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RESEARCH ARTICLE

Left atrial enlargement is associated with pulmonary vascular disease in heart failure with preserved ejection fraction

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Aims Elevated left atrial (LA) pressure is a pathophysiologic hallmark of heart failure with preserved ejection fraction (HFpEF). Chronically elevated LA pressure leads to LA enlargement, which may impair LA function and increase pulmonary pressures. We sought to evaluate the relationship between LA volume and pulmonary arterial haemodynamics in patients with HFpEF.

Methods and results Data from 85 patients (aged 69 ± 8 years) who underwent exercise right heart catheterization and echocardiography were retrospectively analysed. All had symptoms of heart failure, left ventricular ejection fraction ≥50% and haemodynamic features of HFpEF. Patients were divided into LA volume index-based tertiles (≤34 ml/m^2, >34 to ≤45 ml/m^2, >45 ml/m^2). A subgroup analysis was performed in patients with recorded LA global reservoir strain (n = 60), with reduced strain defined as ≤24%. Age, sex, body surface area and left ventricular ejection fraction were similar between volume groups. LA volume was associated with blunted increases in cardiac output with exercise ($p_{adjusted}$ <0.001), higher resting mean pulmonary artery pressure ($p_{adjusted}$ = 0.003), with similar wedge pressure ($p_{adjusted}$ = 1). Pulmonary vascular resistance (PVR) increased with increasing LA volume ($p_{adjusted}$ <0.001). Larger LA volumes featured reduced LA strain ($p_{adjusted}$ <0.001), with reduced strain associated with reduced PVR–compliance time (0.34 [0.28–0.40] vs. 0.38 [0.33–0.43], p = 0.03).

Conclusion Increasing LA volume may be associated with more advanced pulmonary vascular disease in HFpEF, featuring higher PVR and pulmonary pressures. Reduced LA function, worse at increasing LA volumes, is associated with a disrupted PVR–compliance relationship, further augmenting impaired pulmonary haemodynamics.

Keywords Heart failure with preserved ejection fraction • Exercise haemodynamics • Left atrium • Echocardiography • Cardiac catheterization • Pulmonary hypertension

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Introduction

It is widely accepted that heart failure with preserved ejection fraction (HFpEF) has emerged as the predominant of heart failure and that in contrast to heart failure with reduced ejection fraction, management is particularly challenging.[1,2] The pathophysiology of HFpEF is complex, including key cardiovascular elements together with closely related non-cardiovascular features.[2] Impaired left ventricular (LV) relaxation and increased LV stiffness resulting in elevated LV filling pressures are considered hallmarks of the disease, often only evident during exertion.[3,4] As a consequence, left atrial (LA) afterload is elevated[5] and contributes to LA remodelling, ultimately with disturbed atrial mechanical and electrical function.[6] Beyond the passive haemodynamic effect of increased LA pressure on pulmonary pressures,[1,4] this also leads to remodelling of the pulmonary vasculature with reduced compliance, particularly when atrial fibrillation (AF) is present.[6] In the context of HFpEF, LA size is also an independent predictor of morbidity and mortality,[3] suggesting that remodelling of the left atrium in HFpEF patients may further contribute to poor outcomes in already progressed disease.

In the current study we investigated the hypothesis that the mechanical properties of the left atrium in HFpEF influence the remodelling of the pulmonary vasculature beyond the elevation of LA pressure *per se*. Specifically we examined the relationship between LA strain and the mechanical properties of the pulmonary vasculature.

Methods

Study design and participants

Two cohorts were included for a total of 85 patients. The first consisted of baseline data of 21 patients who were assessed for the REDUCE LAP-HF trial, an open-label study assessing the role of an atrial shunt device for patients with HFpEF or heart failure with mildly reduced ejection fraction. Complete selection criteria specific to the REDUCE LAP-HF subset are described elsewhere.[7] Patients with moderate or worse aortic or mitral valvular disease, or an atrial septal defect (ASD) were excluded, as well as those with significant respiratory disease or significant coronary lesions. These data were combined with a cohort of 64 consecutive patients from the Alfred Hospital Haemodynamic Database undergoing haemodynamic evaluation for exertional dyspnoea. Criteria for inclusion in the current analysis across both cohorts included the presence of heart failure symptoms, LV ejection fraction (LVEF) $\geq$50%, and an elevated pulmonary capillary wedge pressure (PCWP) $\geq$15 mmHg at rest (47%) and/or $\geq$25 mmHg with supine exercise (96%), consistent with guideline definitions of HFpEF.[8] The Alfred and REDUCE LAP-HF cohorts had similar baseline characteristics, both predominantly female, with similar mean age, body mass index, body surface area (BSA), and rates of AF. This study complies with the Declaration of Helsinki. Approval was granted by the local ethics committee at each institution for the REDUCE LAP-HF cohort, and by the Alfred Hospital Research and Ethics Committee for the present study.

The combined cohort was divided based on LA volume index (LAVI) into three tertiles: $\leq$34 ml/m^2 (29 patients), >34 to $\leq$45 ml/m^2 (28 patients), >45 ml/m^2 (28 patients). A subgroup analysis was performed with patients who also had LA global reservoir strain assessed on echo (n = 60), with reduced strain defined as $\leq$24%, guided by previously used cut-offs.[9]

Procedures

Right heart catheterization (RHC) was performed from the brachial or jugular venous approach. End-expiratory measurements were taken at rest and peak exercise from the right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge position. Symptom-limited (leg fatigue and/or dyspnoea) exercise was performed using supine cycle ergometry at 60 rpm. For the REDUCE LAP-HF subset, this consisted of 20 W increases every 3 min until symptom-limited maximum exertion was reached. A similar protocol was implemented for the Alfred subset, with a graded increase in resistance every 3 min to a maximum of 1.5 W/kg until volitional fatigue. Cardiac output (CO) was measured at both rest and exercise via thermodilution as an average of $\geq$3 measurements. Stroke volume (SV) was calculated based on thermodilution-derived CO and heart rate at time of measurement. PCWP was consistently measured at end-expiration at rest and during exercise, in keeping with accepted practice.[7,10]

