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Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction

Association With Exercise Capacity, Left Ventricular Filling Pressures, Natriuretic Peptides, and Left Atrial Volume

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ABSTRACT

OBJECTIVES This study sought to study the association of atrial fibrillation (AF) with exercise capacity, left ventricular filling pressure, natriuretic peptides, and left atrial size in heart failure with preserved ejection fraction (HFpEF).

BACKGROUND The diagnosis of heart failure with preserved ejection fraction (HFpEF) in patients with AF remains a challenge because both contribute to impaired exercise capacity, and increased natriuretic peptides and left atrial volume.

METHODS We studied 94 patients with symptomatic heart failure and left ventricular ejection fractions ≥45% using treadmill cardiopulmonary exercise testing and right- and/or left-sided cardiac catheterization with simultaneous echocardiography.

RESULTS During catheterization, 62 patients were in sinus rhythm, and 32 patients had AF. There were no significant differences in age, sex, body size, comorbidities, or medications between groups; however, patients with AF had lower peak oxygen consumption (VO_2) compared with those with sinus rhythm (10.8 ± 3.1 ml/min/kg vs. 13.5 ± 3.8 ml/min/kg; $p = 0.002$). Median (25th to 75th percentile) N-terminal pro–B-type natriuretic peptide (NT-proBNP) was higher in AF versus sinus rhythm (1,689; 851 to 2,637 pg/ml vs. 490; 272 to 1,019 pg/ml; $p < 0.0001$). Left atrial volume index (LAVI) was higher in AF than sinus rhythm (57.8 ± 17.0 ml/m^2 vs. 42.5 ± 15.1 ml/m^2; $p = 0.001$). Invasive hemodynamics showed higher mean pulmonary capillary wedge pressure (PCWP) (19.9 ± 3.7 vs. 15.2 ± 6.8) in AF versus sinus rhythm (all $p < 0.001$), with a trend toward higher left ventricular end-diastolic pressure (17.7 ± 3.0 mm Hg vs. 15.7 ± 6.9 mm Hg; $p = 0.06$). After adjusting for clinical covariates and mean PCWP, AF remained associated with reduced peak VO_2 increased log NT-proBNP, and enlarged LAVI (all $p \leq 0.005$).

CONCLUSIONS AF is independently associated with greater exertional intolerance, natriuretic peptide elevation, and left atrial remodeling in HFpEF. These data support the application of different thresholds of NT-proBNP and LAVI for the diagnosis of HFpEF in the presence of AF versus the absence of AF. (J Am Coll Cardiol HF 2016;■:■–■)

Atrial fibrillation (AF) is the most common arrhythmia in heart failure with preserved ejection fraction (HFpEF), with a prevalence of 20% to 40% at the time of presentation (1). It occurs in two-thirds of patients at some point during the course of HFpEF (2,3). Patients with HFpEF are more likely to have prevalent AF or AF at any time compared with those with heart failure and reduced ejection

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

EF = ejection fraction

eGFR = estimated glomerular filtration rate

HFpEF = heart failure with preserved ejection fraction

LAVI = left atrial volume index

LV = left ventricular

LVEDP = LV end-diastolic pressure

NT-proBNP = N-terminal pro–B-type natriuretic peptide

NYHA = New York Heart Association

PCWP = pulmonary capillary wedge pressure

TAPSE = tricuspid annular plane systolic excursion

VO_2 = oxygen consumption

fraction (2). Furthermore, AF has an independent prognostic impact in HFpEF (2–4).

AF is an important confounder of the diagnosis of HFpEF because of its close association with both HFpEF and the diagnostic criteria used to define HFpEF. The diagnosis of HFpEF is made when there are: 1) typical symptoms and signs of heart failure (e.g., exercise intolerance); 2) a preserved left ventricular (LV) EF; and 3) evidence of LV diastolic dysfunction (e.g., left atrial enlargement) (5). Circulating natriuretic peptides such as N-terminal pro–B-type natriuretic peptide (NT-proBNP) are often used to confirm the diagnosis, particularly in clinical trials (6–8). However, AF itself and its comorbidities cause exercise intolerance, left atrial enlargement, and increased NT-proBNP, even in the absence of overt heart failure (9). Clinical trials have attempted to account for this by proposing different left atrial volume index (LAVI) and NT-proBNP cutoffs for the concurrent diagnosis of HFpEF in the presence of AF. However, these cutoffs are arbitrary and not uniformly applied (e.g., NT-proBNP ≥600 pg/ml in the SOCRATES [Soluble Guanylate Cyclase Stimulator in Heart Failure Studies-Preserved] (8) and >900 pg/ml in PARAGON [Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction]-HF trials), reflecting the continued lack of understanding regarding the extent to which AF increases NT-proBNP or LAVI independent of LV filling pressures in HFpEF.

