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 catheterisation and echocardiography were retrospectively analysed. All had symptoms of heart failure, LVEF ≥50% and haemodynamic features of HFpEF. Patients were divided into LAVI-based tertiles (≤34mL/m^2, >34 to ≤45mL/m^2, >45mL/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, BSA and LVEF were similar between volume groups. LA volume was associated with blunted increases in cardiac output with exercise (ΔCO) ($P_{adjusted}$ < .001), higher resting mean pulmonary artery pressure (mPAP) ($P_{adjusted}$ = .003), with similar wedge pressure (PCWP) ($P_{adjusted}$ = 1). Pulmonary vascular resistance (PVR) increased with increasing LA volume ($P_{adjusted}$ < .001). Larger LA volumes featured reduced LA strain ($P_{adjusted}$ < .001), with reduced strain associated with reduced pulmonary vascular resistance-compliance (RC) time (0.34 [0.28–0.40] vs 0.38 [0.33–0.43], P = .03).

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

Key Words: heart failure with preserved ejection fraction, exercise haemodynamics, left atrium, echocardiography, cardiac catheterisation, pulmonary hypertension

1. INTRODUCTION

It is widely accepted that HFpEF has emerged as the predominant of HF and that in contrast to HFrEF, 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 LV relaxation and increased LV stiffness resulting in elevated left ventricular filling pressures (LVFP) are considered hallmarks of the disease, often only evident during exertion.[3, 4] As a consequence, left atrial 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 remodeling of the pulmonary vasculature with reduced compliance, particularly when AF is present.[6] In the context of HFpEF, LA size is also an independent predictor of morbidity and mortality,[3] suggesting that remodeling of the LA 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 LA in HFpEF influence the remodeling 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.

2. METHODS

2.1 Study design and participants

Two cohorts of patients were included for a total of 85. 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 HFmrEF. 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. This data was 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, LVEF ≥50%, and an elevated pulmonary capillary wedge pressure (PCWP) ≥15mmHg at rest (47%) and/or ≥25mmHg 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, BMI, 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 left atrial volume index (LAVI) into three tertiles: ≤34mL/m^2 (29 patients), >34 to ≤45mL/m^2 (28 patients), >45mL/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 ≤24%, guided by previously used cut-offs.[9]

2.2 Procedures

Right heart catheterisation (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 dyspnea) exercise was performed using supine cycle ergometry at 60 revolutions per minute. For the REDUCE LAP-HF subset, this consisted of 20W increases every three minutes until symptom-limited maximum exertion was reached. A similar protocol was implemented for the Alfred subset, with a graded increase in resistance every 3 minutes to a maximum of 1.5 watts/kg until volitional fatigue. Cardiac output (CO) was measured at both rest and exercise via thermodilution as an average of ≥3 measurements. Stroke volume (SV) was calculated based on thermodilution derived cardiac output and heart rate at time of measurement. Pulmonary capillary wedge pressure (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), with views and calculations in line with ASE guidelines.[11] Simpson's method of discs was used for volume calculations. Focused apical four-chamber left atrial 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).

2.3 Definitions

Body surface area (BSA) was derived using the Dubois equation. LA end-systolic volume, and left ventricular mass were indexed to BSA to calculate left atrial volume index (LAVI) and left ventricular mass index (LVMI). Significantly reduced LA reservoir strain was defined as ≤24% guided by previously used cut-offs.[9] Pulmonary vascular resistance (PVR) was calculated as the difference between mean pulmonary artery pressures (mPAP) and pulmonary capillary wedge pressure (PCWP) divided by cardiac output. Pulmonary arterial compliance (PAC) was calculated as stroke volume (derived from thermodilution cardiac output) divided by pulmonary artery pulse pressure. PVR (with Wood units converted to mmHg sec mL^{-1}) was multiplied by PAC (in mL/mmHg) to calculate the pulmonary RC time constant (expressed in seconds), as per previous studies.[13] The presence of atrial fibrillation (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, NY, USA), and echocardiograms at the University of Pennsylvania (PA, USA). The Alfred subset were analysed locally and verified by two separate investigators.

2.4 Statistical analysis

Normally distributed data are represented as mean ± SD and non-parametric as median (IQR). 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 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 $P < .05$.