Transthoracic echocardiography was performed using a commercially available Philips iE33 cardiology ultrasound system (Andover, MA, USA), with views and calculations in line with the American Society of Echocardiography guidelines.[11] Simpson's method of discs was used for volume calculations. Focused apical four-chamber LA views were obtained to maximize frame rate for two-dimensional speckle tracking analysis, and images were saved in raw data format. Consistent between patient cohorts, speckle tracking was only performed in patients where images were deemed to be of adequate quality, with images having >1 segment dropout, missing views or significant foreshortening excluded from strain analysis. A full description of the strain measurement technique has been described previously.[12] Standard image analysis was performed off-line in accordance with clinical guidelines using Philips Xcelera 4.1 software (Andover, MA, USA).

Definitions

Body surface area was derived using the Dubois equation. LA end-systolic volume and LV mass were indexed to BSA to calculate LAVI and LV mass index (LVMI). Significantly reduced LA reservoir strain was defined as $\leq$24% guided by previously used cut-offs.[9] Pulmonary vascular resistance (PVR) was calculated as the difference between mean pulmonary artery pressures (mPAP) and PCWP divided by CO. Pulmonary arterial compliance (PAC) was calculated as SV (derived from thermodilution CO) divided by pulmonary artery pulse pressure. PVR (with Wood units converted to mmHg s ml^{-1}) was multiplied by PAC (in ml/mmHg) to calculate the PVR–PAC (RC) time constant (expressed in s), as per previous studies.[13] The presence of AF was defined as a history of paroxysmal or persistent AF. For the REDUCE LAP-HF subset of patients, haemodynamic traces were independently analysed at a core laboratory (PVLoops LLC, New York, NY, USA), and echocardiograms at the University of Pennsylvania (PA, USA). The Alfred subset were analysed locally and verified by two separate investigators.

Statistical analysis

Normally distributed data are represented as mean $\pm$ standard deviation and non-parametric as median (interquartile range).

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Table 1 Baseline characteristics by left atrial volume index group

Variable	All ($n = 85$)	≤34 ml/m^2 ($n = 29$)	>34–45 ml/m^2 ($n = 28$)	>45 ml/m^2 ($n = 28$)	p_{raw}	$p_{adjusted}$
Age (years)	69 ± 8	69 ± 7	68 ± 10	71 ± 5	0.32	1
Male sex (%)	28	24	29	32	0.50*	
Height (cm)	165 ± 9	165 ± 10	165 ± 9	165 ± 9	0.78	1
Weight (kg)	85 ± 19	85 ± 16	86 ± 18	84 ± 22	0.45	1
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.42	1
BMI (kg/m^2)	31 ± 6	31 ± 5	31 ± 7	31 ± 7	0.44	1
Obesity (%)	48	45	57	54	0.50*	
Hypertension (%)	69	55	75	81	0.03*†	
History of atrial fibrillation (%)	33	3	36	61	<0.001*†	
REDUCE LAP-HF cohort (%)	25	45	18	11	0.003*†	
Baseline bloods						
NT-proBNP (ng/L) ($n = 46$)	539 ± 685	185 ± 153	689 ± 839	1067 ± 778	<0.001	0.007†
Creatinine (μmol/L) ($n = 72$)	84 ± 21	81 ± 15	79 ± 21	92 ± 25	0.13	1
Haemoglobin (g/L) ($n = 78$)	134 ± 13	134 ± 13	133 ± 12	134 ± 14	0.66	1

BMI, body mass index; BSA, body surface area; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*Chi square test for trend. All other *p*-values relate to linear regression (with Benjamini–Hochberg correction).
†Significant at $p < 0.05$.

Linear regression was used for continuous variables to assess the significance of the relationship with increasing LAVI. Benjamini–Hochberg correction was applied to linear regression results across *Tables 1* and *2* owing to the high number of multiple comparisons, adjusting for the number of observations in each table subset separately (baseline data, haemodynamics and echocardiographic features), with unadjusted *p*-values reported as p_{raw}, and $p_{adjusted}$ after Benjamini–Hochberg correction. Chi-square test for trend using LAVI tertiles was used for categorical data. Two-sided *t*-test or Mann–Whitney U test were used as appropriate for strain analysis. Statistical analysis was performed with R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). The null hypothesis was rejected at $p < 0.05$.

Results

The total cohort included 85 patients, with data collected between 2014 and 2018. The study population had characteristics consistent with established epidemiology of HFpEF,[2,6] being predominantly elderly (mean age 69 ± 8 years), female (72%) and obese (48%), with high rates of AF (33%) as detailed in *Table 1*. Sex and body mass index were similar across LAVI groups. Rates of AF increased in prevalence with larger LA size ($p < 0.001$). N-terminal pro-B-type natriuretic peptide (NT-proBNP) was available for a subset of patients ($n = 46$) and increased across LA groups ($p_{adjusted} = 0.007$).

Haemodynamics

Invasive haemodynamic data are summarized in *Table 2*. LAVI groups were similar in respect to heart rate and systemic pressures. Exercise capacity, indicated by time to maximal exercise and peak workload reached, was comparable between groups.

As shown in *Table 2*, increased LAVI was associated with higher mPAP at rest ($p_{adjusted} = 0.003$). There appeared to be a small directional increase in resting PCWP across LA groups ($p_{raw} = 0.049$) that was not significant after adjustment ($p_{adjusted} = 1$), and similar elevations in exercise PCWP across groups ($p_{raw} = 0.34$, $p_{adjusted} = 1$). Larger LA size was associated with increased PVR at rest ($p_{adjusted} < 0.001$), with a corresponding decrease in PAC ($p_{adjusted} = 0.003$). Similar results were seen during exercise. There were no differences between groups in respect to RC time constant ($p_{raw} = 0.08$, $p_{adjusted} = 1$). Transpulmonary gradient rose with increasing LAVI ($p_{adjusted} = 0.005$), although diastolic pulmonary gradient (DPG) remained low and similar across increasing LAVI ($p_{raw} = 0.11$, $p_{adjusted} = 1$).