Accordingly, we aimed to study the association of AF with exercise capacity, NT-proBNP, and LAVI in a HFpEF population uniformly characterized by gold standard invasive measurements of LV end-diastolic pressure (LVEDP) and mean pulmonary capillary wedge pressure (PCWP).

METHODS

STUDY POPULATION. The study population was identified from 102 patients with HFpEF based on severe heart failure symptoms (New York Heart Association [NYHA] functional class ≥II) and LVEF ≥45% who were referred for routine left- and right-sided cardiac catheterization with simultaneous echocardiography because of signs of pulmonary hypertension on a previous echocardiogram. These patients represented the screening cohort for a trial of sildenafil in HFpEF with pulmonary hypertension (10). Of the 102 patients, 32 (31%) had AF, 62 (61%) had sinus rhythm, and 8 (8%) had paced rhythms during catheterization. We excluded the 8 patients with paced rhythms from the analyses, leaving 94 patients in the final study population with right heart catheterization. Of these, 90 had simultaneous echocardiography, and 84 had combined left and right heart catheterization. This study was conducted in accordance with local and national regulations regarding retrospective clinical research, and approved by the Institutional Review Board of the University Medical Center Groningen.

STUDY PROCEDURES. Detailed study procedures have been previously published (10). In brief, patients underwent standardized clinical evaluation and 12-lead electrocardiography at rest. Treadmill exercise cardiopulmonary oxygen gas exchange was performed, with peak oxygen consumption (VO_2) determined at maximal exertion (when the patient either reached a plateau phase for 1 minute, could not walk further, was unable to maintain walking speed, or displayed a reduction in breathing reserve and oxygen heart rate).

Cardiac catheterization with simultaneous echocardiography was performed under stable, fasting conditions with the patient in supine position. All echocardiograms were measured by the same investigator (YMH), and all cardiac catheterizations were performed by the same cardiologist (ESH). Intraobserver reproducibility for standard echo measurements was evaluated in a subset of 20 randomly selected examinations and showed excellent reproducibility (correlation >0.8 for all 2-dimensional and Doppler parameters). During cardiac catheterization, a 7-F thermodilution balloon-tipped catheter was inserted into the right femoral vein, floated under fluoroscopy to the right atrium, advanced to the right ventricle, and positioned in the pulmonary artery. Change from the pulmonary artery waveform to the typical pulmonary wedge pressure waveform on inflation of the balloon catheter and the expected fluoroscopic position of the catheter were ensured for satisfactory pulmonary wedge pressure determination. PCWP was measured at end-expiration and used as a surrogate measure of the LVEDP as previously validated (11). Left heart catheterization was performed to exclude significant coronary artery disease or left-sided valve disease, and LVEDP was measured. All hemodynamic measurements were performed before contrast injections.

Simultaneous echocardiographic image acquisition was performed according to a pre-specified protocol using a Vivid S6 (GE, Horton, Norway) and a 2.5- to 3.5-mHz probe. Standard evaluation of cardiac dimensions and LV function were performed according to the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging (12). LAVI was measured

using the biplane area–length method. All measurements were determined using the average of at least 3 cardiac cycles in patients with AF.

Blood draw was performed at baseline for measurements of NT-proBNP by the Elecsys proBNP enzyme-linked immunosorbent assay (Roche Diagnostics, Mannheim, Germany). The assay has a lower detection limit of 5.00 pg/ml and an analytical variability of 3.3% in our laboratory.

