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CLINICAL RESEARCH
Heart failure/cardiomyopathy

The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction

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Aims Increases in extravascular lung water (EVLW) during exercise contribute to symptoms, morbidity, and mortality in patients with heart failure and preserved ejection fraction (HFpEF), but the mechanisms leading to pulmonary congestion during exercise are not well-understood.

Methods and results Compensated, ambulatory patients with HFpEF ($n = 61$) underwent invasive haemodynamic exercise testing using high-fidelity micromanometers with simultaneous lung ultrasound, echocardiography, and expired gas analysis at rest and during submaximal exercise. The presence or absence of EVLW was determined by lung ultrasound to evaluate for sonographic B-line artefacts. An increase in EVLW during exercise was observed in 33 patients ($HFpEF_{LW+}$, 54%), while 28 (46%) did not develop EVLW ($HFpEF_{LW-}$). Resting left ventricular function was similar in the groups, but right ventricular (RV) dysfunction was two-fold more common in $HFpEF_{LW+}$ (64 vs. 31%), with lower RV systolic velocity and RV fractional area change. As compared to $HFpEF_{LW-}$, the $HFpEF_{LW+}$ group displayed higher pulmonary capillary wedge pressure (PCWP), higher pulmonary artery (PA) pressures, worse RV-PA coupling, and higher right atrial (RA) pressures during exercise, with increased haemoconcentration indicating greater loss of water from the vascular space. The development of lung congestion during exercise was significantly associated with elevations in PCWP and RA pressure as well as impairments in RV-PA coupling (area under the curve values 0.76–0.84).

Conclusion Over half of stable outpatients with HFpEF develop increases in interstitial lung water, even during submaximal exercise. The acute development of lung congestion is correlated with increases in pulmonary capillary hydrostatic pressure that favours fluid filtration, and systemic venous hypertension due to altered RV-PA coupling, which may interfere with fluid clearance.

Clinical trial registration NCT02885636.

Keywords Heart failure • Pulmonary oedema • Heart failure with preserved ejection fraction • Exercise haemodynamics

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Introduction

The central pathognomonic feature in heart failure (HF) with preserved ejection fraction (HFpEF) is an elevation in cardiac filling pressures during exercise.[1,2] These haemodynamic perturbations are correlated with dyspnoea severity, pulmonary limitations, impairments in aerobic capacity, and increased risk of death in HFpEF.[3–6] The linkage between haemodynamics, symptoms, and clinical outcomes is believed to be related in large part to lung congestion. This develops when left atrial pressure increases beyond a critical threshold in animal models,[7,8] but the invasive haemodynamic mechanisms underlying lung congestion during exercise in humans remain unclear.

An increase in extravascular lung water (EVLW) develops in HF when fluid filtration increases due to pulmonary capillary hypertension due to left HF. However, there also may be an important role for right HF. In experimental animal preparations, acute increases in systemic venous pressure cause increased lung congestion in animals with elevated left atrial pressure due to impaired pulmonary lymphatic drainage.[9] Accordingly, we hypothesized that patients with HFpEF who develop lung congestion with exercise would display higher pulmonary capillary pressures causing excessive fluid filtration, but also higher systemic venous pressures due to impairments in right ventricular (RV) pulmonary artery (PA) coupling, as compared to HFpEF patients that do not develop increased EVLW.

To test this hypothesis, we performed a comprehensive, simultaneous assessment of invasive haemodynamics, lung ultrasound, echocardiography, blood sampling, and expired gas analysis to explore the mechanisms governing the development of EVLW during exercise in patients with HFpEF.

Methods

Patients referred to the Mayo Clinic cardiac catheterization laboratory for invasive haemodynamic exercise testing in the evaluation of unexplained dyspnoea were enrolled prospectively to two different studies employing the same protocol of simultaneous echocardiography, lung ultrasound, high-fidelity micromanometer invasive catheterization, blood gas sampling, and expired gas analysis at rest and during supine cycle ergometry at a matched workload of 20 W. Data from some of these patients have been published, but not as they relate to assessment of EVLW.[10] Written informed consent was obtained from all patients and both studies were approved by the Mayo Clinic Institutional Review Board.

Study population

The diagnosis of HFpEF was defined by lifestyle-limiting symptoms of exertional dyspnoea and fatigue, left ventricular (LV) ejection fraction (EF) ≥50%, and pulmonary capillary wedge pressure (PCWP) of ≥15 mmHg at rest or ≥25 mmHg during exercise.[1,2] Patients with decompensated HF, prior EF <50%, significant left-sided valvular heart disease (>mild stenosis, >moderate regurgitation), coronary disease requiring revascularization, infiltrative, restrictive or hypertrophic cardiomyopathies, constrictive pericarditis, obstructive or restrictive pulmonary disease, high-output HF, and primary RV myopathies were excluded.

Haemodynamic assessment

All studies were performed in the supine position on chronic medications in the fasting state as previously described.[2,10,11] Following assessment of baseline (resting) haemodynamics, subjects underwent supine cycle ergometry with simultaneous expired gas analysis at a workload of 20 W (pedal speed 60 rpm) for 5 min. Right heart catheterization was performed through a 9-Fr sheath via the right internal jugular vein. Right atrial (RA) pressure, PA pressures, and PCWP were measured using high-fidelity micromanometers advanced through a balloon-tipped, end-hole catheter. PCWP position was confirmed by appearance on fluoroscopy, characteristic pressure waveforms, and oximetry (saturation ≥ 94%).

Expired gas analysis was measured continuously throughout each phase of the study (MedGraphics, St. Paul, MN, USA) to measure oxygen consumption (VO_2). A 4–6-Fr radial arterial cannula was used to measure arterial blood pressure and allow sampling of arterial blood gases and measurement of haemoglobin concentration. Simultaneous PA blood samples were obtained to measure mixed venous O_2 contents. Cardiac output or pulmonary blood flow (Q_P) was then calculated by the direct Fick method.