There was a small trend toward lower CO at rest that was not significant after adjustment ($p_{raw} = 0.008$, $p_{adjusted} = 0.34$). In response to exercise, we observed significantly lower CO in relation to larger LAVI ($p_{adjusted} < 0.001$). In particular, the magnitude of CO augmentation during exercise decreased significantly across increasing LAVI groups ($p_{adjusted} < 0.001$). Right ventricular (RV) stroke work index was similar between groups at rest and exercise.

Echocardiography

Overall mean LAVI was 40 ± 10 ml/m^2, as detailed in *Table 2*. There was no clear trend in terms of mean E/e' ($p_{raw} = 0.44$, $p_{adjusted} = 1$). Patients had an overall mean LVEF of 60 ± 6%, with similar results between LA size groups ($p_{raw} = 0.56$, $p_{adjusted} = 1$). LVMI did not differ between groups ($p_{raw} = 0.43$, $p_{adjusted} = 1$).

Left atrial function, as measured by LA global reservoir strain in a subset of patients ($n = 60$), was reduced across the cohort, with an overall mean strain of 25 ± 9%, which decreased with increasing LAVI ($p_{adjusted} < 0.001$). In patients with data on LA

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Table 2 Haemodynamics and echocardiographic findings by left atrial volume index group

	All ($n = 85$)	≤34 ml/m^2 ($n = 29$)	>34–45 ml/m^2 ($n = 28$)	>45 ml/m^2 ($n = 28$)	p_{raw}	$p_{adjusted}$
Peak (W)	51 ± 27	54 ± 31	53 ± 28	46 ± 20	0.24	1
Peak time (min)	6.5 ± 2.8	7.0 ± 2.6	6.4 ± 3.0	6.2 ± 2.8	0.41	1
Heart rate (bpm)						
Rest	68 ± 12	68 ± 10	70 ± 15	66 ± 10	0.66	1
Exercise	103 ± 22	104 ± 19	106 ± 25	99 ± 21	0.89	1
Change	35 ± 18	35 ± 19	36 ± 19	32 ± 17	0.98	1
BP (mmHg)						
Rest	150 ± 26	143 ± 20	152 ± 26	156 ± 30	0.02*	0.86
Exercise	176 ± 30	180 ± 26	179 ± 29	169 ± 34	0.77	1
Change	26 ± 29	36 ± 30	27 ± 28	14 ± 24	0.02*	0.89
RAP (mmHg)						
Rest	8 ± 3	7 ± 4	8 ± 3	9 ± 4	0.12	1
Exercise	17 ± 5	15 ± 5	17 ± 6	19 ± 5	0.04*	1
Change	9 ± 5	8 ± 4	9 ± 5	9 ± 4	0.16	1
mPAP (mmHg)						
Rest	24 ± 7	20 ± 5	24 ± 8	27 ± 7	<0.001*	0.003*
Exercise	44 ± 10	41 ± 7	45 ± 12	47 ± 8	0.053	1
Change	21 ± 7	21 ± 6	21 ± 8	20 ± 8	0.32	1
PCWP (mmHg)						
Rest	15 ± 5	13 ± 5	14 ± 4	17 ± 5	0.049*	1
Exercise	31 ± 5	29 ± 4	31 ± 4	32 ± 6	0.34	1
Change	16 ± 5	16 ± 5	17 ± 5	16 ± 6	0.48	1
CO (L/min)						
Rest	5.1 ± 1.3	5.3 ± 1.2	5.3 ± 1.5	4.6 ± 0.9	0.008*	0.34
Exercise	8.5 ± 2.6	9.7 ± 2.3	8.7 ± 2.8	7.0 ± 1.7	<0.001*	<0.001*
Change	3.5 ± 1.9	4.5 ± 1.9	3.5 ± 2.0	3.5 ± 1.3	<0.001*	<0.001*
SV (ml)						
Rest	76 ± 20	78 ± 16	78 ± 24	71 ± 18	0.04*	1
Exercise	87 ± 26	94 ± 21	89 ± 31	76 ± 21	<0.001*	0.01*
Change	10 ± 16	17 ± 14	10 ± 19	4 ± 11	<0.001*	0.04*
TPG (mmHg)						
Rest	9.0 ± 4.9	6.9 ± 3.6	9.6 ± 5.1	10.7 ± 5.2	<0.001*	0.005*
Exercise	12.8 ± 6.8	12.1 ± 6.6	12.0 ± 7.3	14.4 ± 6.5	0.10	1
Change	3.7 ± 5.7	8.8 ± 5.4	6.3 ± 6.5	3.3 ± 5.3	0.39	1
DPG (mmHg)						
Rest	0.6 ± 3.9	0.0 ± 3.0	1.4 ± 3.4	0.5 ± 4.5	0.11	1
Exercise	−2.7 ± 6.2	−1.7 ± 6.3	−2.8 ± 6.3	−3.6 ± 6.1	0.31	1
Change	−3.4 ± 5.9	−2.1 ± 6.3	−3.7 ± 6.4	−4.4 ± 4.8	0.053	1
PVR (Wood units)						
Rest	2.0 ± 1.2	1.4 ± 0.8	2.0 ± 1.4	2.4 ± 1.3	<0.001*	<0.001*
Exercise	1.7 ± 1.1	1.3 ± 0.7	1.7 ± 1.2	2.2 ± 1.2	<0.001*	0.005*
Change	−0.2 ± 0.9	−0.1 ± 0.8	−0.2 ± 1.1	−0.4 ± 0.9	0.14	1
PA compliance (ml/mmHg)						
Rest	4.0 ± 1.7	4.8 ± 1.5	4.0 ± 1.6	3.2 ± 1.6	<0.001*	0.003*
Exercise	2.8 ± 1.5	3.3 ± 1.8	3.0 ± 1.5	2.0 ± 0.9	<0.001*	0.02*
Change	−1.3 ± 1.5	−1.6 ± 1.8	−1.2 ± 1.1	−1.2 ± 1.4	0.54	1
RC time (s)						
Rest	0.39 ± 0.14	0.36 ± 0.14	0.40 ± 0.14	0.40 ± 0.14	0.08	1
Exercise	0.23 ± 0.13	0.22 ± 0.12	0.22 ± 0.09	0.25 ± 0.17	0.58	1
Change	−0.15 ± 0.18	−0.13 ± 0.19	−0.18 ± 0.14	−0.14 ± 0.19	0.41	1
RVSWI						
Rest	8 ± 4	7 ± 3	9 ± 5	9 ± 4	0.06	1
Exercise	17 ± 6	17 ± 5	18 ± 7	16 ± 7	0.21	1
Change	9 ± 5	10 ± 5	8 ± 5	7 ± 6	0.005*	0.20
Echocardiographic features						
LVEDV (ml)	111 ± 28	105 ± 28	116 ± 29	112 ± 25	0.54	1
LVEF (%)	60 ± 6	60 ± 7	60 ± 5	60 ± 6	0.56	1
LVMI (g/m^2)	98 ± 30	94 ± 23	100 ± 29	101 ± 38	0.43	1
LA volume (ml)	77 ± 29	47 ± 13	76 ± 11	108 ± 19		
LAVI (ml/m^2)	40 ± 10	24 ± 5	40 ± 3	57 ± 10		
Mean E/e'	13 ± 5	13 ± 7	13 ± 4	14 ± 5	0.44	1
LAEF (%) ($n = 20$)	34 ± 12	41 ± 7	26 ± 10	19 ± 5	<0.001*	<0.001*
LA strain (%) ($n = 60$)	25 ± 9	31 ± 7	26 ± 7	16 ± 7	<0.001*	<0.001*
LV strain (%) ($n = 47$)	−19 ± 2	−20 ± 2	−18 ± 2	−19 ± 2	0.007	0.052

