The prognostic impact of mechanical atrial dysfunction and atrial fibrillation in heart failure with preserved ejection fraction

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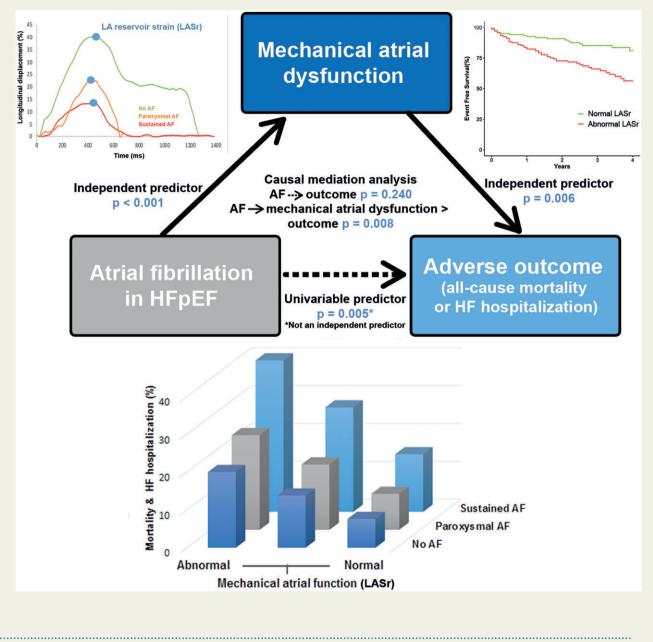|	
Aims	This study assessed the prognostic implications of mechanical atrial dysfunction in heart failure with preserved ejection fraction (HFpEF) patients with different stages of atrial fibrillation (AF) in detail.
Methods and results	HFpEF patients (*n* = 258) systemically underwent an extensive clinical characterization, including 24-h Holter monitoring and speckle-tracking echocardiography. Patients were categorized according to rhythm and stages of AF: 112 with no history of AF (no AF), 56 with paroxysmal AF (PAF), and 90 with sustained (persistent/permanent) AF (SAF). A progressive decrease in mechanical atrial function was seen: left atrial reservoir strain (LASr) 30.5 ± 10.5% (no AF), 22.3 ± 10.5% (PAF), and 13.9 ± 7.8% (SAF), *P* < 0.001. Independent predictors for lower LASr values were AF, absence of chronic obstructive pulmonary disease, higher N-terminal-pro hormone B-type natriuretic peptide, left atrial volume index, and relative wall thickness, lower left ventricular global longitudinal strain, and echocardiographic signs of elevated left ventricular filling pressure. LASr was an independent predictor of adverse outcome (hazard ratio per 1% decrease =1.049, 95% confidence interval 1.014–1.085, *P* = 0.006), whereas AF was not when the multivariable model included LASr. Moreover, LASr mediated the adverse outcome associated with AF in HFpEF (*P* = 0.008).
Conclusion	Mechanical atrial dysfunction has a possible greater prognostic role in HFpEF compared to AF status alone. Mechanical atrial dysfunction is a predictor of adverse outcome independently of AF presence or stage, and may be an underlying mechanism (mediator) for the worse outcome associated with AF in HFpEF. This may suggest mechanical atrial dysfunction plays a crucial role in disease progression in HFpEF patients with AF, and possibly also in HFpEF patients without AF.

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Graphical Abstract

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is frequently seen in elderly patients and its incidence is increasing.[1] Many HFpEF patients present with atrial fibrillation (AF) during the course of their disease.[2] Of note, the occurrence of AF worsens prognosis, but clear evidence for the exact mechanism is lacking.[2] A better understanding of the interplay between HFpEF and AF is clearly needed, also to optimize clinical management and treatment strategies in HFpEF.[3]

An obvious common denominator in both HFpEF and AF is atrial dysfunction, defined as any structural or functional abnormality of the atria (histological, anatomical, mechanical, electrical, and/or rheological).[4] Specific anatomical and electrical atrial abnormalities have been described in HFpEF and are represented in its clinical definition [increased left atrial volume index (LAVI) and presence of AF].[5–7] Mechanical atrial dysfunction assessed by strain analysis with speckle-tracking echocardiography appears to have more diagnostic relevance in HFpEF than conventional echocardiographic markers,[8] yet mechanistic insight is still limited.[4] Previous prognostic studies on

mechanical atrial dysfunction have mainly focused on left atrial (LA) strain in HFpEF patients during sinus rhythm.[9,10] However, atrial arrhythmias affect mechanical atrial function on their own independently from HFpEF, and more so if stage of AF has advanced to paroxysmal AF (PAF) or more persistent forms.[11,12] Considering the above, a deeper understanding of the interplay between mechanical atrial function and stage of AF, and, importantly, how this relates to clinical outcome, may help in understanding the pathophysiology of HFpEF.

Thus, this study aims to evaluate the presence and prognostic relevance of mechanical atrial dysfunction as the common denominator in HFpEF and AF.