Haemodynamic pressure tracings were recorded, digitized (240 Hz), and stored for offline analysis. Pressures were taken at end-expiration as the average of three beats. To assess the total hydrostatic pressure favouring capillary filtration, PCWP was defined as the area under the curve including both the A and V waves at end-expiration, where intrathoracic pressure approximates atmospheric pressure. Because some authors have suggested that pressures be averaged over the entire respiratory cycle during exercise,[12] we also determined mean pressures averaged over three respiratory cycles as a sensitivity analysis, were P_{resp} indicates respiratory cycle averaged pressures.

Pulmonary vascular resistance was calculated as (mean PA-PCWP)/Q_P, PA compliance by the ratio of SV/PA pulse pressure, and pulmonary elastance by the ratio of PA systolic pressure/SV. The slope of increase in mean PA pressure, PCWP, and right atrial pressure (RAP) as a function of cardiac output (PAP/Q_P, PCWP/Q_P, RA/Q_P) were calculated from rest and exercise values.[5,12] Left ventricular transmural pressure, which reflects the net distending pressure that favours LV filling, was calculated as PCWP - RA, given that RA pressure is an accurate estimate of pericardial pressure.[13–15]

Assessment of extravascular lung water

Lung ultrasound was performed simultaneously at rest and during exercise to detect the presence of EVLW. The sonographic signature of EVLW are 'B-Lines' which present as vertical, hyperechoic lines that originate from the pleural line and extend to the bottom of the ultrasound screen while moving synchronously with respirophasic motion of the visceral pleura.[16–19] B-lines have been demonstrated to reflect both an increase in EVLW and to change dynamically with EVLW content.[19–24]

Lung ultrasound was performed using a phased array transducer in the left third intercostal space in two positions along the mid-axillary and mid-clavicular lines. The right chest was not imaged due to unavailability during cardiac catheterization. Imaging depth was optimized to ensure that B-lines were continuous from the pleural edge to the bottom of the lung window and moved with respiration. Because B-lines may also be caused by parenchymal lung disease (so-called 'dry B-lines'), exercise EVLW was only considered to be present if B-lines appeared only during exercise, or if the number of B-lines increased during exercise as compared to rest.[19]

Assessment of right ventricular function and right ventricular pulmonary artery coupling

Prior to cardiac catheterization, comprehensive echocardiography was performed to assess left heart structure and function in accordance with current guidelines.[25] Focused evaluation of right heart function was performed simultaneously with invasive measurements at rest and during exercise as previously described.[11] Tricuspid annular plane systolic

excursion (TAPSE), RV systolic tissue velocity at the lateral tricuspid annulus (RV s'), and fractional area change (FAC) were measured during rest and exercise.[26] RV dysfunction was defined according to the American Society of Echocardiography recommendations as RV FAC < 35% or RV s' <10 cm/s.[26] Right ventricular-PA coupling was assessed by the ratio of TAPSE to PA pressure as in prior studies.[27] Ratios of FAC and RV s' to PA pressure were also examined as complementary indices of RV-PA coupling analogous to TAPSE/PA pressure ratio. Additionally, LA reservoir strain and LA compliance were measured as previously described.[28]

Assessment of oncotic pressure, haemoconcentration, and pulmonary ventilation

Plasma oncotic pressure was estimated by pre-exercise albumin levels. Acute changes in arterial haemoglobin during exercise were assessed as a measure of intravascular water content relative to baseline, whereby increases in haemoglobin identify an acute reduction in intravascular fluid content due to filtration of water out of the vascular space and into the interstitium during exercise in the setting of pulmonary and systemic venous congestion.[29] Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (V_E) were measured continuously using a portable metabolic cart (MedGraphics, St. Paul, MN, USA).[3,30] Pulmonary dead-space fraction or the ratio of dead space ventilation to tidal volume (V_D/V_T) was determined using the modified alveolar gas equation.[30] The V_E/VCO_2 slope was calculated from the slope of all V_E and VCO_2 data points during exercise.

Statistical analysis

Data are presented as mean (standard deviation), median (interquartile range), or number (%). Between-group differences were compared by unpaired *t*-test, Wilcoxon rank-sum test, χ^2 or Fisher's exact test as appropriate. Linear regression analyses and Pearson correlation coefficients were used to assess relationships between changes in variables of interest. Logistic regression was used to identify predictors for the development of EVLW during exercise. Analysis was performed using JMP 13.0.0 (SAS). A *P*-value of <0.05 was considered statistically significant. Standardized mean differences (SMD) were also calculated to provide estimates of effect size for differences between groups independent of traditional null hypothesis testing. Higher SMD indicates greater magnitude of differences between the two groups.

Results

Prevalence of lung water during exercise

Among 61 consecutive HFpEF patients without clinically apparent congestion prior to assessment, 54% ($n = 33$) either developed new B-lines ($n = 23$, 38%) or developed an increase in the number B-lines ($n = 10$, 16%) during exercise, indicating development of lung congestion ($HFpEF_{LW+}$), while 46% ($n = 28$) did not develop B-lines ($HFpEF_{LW-}$). As compared to $HFpEF_{LW-}$ subjects, the $HFpEF_{LW+}$ group had slightly higher plasma NT-proBNP levels but other baseline characteristics, including atrial fibrillation and measures of oncotic pressure, were similar in the groups (*Table 1*).

Baseline cardiac structure and function

Left ventricular structure and function were similar in the $HFpEF_{LW+}$ and $HFpEF_{LW-}$ groups, with similar LV chamber size, EF, and diastolic function indices (*Table 1*). In contrast, LA reservoir strain and LA compliance were lower in the $HFpEF_{LW+}$ group. Despite similarities in LV function, there was a markedly higher prevalence of RV dysfunction in $HFpEF_{LW+}$ (64% vs. 31%, $P = 0.011$; *Table 1* and *Figure 1*), with lower RV s' and FAC as compared to $HFpEF_{LW-}$ at rest (*Table 2*).