3. 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), female (72%) and obese (48%), with high rates of atrial fibrillation (AF) (33%) as detailed in Table 1. Sex and BMI were similar across LAVI groups. Rates of AF increased in prevalence with larger LA size ($P < .001$). NT-proBNP was available for a subset of patients (n=46) and increased across LA groups ($P_{adjusted} = .007$).

3.1 Haemodynamics

Invasive haemodynamic data is summarised 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 mean pulmonary artery pressure (mPAP) at rest ($P_{adjusted}$ = .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 pulmonary vascular resistance (PVR) at rest ($P_{adjusted}$ < .001), with a corresponding decrease in pulmonary artery compliance (PAC) ($P_{adjusted}$ = .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 (TPG) rose with increasing LAVI ($P_{adjusted}$ = .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 cardiac output 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 ($P_{adjusted}$ < .001). In particular, the magnitude of CO augmentation during exercise (ΔCO) decreased significantly across increasing LAVI groups ($P_{adjusted}$ < .001). Right ventricular stroke work index (RVSWI) was similar between groups at rest and exercise.

3.2 Echocardiography

Overall mean LAVI was 40 ± 10mL/m^2, 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). Left ventricular mass index (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 ($P_{adjusted}$ <.001). In patients with data on LA emptying fraction (LAEF) (n = 20), this also decreased with increasing LAVI ($P_{adjusted}$ < .001).

3.3 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], $P < .001$), with an increase in PVR that did not reach significance (1.9 [1.4 – 3.0] vs 1.6 [1.1 – 2.0], $P = .06$). There was a decrease in RC time constant (0.34 [0.28 – 0.40] vs 0.38 [0.33 – 0.43], $P < .001$). 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 Supplementary Tables 1 and 2.

4. DISCUSSION

This study evaluated the relationship between left atrial 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 pulmonary vascular resistance. Our secondary analysis of patients with LA strain data suggests that decreased LA function is associated with decreased pulmonary arterial compliance and reduced RC time constant.

4.1 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 LAEF 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, pulmonary hypertension 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 pulmonary hypertension (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 (PVD) in HFpEF.[1, 6] Of note, the haemodynamic changes noted persisted even in the absence of atrial fibrillation (Supplementary Table 1-2). 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 remodeling. A degree of Cpc-PH among patients with larger LA is supported by a higher TPG 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 challenges the notion that simple chronic elevation of LA pressure leads in a direct closely proportionate manner to LA 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-HF2 trial in which a significant interaction between clinical response to an inter-atrial shunt device and PVR were observed.[10, 18]

4.2 Relationship of pulmonary resistance and compliance with LA 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 pulmonary hypertension (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 remodeling 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 – ie 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 HF,[22-24] as well as a corresponding increase in RC time after reduction in PCWP with HF therapy.[21] Changes in RC time as a result of pre-capillary hypertension 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 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.

4.3 Cardiac output and systolic reserve

We found that patients with increased LAVI had significantly blunted increases in stroke volume and cardiac output, 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 left ventricular end diastolic volume (LVEDV) at exercise, subsequently limiting SV and CO.[5, 26] Furthermore, studies reporting LA dysfunction in HFpEF have recognised 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 right ventricular dysfunction due to progressive PVD which further contributes to LV underfilling and impaired CO partly related to impaired Frank-Starling reserve.[6]

4.4 HFpEF 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 NTproBNP 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 LA during exercise, consistent with a recent report from our group.[29]

4.5 Limitations

Left atrial volume was measured using 2D echocardiography, which underestimates volume measurements when compared to cardiac CT, cardiac MRI 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 (Supplementary Table 3 for P values). There was no direct invasive measure of left ventricular 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 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 minimised. 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 ischemia or un-revascularised 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.

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

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FIGURE LEGENDS

Figure 1: Mean Pulmonary Pressure at Increasing LA Volume

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

Figure 2: Pulmonary Vascular Resistance at Increasing LA Volume

Pulmonary vascular resistance (PVR) increased with higher left atrial volume index (LAVI). Distribution by left atrial (LA) volume tertiles displayed.

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 (LA) volume predominantly focus on the flatter point of this curve, demonstrating higher pulmonary vascular resistance and lower pulmonary arterial compliance. Smaller LA volumes 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 LA volume 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 (LA) strain. The curve is displaced down and to the left in patients with reduced LA strain compared to those with normal strain. The change in the relationship between resistance and compliance among these patients, and the corresponding reduction in pulmonary resistance-compliance (RC) time, indicates for any given resistance, the corresponding expected pulmonary arterial compliance is significantly reduced. This further augments RV afterload which is already increased as a result of elevated pulmonary pressures among these patients.