Methods

Study population

Consecutive patients referred to our outpatient HFpEF clinic and diagnosed with HFpEF between December 2014 and June 2019 were included in this prospective study. All patients systematically underwent a comprehensive diagnostic work-up at baseline. The diagnosis HFpEF was based on the European Society of Cardiology HF guidelines,[7] as described previously.[13]

To analyse mechanical atrial function changes in relation to stage of AF, patients were grouped into (i) no history of AF (no AF), (ii) history of PAF (defined as any history of AF episodes with a duration <7 days), and (iii) history of sustained (persistent/permanent) AF (SAF, defined as any history of AF episodes with a duration >7 days). Grouping was based on medical history (available in 100%) and prior as well as baseline 12-lead electrocardiogram (available in 100%) and 24-h Holter monitor (available in 93%). Exclusion criteria were history of cardiac valve replacement, paced cardiac rhythm, missing LA echocardiography, or insufficient image quality for speckle tracking echocardiography. This study was approved by the Institutional Review Board/Ethics Committee and performed according to the principles of the Declaration of Helsinki. All patients provided written informed consent.

In order to assess the influence of congestion on LA strain, we defined several categories: (i) *Clinical signs* of congestion were defined by the presence of orthopnoea, pulmonary crackles, or peripheral oedema, without a primary cause other than HF;[7] (ii) *Echocardiographic signs* of elevated filling pressure were defined by an E/A ratio $\geq$2, or an E/e' average >14 with a tricuspid regurgitation speed >2.8 m/s, or echocardiographic signs of congestion defined as an inferior vena cava diameter >2.1 cm with <50% collapse.[7,14] Regardless, patients with an E/A ratio $\leq$0.8 or E-peak $\leq$50 cm/s were considered to have no echocardiographic signs of elevated filling pressure. N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) levels were not used to define or categorize congestion as exact NT-proBNP cut-off values for elevated filling pressure in HFpEF are yet to be elucidated.[15]

Transthoracic echocardiography and strain analyses

Echocardiography was performed during routine clinical care according to guideline recommendations (Supplementary data online, *Methods*).[16,17] All volumetric data and left ventricle (LV) ejection fraction were harmonized by reassessment using automated software (AutoLV, ImageArena v4.6, TOMTEC Imaging Systems, Unterschleissheim, Germany).[18] Strain analyses using speckle-tracking echocardiography were performed with dedicated software (2D Cardiac Performance Analysis v1.4, ImageArena v4.6) according to current consensus statements to obtain left ventricular

global longitudinal strain (LV-GLS) and LA filling/reservoir strain (LASr) (Supplementary data online, *Methods*).[19] LA conduit and contraction strain were also assessed if sinus rhythm was present during echocardiography. LASr was used as the key parameter in this study because it can be measured in both patients with and without AF, and it seems to be the most characteristic marker of atrial dysfunction in HFpEF.[10]

Clinical outcome

The clinical outcome was defined as a composite of HF hospitalization or all-cause mortality. Outcome was assessed after baseline visit using patient records, hospital databases, and municipality records through 1 July 2020. Patients were censored at 4 years or on the last day of follow-up if lost-to-follow-up occurred earlier.

Statistical analysis

Statistical analyses are fully detailed in Supplementary data online, *Methods*.

Results

Clinical characteristics

This study included 258 HFpEF patients: 112 (43%) without a history of AF, 56 (22%) with PAF, and 90 (35%) patients with SAF (flowchart; Supplementary data online, *Figure S1*). Clinical characteristics were similar between the three groups (*Table 1*). Patients with AF were less often female, slightly older, and had higher NT-proBNP levels compared to patients without a history of AF. Also, AF was associated with a slightly lower LV ejection fraction (but still within the HFpEF range), a higher LAVI, higher estimated right ventricular (RV) systolic pressure, and a higher prevalence of mitral valve regurgitation (*Table 2*). Sex-stratified data are available in Supplementary data online, *Tables S1 and S2*. Patients excluded due to missing LA images or insufficient image quality (n = 21, 7.5%) were more often obese and New York Heart Association (NYHA) Class $\geq$3, had slightly more comorbidities, and had lower exercise capacity than patients included in this study (Supplementary data online, *Table S3*).

Mechanical atrial dysfunction in HFpEF

More severe mechanical atrial dysfunction, in other words, progressively lower LASr, was observed with more advanced stages of AF (*Figure 1* and *Table 2*). Progressively lower LV-GLS values with more advanced AF stages were less distinct than LASr; lower LV-GLS values were mainly seen in patients with SAF (Supplementary data online, *Figure S2*). Selecting only patients in sinus rhythm during echocardiography revealed similar results for LASr, while no clear differences remained for LV-GLS (Supplementary data online, *Figure S3*).

Predictors of lower LA reservoir strain

Adjusted multivariable linear regression analyses showed that independent predictors for lower LASr were the presence of PAF or SAF, absence of chronic obstructive pulmonary disease (COPD), higher NT-proBNP levels, higher LAVI, lower LV-GLS, higher relative wall thickness, and echocardiographic signs of elevated LV filling pressure (*Table 3*). No interaction existed between sex or age and any of these independent predictors for their association with LASr.