BP, blood pressure; CO, cardiac output; DPG, diastolic pulmonary gradient; LA, left atrial; LAEF, left atrial emptying fraction; LAVI, left atrial volume index; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC, resistance–compliance; RVSWI, right ventricular stroke work index; SV, stroke volume; TPG, transpulmonary gradient.

*Significant at $p < 0.05$.

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Table 3 Differences between left atrial strain groups

	Total ($n = 60$)	Significantly reduced strain (≤24%) ($n = 27$)	Low to normal strain (>24%) ($n = 33$)	*p*-value
Rest PVR (Wood units)	1.7 (1.2–2.3)	1.9 (1.4–3.0)	1.6 (1.1–2.0)	0.06
Exercise PVR (Wood units)	1.5 (1.0–2.2)	1.9 (1.5–2.8)	1.2 (0.7–1.5)	<0.001*
Rest PAC (ml/mmHg)	3.6 (2.9–5.0)	3.0 (2.3–3.7)	4.3 (3.5–5.7)	<0.001*
Exercise PAC (ml/mmHg)	2.4 (1.8–3.5)	1.8 (1.6–2.1)	3.4 (2.2–3.5)	<0.001*
Rest RC (s)	0.36 (0.30–0.43)	0.34 (0.28–0.40)	0.38 (0.33–0.43)	0.03*
Exercise RC (s)	0.20 (0.16–0.28)	0.19 (0.16–0.26)	0.22 (0.16–0.28)	0.73
Rest mPAP (mmHg)	22 (19–27)	26 (22–30)	21 (17–22)	<0.001*
Exercise mPAP (mmHg)	43 (38–44)	48 (43–52)	40 (36–43)	<0.001*
Rest PCWP (mmHg)	14 (12–17)	17 (14–21)	13 (10–15)	<0.001*
Exercise PCWP (mmHg)	30 (27–34)	34 (29–37)	27 (26–32)	0.002*

mPAP, mean pulmonary artery pressure; PAC, pulmonary arterial compliance; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RC, resistance–compliance.
*Significant at $p < 0.05$.

emptying fraction ($n = 20$), this also decreased with increasing LAVI ($p_{adjusted}$ <0.001).

Subgroup analysis

Results on patients with reduced LA strain are shown in *Table 3*. Patients with significantly reduced strain exhibited reduced PAC (3.0 [2.3–3.7] vs. 4.3 [3.5–5.7], $p < 0.001$), with an increase in PVR that did not reach significance (1.9 [1.4–3.0] vs. 1.6 [1.1–2.0], $p = 0.06$). There was a decrease in RC time constant (0.34 [0.28–0.40] vs. 0.38 [0.33–0.43], $p = 0.03$). Patients with significantly reduced LA strain also featured increased pulmonary arterial and wedge pressures.

Owing to the potential influence of AF on haemodynamics, all results were re-analysed using only patients that were confirmed to be in sinus rhythm at the time echocardiography and RHC ($n = 62$). Significant results were unchanged and are displayed in online supplementary *Tables S1* and *S2*.

Discussion

This study evaluated the relationship between LA enlargement (LAVI) and resting and exercise haemodynamics among patients with HFpEF. Our main findings were that HFpEF patients with increased LAVI demonstrated elevated pulmonary pressures and elevated PVR. Our secondary analysis of patients with LA strain data suggests that decreased LA function is associated with decreased PAC and reduced RC time constant.

The left atrium and pulmonary circulation

Consistent with previous results,[1,6] our study showed that an enlarged LA was associated with LA dysfunction, as demonstrated by reduced LA emptying fraction and LA global reservoir strain, as well as AF and increased pulmonary pressure. While PCWP was elevated in patients with reduced strain, as noted previously,[9,12] there was no observable relationship between PCWP and LAVI.