Baseline haemodynamics

As compared to $HFpEF_{LW-}$, subjects with $HFpEF_{LW+}$ displayed higher PCWP and greater V wave amplitude at rest (*Table 2* and *Figure 1*). Similarly, RAP, PA systolic pressures, PA mean pressures, and PA Ea were higher in the $HFpEF_{LW+}$ group as compared to $HFpEF_{LW-}$. In contrast, LV transmural pressure was similar in the two groups. The $HFpEF_{LW+}$ group displayed more deranged RV-PA coupling at rest, manifest by lower ratios of TAPSE, FAC, and RV s' to PA mean pressure. Vital signs, cardiac output, arterial saturation, and ventilatory measures were similar in the groups at rest (*Table 2*).

Haemodynamics, ventricular function, and ventilation during exercise

With exercise, patients in the $HFpEF_{LW+}$ group developed higher RAP, PCWP, and greater increase in the amplitude of the PCWP V wave (*Table 3* and *Figure 1*). Patients in the $HFpEF_{LW+}$ group also displayed more severe exercise-induced pulmonary hypertension, worse RV-PA coupling, and greater increases in pulsatile RV load (higher PA Ea) compared to the $HFpEF_{LW-}$ group (*Figure 2*). The increase in RA pressure observed was correlated with the magnitude of RV-PA uncoupling during exercise (*Figure 2*). Even though the PCWP was higher in the $HFpEF_{LW+}$ group this was associated with a lower transmural pressure during exercise, indicating that the PCWP elevation was in part driven by the right heart and relative pericardial restraint.[15] There was no difference in heart rate or Q_P between the groups during exercise (*Table 3*).

Patients in the $HFpEF_{LW+}$ group displayed greater haemoconcentration with exercise as compared to $HFpEF_{LW-}$, indicating greater translocation of fluid from the vascular space to the extravascular space (*Figure 3*). Patients in the $HFpEF_{LW+}$ group also displayed greater increases in pulmonary dead space fraction and minute ventilation compared to the $HFpEF_{LW-}$ group. The V_E/VCO_2 ratio tended to be higher in the $HFpEF_{LW+}$ group ($P = 0.060$) but the V_E/VCO_2 slope was not different between groups (*Table 3*).

Predictors of development of increased lung water

Elevation in PCWP and RA pressures during exercise distinguished patients developing EVLW from those who did not [area under the curve (AUC) 0.77 and 0.80, *Table 4*]. Discrimination was numerically better for pressures measured at end-expiration than for pressure averaged over the respiratory cycle, though both methods were predictive. There was no association between markers of LV function at rest and development of EVLW, but measures of LA reservoir strain, LA compliance, and PCWP V wave height were predictive. In contrast, all measures of abnormal RV-PA coupling at rest and during exercise were strongly predictive of developing EVLW during exercise (AUC 0.76–0.84, *Table 4*).

Table 1 Baseline characteristics

	$HFpEF_{LW-}$ ($n = 28$)	$HFpEF_{LW+}$ ($n = 33$)	*P*-value	SMD (95% CI)
Age (years)	66 ± 10	66 ± 13	0.89	0.04 (-0.47 to 0.54)
Female (%)	61	42	0.20	—
Body mass index (kg/m^2)	33 ± 7	35 ± 8	0.32	0.26 (-0.25 to 0.76)
Comorbidities				
Coronary disease (%)	26	27	1.00	—
Diabetes mellitus (%)	18	33	0.24	—
Hypertension (%)	100	91	0.24	—
Atrial fibrillation (%)	21	28	0.55	—
Medications				
ACE or ARB (%)	57	39	0.20	—
Beta-blocker (%)	32	55	0.12	—
Loop diuretic (%)	52	69	0.28	—
Laboratories				
Creatinine (mg/dL)	1.0 ± 0.3	1.3 ± 0.8	0.067	-0.48 (-0.99 to 0.03)
Haemoglobin (g/dL)	12.5 ± 1.3	12.0 ± 1.5	0.25	-0.30 (-0.80 to 0.21)
Albumin (n = 39/61) (g/dL)	4.0 ± 0.3	3.9 ± 0.4	0.21	-0.40 (-1.03 to 0.24)
NT-proBNP (n = 46/61) (pg/mL)	91 (30–423)	336 (93–1058)	0.017	—
Echocardiography				
LV ejection fraction (%)	62 ± 5	60 ± 5	0.17	-0.37 (-0.90 to 0.17)
LV diastolic dimension (mm)	51 ± 4	52 ± 5	0.64	0.14 (-0.43 to 0.70)
LV mass index (g/m^2)	94 ± 20	92 ± 19	0.81	-0.07 (-0.66 to 0.51)
LA volume index (mL/m^2)	32 ± 10	37 ± 15	0.23	0.36 (-0.23 to 0.93)
LA reservoir strain (%) (n = 57/61)	32 ± 14	24 ± 15	0.037	-0.57 (-1.09 to -0.03)
LA compliance (%/mmHg) (n = 57/61)	1.62 ± 0.86	1.00 ± 0.84	0.008	-0.73 (-1.25 to -0.18)
LV e' velocity (cm/s)	7 ± 2	7 ± 2	0.88	0.05 (-0.49 to 0.58)
LV *E*/e' ratio	11.6 ± 4.9	12.9 ± 6.1	0.40	0.23 (-0.31 to 0.76)
MR (%) (no/mild/moderate)	56/44/0	43/54/3	0.37	—
TR (%) (no/mild/moderate)	68/24/8	46/29/25	0.17	—
RV dysfunction[a] (%)	31	64	0.011	—

Values are represented as mean ± standard deviation or median (interquartile range).
ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; *E*/e', ratio of early diastolic transmitral filling velocity (*E*) and early diastolic mitral annular tissue velocity (e'); LA, left atrial; LV, left ventricular; MR, mitral regurgitation; NT-proBNP, N-terminal pro brain natriuretic peptide; RV, right ventricular; SMD, standardized mean difference; TR, tricuspid regurgitation.
[a]RV dysfunction was defined by American Society of Echocardiography recommendations as either RV FAC <35% or RV s' <10 cm/s.