Table 1   Clinical characteristics

	No AF (n = 112)	Paroxysmal AF (n = 56)	Sustained AF (n = 90)	P-value for trend
Female sex, n (%)	90 (80)	43 (77)	46 (51)	<0.001
Age (years)	74 ± 9	76 ± 5	77 ± 7	0.013
Medical history, n (%)				
Hypertension	97 (87)	49 (88)	74 (82)	0.592
Significant CAD	28 (25)	11 (20)	20 (22)	0.726
Hypercholesterolaemia	74 (67)	30 (54)	49 (54)	0.126
Stroke	13 (12)	7 (13)	17 (19)	0.309
AF ablation	0 (0)	6 (11)	13 (15)	<0.001
Diabetes mellitus	35 (31)	17 (30)	28 (31)	0.993
Obesity	91 (81)	42 (75)	77 (86)	0.280
Sleep apnoea	36 (32)	18 (32)	42 (47)	0.071
Chronic obstructive pulmonary disease	19 (17)	6 (11)	14 (16)	0.572
Pulmonary embolism	4 (4)	0 (0)	5 (6)	0.184
Iron deficiency	56 (52)	26 (48)	49 (57)	0.574
Thyroid disease	15 (14)	7 (13)	9 (11)	0.786
Chronic kidney disease	40 (37)	17 (32)	34 (40)	0.626
Gout	11 (10)	4 (7)	10 (12)	0.708
Symptoms, n (%)				
NYHA class				0.174
1	1 (1)	0 (0)	2 (2)	
2	60 (54)	20 (37)	42 (47)	
3	45 (41)	32 (59)	44 (50)	
4	5 (4)	2 (4)	1 (1)	
Orthopnoea	24 (21)	11 (20)	14 (16)	0.566
Physical characteristics				
Body mass index (kg/m^2)	30.5 ± 6.1	29.3 ± 5.6	30.1 ± 5.4	0.466
Pulmonary crackles, n (%)	10 (9)	6 (11)	13 (14)	0.463
Peripheral oedema, n (%)	26 (26)	10 (23)	23 (30)	0.771
Systolic BP (mmHg)	149 ± 22	148 ± 23	146 ± 21	0.732
Diastolic BP (mmHg)	76 ± 13	77 ± 12	79 ± 14	0.354
Pulse pressure (mmHg)	72 ± 18	71 ± 22	67 ± 18	0.163
Clinical signs of congestion, n (%)	45 (40)	23 (41)	35 (39)	0.964
Echocardiographic signs of elevated FP/congestion, n (%)	22 (20)	15 (27)	30 (33)	0.087
Laboratory values				
eGFR-MDRD (mL/min/1.73 m^2)	55 [38–60]	53 [39–60]	52 [42–60]	0.844
NT-proBNP (pg/mL)	364 [214–710]	554 [309–1364]	1480 [913–1924]	<0.001
HbA1c (mmol/mol)	42 [38–49]	45 [39–53]	44 [39–52]	0.563
High-sensitive C-reactive protein (mg/L)	2.21 [1.09–4.59]	2.91 [1.21–5.71]	2.40 [1.21–5.90]	0.490
Medication, n (%)				
ACEi/ARB	71 (66)	40 (74)	58 (67)	0.554
Beta-blocker	74 (69)	39 (72)	58 (67)	0.831
Loop diuretic	51 (47)	34 (63)	56 (65)	0.026
Thiazide diuretic	27 (25)	13 (24)	18 (21)	0.794
Aldosterone receptor antagonist	11 (10)	16 (30)	15 (17)	0.008
Statin	63 (58)	27 (50)	49 (57)	0.588
Calcium channel blocker	40 (37)	11 (20)	23 (27)	0.068
Nitrate	29 (27)	11 (20)	22 (26)	0.660
Anticoagulants	16 (14)	47 (84)	76 (84)	<0.001
6-min walk test				
Distance walked (meters)	375 ± 116	368 ± 103	368 ± 141	0.907
Distance walked of predicted (%)	64 ± 20	64 ± 20	61 ± 20	0.465

Continued

Table 1 *Continued*

	No AF (*n* = 112)	Paroxysmal AF (*n* = 56)	Sustained AF (*n* = 90)	*P*-value for trend
Pulmonary function test				
Forced expiratory volume of predicted (%)	91 ± 21	88 ± 24	85 ± 20	0.195
Forced vital capacity of predicted (%)	94 ± 17	91 ± 21	90 ± 18	0.241
Tiffeneau index of predicted (%)	95 ± 14	93 ± 16	96 ± 37	0.837
Cardiac exercise test				
Metabolic equivalent	4.7 ± 2.5	4.6 ± 2.1	4.4 ± 2.7	0.676
Heart rate at submaximal exercise (bpm)	112 ± 24	116 ± 21	123 ± 26	0.013
24-h Holter				
Mean heart rate (bpm)	68 ± 10	66 ± 10	72 ± 12	0.007

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CAD, coronary artery disease; eGFR-MDRD, estimated glomerular filtration rate calculated with modification of diet in renal disease study equation; FP, filling pressure; HbA1c, haemoglobin A1c; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; NYHA, New York Heart Association.