Table 1. Baseline Characteristics by LAVI group

Variable	All (n=85)	≤34mL/m² (n=29)	>34 – 45mL/m² (n=28)	>45mL/m² (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[b]	
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[b]	
Hypertension (%)	69	55	75	81	0.03[a b]	
History of atrial fibrillation (%)	33	3	36	61	<0.001[a b]	
REDUCE LAP cohort (%)	25	45	18	11	0.003[a b]	
Baseline bloods						
NT-proBNP (ng/L) (n=46)	539 ± 685	185 ± 153	689 ± 839	1067 ± 778	<0.001	0.007[a]
Creatinine (µmol/L) (n=72)	84 ± 21	81 ± 15	79 ± 21	92 ± 25	0.13	1
Hemoglobin (g/L) (n=78)	134 ± 13	134 ± 13	133 ± 12	134 ± 14	0.66	1

[a] *Significant at P <0.05*

[b] *Chi square test for trend. All other P values relate to linear regression (with Benjamini-Holchberg correction).*

Table 2. Haemodynamics and echocardiogram findings by LAVI group

	All (n=85)	**≤34mL/m²** (n=29)	**>34 – 45mL/m²** (n=28)	**>45mL/m²** (n=28)	**P_{raw}**	**$P_{adjusted}$**
Peak watts	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
BPs (mmHg)						
Rest	150 ± 26	143 ± 20	152 ± 26	156 ± 30	0.02[a]	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[a]	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[a]	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[a]	0.003[a]
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[a]	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[a]	0.34
Exercise	8.5 ± 2.6	9.7 ± 2.3	8.7 ± 2.8	7.0 ± 1.7	<0.001[a]	<0.001[a]
Change	3.5 ± 1.9	4.5 ± 1.9	3.5 ± 2.0	3.5 ± 1.3	<0.001[a]	<0.001[a]
SV (mL)						
Rest	76 ± 20	78 ± 16	78 ± 24	71 ± 18	0.04[a]	1
Exercise	87 ± 26	94 ± 21	89 ± 31	76 ± 21	<0.001[a]	0.01[a]
Change	10 ± 16	17 ± 14	10 ± 19	4 ± 11	<0.001[a]	0.04[a]
TPG (mmHg)						
Rest	9.0 ± 4.9	6.9 ± 3.6	9.6 ± 5.1	10.7 ± 5.2	<0.001[a]	0.005[a]
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[a]	<0.001[a]
Exercise	1.7 ± 1.1	1.3 ± 0.7	1.7 ± 1.2	2.2 ± 1.2	<0.001[a]	0.005[a]
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[a]	0.003[a]
Exercise	2.8 ± 1.5	3.3 ± 1.8	3.0 ± 1.5	2.0 ± 0.9	<0.001[a]	0.02[a]
Change	-1.3 ± 1.5	-1.6 ± 1.8	-1.2 ± 1.1	-1.2 ± 1.4	0.54	1

