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Atrial function in paroxysmal AF patients with and without heart failure with preserved ejection fraction: Data from the AF-RISK study

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Abstract Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) are 2 cardiovascular conditions that often coexist. Strain phases of both the left and right atria are more impaired in paroxysmal AF patients with HFpEF than those without HFpEF in spite of comparable global longitudinal strain of the left ventricle. Atrial function may differentiate paroxysmal AF patients with HFpEF from those without HFpEF. (Am Heart J 2022;244:36–41.)

Keywords: Atrial fibrillation; Heart failure with preserved ejection fraction; Echocardiography; Left atrial function; Right atrial function; Speckle-tracking echocardiography

Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are 2 cardiovascular conditions that often coexist. Both conditions are associated with aging, hypertension, obesity, and sleep apnea.[1, 2] The presence of 1 of both conditions leads to an increased risk of the other. However, the overlap in symptoms, biomarker profile, and echocardiographic changes hinder the diagnosis of underlying HFpEF in patients with AF and suggests that both conditions might reflect similar remodeling processes in the heart.[1, 2] The aim of this study was therefore to assess cardiac remodeling in AF patients with vs without concomitant HFpEF by transthoracic echocardiography, focusing on atrial dimension and speckle tracking of the left and right atria.

We included patients from the identification of a risk profile to guide atrial fibrillation therapy study (AF-RISK), a prospective, observational, multicenter study (NCT01510210).[3] In brief, inclusion criteria were patients aged ≥18 years, with paroxysmal AF (total AF history <2 years, or total AF history <3 years in case of ≤2 AF episodes of ≤48 hours per month terminating spontaneously) or persistent AF (total AF history <2 years, and total persistent AF duration >7 days and <1 year). Exclusion criteria were patients with history of heart failure >3 years, severe valvular disease, acute coronary syndrome <1 month, post-operative AF or history of pulmonary vein isolation. For this subanalysis, 287 patients had paroxysmal AF, had a left ventricular ejection fraction (LVEF) ≥50%, were in SR (sinus rhythm) at the moment of performing echocardiography and blood sampling (Supplementary figure S-1). The diagnosis of HFpEF was based on the 2016 ESC heart failure guidelines, including symptoms and signs heart failure (dyspnea and fatigue, equivalent to NYHA ≥ II) or history of HF hospitalization and N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥125pg/ml, and 1 of the following echocardiographic measures: left atrium volume index (LAVI) >34ml/m^2, left ventricular mass index ≥115g/m^2 for men and ≥95g/m^2 for women, average E/e' ≥13cm/s and average e' <9cm/s.[4] Due to imbalances in age and sex between AF patients with HFpEF in comparison to those without HFpEF, patients were selected using propensity score matching by nearest neighbor. A 1:1 ratio created balanced differences in age and sex resulting in two groups: 1) AF with HFpEF ($n = 60$) and 2) AF without HFpEF ($n = 60$). A sensitivity analysis was performed in pa-

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Abbreviation

ACE	Angiotensin-converting enzyme
AAD	Anti-arrhythmic drug
AF	Atrial fibrillation
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
ECV	Electrical cardioversion
EHRA	European heart rhythm association symptom classification
GLS	Global longitudinal strain
GDF-15	Chronic obstructive pulmonary disease
HF_pEF	Heart failure with preserved ejection fraction
AF-RISK	Identification of a risk profile to guide atrial fibrillation therapy study
LAVI	Left atrium volume index
LVEF	Left ventricular ejection fraction
NT-proBNP	n-terminal pro-b-type natriuretic peptide
SR	Sinus rhythm

tients with cutoff of NT-proBNP≥400pg/ml into the HFpEF definition.[5] This work was supported by the Dutch Heart Foundation (NHS2010B233). This project received funding from European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie [agreement 754425].

Atrial function was determined by speckle tracking as it is less affected by loading conditions in comparison to volumetric methods .[6] Reservoir, conduit and contraction strain of both atria was performed in apical four-chamber view by manually selecting endocardial borders from 1 cardiac cycle R-R gated (GE, EchoPac BT12). Tracking was manually adjusted for accuracy if needed. An independent observer, blinded to results, measured 10% of the strains to calculate inter-observer reliability. The average intraclass correlation coefficient of strain measures was 0.831, using average consistency two way random effects method. Associations of clinical and echocardiographic characteristics were tested for collinearity and by multivariable logistic regression analyses. LAVI, LV mass index and NT-proBNP were excluded from multivariable analysis since these markers were part of the HFpEF diagnostic criteria. A two-tailed *P*-value of $<.05$ was considered statistically significant. The study was performed in accordance with the Declaration of Helsinki and after local research ethics committee approval.