Clinical outcomes

During a mean follow-up of 3 years, AF was associated with a higher occurrence of adverse outcome: all-cause mortality or HF hospitalization occurred in 18 (16%) patients without a history of AF, 14 (25%) with PAF, and 34 (38%) with SAF, respectively (*P* = 0.005) (*Figure 2*). After adjustment for multiple testing, only significant differences were found between no AF and SAF (*P* = 0.003). Nine patients (8%) without a history of AF died, compared to 9 (16%) with PAF, and 27 (30%) with SAF (*P* < 0.001), in which sudden death or cardiac death was more often identified in patients with AF [2 (2%), 6 (11%), and 8 (9%), respectively]. Rates for HF hospitalization were 14 (12%) in patients without history of AF, 10 (18%) with PAF, and 17 (19%) with SAF (*P* = 0.513), with no difference in HF hospitalization number in hospitalized patients (*P* = 0.540). No death or HF hospitalization was attributed to a SARS-Cov-2 (COVID-19) infection during this study. Baseline differences between patients with and without the combined endpoint are shown in Supplementary data online, *Table S4*.

LA strain predicts HF hospitalization or all-cause mortality

Patients with abnormal LASr (regardless of rhythm) showed a worse outcome compared to those with normal LASr (*Figure 3*). Similarly, patients without a history of AF displayed a worse outcome if abnormal LASr was present (*P* = 0.048) (data not shown). Combining abnormal LASr and AF status showed a worse prognosis in particularly in those patients with abnormal LASr.

Independent predictors for an adverse outcome adjusted for sex and age were lower LASr values (per 1% decrease), higher estimated RV systolic pressure, higher LV mass index, lower exercise capacity (per 1 metabolic equivalent), and a medical history of significant coronary artery disease (*Table 4*). Changing LASr as a continuous variable in the multivariable model into abnormal LASr defined by <22.7%[20] or <24.0% (optimal cut-off from receiver operating characteristic curve) showed a hazard ratio of 2.95 and 2.85, respectively (Supplementary data online, *Table S5*). Changing LASr into LA fractional area change or emptying fraction showed comparable results (Supplementary data online, *Table S5*). Presence or stage of AF was a predictor for adverse outcome. However, when both AF and LASr

were put in the multivariable model, only LASr remained an independent predictor for adverse outcome (Graphical Abstract). In addition, a causal mediation analysis between AF status (no history of AF vs. history of AF) and LASr showed no direct effect of AF on clinical outcome [bootstrapped average direct effect 7.6%, 95% confidence interval (CI) -4.9% to 20%, *P* = 0.240]. In contrast, this evaluation showed that the adverse outcome in both patients with and without a history of AF was mediated by LASr (bootstrapped average causal mediation effect in AF 10.6%, 95% CI 3.0–17%, without AF 8.6%, 95% CI 1.6–17%, average 9.6%, 95% CI 2.4–17%, *P* = 0.008; total effect 17.2%, 95% CI 6.6–27%, *P* < 0.001).

Discussion

Mechanical atrial dysfunction was an independent predictor of adverse outcome (HF hospitalization or all-cause mortality) and was an underlying mechanism (mediator) for the worse outcome associated with AF in HFpEF. These findings were independent of heart rate and remained after a comprehensive correction of potential confounders. Besides that, this study provides a deeper understanding of AF and HFpEF by showing that occurrence and more advanced stages of AF were associated with progressive mechanical LA dysfunction (decreased LASr) in a prospectively, extensively phenotyped cohort of HFpEF patients.

The current results show the interplay between mechanical and electrical atrial dysfunction in HFpEF. Particularly decreased LA reservoir strain clearly associates with more advanced stages of AF, which confirms recent findings by Reddy *et al.*[21] The current study, however, goes beyond the latter report and adds novel prognostic insight between electrical and mechanical atrial dysfunction in HFpEF. The cohort of the current study was more broadly phenotyped, more balanced in terms of comorbidities and age between study groups (stages of AF), and representative of real-world European HFpEF populations.[13] Our study also had relatively higher PAF and SAF prevalence. These factors allowed us to employ detailed multivariable analyses to observe the independent association of LASr with AF in HFpEF and its prognostic consequences.
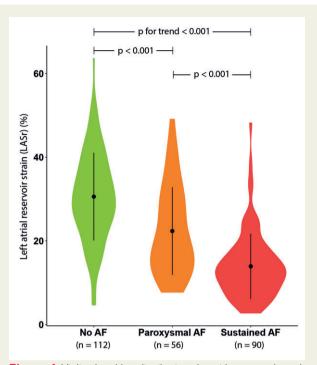
Table 2 Echocardiographic characteristics