STATISTICAL ANALYSES. Study groups (AF vs. sinus rhythm) were compared using chi-square tests for discrete variables and Student *t* tests for normally distributed continuous variables. Log transformation was performed for variables with skewed distribution. In our study with 32 patients with AF and 62 patients with sinus rhythm, we were able to detect minimum differences in the means of peak VO_2, log NT-proBNP, and LAVI of −0.45 ml/min/kg, 0.11 pg/ml, and 3.16 ml/m^2, respectively, at 90% power and 5% level of significance. We used multivariable linear regression to test the independent association of AF with peak VO_2, log NT-proBNP, and LAVI, in which the dependent variable was peak VO_2, log NT-proBNP, or LAVI; covariates included group (AF vs. sinus rhythm), age, sex, heart rate, body mass index, LVEF, estimated glomerular filtration rate (eGFR), diabetes, hypertension, history of myocardial infarction, history of stroke, and mean PCWP or LVEDP. Covariates were selected based on a priori clinical knowledge and entered into models in a stepwise manner to select the most parsimonious model. The adjusted R^2, which incorporates the model's degree of freedom and/or number of terms, was used to assess the model fit in the linear regression. To determine the percent variability of each outcome variable (peak VO_2, log NT-proBNP, LAVI) that was attributable to AF, we compared the type I sum of squares with the type III sum of squares before and after the addition of AF to the model, adjusting for all other covariates. In secondary analyses, we further adjusted for type of AF (permanent vs. paroxysmal). Finally, in sensitivity analyses, we excluded 12 patients with a history of AF who were in sinus rhythm at catheterization. All analyses were performed using SAS for Windows version 9.3 (SAS Institute, Cary, North Carolina) and SPSS version 22 (IBM, Armonk, New York). A 2-tailed p value < 0.05 was considered significant. We accounted for multiple testing in the primary analyses using the Bonferroni correction.

RESULTS

CLINICAL CHARACTERISTICS. Compared with patients in sinus rhythm (n = 62) at catheterization, there were no statistically significant differences in age, sex, body size, comorbidity burden, or treatment in those with AF (n = 32) (Table 1). Mean heart rate was slightly higher in the AF group compared with the sinus rhythm group (75 ± 15 beats/min vs. 69 ± 11 beats/min; p = 0.04), but only 1 patient with AF had uncontrolled tachycardia (heart rate >110 beats/min) compared with 2 patients in sinus rhythm. Among patients with AF at catheterization, 30 (94%) had a history of permanent AF, and 2 (6%) had paroxysmal AF. Despite the similarities in demographics and comorbidities, patients with AF displayed more severe NYHA functional class status and poorer exercise capacity compared with those in sinus rhythm, with lower peak VO_2 (10.8 ± 3.1 ml/min/kg vs. 13.5 ± 3.8 ml/min/kg; p = 0.002) (Figure 1A). Median (25th, 75th percentile) NT-proBNP was markedly higher in the AF group compared with those in sinus rhythm (1,689; 851 to 2,637 pg/ml vs. 490; 272 to 1,019 pg/ml; $p < 0.0001$) (Figure 1B).