Patients with paroxysmal AF and concomitant HFpEF had more often beta-blocker and angiotensin-converting enzyme (ACE) inhibitors medication, had more often impaired strain phases of both the left and right atria as compared to those without HFpEF, and comparable time of AF diagnosis, AF burden, global longitudinal strain (GLS) of the left ventricle and LVEF (Table I) (Figure 1). In multivariable analyses including age, sex, use of ACE inhibitor and beta-blockers, LA reservoir and contraction decrease was associated with presence of HFpEF (OR per 5% decrease in LA reservoir 1.39, 95% CI 1.11 – 1.81, $P = .008$; OR per 5% decrease in LA contraction 1.96, 95% CI 1.26 – 3.33, $P = .006$) (Table II). LA reservoir and contraction phases were not placed in the same model due to collinearity (Supplementary figure S-2). LA reservoir and contraction were not correlated with LAVI in AF patients with concomitant HFpEF and moderately correlated in patients with AF (Supplementary table S-1). Similar results were observed in a sensitivity analysis of AF patients with HFpEF patients classified by a cutoff of NT-proBNP≥400pg/ml (Supplementary table S-3 and figure S-2)

Our results show that atrial function discriminates AF patients with HFpEF from those without HFpEF. In patients with AF, a more impaired structure and function of the left and right atria were associated with concomitant HFpEF, whereas ventricular function, reflected by GLS and LVEF, was comparable. LAVI was a criteria to classify patients with HFpEF and could therefore explain decrease in LA strain[7]; however, LA strains were not correlated with LAVI in our study. Our results are in accordance to previous studies suggesting LA strains as markers for improving the diagnosis of HFpEF.[8] Katbeh et al found that LA reservoir and, followed by, LA contraction were associated with the probability of HFpEF in patients with paroxysmal AF and dyspnea, using two scores, H_2FPEF and HFA-PEFF.[9] It has been shown that contraction function is reduced in advanced stages of AF,[10] however in this study AF burden and time of AF history in both groups were comparable, possibly attributing the differences to having concomitant HFpEF. Even though we could only speculate about the explanations for these results, HFpEF plausible mechanisms imply higher cardiac energy consumption and production of reactive oxygen species;[11] the latter have been associated with decreased atrial myocardial energetics more than in the ventricles, predominantly in the LA.[12] This could increase remodeling of the atria in AF patients with concomitant HFpEF.

This analysis has limitations since the results are based on *post hoc* analyses and classification of HFpEF was performed after inclusion. The AFRISK study had already