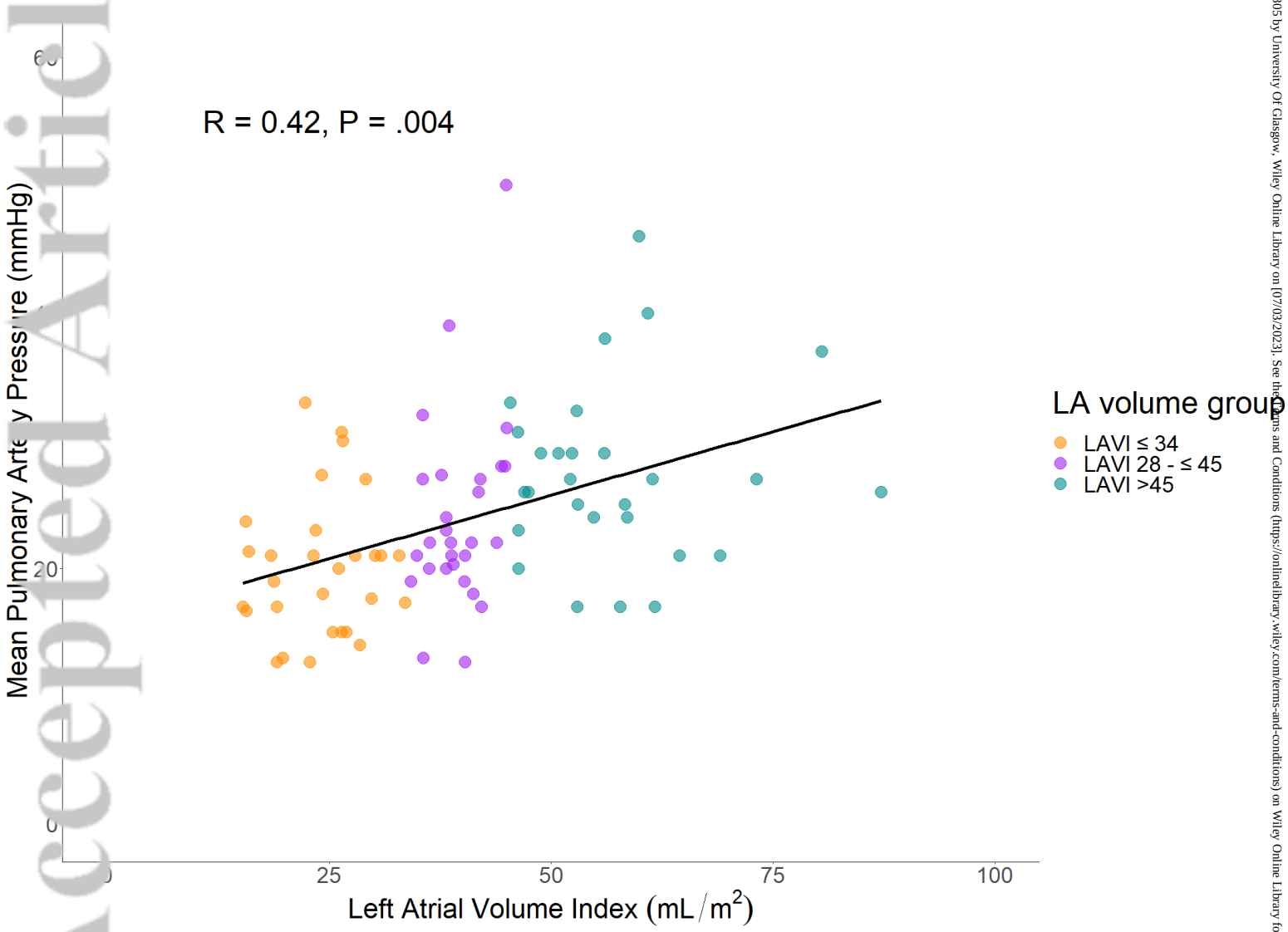
RC time (sec)						
Rest	0.39 ± 0.14	0.36 ± 0.14	0.40 ± 0.14	0.40 ± 0.14	0.08	1
Exercise	0.23 ± 0.13	0.22 ± 0.12	0.22 ± 0.09	0.25 ± 0.17	0.58	1
Change	-0.15 ± 0.18	-0.13 ± 0.19	-0.18 ± 0.14	-0.14 ± 0.19	0.41	1
RVSWI						
Rest	8 ± 4	7 ± 3	9 ± 5	9 ± 4	0.06	1
Exercise	17 ± 6	17 ± 5	18 ± 7	16 ± 7	0.21	1
Change	9 ± 5	10 ± 5	8 ± 5	7 ± 6	0.005[a]	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[a]	<0.001[a]
LA strain (%) (n=60)	25 ± 9	31 ± 7	26 ± 7	16 ± 7	<0.001[a]	<0.001[a]
LV strain (%) (n=47)	-19 ± 2	-20 ± 2	-18 ± 2	-19 ± 2	0.007	0.052