TABLE 1 Clinical Characteristics by AF Status

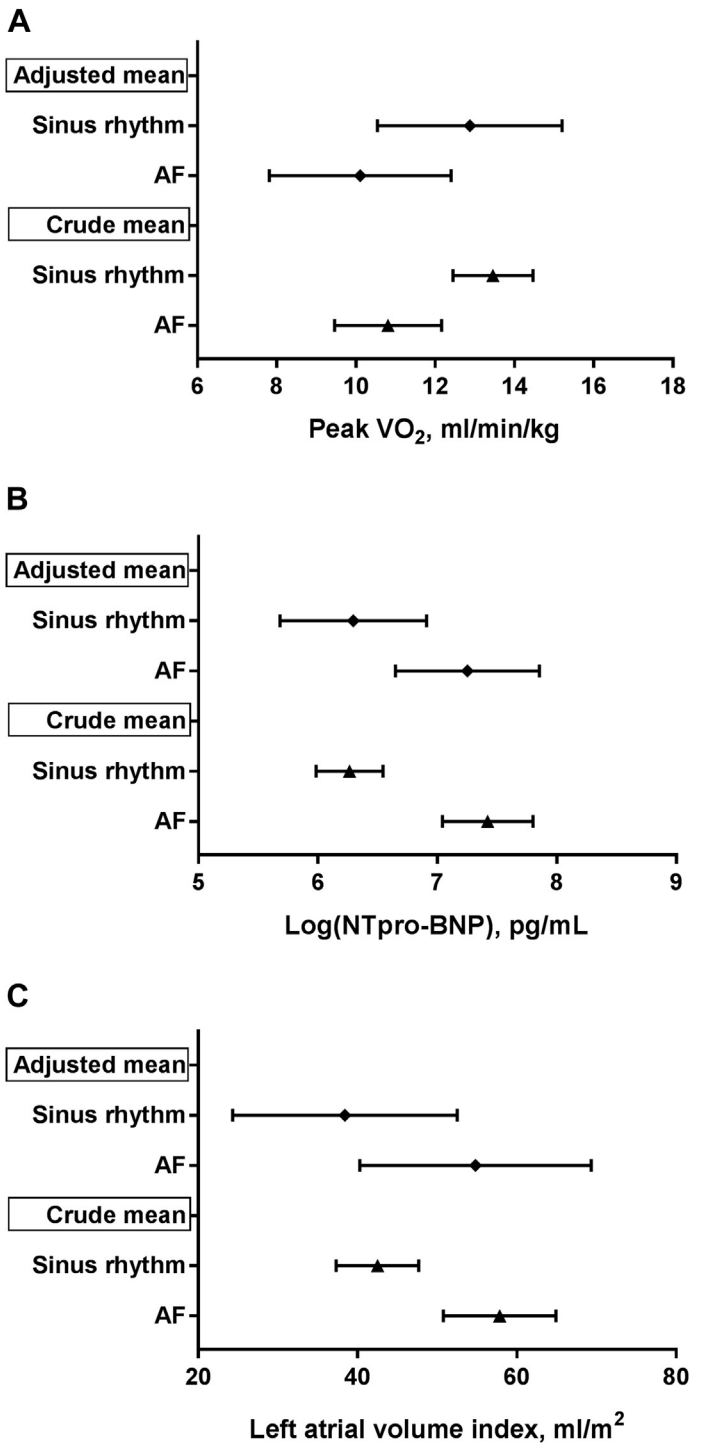
	AF (n = 32)	Sinus Rhythm (n = 62)	p Value
Age, yrs	73.9 ± 10.3	72.6 ± 7.9	0.505
Female	20 (62.5)	46 (74.2)	0.240
Heart rate, beats/min	75.3 ± 15.0	69.0 ± 10.9	0.041
Body mass index, kg/m^2	29.0 ± 6.7	28.2 ± 5.2	0.531
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2	0.134
Comorbidites, %			
History of diabetes mellitus	8 (25.0)	21 (33.9)	0.378
History of hypertension	21 (65.6)	41 (66.1)	0.961
History of myocardial infarction	2 (6.3)	11 (17.7)	0.126
History of cerebrovascular disease	3 (9.4)	1 (1.6)	0.077
Medications at enrollment, %			
ACEI	15 (48.4)	20 (32.3)	0.130
ARB	12 (38.7)	13 (21.0)	0.069
Beta-blocker	26 (81.3)	49 (79.0)	0.800
Angiotensin antagonist	9 (29.0)	22 (35.5)	0.534
Diuretic	26 (83.9)	43 (69.4)	0.132
Laboratory values			
Creatinine, μmol/l	97.0 (75.5–118.3)	91.0 (65.0–109.3)	0.413
eGFR, ml/min/1.73 m^2	58.0 ± 25.0	61.5 ± 22.1	0.521
Hemoglobin, mmol/l	8.2 ± 1.1	8.1 ± 1.1	0.753
NT-proBNP, pg/ml	1,689 (851–2,637)	490 (272–1,019)	<0.001
Exercise capacity			
NYHA functional class III/IV	24 (77.4)	28 (45.9)	0.004
Peak VO_2, ml/min/kg	10.8 ± 3.1	13.5 ± 3.8	0.002

Values are mean ± SD, n (%), or median (interquartile range).

ACEI = angiotensin-converting-enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; VO_2 = oxygen consumption.

ECHOCARDIOGRAPHIC CHARACTERISTICS. According to the echocardiograms (Table 2), there were no statistically significant differences in LV ejection fraction,

FIGURE 1 Peak VO_2, Log NT-proBNP, and LAVI in Patients With Sinus Rhythm Versus AF



Forest plots showing **(A)** peak oxygen consumption (peak VO_2), **(B)** log N-terminal pro–B-type natriuretic peptide (NT-proBNP), and **(C)** left atrial volume index (LAVI) in patients with sinus rhythm versus atrial fibrillation (AF). **Dots and bars** represent mean ± SE.