Pulmonary hypertension (PH) is present in a significant portion of HFpEF patients, and is independently linked to morbidity and mortality.[4] In the majority of HFpEF patients, PH is driven by post-capillary mechanisms in the setting of elevated left-sided pressures and pulmonary venous congestion.[4,14] There appears to be a pre-capillary component in a subset of these patients where pulmonary pressures exceed that expected based on PCWP alone.[4,15] Combined pre- and post-capillary PH (CpcPH) is estimated to affect up to 28% of patients with HFpEF, the underlying mechanisms of which are not fully understood, and haemodynamic definitions imperfect.[4,15]

Our cohort of patients featured higher mean pulmonary pressures (*Figure 1*) with increasing LAVI. PVR increased with LAVI (*Figure 2*), confirming and extending upon earlier studies showing significant relationships between LA function, compliance, and AF with severity of pulmonary vascular disease in HFpEF.[1,6] Of note, the haemodynamic changes noted persisted even in the absence of AF (online supplementary *Table S1* and *S2*). Rising PVR with increasing LAVI, without rising PCWP suggests an element of intrinsic pulmonary vascular disease, although in the present study it is unclear if this results from vasoconstriction or vascular remodelling. A degree of Cpc-PH among patients with larger LA is supported by a higher transpulmonary gradient in these patients. While there were no observable differences in DPG, this measurement had a relatively high proportion of mechanistically implausible negative DPG values. This is not out of keeping with previous studies showing a high proportion of negative DPG values in heart failure patients, with DPG calculation prone to error when derived from usual end-expiratory timed PCWP measurements,[16,17] and hence interpretation of this value is limited.

Our data challenge the notion that simple chronic elevation of LA pressure leads in a direct closely proportionate manner to LA

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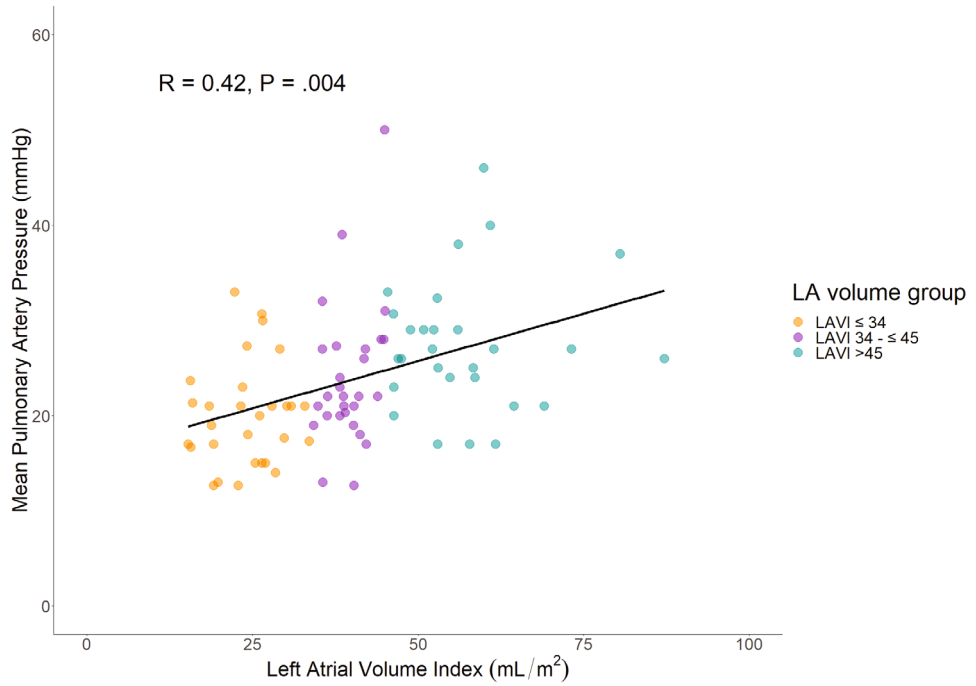

Figure 1 Mean pulmonary pressure at increasing left atrial (LA) volume. Mean pulmonary artery pressure increased with higher LA volume index (LAVI). Distribution by LA volume tertiles displayed.

enlargement and to increased PVR. We demonstrate the important relationship of LA strain and rhythm with LA enlargement, suggesting factors other than pressure *per se* also influence LA size. Similarly, whilst we confirm a statistically significant association of LAVI with PVR, this only accounts for 17% of the variance in PVR. These data are of relevance to the recent REDUCE LAP-HF II trial in which a significant interaction between clinical response to an inter-atrial shunt device and PVR was observed.[10,18]

Relationship of pulmonary resistance and compliance with left atrial size and function

In keeping with larger LAVI and higher pulmonary pressures, our study shows that increased LAVI is associated with higher PVR and lower PAC. This statistical difference is visually demonstrated by the position of LA subgroups on the RC curve depicted in *Figure 3*. Both resistance and compliance are important contributors to RV afterload, although compliance has been suggested as a more important factor as it incorporates pulsatile pressure variations,[19,20] and appears to be a better predictor than resistance of RV dysfunction, heart failure symptoms and prognosis.[21–23] Resistance and compliance have a dependent inverse hyperbolic relationship.[19,20] As such, having a higher PVR, as seen in patients with an increased LAVI, means that a substantial reduction in pulmonary resistance is required before there will be a significant improvement in compliance. The change in distribution along the RC curve for increased LAVI is similar to that shown by Dragu *et al.*[22] where heart failure patients with reactive PH (compared to no PH or passive PH) having the lowest compliance and occupying the flattest section of the curve. These changes in PVR and PAC seen at larger LA volumes may mark a degree of pulmonary remodelling and pre-capillary pulmonary hypertensive changes, and as such a larger LAVI may be reflective of either chronicity or severity of disease.