	No AF (n = 112)	Paroxysmal AF (n = 56)	Sustained AF (n = 90)	P-value for trend
LV ejection fraction (%)	61 ± 7	60 ± 6	57 ± 6	<0.001
LV global longitudinal strain (%)	19.6 ± 4.2	18.3 ± 4.5	15.3 ± 4.5	<0.001
LV end-diastolic volume (mL)	98 ± 25	94 ± 26	96 ± 30	0.596
LV end-diastolic volume/BSA (mL/m^2)	51 ± 11	49 ± 11	48 ± 13	0.115
LV end-systolic volume (mL)	40 ± 15	38 ± 12	42 ± 13	0.202
LV end-systolic volume/BSA (mL/m^2)	20 ± 7	20 ± 6	21 ± 6	0.652
LA volume index (mL/m^2)	39 ± 12	50 ± 16	59 ± 20	<0.001
LV mass index (g/m^2)	85 ± 20	84 ± 19	86 ± 21	0.879
Relative wall thickness	0.38 ± 0.06	0.40 ± 0.06	0.40 ± 0.08	0.121
E peak (m/s)	77 ± 24	82 ± 23	99 ± 23	<0.001
A peak (m/s)	84 ± 23	73 ± 25	62 ± 32	0.002
E/A ratio	1.0 ± 0.4	1.2 ± 0.7	1.7 ± 1.1	<0.001
E′ septal (cm/s)	6.2 ± 1.7	6.9 ± 2.4	7.9 ± 2.5	<0.001
E′ lateral (cm/s)	8.1 ± 2.6	9.9 ± 3.5	10.5 ± 3.2	<0.001
E/e′ average	13.4 ± 5.5	13.1 ± 5.0	13.8 ± 5.4	0.812
Inferior vena cava collapse (%)	68 ± 15	69 ± 17	65 ± 20	0.374
Tricuspid regurgitation peak velocity (m/s)	2.6 ± 0.4	2.7 ± 0.4	2.8 ± 0.5	0.071
Estimated RV systolic pressure (mmHg)	33 ± 11	35 ± 10	38 ± 12	0.034
Mitral valve regurgitation, n (%)				0.001
Absent	99 (92)	40 (74)	64 (74)	
Mild	5 (4)	13 (24)	17 (20)	
Moderate	4 (4)	1 (2)	5 (6)	
Cardiac rate and rhythm during echocardiography				
Heart rate (bpm)	65 ± 10	67 ± 13	75 ± 16	<0.001
AF, n (%)	0 (0)	16 (29)	74 (82)	<0.001
Additional left atrial features				
LA reservoir strain (%)	30.5 ± 10.5	22.3 ± 10.5	13.9 ± 7.8	<0.001
Abnormal LA reservoir strain, n (%)	25 (22)	32 (57)	79 (88)	<0.001
LA reservoir strain rate (%/s)	2.98 ± 1.17	2.27 ± 1.14	2.00 ± 1.42	<0.001
LA stiffness (E/e′/LA reservoir strain)	0.46 [0.28–0.62]	0.62 [0.40–1.02]	1.01 [0.71–1.65]	<0.001
LA fractional area change (%)	42.0 ± 11.0	32.2 ± 12.4	22.5 ± 10.1	<0.001
Biplane LA emptying fraction (%)	56.8 ± 11.8	43.7 ± 16.0	29.9 ± 11.4	<0.001
Abnormal LA emptying fraction, n (%)	12 (14)	23 (50)	71 (91)	<0.001
LA conduit strain (%)	18.6 ± 7.2	15.6 ± 5.7	15.8 ± 7.6	0.040
LA contraction strain (%)	13.5 ± 6.7	12.1 ± 6.3	7.7 ± 6.2	0.001

AF, atrial fibrillation; BSA, body surface area; LA, left atrial; LV, left ventricular; RV, right ventricular.

Prognostic implications of mechanical atrial dysfunction in HFpEF and AF

Perhaps the most important finding of the present study concerns the prognostic role of mechanical atrial dysfunction in HFpEF and AF. Prognostic implications of either a history of AF or mechanical atrial dysfunction during sinus rhythm have previously been reported in HFpEF[2,9,10] and were validated in our study. Interestingly, however, our data show the direct association between AF and adverse outcome completely disappeared when mechanical atrial dysfunction was taken into account (both in multivariable Cox regression and mediation analyses). Meanwhile, mechanical atrial dysfunction remained an independent predictor of adverse outcome in adjusted multivariable analyses. This novel finding might indicate that the worse outcome seen in HFpEF patients with AF is largely mediated

through mechanical atrial dysfunction, thus proposing the hypothesis that mechanical atrial dysfunction is one of the underlying mechanisms for adverse outcome in these patients. Additionally, LV-GLS was not an independent predictor of an adverse outcome when mechanical atrial dysfunction was added to the model, although it correlated with lower values of mechanical atrial function. These findings may suggest that mechanical atrial dysfunction, particularly a decreased LA reservoir function, plays a crucial role in disease progression and worse outcome in HFpEF and AF. Moreover, based on our outcome data in patients without a history of AF (both univariable survival and mediation analyses), mechanical atrial dysfunction likely also plays an important role in disease progression in HFpEF patients without AF, but the underlying process needs further investigation.

Figure 1 Violin plots (data distribution plot with mean and standard deviation) showing mechanical atrial dysfunction at different atrial fibrillation (AF) stages in HFpEF.