LV size, and LV mass between groups; however, the LV diastolic indexes differed: the AF group had higher E waves and shorter deceleration times, whereas the sinus rhythm group had lower e′ velocities. The E/e′ ratio was therefore balanced between the groups. LAVI was larger in AF than in sinus rhythm (57.8 ± 17.0 ml/m^2 vs. 42.5 ± 15.1 ml/m^2; p = 0.001) (Figure 1C). Interestingly, right ventricular systolic function (tricuspid annular plane systolic excursion [TAPSE]) was more impaired in the AF group. The reduction in TAPSE in AF patients persisted after adjusting for age, sex, heart rate, body mass index, eGFR, diabetes, hypertension, LV ejection fraction, and history of myocardial infarction or stroke.

CARDIAC CATHETERIZATION. Invasive hemodynamics (Table 3) showed higher mean right atrial pressure (11.3 ± 5.3 mm Hg vs. 6.3 ± 3.7 mm Hg), pulmonary artery pressure (35.9 ± 9.1 mm Hg vs. 27.9 ± 10.2 mm Hg), and PCWP (19.9 ± 3.7 vs. 15.2 ± 6.8) in the AF group compared with the sinus rhythm group (all p < 0.001), with a trend toward higher LVEDP (17.7 ± 3.0 mm Hg vs. 15.7 ± 6.9 mm Hg; p = 0.06). LVEDP and mean PCWP were closely correlated in the entire cohort (r = 0.92; p < 0.001).

ASSOCIATION OF AF WITH PEAK VO_2, NT-proBNP, AND LAVI. The presence of AF was associated with reduced peak VO_2, increased log NT-proBNP, and enlarged LAVI (all p ≤ 0.005; Table 4), even after adjusting for clinical covariates (age, sex, heart rate, body mass index, LV ejection fraction, eGFR, diabetes, hypertension, history of myocardial infarction or stroke) and mean PCWP (adjusted beta coefficient = −2.83, 1.11, and 18.63, respectively; all p ≤ 0.005). Before multivariable adjustment, AF explained 11.4%, 21.7%, and 18.2% of the variability in peak VO_2, log NT-proBNP, and LAVI, respectively. After multivariable adjustment for clinical covariates (as discussed previously) and mean PCWP, AF still explained 9.7%, 14.6%, and 17.8% of the variability in peak VO_2, log NT-proBNP, and LAVI, respectively. Results were similar after adjusting for LVEDP instead of mean PCWP (Table 4). Results were also similar after further adjusting for medications (including angiotensin-converting enzyme inhibitors, angiotension receptor blockers, beta-blockers, angiotensin antagonists, digoxin, and diuretics) (adjusted beta coefficient for VO_2, log NT-proBNP, and LAVI = −3.50, 1.39, and 15.37, respectively; all p ≤0.012). To account for potential overfitting due to limited sample size, we performed bootstrapping of the estimates with 1,000 iterations to correct for optimism in the models, and demonstrated that the models were adequate (results not shown).

TABLE 2 Echocardiographic Characteristics by AF Status

	AF (n = 32)	Sinus Rhythm (n = 62)	p Value
Left ventricular ejection fraction, %	56 ± 5.0	58 ± 5.0	0.174
Left ventricular mass index, g/m^2	96.7 ± 24.3	92.1 ± 35.4	0.522
Left ventricular end diastolic dimension, mm	48.9 ± 6.0	46.0 ± 11.0	0.188
Left ventricular end systolic dimension, mm	35.1 ± 6.2	33.0 ± 7.7	0.199
Intraventricular septum thickness, mm	10.7 ± 1.8	10.4 ± 2.1	0.514
Left ventricular posterior wall thickness, mm	9.9 ± 1.5	9.6 ± 2.1	0.416
Mitral valve early inflow velocity E, m/s	1.2 ± 0.3	0.9 ± 0.3	0.001
Mitral valve inflow deceleration time, ms	176.9 ± 54.4	213.1 ± 63.5	0.011
e′ lateral, cm/s	10.8 ± 4.4	8.2 ± 2.8	0.004
e′ septal, cm/s	8.2 ± 3.1	6.4 ± 2.2	0.002
E/e′ ratio	14.1 ± 7.3	13.6 ± 6.1	0.707
Isovolumetric relaxation time, ms	82.8 ± 22.0	91.2 ± 22.9	0.153
Left atrial volume index, ml/m^2	57.8 ± 17.0	42.5 ± 15.1	0.001
Left atrial diameter, mm	49.4 ± 8.3	41.4 ± 8.5	<0.001
TAPSE	16.6 ± 4.9	22.5 ± 5.5	<0.001
Tricuspid regurgitant maximum gradient, mm Hg	42.1 ± 12.1	38.1 ± 15.5	0.274

Values are mean ± SD.
AF = atrial fibrillation; TAPSE = tricuspid annular plane systolic excursion.

