02 (1.47, 2.64)	0.760
Serum creatinine (mmol/L)	98 (77, 116.5)	88 (71, 114)	0.090
HbA1c (%)	5.8 (5.6, 6.2)	5.8 (5.6, 6.5)	0.310
B-type natriuretic peptide (pg/ml)+	349 (128, 777)	111 (33, 339)	<0.001
Left ventricular ejection fraction (%)	60 (55, 65)	60 (55, 60)	0.210

+ BNP data were available in 36 individuals with atrial fibrillation and 85 individuals in with normal sinus rhythm group
Data on heart rate was not collected

Table 2: Summary of echocardiographic findings

	Atrial fibrillation (N=49)	Sinus rhythm (N=147)	p-value
Right ventricle diameter (mm)	36 (34, 39)	35 (30, 38)	0.071
Tricuspid annular plane systolic excursion (mm)	21 (20, 27)	23 (19, 26)	0.800
Left atrial volume index (mL/m2)	50 (39, 57)	36.5 (32, 45)	<0.001
Left ventricle end-diastolic diameter index (mm/m2)	26 (24, 29)	26 (23, 29)	0.480
Left ventricle mass index (g/m2)	97 (80, 112)	92 (74, 109)	0.340
Mitral valve E/A ratio+	1.35 (0.95, 1.9)	0.91 (0.7, 1.2)	<0.001
Average E/e' ratio++	15 (11.8, 19.5)	13.9 (10, 16.6)	0.047
Pulmonary artery pressure (mmHg)	34 (26.5, 40)	28 (24, 35)	0.036
Elevated LV filling pressure (%)	84	57	<0.001
Moderate diastolic dysfunction (%)	57	50	<0.001
Severe diastolic dysfunction (%)	16	3	<0.001
Moderate MR (%)	41	23	<0.001
Moderate AS (%)	4	7	0.540
Moderate AR (%)	10	10	0.999
Moderate TR (%)	45	17	<0.001

• + E/A was available in 46 individuals in the atrial fibrillation group and 146 of the individuals in the sinus rhythm group
• ++E/e' was available in all 49 in the atrial fibrillation group and 147 in the sinus rhythm group

level of BNP in the patients with atrial fibrillation compared to those without atrial fibrillation. Whether the rapid ventricular rate that may be associated with AF, is responsible for the adverse outcome when AF coexists with HFpEF is uncertain. There are some data that support this contention [18] while others refute it [19]. The nature of both of those ad hoc analyses requires a prospective clinic trial to answer the question. While our study does not by itself provide incontrovertible evidence for the relationship of HFpEF leading to atrial dilatation and eventual atrial fibrillation, this construct can be supported by other evidence. Left atrial enlargement in HFpEF is associated with alterations in left atrial compliance, reductions in atrial pump function and impairment in atrial contractile reserve [20]. In aged female Fischer F344 rats, a model of HFpEF with left atrial enlargement, there is a high frequency of inducible atrial fibrillation and atrial electrical activation mapping revealed abnormal beta-adrenergic responsiveness and slowed conduction velocity [21]. In addition, in our study left atrial volume was a significant independent factor distinguishing patients with atrial fibrillation compared to those without atrial fibrillation even after considering factors such as age, left ventricular size, and two indices of left ventricular stiffness (the ratios E/A and E/e').

Cellular pathways linking atrial fibrillation and HFpEF

A number of cellular pathways have been proposed to explain HFpEF, including abnormalities of cardiomyocyte relaxation processes that include intracellular calcium kinetics, different autocrine or paracrine factors, endothelial dysfunction, inflammation, dysregulated oxidative and nitrosative stress, dysfunctional nitric oxide and cGMP signaling, titin hypophosphorylation, abnormal metabolism including mitochondrial defects, and abnormalities of small arteries and the microvasculature [22–25].

While we recognize that elevated left ventricular diastolic pressure by passively increasing left atrial pressure may simply distend the atrium leading to atrial fibrillation, we speculate that there are two likely potential unifying molecular and cellular concept to link atrial fibrillation and HFpEF, recognizing that they are speculations and were not addressed directly in our research. Cardiac inflammation and fibrosis are two separate but interwoven processes that might explain AF and HFpEF. Infiltration of immune cells and proteins that mediate the inflammatory response alter atrial electrophysiology and structural substrates increasing vulnerability to AF [26,27]. Cardiac inflammation is evident in animal models of HFpEF. Rabbits fed with a cholesterol-enriched diet develop LVDD with preserved systolic function and evidence of cardiac inflammation and oxidative stress. Increased cardiac expression of mRNA for Nox2, Vcam1, Mmp12, Mmp12/Timp1, Il1b and Col1/Col3 ratios was also higher in these rabbits [28]. Toll-like receptor 9 activation produces cardiac inflammation, and deterioration of diastolic function in the SERCA2a depletion-mediated mouse model of diastolic heart failure [29]. Patients with HFpEF have increased serum levels of pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL) 12, IL-6, monocyte chemoattractant protein 1, C-X-C motif chemokine 10 [30]. The percentage of peripheral monocytes was not only increased in HFpEF but also correlated with echocardiographic indices of diastolic dysfunction [30]. Inflammation can also activate fibrotic pathways leading to cardiac fibrosis with structural remodelling of the atria [26].