Table I. Clinical characteristics and echocardiographic measurements

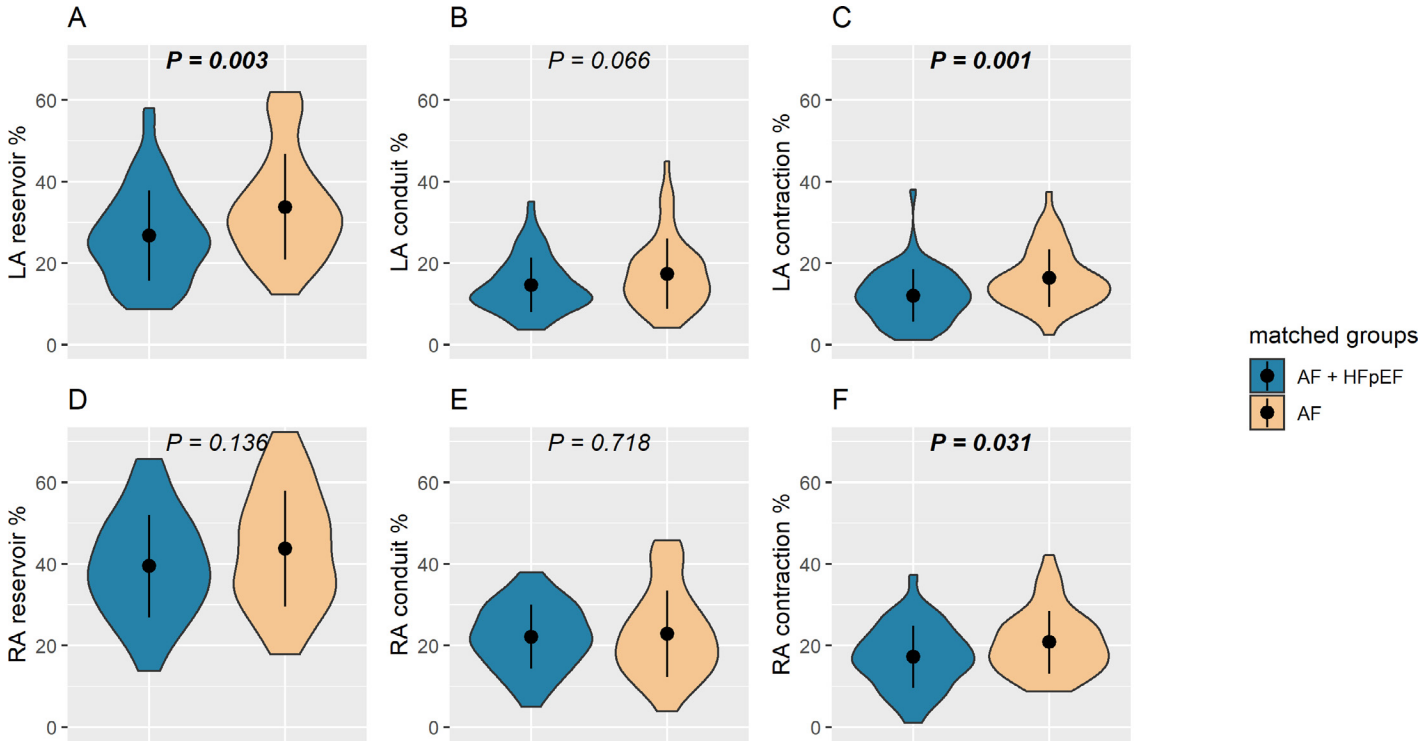
Characteristic	Total population ($n = 120$)	AF with HFpEF($n = 60$)	AF without HFpEF($n = 60$)	*P*-value
Age(ys)	65±8	66±8	65±8	.807
Women %	58 (48)	31 (52)	27 (45)	.584
Diagnosis of AF(months)	7(2-20)	10(2-23)	4(2-15)	.142
Percentage AF %				.293
<5	97 (87)	46 (82)	51 (91)	
5 – 50	10(9)	6(11)	4(7)	
>50	5(4)	4 (7.1)	1(2)	
Hypertension %	107 (90)	57 (95)	50 (83)	.078
Diabetes mellitus %	17 (14)	7(12)	10 (17)	.601
Coronary artery disease %	8(7)	6(10)	2(3)	.272
Peripheral artery disease %	7(6)	2(3)	5(8)	.436
Stroke or TIA %	6(5)	3(5)	3(5)	.000
COPD %	9(8)	5(8)	4(7)	.000
BMI(kg/m^2)	27±4	28±4	26±4	.129
Obesity(BMI>30) %	30 (25)	18 (30)	12 (20)	.292
CHA_2DS_2-VASc score*	2.2±1.4	2.5±1.4	2.0±1.3	.061
Comorbidities†	2.5±1.2	2.7±1.2	2.4±1.2	.150
Fatigue	110 (92)	57 (95)	53 (88)	.322
Dyspnea	63 (53)	29 (48)	34 (58)	.405
EHRA class % I II III				.681
	30 (25)	13 (22)	17 (28)	
	68 (57)	36 (60)	32 (53)	
	22 (18)	11 (18)	11 (18)	
Medications				
β-Blocker %	82 (68)	48 (80)	34 (57)	.011
Verapamil/Diltiazem %	10(8)	6(10)	4(7)	.741
Digoxin %	4(3)	4(7)	0 (0)	.127
ACE-inhibitor %	40 (33)	27 (45)	13 (22)	.012
Anticoagulant %	81 (68)	45 (75)	36 (60)	.119
Class Ic AAD %	7(6)	4(7)	3(5)	.000
Class III AAD %	8(7)	5(8)	3(5)	.714
Previous ECV %	29 (24)	18 (30)	11 (18)	.201
Biomarkers				
NTproBNP (pg/ml)	189 (93 – 324)	268 (190 – 464)	87 (59 – 159)	<.001
GDF15 pg/ml	1033 (821-1422)	1141 (854 – 1480)	1002 (780 – 1339)	.287
Troponin-T pg/ml	6.4 (4.3 – 9.9)	6.9 (3.7 – 11.2)	6.1 (4.7 – 7.7)	.271
Echocardiography				
LAVI(mL/m^2)	35±10	40±8	29±8	<.001
RAVI(mL/m^2)	36±12	39±12	33±12	.013
LV ejection fraction(%)	58±3	57±3	58±3	.168
LV mass index(g/m^2)	86±21	89±22	82±21	.087
e′	8.8±1.9	8.8±1.9	8.8 ±2.0	.879
E/A ratio	1.0 (0.9 – 1.3)	1.1(0.9 – 1.3)	1.0 (0.8 – 1.2)	.078
E/e′	7.7 (6.6 – 9.8)	8.8(6.9 – 10.3)	7.2 (6.2 – 8.6)	.004
Left atrial strain(%)				
Reservoir	30.1±12.5	26.8±11.1	33.8±12.9	.003
Conduit	16.0± 7.7	14.7±6.7	17.4±8.6	.066
Contraction	14.1± 7.0	12.1±6.5	16.3±7.0	.001
Right atrial strain(%)				
Reservoir	41.6±13.5	39.4±12.5	43.7±14.2	.136
Conduit	22.5±9.3	22.2±7.8	22.9±10.6	.718
Contraction	19.1±7.8	17.3±7.6	20.9±7.7	.031
GLS (%)	-19.3±3.2	-18.9±3.4	-19.7±3.1	.212