TABLE 3 Cardiac Catheterization Characteristics by AF Status

	AF (n = 32)	Sinus Rhythm (n = 62)	p Value
Mean right atrial pressure, mm Hg	11.3 ± 5.3	6.3 ± 3.7	<0.001
Right ventricular systolic pressure, mm Hg	56 ± 16.1	46.6 ± 16.3	0.009
Right ventricular end diastolic pressure, mm Hg	11.0 ± 4.8	7.9 ± 4.1	0.001
Systolic pulmonary artery pressure, mm Hg	55.8 ± 15.3	45.2 ± 16.3	0.003
Diastolic pulmonary artery pressure, mm Hg	21 ± 7.8	16.2 ± 6.0	0.001
Mean pulmonary artery pressure, mm Hg	35.9 ± 9.1	27.9 ± 10.2	<0.001
Mean PCWP, mm Hg	19.9 ± 3.7	15.2 ± 6.8	<0.001
Mean PCWP ≥15, mm Hg	30 (93.8)	36 (58.1)	<0.001
Left ventricular systolic pressure, mm Hg	142.7 ± 22.1	156.4 ± 24.2	0.017
Left ventricular end-diastolic pressure, mm Hg	17.7 ± 3.0	15.7 ± 6.9	0.062
Aortic systolic pressure, mm Hg	139.9 ± 24.0	155 ± 23.0	0.004
Aortic diastolic pressure, mm Hg	69.7 ± 13.3	69.0 ± 13.4	0.81
Mean aortic pressure, mm Hg	97.2 ± 13.1	102.6 ± 16.4	0.111
Cardiac output (Fick), l/min	5.3 ± 1.4	5.9 ± 1.6	0.063
Cardiac index, l/min/m^2	3.5 ± 4.1	3.2 ± 0.8	0.691
Pulmonary vascular resistance, dynes/s/cm^{-5}	273.4 ± 172.2	189 ± 161.5	0.025

Values are mean ± SD.
AF = atrial fibrillation; PCWP = pulmonary capillary wedge pressure.

HISTORY AND TYPE OF AF. Further adjusting for type of AF in the multivariable models produced similar results for the association of AF with peak VO_2 (adjusted beta coefficient: −2.85; 95% confidence interval [CI]: −5.05 to −0.66; p = 0.012), log NT-proBNP (adjusted beta coefficient: 0.98; 95% CI: 0.42 to 1.54; p = 0.001), and LAVI (adjusted beta coefficient: 16.96; 95% CI: 4.18 to 29.75; p = 0.011), adjusting for age, sex, heart rate, body mass index, LVEF, eGFR, diabetes, hypertension, history of myocardial infarction or stroke, and mean PCWP.

Among patients in sinus rhythm at catheterization, 12 (19%) had a history of AF. Excluding these patients from analysis provided similar results for the association of AF with peak VO_2, log NT-proBNP, and LAVI (all p ≤ 0.008).

DISCUSSION

In our cohort of patients with HFpEF who underwent simultaneous cardiac catheterization and echocardiography, those with AF were more severely diseased than those in sinus rhythm. However, even after adjustment for clinical factors and invasively measured LVEDP or mean PCWP, the presence of AF was still related to poorer exercise capacity, higher circulating NT-proBNP, and left atrial enlargement compared with sinus rhythm. The associations of AF with key symptom, biomarker, and echocardiographic domains of HFpEF carry important implications for cutoffs used to confirm the presence of pulmonary venous congestion in HFpEF with concomitant AF versus without concomitant AF.