[a] *Significant at P <0.05*

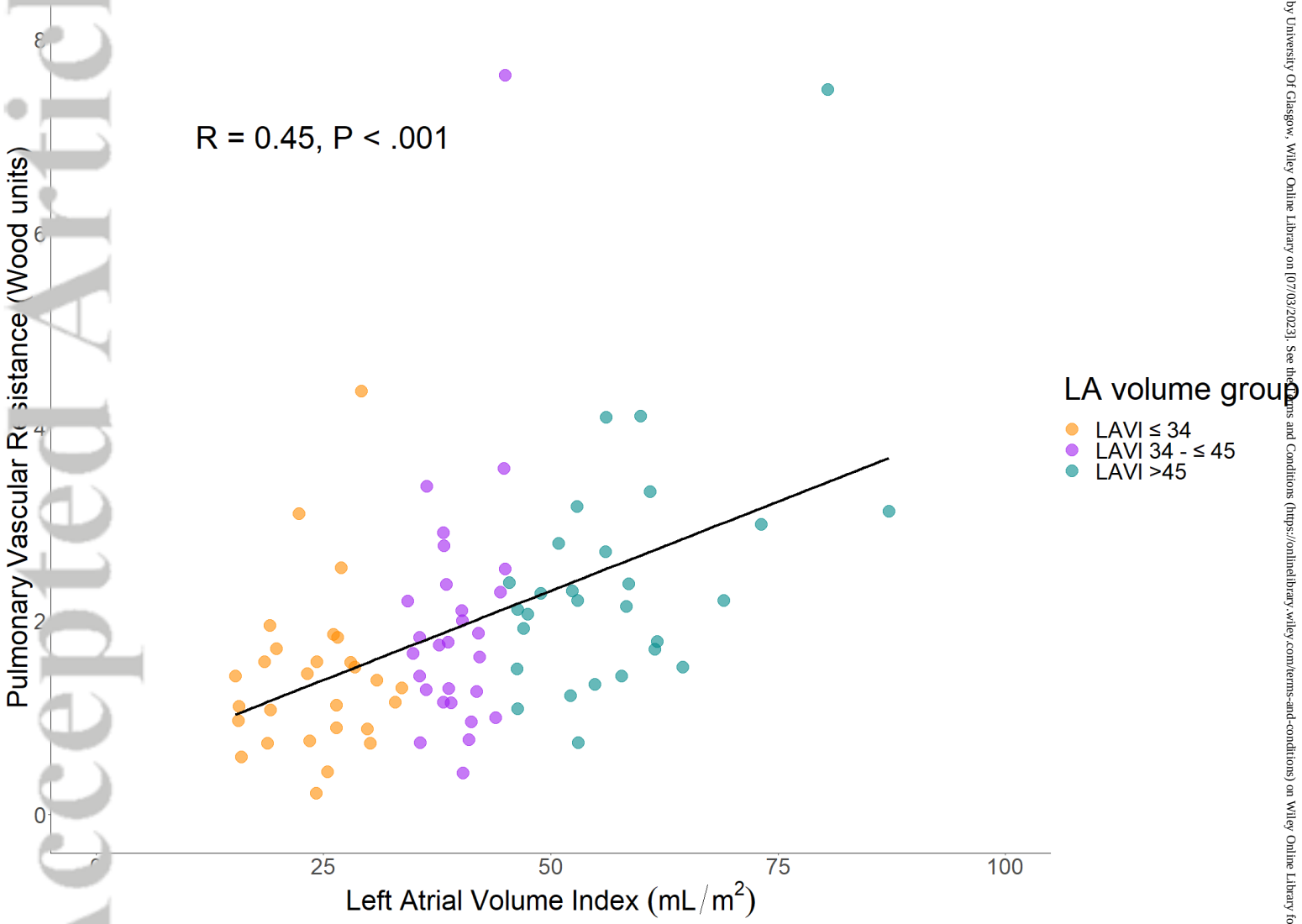
Table 3. Differences between LA strain groups

	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[a]
Rest PAC (mL/mmHg)	3.6 (2.9 – 5.0)	3.0 (2.3 – 3.7)	4.3 (3.5 – 5.7)	<0.001[a]
Exercise PAC (mL/mmHg)	2.4 (1.8 – 3.5)	1.8 (1.6 – 2.1)	3.4 (2.2 – 3.5)	<0.001[a]
Rest RC (sec)	0.36 (0.30 – 0.43)	0.34 (0.28 – 0.40)	0.38 (0.33 – 0.43)	0.03[a]
Exercise RC (sec)	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[a]
Exercise mPAP (mmHg)	43 (38 – 44)	48 (43 – 52)	40 (36 – 43)	<0.001[a]
Rest PCWP (mmHg)	14 (12 – 17)	17 (14 – 21)	13 (10 – 15)	<0.001[a]
Exercise PCWP (mmHg)	30 (27 – 34)	34 (29 – 37)	27 (26 – 32)	0.002[a]