Sensitivity analyses

Sensitivity analyses excluding the HFpEF patients with B-lines at rest, and using systolic PA pressure in place of mean PA pressure for RV-PA coupling assessments demonstrated similar results as in the overall population (Supplementary material online, *Tables S1–S3*).

Discussion

In this study, we directly evaluated for the development of increased EVLW during exercise and related it to simultaneously assessed invasive haemodynamics and measurements of ventricular function, ventricular-arterial coupling, and pulmonary mechanics, allowing for exploration of the relationships between haemodynamic perturbations and lung congestion during exercise in patients with HFpEF. We observed that development of increased EVLW during exercise is related not only to increases in pulmonary capillary pressures but also to increases in central venous pressures, which were observed to develop secondary to abnormalities in RV function and RV-PA coupling. These data provide new pathophysiologic insight on the complex interactions between haemodynamics and lung congestion in patients with HFpEF and identify an important and previously unappreciated role for abnormalities in RV-PA coupling in the pathogenesis of increased lung water.

Assessment of lung congestion

An emerging body of evidence has shown that increases in EVLW at rest and during exercise can be reliably demonstrated by lung ultrasound in patients with HF.[16–19] The development of B-lines has been shown to reflect acute increases in lung congestion and to change dynamically with EVLW content.[19–24] Increases in EVLW are associated with adverse outcomes, increased risk for HF hospitalization, and are currently being evaluated as novel treatment targets.

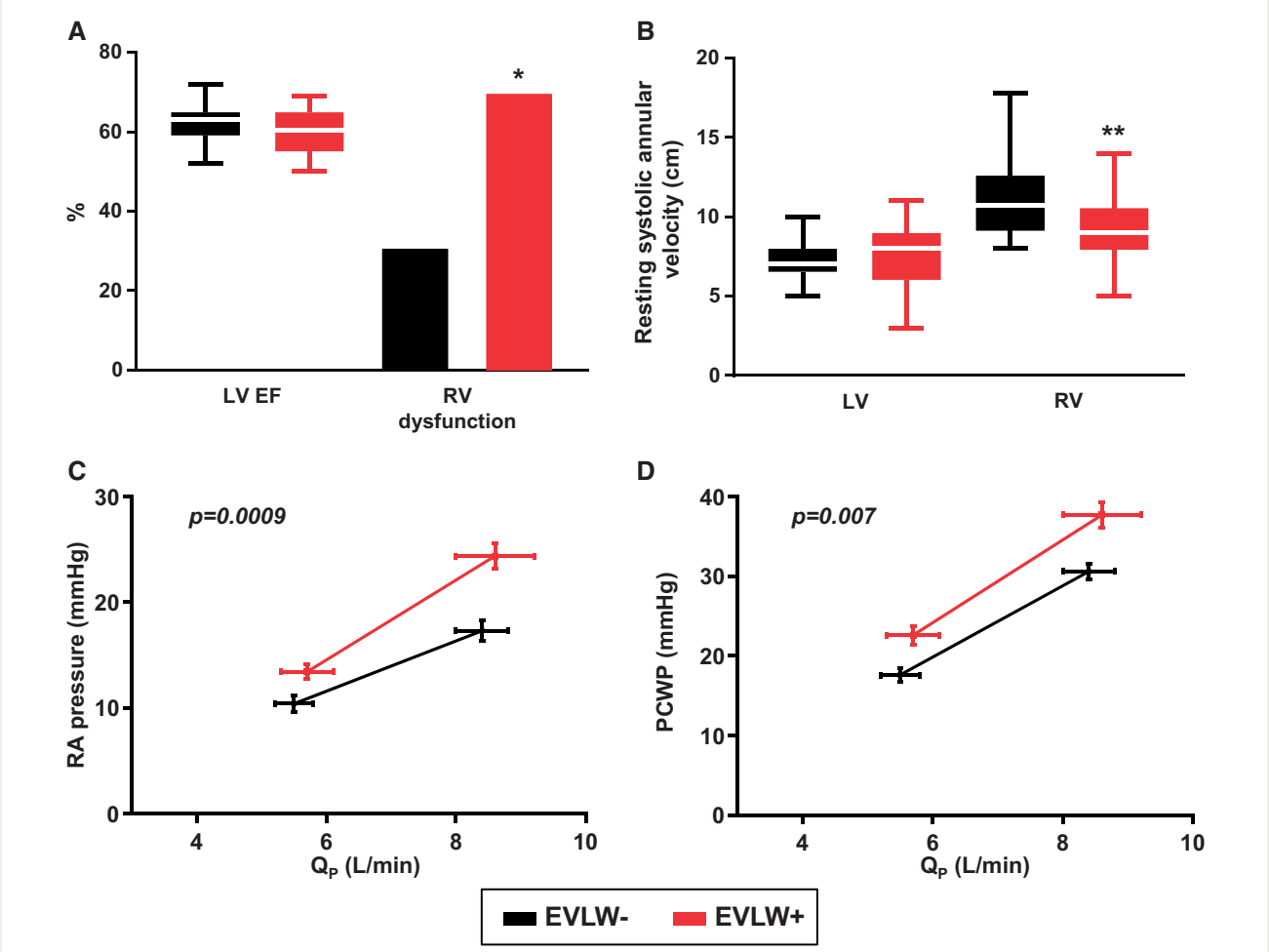


Figure 1 The HFpEF group with extravascular lung water (EVLW+) had similar left ventricular function but worse right ventricular function compared with the HFpEF group without extravascular lung water (EVLW-) (*A* and *B*). Right atrial and pulmonary capillary wedge pressure were higher during exercise in the EVLW+ HFpEF group (*C* and *D*). *P=0.01, **P=0.001.