The RC time constant, the product of PVR and PAC, reflects the diastolic decay constant of pulmonary artery pressure. Changes in RC time reflect an alteration to the usual relationship between PVR and PAC – i.e. a reduced RC time indicates that for any given resistance, the corresponding compliance will be lower than expected, suggestive of a resulting increase in RV pulsatile load. An elevated PCWP has been associated with reductions in RC time among patients with heart failure,[22–24] as well as a corresponding increase in RC time after reduction in PCWP with heart failure therapy.[21] Changes in RC time as a result of pre-capillary PH appear to be more variable,[20,25] and RC time may be overestimated when using calculated estimates of compliance and resistance,[13] and inaccurate at the extremes of resistance and compliance measurements owing to their hyperbolic relationship.[20]

The RC time constant in the present study appears to be consistent across LAVI groups. However, in the sub-analysis of LA function groups, it was apparent that significantly reduced strain (≤24%) was associated with reduced RC time. The reduction in RC time is visually shown by the shifting of the RC curve down and to the left (*Figure 3*). Among patients with reduced

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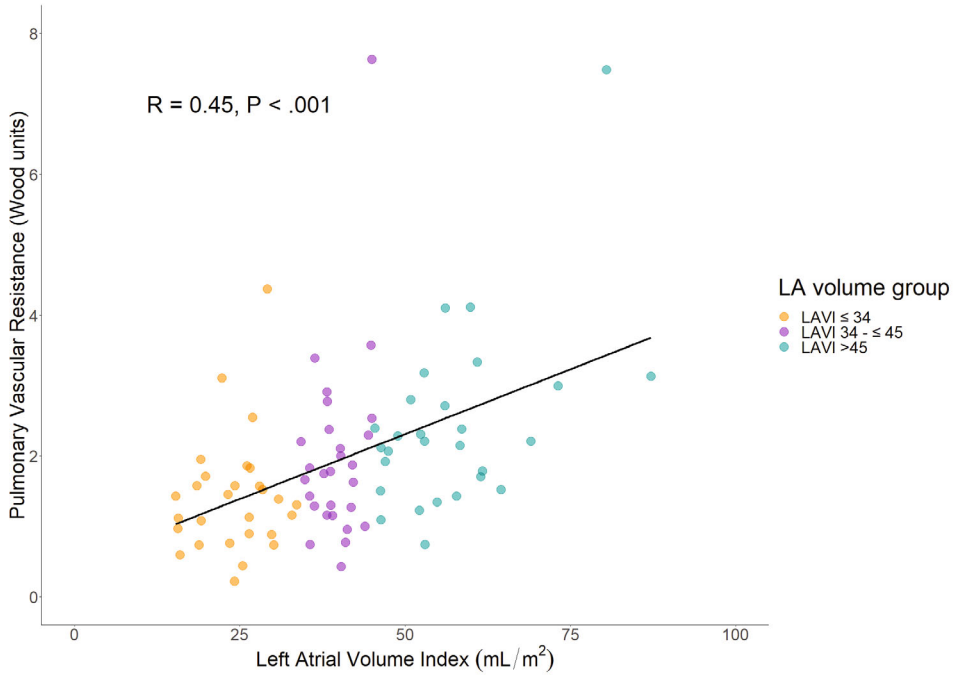

Figure 2 Pulmonary vascular resistance at increasing left atrial (LA) volume. Pulmonary vascular resistance increased with higher LA volume index (LAVI). Distribution by LA volume tertiles displayed.

strain, who feature elevated pulmonary pressures, reduced RV time further augments increased RV afterload, with likely negative clinical and prognostic implications. Whether the effect of LA function on pulmonary haemodynamics and RC time is related only to its association with increased LA pressures, or if there is an independent driving factor is unclear, but in the absence of invasive RHC measurements, LA strain does present valuable clinical information in relation to concurrent pulmonary vascular disease.

Cardiac output and systolic reserve

We found that patients with increased LAVI had significantly blunted increases in SV and CO, highlighting a reduced systolic reserve, consistent with prior studies.[1,6] Inadequate LV reserve has been noted in HFpEF patients, with increased LV stiffness limiting the ability to increase LV end-diastolic volume at exercise, subsequently limiting SV and CO.[5,26] Furthermore, studies reporting LA dysfunction in HFpEF have recognized impairment in reservoir, conduit and contractile function.[6,9] Worsening atrial dysfunction seen at larger LA volumes may lead to poor LV filling and subsequently reduced CO. This is compounded by the increasing incidence of AF at larger LA volumes, resulting in the loss of LA contractile function and the late diastolic component of LV filling, as well as development of RV dysfunction due to progressive pulmonary vascular disease which further contributes to LV underfilling and impaired CO partly related to impaired Frank–Starling reserve.[6]

Heart failure with preserved ejection fraction and the normal left atrium

Classification of HFpEF patients into LAVI tertiles identified a group of patients with LA volumes within the normal range. These patients had a low prevalence of AF and as may be expected low NT-proBNP levels.[27] Nevertheless exercise PCWP levels were broadly similar to that in the other groups. Whilst potentially representing an earlier phase in the progression of HFpEF,[28] it is possible that the exercise PCWP value observed reflects greater RV delivery to the left atrium during exercise, consistent with a recent report from our group.[29]

Limitations

Left atrial volume was measured using two-dimensional echocardiography, which underestimates volume measurements when compared to cardiac computed tomography, cardiac magnetic resonance imaging or three-dimensional echocardiography.[30,31] Indexing of volume to BSA may result in underestimation of LA dilatation and associated risk, particularly among obese patients.[32,33] To account for this, we ran a supplementary analysis indexing LA volume to height to the power of 1.7, as previously evidenced to be an improved method of scaling,[33] and results remained essentially unchanged (*Table 3* for *p*-values). There was no direct invasive measure of LV end-diastolic pressure, the inclusion of which would have been valuable to compare across LAVI groups and add to our discussion regarding pressure changes and reflections on the pulmonary system. Pulmonary vascular pressures were recorded