Our study confirms that approximately one-third of patients with HFpEF have concomitant AF at presentation, similar to findings from other HFpEF trials (13) or epidemiological studies (2,3). Similar to the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in HFpEF) trial (13), HFpEF patients with AF had similar comorbidities, hemoglobin, and renal function compared with those in sinus rhythm. However, the RELAX investigators also found significantly older age and more frequent use of diuretics in patients with AF compared with those in sinus rhythm. Our data showed similar trends that may not have reached statistical significance due to smaller numbers.

TABLE 4 Association of AF With Peak VO_2, NT-proBNP, and LAVI in HFpEF

	Peak VO_2		NT-proBNP		LAVI	
	Beta Coefficient (95% CI)	p Value	Beta Coefficient (95% CI)	p Value	Beta Coefficient (95% CI)	p Value
Unadjusted	−2.65 (−4.33 to −0.96)	0.002	1.16 (0.69 to 1.63)	<0.001	15.33 (6.56 to 24.11)	0.001
Adjusted for						
Age and sex	−2.68 (−4.34 to −1.02)	0.002	1.09 (0.63 to 1.56)	<0.001	14.61 (5.76 to 23.47)	0.002
Age, sex, heart rate, BMI, eGFR, diabetes, hypertension, previous MI/stroke, LVEF	−2.80 (−4.66 to −0.93)	0.004	1.23 (0.73 to 1.72)	<0.001	19.49 (8.93 to 30.06)	0.001
Age, sex, heart rate, BMI, eGFR, diabetes, hypertension, previous MI/stroke, LVEF, mean PCWP	−2.83 (−4.76 to −0.90)	0.005	1.11 (0.60 to 1.61)	<0.001	18.63 (7.39 to 29.86)	0.002
Age, sex, heart rate, BMI, eGFR, diabetes, hypertension, previous MI/stroke, LVEF, LVEDP	−2.86 (−4.77 to −0.95)	0.004	1.27 (0.75 to 1.80)	<0.001	19.53 (8.48 to 30.58)	0.001

BMI = body mass index; CI = confidence interval; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; MI = myocardial infarction; LVEDP = left ventricular end-diastolic pressure; other abbreviations as in Table 1.

The RELAX investigators also found similar E/e′ ratios but shorter deceleration time, higher right atrial pressure, higher pulmonary artery systolic pressure, and larger left atria in their patients with AF compared with those in sinus rhythm (13). Invasive hemodynamics and right ventricular function were not reported. Our echocardiographic results are consistent with RELAX, and extend the prior results, with invasive data showing that despite similar E/e′ ratios, invasively measured mean PCWP was higher in patients with AF versus patients with sinus rhythm, with a similar trend for LVEDP. Furthermore, invasively measured right atrial, right ventricular, and pulmonary artery pressures, as well as pulmonary vascular resistance, were all elevated in AF with HFpEF compared with sinus rhythm. Finally, AF with HFpEF was related to evidence of right ventricular systolic dysfunction (reduced TAPSE) on echocardiography. Other investigators have suggested that AF may contribute to right ventricular dysfunction in HFpEF, independent of pulmonary pressure overload (14,15).

Both RELAX and our current data showed that HFpEF patients with AF had poorer exercise capacity, higher NT-proBNP, and larger left atria compared with those in sinus rhythm. In aggregate, the clinical, hemodynamic, echocardiographic, and biomarker correlates may suggest that AF with HFpEF can represent a more advanced form of HFpEF with greater exertional intolerance (16), pulmonary venous congestion, natriuretic peptide elevation, and left atrial remodeling compared with those in sinus rhythm.

However, AF is also a confounder in the diagnosis of HFpEF (16). Our data show, after adjusting for severity of HFpEF (mean PCWP or LVEDP), that AF is associated with the key domains of HFpEF; namely: 1) symptoms (exercise intolerance); 2) circulating biomarkers (NT-proBNP); and 3) left atrial remodeling. This is especially important because all 3 domains are used for the diagnosis of HFpEF (5) and used as surrogate outcomes in HFpEF trials (6,8). Thus, the diagnosis of raised LV filling pressures in HFpEF cannot be made with certainty based on the presence of exercise tolerance, raised NT-proBNP, or left atrial enlargement (at their usual cutoffs) when there is concomitant AF. HFpEF trials have dealt with these challenges by imposing a limit on the number of patients with AF that can be recruited (6) or using different qualifying cutoffs for HFpEF, depending on the presence of AF. For example, in the SOCRATES-Preserved trial (8), NT-proBNP cutoffs of ≥300 and ≥600 pg/ml were used in sinus rhythm and AF, respectively; whereas in the PARAGON-HF trial, corresponding NT-proBNP cutoffs were >300 and >900 pg/ml, respectively. The variability of proposed cutoffs illustrates the lack of consensus and/or supporting data to select cutoffs. Such cutoffs would ideally be derived from cohorts of AF with and without HFpEF, with the latter defined by invasive diagnostic criteria. Our study does not provide this comparison for derivation of cutoffs, but provides invasive data supporting the need for different cutoffs in the presence of AF in HFpEF. Interestingly, the PARAGON-HF cutoffs were similar to the 25th percentile NT-proBNP values in our HFpEF patients with sinus rhythm (272 pg/ml) and AF (851 pg/ml).