Normal and abnormal exercise responses

The normal lung can accommodate a 300% increase in blood flow during exercise without developing significant congestion. This is achieved by maintenance of low pulmonary capillary hydrostatic pressures through enhancement in left heart function and rapid, efficient clearance of any EVLW that is filtered across the alveolar-capillary membrane through pulmonary lymphatics.[9,31,32] We observed that HFpEF patients developing lung congestion displayed similar increase in lung blood flow to those without congestion, but the $HFpEF_{LW+}$ group displayed significantly greater increase in PCWP, shifting the balance in Starling forces favouring greater fluid filtration out of the capillaries.[7,8] The greater loss of fluid from the vascular space in the $HFpEF_{LW+}$ group was further evidenced by the greater degree of dynamic haemoconcentration during stress (*Figure 3*).

We also hypothesized the lung congestion would be greater in patients with higher systemic venous pressures due to abnormalities in right heart reserve. This idea was based upon studies in sheep where combined increases in left atrial and systemic venous pressure induced by balloon occlusion were shown to increase lung congestion far beyond that seen with isolated left atrial hypertension alone.[9] Consistent with this hypothesis, we observed that the $HFpEF_{LW+}$ group displayed higher RAP, which was associated with greater impairment in RV-PA coupling at rest and during exercise. We speculate that this relationship is caused by impaired lymphatic clearance of lung water in the setting of high central venous pressures from RV dysfunction, since the pulmonary lymphatics drain passively into the central veins,[9,31,32] though the current data cannot address this potential mechanism directly.

Historically, patients developing right-sided HF have been conceptualized as having dry lungs, because the development of pulmonary congestion by definition requires RV output to exceed that of the LV.[33] We show that even with the same rate of lung perfusion during exercise (similar increase in Q_P) and equivalent pulmonary transit time [similar heart rate (HR)], the combination of increased filtration pressure (elevated PCWP) and increased lymphatic 'afterload' (RA hypertension) caused by impaired RV-PA coupling was associated with an increase in lung congestion during stress (*Take home figure*).

Table 2 Resting haemodynamics, right heart function, and ventilatory measures

	$HFpEF_{LW-}$ ($n = 28$)	$HFpEF_{LW+}$ ($n = 33$)	*P*-value	SMD (95% CI)
Heart rate (b.p.m.)	71 ± 12	72 ± 9	0.76	0.08 (-0.42 to 0.58)
Mean BP (mmHg)	106 ± 13	104 ± 13	0.60	-0.14 (-0.67 to 0.39)
Qp (L/min)	5.5 ± 1.5	5.7 ± 2.2	0.69	0.11 (-0.40 to 0.61)
Ventricular filling pressures				
RA mean (mmHg)	10 ± 4	13 ± 4	0.007	0.72 (0.19–1.24)
RA_{resp} mean (mmHg)	9 ± 5	12 ± 5	0.023	0.60 (0.08–1.11)
PCWP mean (mmHg)	18 ± 5	23 ± 7	0.002	0.83 (0.30–1.35)
$PCWP_{resp}$ mean (mmHg)	15 ± 5	19 ± 6	0.005	0.75 (0.22–1.26)
PCWP V wave (mmHg)	22 ± 7	31 ± 12	0.001	0.88 (0.34–1.40)
LV transmural pressure (mmHg)	7 ± 3	7 ± 3	0.46	0.19 (-0.31 to 0.70)
Pulmonary vascular function				
PA systolic pressure (mmHg)	38 ± 7	49 ± 16	0.002	0.83 (0.30–1.34)
PA mean (mmHg)	27 ± 5	34 ± 10	0.0003	1.24 (0.68–1.78)
PA_{resp} mean (mmHg)	24 ± 6	31 ± 10	0.002	0.83 (0.30–1.34)
PVR (Wood units)	1.8 ± 1.0	2.4 ± 1.8	0.10	0.42 (-0.09 to 0.93)
PA compliance (mL/mmHg)	4.5 ± 2.0	3.8 ± 1.9	0.17	-0.36 (-0.86 to 0.16)
PA Ea (mmHg/mL)	0.53 ± 0.18	0.68 ± 0.33	0.034	0.56 (0.04–1.06)
RV function				
RV s' (cm/s)	11 ± 2	9 ± 2	0.001	-0.87 (-1.39 to -0.33)
TAPSE (mm) (n = 58/61)	19 ± 4	17 ± 4	0.11	-0.42 (-0.94 to 0.10)
RV FAC (%) (n = 55/61)	52 ± 7	46 ± 9	0.006	-0.77 (-1.31 to -0.21)
RV s'/PA mean ($cm \cdot s^{-1}$/mmHg)	0.44 ± 0.16	0.29 ± 0.11	<0.0001	-1.11 (-1.64 to -0.55)
TAPSE/PA mean (mm/mmHg) (n = 58/61)	0.72 ± 0.19	0.52 ± 0.17	0.0001	-1.11 (-1.65 to -0.54)
FAC/PA mean (%/mmHg) (n = 55/61)	2.05 ± 0.56	1.48 ± 0.58	0.0005	-1.00 (-1.54 to -0.42)
Ventilation and gas exchange				
Arterial saturation (%)	95 ± 2	95 ± 3	0.97	0.00 (-0.50 to 0.50)
V_E (L/min)	6.7 ± 1.5	7.5 ± 2.3	0.14	0.38 (-0.13 to 0.88)
V_D/V_T	0.36 ± 0.05	0.37 ± 0.06	0.70	0.09 (-0.41 to 0.59)

Values are represented as mean ± SD.
$Ca_{O2} - Cv_{O2}$, arterial-venous O2 content difference; Ea, elastance; FAC, fractional area change; f_b, respiratory rate; LV, left ventricular; PCWP, pulmonary capillary wedge pressure; $PCWP_{resp}$, average pressure throughout respiration; PVR, pulmonary vascular resistance; Qp, pulmonary flow/cardiac output; RA, right atrial; RV, right ventricular; s', systolic tissue Doppler velocity; SMD, standardized mean difference; TAPSE, tricuspid annular plane systolic excursion; V_D/V_T, dead space fraction; V_E, minute ventilation; V_E/VCO_2, ventilatory efficiency; V_T, tidal volume.