Mechanical atrial dysfunction within the clinical entity of HFpEF

Several factors were associated with mechanical atrial dysfunction (lower LASr values) in HFpEF patients in the current study, which may be related to the different phenotypes in HFpEF and may also indicate different underlying pathophysiology.[22] In particular, we found more advanced stages of AF (electrical alterations), higher LAVI (anatomic alterations), and higher NT-proBNP levels (pressure/compliance alterations) were associated with worse mechanical atrial function, showing that atrial dysfunction comprises a variety of elements. Moreover, mechanical LA dysfunction was correlated with LV ejection fraction and LV-GLS. A similar correlation has been found in HFpEF patients,[9,10] and mechanical atrial dysfunction and LV-GLS have been separately reported in advanced stages of AF.[21] Relative wall thickness was also inversely correlated with mechanical atrial dysfunction. One could speculate that this finding may reflect underlying LV hypertrophy that decreases the LV compliance, which consequently impacts the LA; still, this requires future research as current data are scarce.[10] Mechanical atrial dysfunction was also associated with echocardiographic signs of elevated LV filling pressure, a finding that is in line with results from prior studies.[9,10,23] Hence, it is suggestive that the thin-walled LA is susceptible to elevated left-sided intracardiac filling pressures, resulting in decreased LA reservoir function. Finally, patients without COPD had lower mechanical atrial function values than those with COPD. This unexpected finding may warrant future research but should be interpreted with caution, as only 15% (*n* = 39) of the study population had COPD, and

pulmonary function test values (including Tiffeneau index) were not independently associated with LASr. Based on previous studies, HFpEF patients with COPD possibly represent a separate phenotype in which LV impairments together with RV impairments lead to HF,[22] perhaps more so than LA impairments. Another possible explanation is that patients with both COPD and HF are more symptomatic than those without COPD,[24] and therefore, it may be speculated that HFpEF was less severe in COPD patients despite similar symptoms.

Implications for treatment of electrical atrial dysfunction in HFpEF

Findings from prior studies suggest that HFpEF patients could benefit from rhythm control therapy to restore normal sinus rhythm. The recent EAST-AFNET 4 trial showed that patients aged above 65 years recently diagnosed with AF benefitted from rhythm control (both anti-arrhythmic drugs and ablation) rather than rate control with a modest yearly risk reduction of 1.1% for cardiovascular death or hospitalization, or stroke.[25] In addition, a small prospective study on patients with symptomatic AF and HFpEF reported HFpEF patients who remained arrhythmia free after AF ablation had a clear improvement in peak exercise pulmonary capillary wedge pressure after 6 months.[26] However, the beneficial effects and underlying mechanisms of rhythm control treatment in HFpEF patients remain unclear.[25–27] Randomized trials on rhythm control in HFpEF are clearly needed. The association between AF, mechanical atrial dysfunction, and adverse prognosis found in our study suggests that treatments targeting AF in HFpEF should take mechanical atrial dysfunction into account. In this regard, functional atrial assessment may be useful to improve the efficacy of rhythm control in HFpEF, as assessing mechanical atrial dysfunction may allow better characterization of atrial function and pathological substrate.[12] Mechanical atrial dysfunction could predict future AF development, AF progression or recurrence,[11,21] and might predict successful sinus rhythm restoration after cardioversion.[28]

Still, anti-arrhythmic therapies may insufficiently modulate or halter progression of the underlying atrial disease substrate: patients with lone AF had further adverse electrical remodelling 10 months after sinus rhythm initiation.[29] Hence, attention should also be given to the treatment of underlying risk factors and comorbidities, such as anti-hypertensive therapy, with the aim to halting further adverse remodelling.

Future perspectives on mechanical atrial dysfunction in HFpEF

The current study results may suggest a greater role for atrial function assessment in HFpEF compared to rhythm status or atrial morphological features alone. Several pathological mechanisms associated with mechanical atrial dysfunction may occur concurrently in HFpEF, including increased fibrosis (resulting in decreased compliance), suboptimal actin–myosin coupling due to enlarged atrial volumes, fat deposition, local inflammation, and pericardial constraint.[21,30] Therapies targeting these specific substrates, such as cardiac fibrosis or inflammation, could consider using functional atrial assessment to monitor disease progression regardless of AF stage.
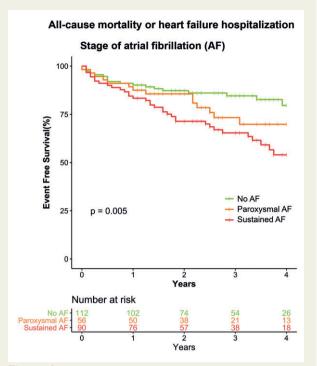
Table 3 Predictors for LASr values (continuous)