ACE,angiotensin-converting enzyme; AF,atrial fibrillation; BMI,body mass index; COPD,chronic obstructive pulmonary disease; ECV, electrical cardioversion; GDF-15,growth differentiation factor 15; EHRA,European Heart Rhythm Association symptom classification; HFpEF,heart failure with preserved ejection fraction; LAVI,left atrial volume index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TIA,transient ischemic attack.

*The CHA_2DS_2-VASc score assesses thromboembolic risk. C, congestive heart failure/LV dysfunction; H, hypertension; A2, age ≥ 75 years; D, diabetes mellitus; S2, stroke/transient ischaemic attack/systemic embolism; V, vascular disease; A, age 65–74 years; Sc, sex category (female sex).

†The number of comorbidities was calculated by awarding a point for hypertension, age >65 years, diabetes, coronary artery disease, body mass index >25, kidney dysfunction, and moderate or severe mitral valve regurgitation.

Figure



Strain phases distribution of both left and right atria in patients with paroxysmal AF with HFpEF in comparison to those without HFpEF Y axis expresses percentage of deformation measure by 2D speckle tracking by transthoracic echocardiography. Point within the graph expresses mean and lines determine standard deviation.

Table II. Predictors of heart failure with preserved ejection fraction in patients with atrial fibrillation

	OR	CI 95%	*P*
LA reservoir	1.38	1.14 – 1.71	.002
LA contraction	1.89	1.33 – 2.85	<.001
RA contraction	1.57	1.13 – 2.30	.012
LA reservoir +RA contraction	1.391.37	1.11 – 1.810.95 – 2.05	.008.108
LA contraction +RA contraction	1.961.36	1.26 – 3.330.94 – 2.06	.006.122

All models included age, sex, use of ACE inhibitor, use of beta-blockers
Results are shown as 5% reduction per strain phase
LA, Left atria; RA, right atria

small inclusion of patients and propensity score matching generated even smaller comparison groups. These results were performed in a population with paroxysmal AF and cannot be generalized to other forms of AF. Given the transversal analysis of the data, it cannot be determined whether HFpEF set the stage for AF nor inversely. Furthermore, the associations found might be affected by residual cofounding. Echocardiographic B-line were not measured which could have provided insights into the congestive state in AF patients with HFpEF. These findings encourage the need for well phenotyped AF with and without HFpEF cohorts to further understand atrial remodeling processes and underlying AF substrate.

In conclusion, in patients with paroxysmal AF, more impaired strain phases of the left and right atria were associated with concomitant HFpEF, whereas ventricular function, reflected by LVEF and GLS, did not differ.

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Conflict of interest

J.G.L.M.L. has a consultancy agreement with Medtronic. A.A.V reports receiving consulting fees from Amgen, AstraZeneca, Cytokinetics, MyoKardia, Novartis, and Servier, and grant support and consulting fees from Boehringer Ingelheim and Roche Diagnostics.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.10.183.

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