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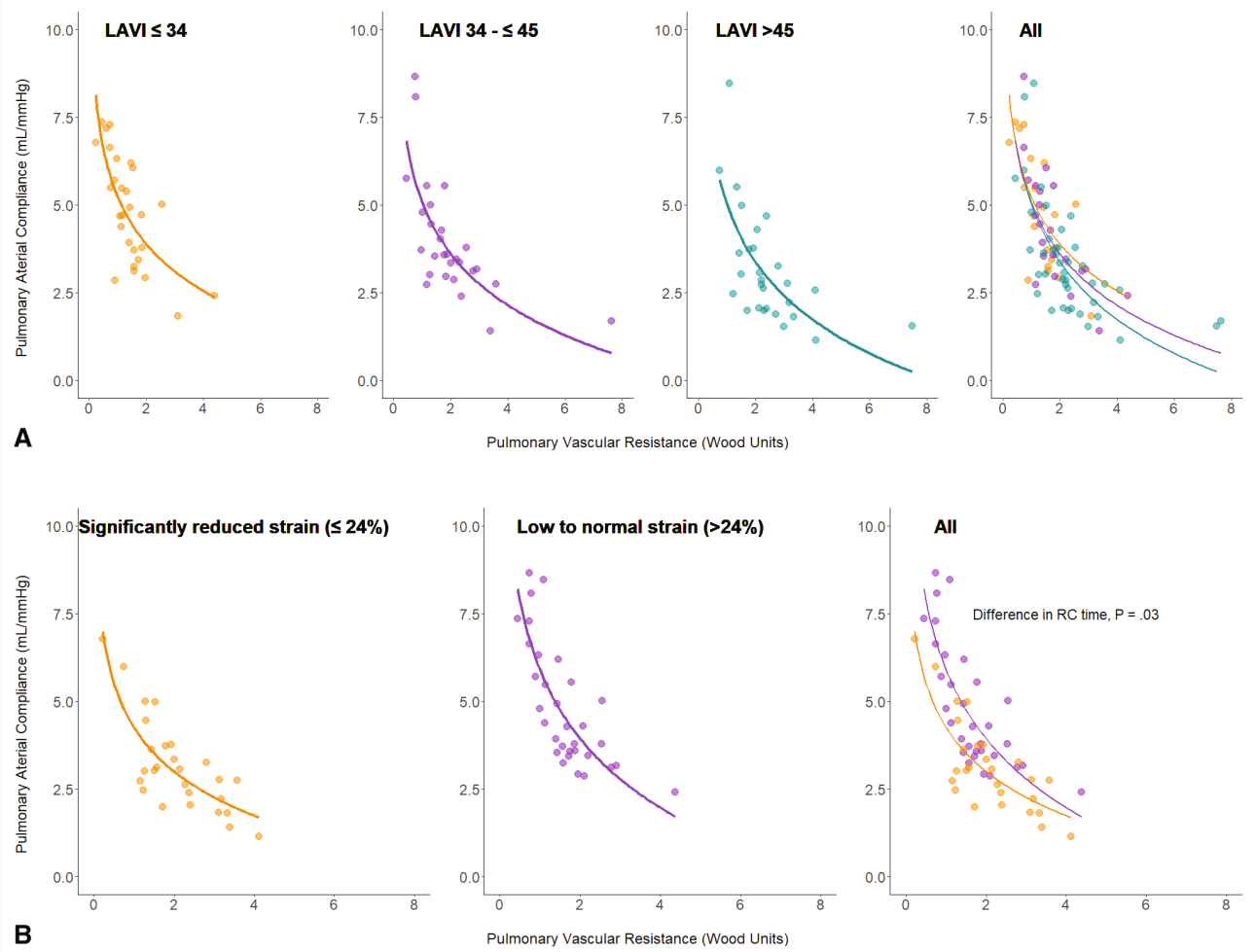

Figure 3 Pulmonary vascular resistance–compliance relationship by left atrial volume and left atrial strain. (*A*) Resistance–compliance curves showing focus of distribution along the curve by left atrial volume index (LAVI) tertiles. Patients with larger left atrial volume predominantly focus on the flatter point of this curve, demonstrating higher pulmonary vascular resistance and lower pulmonary arterial compliance. Smaller left atrialvolumes concentrate on the higher point of the curve, with lower pulmonary vascular resistance and higher compliance. The relationship between resistance and compliance however remains similar across left atrialvolume groups, with no change in curve or pulmonary resistance–compliance (RC) time. (*B*) Resistance–compliance curves showing focus of distribution along the curve by left atrial strain. The curve is displaced down and to the left in patients with reduced left atrial strain compared to those with normal strain. The change in the relationship between resistance and compliance among these patients, and the corresponding reduction in RC time, indicates for any given resistance, the corresponding expected pulmonary arterial compliance is significantly reduced. This further augments right ventricular afterload which is already increased as a result of elevated pulmonary pressures among these patients.

at end-expiration, which may overestimate measurements when compared to averaging across multiple respiratory cycles,[4,34] although this approach was consistent across the cohort so any potential impact is minimized. We did not perform pulmonary function testing in this study and therefore are not able to account for any influence of lung disease on pulmonary vascular function. Nevertheless, patients with significant respiratory disease were excluded from the cohorts, as well as those with clinical evidence of active myocardial ischaemia or un-revascularized known significant coronary lesions were excluded. We combined two cohorts of patients, and while we encouraged homogeneity through the same inclusion criteria and similar exercise protocols, direct validation was not performed, and the potential for bias remains.

Conclusions

In conclusion, echocardiographic evidence of LA enlargement in patients with HFpEF is associated with a heart failure phenotype of more advanced pulmonary vascular disease. Impaired LA function in the form of reduced LA reservoir strain is associated with impaired PAC and a reduced RC time constant, which may have more clinical implications than LA volume alone. These findings appear to be independent of AF.