Processes leading to increases in cardiac fibrosis in the atrium and ventricle have the capacity to produce respectively atrial fibrillation and HFpEF. Patients with HFpEF have an increased content of myocardial type I collagen, enhanced collagen cross-linking, and lysyl-oxidase (LOX) expression [31]. The production of increased collagen may either be a primary phenomenon or a response to injury, inflammation or myocardial stress. Such stressors may be from valvular heart disease or hypertension. Cardiomyocyte-specific deletion of STAT3 (STAT3cKO) mice develop more cardiac fibrosis than wild type controls [32]. These mice had increased BNP and echocardiographic indices of increased cardiac stiffness [32]. They also demonstrated reduced levels of protein kinase G [32] that is consistent with the picture of HFpEF [24]. HFpEF is associated with higher levels of syndecan-4 [33]. Activation of syndecan-4, a transmembrane proteoglycan, acting through its cytosolic domain and calcineurin/nuclear factor to activate T-cells induces collagen, osteopontin, and LOX which in turn induces cardiac fibroblasts [34]. Syndecan-4 acting through its extracellular domain facilitates LOX-dependent collagen cross-linking [34].

Despite atrial dilation in both HFpEF and HFrEF, patients with HFpEF manifest changes in atrium that are distinct from patients with HFrEF [35,36]. Putko et al found that left atrial enlargement is different between HFrEF and HFpEF because in the former there is a significant relationship between LVEF or LV mass and LA volume which is not consistently observed with HFpEF [36]. Melenovsky et al assessing the pressure volume relationships in left atrium of patients with HFpEF and HFrEF found that the HFpEF group was characterized by increased left atrial stiffening and greater atrial wall stress [35]. Increased left atrial stiffness is consistent with increased atrial fibrosis. AF is well known to be associated with increased atrial fibrosis [37–39]. Atrial fibrosis has been demonstrated by cardiac MRI in AF [37]. The increase in cardiac fibroblasts enhances the probability of their contact with cardiomyocytes. Cardiomyocytes and fibroblasts can

develop low-resistance electrical junctions that can enhance phase 4 depolarization and promote ectopic impulse formation leading to re-entrant arrhythmias [38].

Aging is associated with an increased incidence of AF [40] as well as an increased incidence of HFpEF [41]. The mechanisms responsible for the increased incidence of AF with aging encompass aging-induced atrial electrical and structural remodelling, disturbed calcium homeostasis, enhanced atrial ectopic activity, impairment of sinus node function, increased atrial effective refractory period (ERP), slowed conduction in different regions of the atrium and increased vulnerability to re-entry arrhythmias [40, 42]. Fundamental to the aging process, however, is increased organ fibrosis which also takes place in the heart [43]. 'Reactive interstitial fibrosis", a term applied to the expansion of the cardiac interstitial in the absence of significant cardiomyocyte loss [44], is evident with aging and has been attributed, in part, to reactive oxygen species, chemokine growth factors such as TGF-β, endothelin-1 and angiotensin II signaling that increase collagen synthesis [43]. Reductions in collagen degradation pathways may be more important than increased de novo synthesis in the pathogenesis of aging-associated fibrosis [43] as aging is associated with down-regulation of matrix mletalloproteinase-2 (MMP-2) mRNA with reduced MMP-2 levels as well as reduced proMMP-1 activity [45].

TGF)-β, may play a critical role in aging-induced myocardial fibrosis as it can induce myofibroblast transdifferentiation, enhance fibroblast matrix protein synthesis, as well as suppressing MMP activity by inducing synthesis of protease inhibitors, such as PAI-1 and TIMPs [43]

Study limitations

The limitations of our study have been previously been discussed [10] but it is worthwhile to restate that retrospective studies have challenges and limitations mainly with missing data for subjects that met the inclusion criteria. However, for the variables included in our study population, less than 1% were missing and required imputation [10]. This was a significant improvement compared to a number of other HFpEF studies [46–48]. Never the less it limits the ability to do propensity matching to compare the different group assessing the impact of variables such as BNP and E/A between groups. Another issue is referral bias which may have affected the composition of the patient population. However, the mean age of the large study population in iPreserve was 72 years [49] compared to 77 years of age in our study, A younger patient population in a clinical trial would be expected because of the need for follow-up. The predominance of women (66% in our study is comparable to 60% in iPreserve [49] and 60% in the CHARM-preserved study [50]. The percentage of hypertension, 73%, in our study compares to 65% in CHARM-preserved [50] and 88.5% in iPreserve [49]. Left ventricular ejection fraction was similar in the studies being 60% in our study and 54% in CHARM -preserved [50] and 60 % in iPreserve [49]. A consideration is that the patients in the study did not have 24-hour ECGs to determine the 'burden' of atrial fibrillation in the atrial fibrillation group and whether there might have been some cases of atrial fibrillation present in the non-atrial fibrillation group. This issue, however, is always present as even a 24-hour ECG is only a brief time in the course of HFpEF condition. An insertable cardiac monitor is even more effective than conventional follow-up for atrial fibrillation detection in patients with cryptogenic stroke [51,52]. We did not calculate the CHAD-VASC score in our patient population as the objective of our study was to examine the relationship between HFpEF and atrial fibrillation and not the stroke risk in the HFpEF population with or without atrial fibrillation. Another limitation of the study is that we did not have other indicators of heart failure to compare the atrial fibrillation and non-atrial fibrillation groups. However, BNP levels were three times higher in the atrial fibrillation compared to the non-atrial fibrillation group. Recognizing that BNP is not a perfect mirror of heart failure, it is note worthy that BNP levels are similarly elevated in HFpEF as HFrEF [53]

Conclusion

The coexistence of AF and HFpEF indicates the severity of the underlying processes that lead to each of these conditions. When AF is present with HFpEF, there is an increased likelihood of more severe heart failure as indicated by higher circulating BNP levels, worse diastolic function, reflected by echocardiographic indices of diastolic dysfunction and most importantly larger left atrial size.

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