	Univariable				Multivariable			
	β	95% CI	Standardized β	P-value	β	95% CI	Standardized β	P-value
Female sex	5.5	2.4–8.7	0.211	0.001	1.8	-0.5 to 4.1	0.068	0.140
Age	-0.28	-0.47 to -0.09	-0.176	0.005	-0.07	-0.21 to 0.07	-0.044	0.326
Cardiac rhythm								
No AF				ref				ref
Paroxysmal AF	-8.2	-11.3 to -5.1	-0.281	<0.001	-4.0	-6.67 to -1.25	-0.138	0.004
Sustained AF	-16.7	-19.3 to -14.0	-0.658	<0.001	-7.1	-10.13 to -4.00	-0.276	<0.001
Chronic obstructive pulmonary disease	5.3	1.2–9.4	0.157	0.011	4.4	1.6–7.3	0.132	0.002
Hypercholesterolaemia	2.7	-0.2 to 5.7	0.113	0.071				n.s.
Significant CAD	-0.74	-4.3 to 2.8	-0.026	0.679				
Systolic BP	0.04	-0.03 to 0.11	0.077	0.229				
Diastolic BP	-0.08	-0.19 to 0.04	-0.086	0.178				
Clinical signs of congestion	-1.07	-4.10 to 1.96	-0.043	0.490				
Echo signs of elevated LVFP	-5.6	-8.9 to -2.3	-0.205	0.001	-2.7	-5.1 to -0.3	-0.099	0.025
NT-proBNP (log)	-7.0	-8.2 to -5.7	-0.567	<0.001	-2.9	-4.2 to -1.7	-0.238	<0.001
eGFR-MDRD	0.09	-0.02 to 0.21	0.121	0.106				
Aldosterone receptor antagonist	-4.5	-8.4 to -0.5	-0.141	0.027				n.s.
Loop diuretic	-5.3	-8.2 to -2.3	-0.219	0.001				n.s.
LV ejection fraction	0.60	0.40–0.80	0.348	<0.001				n.s.
LV global longitudinal strain	1.2	0.9–1.5	0.478	<0.001	0.58	0.33–0.83	0.228	<0.001
LA volume index	-0.33	-0.40 to -0.26	-0.507	<0.001	-0.13	-0.20 to -0.06	-0.189	<0.001
Inferior vena cava collapse	0.06	-0.03 to 0.15	0.092	0.159				
LV mass index	-0.06	-0.13 to 0.01	-0.099	0.113				
Relative wall thickness	-46.6	-67.9 to -25.4	-0.262	<0.001	-21.0	-36.21 to -5.80	-0.119	0.007
E′ septal	-0.420	-1.1 to 0.31	-0.077	0.255				
E′ lateral	-0.62	-1.1 to -0.10	-0.160	0.020				n.s.
E/e′ average	-0.37	-0.68 to -0.07	-0.162	0.017				n.s.
Mitral valve regurgitation (≥moderate)	-2.9	-6.8 to 1.0	-0.090	0.148				
RV systolic pressure	-0.24	-0.37 to -0.10	-0.214	0.001				n.s.
RR interval during echocardiography	0.01	0.00–0.02	0.160	0.010	0.00	-0.01 to 0.01	-0.012	0.797
Distance walked of predicted during 6MWT	0.08	-0.00 to 0.15	0.128	0.056				n.s.
Metabolic equivalent	0.24	-0.40 to 0.89	0.051	0.454				
Forced vital capacity of predicted	0.09	0.00–0.17	0.132	0.042				n.s.
Forced expiratory volume of predicted	0.03	-0.04 to 0.10	0.056	0.384				
Tiffeneau index of predicted	-0.05	-0.11 to 0.01	-0.098	0.131				

6MWT, 6-min walk test; AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; eGFR-MDRD, estimated glomerular filtration rate calculated with modification of diet in renal disease study equation; LA, left atrial; LASr, left atrial reservoir strain; LV, left ventricular; LVFP, left ventricular filling pressure; n.s., not significant; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; RV, right ventricular.

Therapies focusing on atrial mechanics may improve symptoms and outcomes in HFpEF patients due to favourable unloading effects on intracardiac pressure and the pulmonary vascular bed. Regardless of cardiac rhythm, impaired LA reservoir function causes quicker atrial pressure build-up and backflow of blood to the lungs if atrial pressures are too high, with pulmonary congestion and hypertension as a consequence.[21] Hence, patients with a worse mechanical atrial function are more susceptible to elevated filling pressures. Conversely, we found mechanical atrial dysfunction was significantly associated with echocardiographic signs of elevated LV filling pressure. This finding is supported by a recent study using computer simulations of atrioventricular mechanics and haemodynamics in HFpEF

with and without mechanical atrial dysfunction, which showed that elevated filling pressures and mechanical atrial function might affect each other bi-directionally.[31] Therefore, more stringent use of diuretics to achieve normal filling pressures could potentially be beneficial not only for symptom improvement but also to improve mechanical atrial function and thereby better clinical outcome in HFpEF.

Similar assessments of LA function, such as LA fractional area change or emptying fraction, may also be accessible ways to evaluate mechanical atrial dysfunction and could be considered in future research. Their prognostic power was comparable to LASr in our study. However, 5.2% of patients with a normal LA emptying fraction
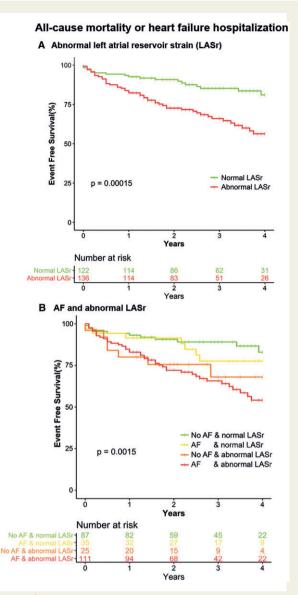
Figure 2 Kaplan–Meier survival curve for freedom of heart failure hospitalization or all-cause mortality for stages of atrial fibrillation (AF).

had an abnormal LASr. Which of these measures is most suitable for clinical practice requires additional research.