[a] *Significant at P <0.05*



EJHF_2805_Figure 1.tiff



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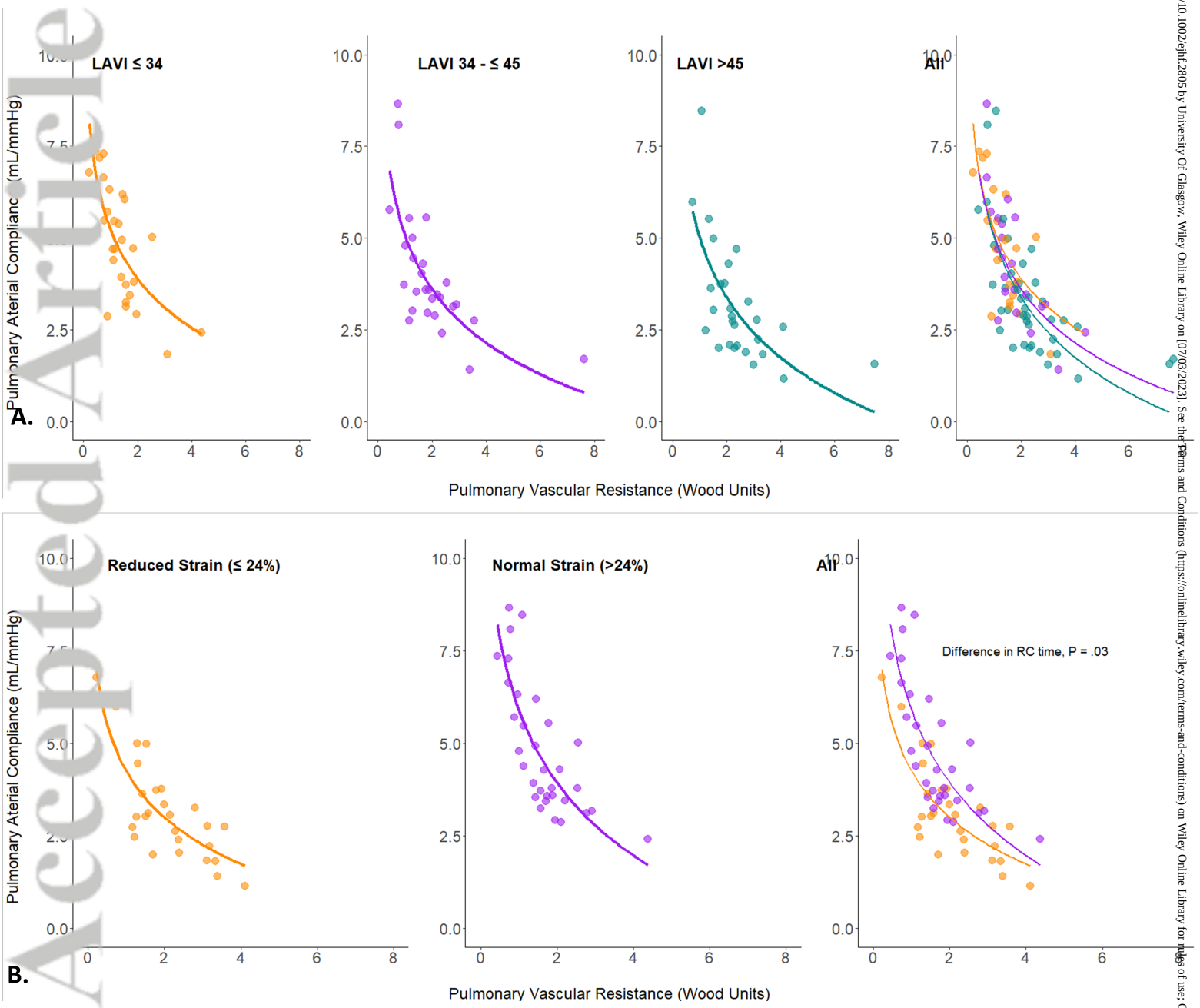

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Table 1. Baseline Characteristics by LAVI group