Patients with HFpEF, pulmonary hypertension (PH), and RV dysfunction are known to display worse functional capacity and clinical outcomes, and the current data may shed new light on the pathophysiology contributing to this observation.[27,34–36]

Chronic remodelling vs. acute congestion

In contrast to the current data, patients with advanced HF often display little evidence of lung congestion, despite high biventricular filling pressures. The discrepant findings may relate to presence or absence of adaptations that develop chronically in the lungs. While pulmonary congestion develops acutely with left atrial hypertension,[7] with more sustained elevations there may be structural remodelling in the lung vasculature, which dampens the elevation in pulmonary capillary pressure even as left atrial pressures are high, while decreasing capillary permeability to reduce oedema formation.[37,38] This remodelling effectively protects the alveoli from oedema but this occurs at the cost of impairments in lung diffusion in advanced HF patients, which are often not reversible even after aggressive decongestion.[33–36]

The patients with HFpEF enrolled in the current study displayed normal or mild elevation in PCWP at rest, but marked elevations in PCWP during exercise. With this ephemeral PCWP elevation, there may be less of a stimulus driving capillary and vascular structural remodelling.[37–42] Earlier stage HFpEF patients have better lung diffusion than advanced HF but may be more vulnerable to the development of acute lung congestion during exercise as capillary pressures rise.

Greater pulmonary vascular disease in patients with lung congestion

Pulmonary vasoconstriction and remodelling are often conceptualized as a means to protect the lung capillaries from barotrauma in PH due to left heart disease, but the $HFpEF_{LW+}$ group displayed more profound pulmonary vascular disease, with higher PA elastance at rest and during exercise. In tandem with worsening left atrial

Table 3 Exercise haemodynamics, right heart function, and ventilatory measures

	$HFpEF_{LW-}$ ($n = 28$)	$HFpEF_{LW+}$ ($n = 33$)	*P*-value	SMD (95% CI)
Heart rate (b.p.m.)	93 ± 16	91 ± 15	0.63	-0.13 (-0.63 to 0.38)
Mean BP (mmHg)	117 ± 13	118 ± 17	0.73	0.09 (-0.42 to 0.63)
Qp (L/min)	8.4 ± 2.2	8.6 ± 3.3	0.73	0.09 (-0.42 to 0.60)
Ventricular filling pressures				
RA mean (mmHg)	17 ± 5	24 ± 7	<0.0001	1.12 (0.56–1.65)
RA_{resp} mean (mmHg)	16 ± 6	22 ± 6	0.0005	0.96 (0.42–1.48)
PCWP mean (mmHg)	31 ± 5	38 ± 9	0.0004	0.97 (0.43–1.49)
$PCWP_{resp}$ mean (mmHg)	26 ± 6	30 ± 7	0.008	0.70 (0.17–1.21)
PCWP V wave (mmHg)	42 ± 9	53 ± 15	0.0007	0.92 (0.38–1.43)
LV transmural pressure (mmHg)	12 ± 4	9 ± 6	0.008	-0.71 (-1.22 to -0.17)
Pulmonary vascular function				
PA systolic pressure (mmHg)	59 ± 10	73 ± 17	0.0002	1.01 (0.46–1.53)
PA mean (mmHg)	44 ± 8	54 ± 11	0.0006	0.93 (0.39–1.46)
PA_{resp} mean (mmHg)	39 ± 7	48 ± 11	0.001	0.88 (0.34–1.40)
PVR (Wood units)	1.8 ± 0.9	2.0 ± 1.3	0.38	0.24 (-0.28 to 0.75)
PA compliance (mL/mmHg)	3.7 ± 1.4	3.2 ± 1.4	0.15	-0.38 (-0.88 to 0.14)
PA Ea (mmHg/mL)	0.68 ± 0.19	0.84 ± 0.32	0.028	0.60 (0.07–1.11)
R function				
RV s' (cm/s) (n = 54/61)	12 ± 2	10 ± 3	0.033	-0.60 (-1.14 to -0.04)
TAPSE (mm) (n = 51/61)	20 ± 4	18 ± 4	0.038	-0.60 (-1.15 to -0.03)
RV FAC (%) (n = 50/61)	55 ± 8	50 ± 10	0.035	-0.62 (-1.17 to -0.04)
RV s'/PA mean ($cm \cdot s^{-1}$/mmHg) (n = 54/61)	0.27 ± 0.07	0.20 ± 0.08	0.001	-0.93 (-1.48 to -0.34)
TAPSE/PA mean (mm/mmHg) (n = 51/61)	0.47 ± 0.12	0.34 ± 0.12	0.0003	-1.08 (-1.66 to -0.47)
FAC/PA mean (%/mmHg) (n = 50/61)	1.34 ± 0.33	0.99 ± 0.35	0.0008	-1.03 (-1.61 to -0.41)
Integrated indices				
ΔPCWP/ΔQp ($mmHg/L \cdot min^{-1}$)	3.7 (2.3–5.0)	5.7 (4.2–8.3)	0.007	—
ΔRA/ΔQp ($mmHg/L \cdot min^{-1}$)	2.1 (1.1–3.0)	3.8 (2.8–7.5)	0.0009	—
ΔPA mean/ΔQp ($mmHg/L \cdot min^{-1}$)	5.2 (3.9–8.9)	6.8 (5.0–10.8)	0.10	—
Ventilation and gas exchange				
Arterial saturation (%)	94 ± 2	95 ± 3	0.16	0.36 (-0.15 to 0.87)
V_E (L/min)	20 ± 6	24 ± 9	0.047	0.52 (0.00–1.03)
V_D/V_T	0.28 ± 0.03	0.30 ± 0.05	0.040	0.53 (0.01–1.04)
V_E/VCO_2	33 ± 7	37 ± 7	0.060	0.49 (-0.03 to 1.00)
V_E/VCO_2 slope	29 ± 6	27 ± 6	0.25	-0.31 (-0.82 to 0.22)