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Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

References

1. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail*. 2015;**8**:295–303.
2. Gevaert AB, Kataria R, Zannad F, Sauer AJ, Damman K, Sharma K, et al. Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management. *Heart*. 2022;**108**:1342–50.
3. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, et al. I-PRESERVE Investigators. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011;**124**:2491–501.
4. Vachiery JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, et al. Pulmonary hypertension due to left heart disease. *Eur Respir J*. 2019;**53**:1801897.
5. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation*. 2008;**117**:2051–60.
6. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol*. 2020;**76**:1051–64.
7. Hasenfuss G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, et al.; REDUCE LAP-HF Study Investigators. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet*. 2016;**387**:1298–304.
8. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;**79**:e263–421.
9. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, et al. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019;**21**:891–900.
10. Shah SJ, Borlaug BA, Chung ES, Cutlip DE, Debonnaire P, Fail PS, et al.; REDUCE LAP-HF II Investigators. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. *Lancet*. 2022;**399**:1130–40.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, 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.
12. Telles F, Nanayakkara S, Evans S, Patel HC, Mariani JA, Vizi D, et al. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019;**21**:495–505.
13. Chemla D, Lau EM, Papelier Y, Attal P, Herve P. Pulmonary vascular resistance and compliance relationship in pulmonary hypertension. *Eur Respir J*. 2015;**46**:1178–89.
14. Thenappan T, Prins KW, Cogswell R, Shah SJ. Pulmonary hypertension secondary to heart failure with preserved ejection fraction. *Can J Cardiol*. 2015;**31**:430–9.
15. Reddy YNV, Borlaug BA. Pulmonary hypertension in left heart disease. *Clin Chest Med*. 2021;**42**:39–58.
16. Naeije R, Gerges M, Vachiery JL, Caravita S, Gerges C, Lang IM. Hemodynamic phenotyping of pulmonary hypertension in left heart failure. *Circ Heart Fail*. 2017;**10**:e004082.
17. Chatterjee NA, Lewis GD. Characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: limitations of a solitary measurement. *JACC Heart Fail*. 2015;**3**:17–21.
18. Borlaug BA, Blair J, Bergmann MW, Bugger H, Burkhoff D, Bruch L, et al.; REDUCE LAP-HF II Investigators. Latent pulmonary vascular disease may alter the response to therapeutic atrial shunt device in heart failure. *Circulation*. 2022;**145**:1592–604.
19. Saouti N, Westerhof N, Postmus PE, Vonk-Noordegraaf A. The arterial load in pulmonary hypertension. *Eur Respir Rev*. 2010;**19**:197–203.
20. Tedford RJ. Determinants of right ventricular afterload (2013 Grover Conference series). *Pulm Circ*. 2014;**4**:211–9.
21. Dupont M, Mullens W, Skouri HN, Abrahams Z, Wu Y, Taylor DO, et al. Prognostic role of pulmonary arterial capacitance in advanced heart failure. *Circ Heart Fail*. 2012;**5**:778–85.
22. Dragu R, Rispler S, Habib M, Sholy H, Hammerman H, Galiè N, et al. Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. *Eur J Heart Fail*. 2015;**17**:74–80.
23. Pellegrini P, Rossi A, Pasotti M, Raineri C, Cicoira M, Bonapace S, et al. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. *Chest*. 2014;**145**:1064–70.
24. Tedford RJ, Hassoun PM, Mathai SC, Girgis RE, Russell SD, Thiemann DR, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation*. 2012;**125**:289–97.
25. Chemla D, Creuze N, Hoette S, Papelier Y, Savale L, Jais X, et al. Relationship between the pulsatile and steady component of right ventricular afterload in patients with precapillary pulmonary hypertension. *Am J Respir Crit Care Med*. 2014;**189**:A1899.
26. Borlaug BA, Jaber WA, Ommen SR, Lam CS, Redfield MM, Nishimura RA. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. *Heart*. 2011;**97**:964–9.
27. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. *Eur Heart J*. 2022;**43**:1941–51.
28. Sorimachi H, Verbrugge FH, Omote K, Omar M, Obokata M, Reddy YNV, et al. Longitudinal evolution of cardiac dysfunction in heart failure and preserved ejection fraction with normal natriuretic peptide levels. *Circulation*. 2022;**146**:500–2.
29. Kaye DM, Wolsk E, Nanayakkara S, Mariani J, Hassager C, Gustafsson F, et al. Comprehensive physiological modeling provides novel insights into heart failure with preserved ejection fraction physiology. *J Am Heart Assoc*. 2021;**10**:e021584.
30. Kuhl JT, Lonborg J, Fuchs A, Andersen MJ, Vejlstrup N, Kelbaek H, et al. Assessment of left atrial volume and function: a comparative study between echocardiography, magnetic resonance imaging and multi slice computed tomography. *Int J Cardiovasc Imaging*. 2012;**28**:1061–71.
31. Perez de Isla L, Feltes G, Moreno J, Martinez W, Saltijeral A, de Agustin JA, et al. Quantification of left atrial volumes using three-dimensional wall motion tracking echocardiographic technology: comparison with cardiac magnetic resonance. *Eur Heart J Cardiovasc. Imaging*. 2014;**15**:793–9.
32. Davis EF, Crousillat DR, He W, Andrews CT, Hung JW, Danik JS. Indexing left atrial volumes: alternative indexing methods better predict outcomes in overweight and obese populations. *JACC Cardiovasc Imaging*. 2022;**15**:989–97.
33. Chirinos JA, Segers P, De Buyzere ML, Kronmal RA, Raja MW, De Bacquer D, et al. Left ventricular mass: allometric scaling, normative values, effect of obesity, and prognostic performance. *Hypertension*. 2010;**56**:91–8.
34. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings. How to handle the problems of zero leveling and respiratory swings. *Am J Respir Crit Care Med*. 2014;**190**:252–7.

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