Variable	**All** (n=85)	**≤34mL/m²** (n=29)	**>34 – 45mL/m²** (n=28)	**>45mL/m²** (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[b]	
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[b]	
Hypertension (%)	69	55	75	81	0.03[a b]	
History of atrial fibrillation (%)	33	3	36	61	<0.001[a b]	
REDUCE LAP cohort (%)	25	45	18	11	0.003[a b]	
Baseline bloods						
NT-proBNP (ng/L) (n=46)	539 ± 685	185 ± 153	689 ± 839	1067 ± 778	<0.001	0.007[a]
Creatinine (µmol/L) (n=72)	84 ± 21	81 ± 15	79 ± 21	92 ± 25	0.13	1
Hemoglobin (g/L) (n=78)	134 ± 13	134 ± 13	133 ± 12	134 ± 14	0.66	1

[a] *Significant at P <0.05*

[b] *Chi square test for trend. All other P values relate to linear regression (with Benjamini-Holchberg correction).*

Table 2. Haemodynamics and echocardiogram findings by LAVI group

	All (n=85)	**≤34mL/m²** (n=29)	**>34 – 45mL/m²** (n=28)	**>45mL/m²** (n=28)	**P_{raw}**	**$P_{adjusted}$**
Peak watts	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
BPs (mmHg)						
Rest	150 ± 26	143 ± 20	152 ± 26	156 ± 30	0.02[a]	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[a]	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[a]	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[a]	0.003[a]
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[a]	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[a]	0.34
Exercise	8.5 ± 2.6	9.7 ± 2.3	8.7 ± 2.8	7.0 ± 1.7	<0.001[a]	<0.001[a]
Change	3.5 ± 1.9	4.5 ± 1.9	3.5 ± 2.0	3.5 ± 1.3	<0.001[a]	<0.001[a]
SV (mL)						
Rest	76 ± 20	78 ± 16	78 ± 24	71 ± 18	0.04[a]	1
Exercise	87 ± 26	94 ± 21	89 ± 31	76 ± 21	<0.001[a]	0.01[a]
Change	10 ± 16	17 ± 14	10 ± 19	4 ± 11	<0.001[a]	0.04[a]
TPG (mmHg)						
Rest	9.0 ± 4.9	6.9 ± 3.6	9.6 ± 5.1	10.7 ± 5.2	<0.001[a]	0.005[a]
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[a]	<0.001[a]
Exercise	1.7 ± 1.1	1.3 ± 0.7	1.7 ± 1.2	2.2 ± 1.2	<0.001[a]	0.005[a]
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[a]	0.003[a]
Exercise	2.8 ± 1.5	3.3 ± 1.8	3.0 ± 1.5	2.0 ± 0.9	<0.001[a]	0.02[a]
Change	-1.3 ± 1.5	-1.6 ± 1.8	-1.2 ± 1.1	-1.2 ± 1.4	0.54	1
RC time (sec)						

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[a]	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[a]	<0.001[a]
LA strain (%) (n=60)	25 ± 9	31 ± 7	26 ± 7	16 ± 7	<0.001[a]	<0.001[a]
LV strain (%) (n=47)	-19 ± 2	-20 ± 2	-18 ± 2	-19 ± 2	0.007	0.052

[a] *Significant at P <0.05*

Table 3. Differences between LA 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[a]
Rest PAC (mL/mmHg)	3.6 (2.9 – 5.0)	3.0 (2.3 – 3.7)	4.3 (3.5 – 5.7)	<0.001[a]
Exercise PAC (mL/mmHg)	2.4 (1.8 – 3.5)	1.8 (1.6 – 2.1)	3.4 (2.2 – 3.5)	<0.001[a]
Rest RC (sec)	0.36 (0.30 – 0.43)	0.34 (0.28 – 0.40)	0.38 (0.33 – 0.43)	0.03[a]
Exercise RC (sec)	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[a]
Exercise mPAP (mmHg)	43 (38 – 44)	48 (43 – 52)	40 (36 – 43)	<0.001[a]
Rest PCWP (mmHg)	14 (12 – 17)	17 (14 – 21)	13 (10 – 15)	<0.001[a]
Exercise PCWP (mmHg)	30 (27 – 34)	34 (29 – 37)	27 (26 – 32)	0.002[a]

[a] *Significant at P <0.05*