Values are represented as mean ± SD or median (interquartile range).
$Ca_{O2} - Cv_{O2}$, arterial-venous O2 content difference; Ea, elastance; FAC, fractional area change; f_b, respiratory rate; LV, left ventricular; PCWP, pulmonary capillary wedge pressure; $PCWP_{resp}$, average pressure throughout respiration; PVR, pulmonary vascular resistance; Qp, pulmonary flow/cardiac output; RA, right atrial; RV, right ventricular; s', systolic tissue Doppler velocity; SMD, standardized mean difference; TAPSE, tricuspid annular plane systolic excursion; V_D/V_T, dead space fraction; V_E, minute ventilation; V_E/VCO_2, ventilatory efficiency; V_T, tidal volume.

hypertension, these abnormalities combined to greatly increase PA pressures and impair RV-PA coupling reserve with stress.

The current data reveal how combined left and right heart limitations during exercise in HFpEF may induce a vicious cycle, whereby left atrial hypertension caused by reduced LA compliance worsens fluid filtration, but also leads to greater PH and impairments in RV-PA coupling, which increase systemic venous pressure to compromise lung lymphatic drainage, further increasing vascular oedema to exacerbate increases in RV afterload. Future study is required to determine the efficacy of novel therapies designed to reduce EVLW, either by directly targeting elevations in PCWP, through medical,[43,44] or interventional approaches[45,46] to enhance LA compliance or LV diastolic function, improving RV-PA coupling through pulmonary vasodilation[10] or enhancement in RV inotropy (NCT03541603), reducing RA pressure through diuresis or alteration in venous tone,[47] or possibly even altering capillary permeability. These data may also have implications for new experimental interventional procedures such as atrial septostomy.[45] If right heart compliance is adequate, the volume load associated with this procedure may be well-tolerated, but in patients that develop RA hypertension, this could mitigate the benefit from LA decompression.

Limitations

The cross-sectional design of the study limits the ability to discern causality. All participants were referred for invasive exercise testing, introducing bias. Measurements were obtained at rest and during

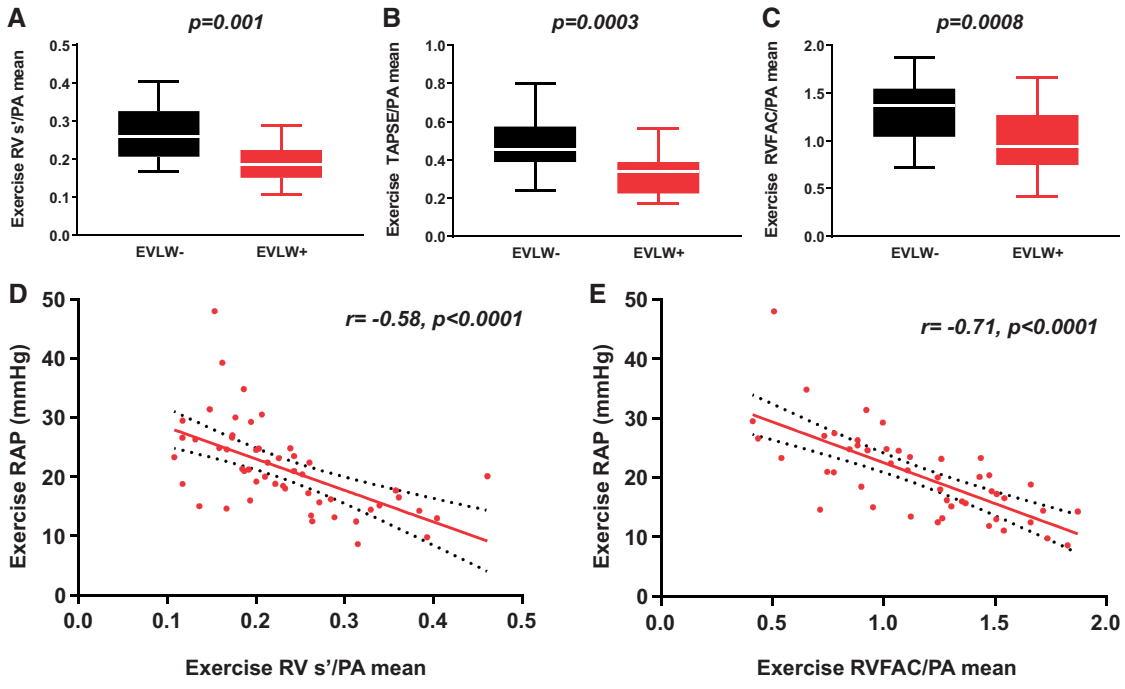


Figure 2 Right ventricular pulmonary artery uncoupling during exercise was worse in the EVLW+ HFpEF group (*A*–*C*) and associated with higher right atrial pressure during exercise (*D* and *E*).