Limitations

It could be argued that categorizing stages of AF based on medical history, electrocardiography, and 24-h Holter monitoring is obscuring the true nature of AF complexity and may lead to AF underdiagnosis.[32] However, AF based on medical history is used by all diagnostic scores for HFpEF[5–7] and does resemble how HFpEF patients are labelled clinically. To the same extent, echocardiographic evaluation of LA function at a single time point is probably an over-simplification of the dynamic electrical and mechanical relationship of both atria and ventricles. In addition, our observational results are hypothesis generating but do not allow to determine causality. Longitudinal data on both cardiac electrical and mechanical function could indicate more clearly the causal role of both phenomena in HFpEF patients. This causality is likely bi-directional, but this needs to be further investigated. Moreover, assessing more aspects of atrial function (reservoir, conduit, and contraction) may enhance mechanical atrial understanding and be of additional prognostic value, but assessment is limited to sinus rhythm.

Although guidelines of LA strain measurements exist,[19,33] there still is a lack of standardization between vendors and software, hindering the external validity of LA strain studies. Dedicated apical views were used in this study, in which care was taken to obtain non-foreshortened images for both LV and LA morphology and function. However, three-dimensional echocardiography was not available, which is preferable to minimize foreshortening.[34] Of course, all

Figure 3 Kaplan–Meier survival curves for freedom of heart failure hospitalization or all-cause mortality for (*A*) abnormal left atrial reservoir strain (LASr) (defined as <22.7%) and (*B*) atrial fibrillation (AF) presence and abnormal LASr combined.

images were reviewed and excluded from the analysis if overt LA foreshortening was present. Nevertheless, LA strain values obtained can potentially be falsely increased compared to three-dimensional LA focused images. This does not affect the internal validity of the current study results, but the potential difference should be considered when comparing absolute values with those of other studies.

Considering the multimodality of the HFpEF syndrome,[22] looking at one specific marker is most likely not fully catching the pathophysiology or prognostic consequence of the entire patient population. Although we employed many multivariable analyses with all available clinical and echocardiographic data to overcome this issue, still certain pathophysiological processes may not have been covered due to limited current knowledge about the syndrome.

Table 4 Independent predictors for heart failure hospitalization or all-cause mortality

	Univariable			Multivariable		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Female sex	0.689	0.419–1.133	0.142	0.806	0.383–1.694	0.569
Age (per year)	1.027	0.993–1.063	0.123	0.985	0.943–1.030	0.511
Cardiac rhythm						
No AF vs. paroxysmal AF	1.622	0.807–3.262	0.175			n.s.
No AF vs. sustained AF	2.493	1.407–4.414	0.002			n.s.
Paroxysmal AF vs. sustained AF	1.537	0.825–2.863	0.176			n.s.
History of significant CAD	1.935	1.166–3.211	0.011	2.366	1.268–4.374	0.006
LV mass index (per 1 g/m^2)	1.023	1.012–1.034	<0.001	1.024	1.009–1.038	0.001
LV global longitudinal strain (per 1%)	0.958	0.909–1.010	0.115			n.s.
RV systolic pressure (per 1 mmHg)	1.042	1.023–1.062	<0.001	1.031	1.008–1.056	0.009
LA reservoir strain (per 1% decrease)	1.046	1.022–1.071	<0.001	1.049	1.014–1.085	0.006
Exercise tolerance (per 1 MET)	0.620	0.505–0.760	<0.001	0.636	0.510–0.792	<0.001
NT-proBNP (per 100 pg/mL)	1.037	1.023–1.051	<0.001			n.s.
LA volume index (per 1 mL/m^2)	1.008	0.996–1.021	0.182			n.s.

Variables independently associated with adverse outcome are shown in this table, with an addition of selected relevant variables. Analyses have been performed on all available clinical, functional, and echocardiographic variables, including confounders of LASr. Variables that are not displayed had no significant association with adverse outcome in the final model.

AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; LA, left atrial; LASr, left atrial reservoir strain; LV, left ventricular; MET, metabolic equivalent; n.s., not significant; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; RV, right ventricular.

Conclusions

This study supports a possible greater role for atrial function in prognosis of HFpEF compared to AF status alone. Mechanical atrial dysfunction in HFpEF patients was an independent predictor of adverse outcome (HF hospitalization or all-cause mortality). Moreover, it was a possible underlying mechanism (mediator) for the adverse clinical outcome associated with AF in HFpEF. These findings remained after a comprehensive correction of potential confounders, including heart rate. In addition, HFpEF patients with occurrence and more advanced stages of AF displayed progressive mechanical LA dysfunction. Mechanical atrial dysfunction may play a crucial role in disease progression in HFpEF patients with AF and warrants future research for improved treatment strategies for these patients. Similarly, the current results suggest mechanical atrial dysfunction may play an important role in HFpEF patients without AF.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

All relevant data are within the paper and its Supplementary material online. The data underlying this article may be shared on a reasonable request to the corresponding author.

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