STUDY LIMITATIONS. Our relatively small patient population was limited to HFpEF with suspected pulmonary hypertension on baseline echocardiography, thus introducing selection bias. However, not all patients had confirmed pulmonary hypertension at cardiac catheterization; thus, our sample included

HFpEF without pulmonary hypertension. We did not include controls without HFpEF. The cross-sectional design precluded definite conclusions about cause-effect relationships. Although all patients had right heart catheterization and echocardiography, not all had combined left and right heart catheterization. However, left-sided invasive measurements were available in most of the patients (89%), and our study provided the first data on invasive hemodynamic correlates of AF in HFpEF combined with simultaneous comprehensive Doppler echocardiography. No information on duration of AF history or current episode was available, nor was detailed information on heart rate control (resting and exercise) available. Repeat measurements pre- and post-exercise or pre- and post-cardioversion would have been informative, but were not available in our study. These represent areas for future study.

CONCLUSIONS

HFpEF with AF is associated with greater exertional intolerance, pulmonary venous congestion, natriuretic peptide elevation, and left atrial remodeling compared with those in sinus rhythm.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our data in patients with HFpEF who underwent simultaneous cardiac catheterization and echocardiography showed that after adjusting for severity of HFpEF (mean PCWP or LVEDP), AF was associated with the key domains of HFpEF; namely: 1) symptoms (exercise intolerance); 2) circulating biomarkers (NT-proBNP); and 3) left atrial remodeling.

TRANSLATIONAL OUTLOOK: These findings have important translational implications for the diagnosis of HFpEF, and suggest that diagnosis of raised LV filling pressures in HFpEF cannot be made with certainty based on the presence of exercise tolerance, raised NT-proBNP, or left atrial enlargement (at the usual cutoffs) when there is concomitant AF.

REFERENCES

1. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13:18–28.

2. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved reduced ejection fraction. Circulation 2016;133:484–92.

3. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. Circulation 2013;128:1085–93.

4. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. Int J Cardiol 2016;203:660–6.

5. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

6. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387–95.

7. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.

8. Pieske B, Butler J, Filippatos G, et al. Rationale and design of the SOluble guanylate Cyclase stimulatoR in heArT failurE Studies (SOCRATES). Eur J Heart Fail 2014;16:1026–38.

9. Mulder BA, Van Veldhuisen DJ, Crijns HJ, et al. Lenient vs. strict rate control in patients with atrial fibrillation and heart failure: a post-hoc analysis of the RACE II study. Eur J Heart Fail 2013;15:1311–8.

10. Hoendermis ES, Liu LC, Hummel YM, et al. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. Eur Heart J 2015;36:2565–73.

11. Forrester JS, Diamond G, McHugh TJ, Swan HJ. Filling pressures in the right and left sides of the heart in acute myocardial infarction. A reappraisal of central-venous-pressure monitoring. N Engl J Med 1971;285:190–3.

12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–70.

13. Zakeri R, Borlaug BA, McNulty SE, et al. Impact of atrial fibrillation on exercise capacity in heart failure with preserved ejection fraction: a RELAX trial ancillary study. Circ Heart Fail 2014;7:123–30.

14. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J 2014;35:3452–62.

15. Mohammed SF, Hussain I, AbouEzzeddine OF, et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. Circulation 2014;130:2310–20.

16. Kelly JP, Mentz RJ, Mebazaa A, et al. Patient selection in heart failure with preserved ejection fraction clinical trials. J Am Coll Cardiol 2015;65:1668–82.

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