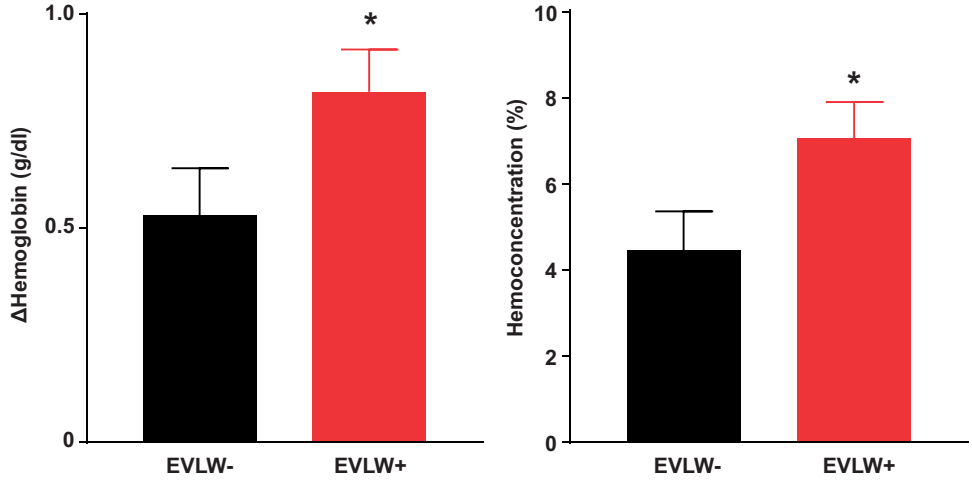


Figure 3 Heart failure and preserved ejection fraction patients that developed extravascular lung water had a greater rise in haemoglobin (*A*) and greater haemoconcentration (*B*) during exercise. *$P<0.05$.

relatively low-level exercise, and we cannot exclude the possibility that some of the $HFpEF_{LW-}$ group would have gone on to develop pulmonary oedema with higher levels of exertion. However, most of the filling pressure elevation occurs at 20 W in HFpEF and studying patients at a common workload removes confounding differences due to differences in functional capacity.[1,2] The $HFpEF_{LW+}$ group had worse LA reservoir and RV function with higher NT-proBNP levels, and a trend to worse renal function. This raises the possibility that patients developing lung water represent a more advanced stage or longer natural history of disease compared to the $HFpEF_{LW-}$ group. Future natural history studies are required to further assess this hypothesis. Notably, even as patients were considered by their primary cardiologists to be clinically euvolaemic, there was evidence of subclinical congestion in the $HFpEF_{LW+}$ group, with

Table 4 Predictors of increased extravascular lung water

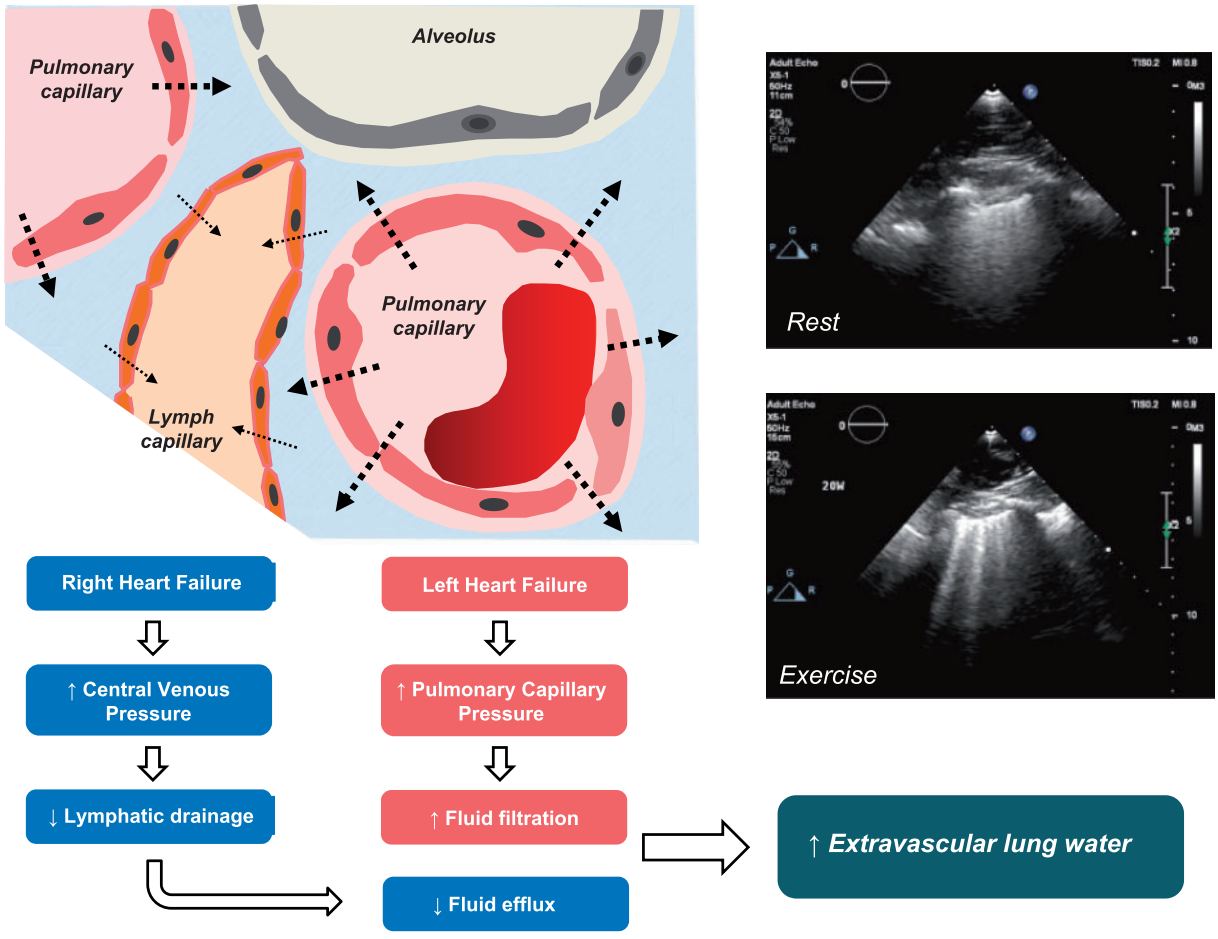
	AUC	95% CI	Optimal cut point	Sens	Spec
Exercise haemodynamics					
RA mean (mmHg)	0.800	0.665–0.890	19	79	67
RA_{resp} mean (mmHg)	0.753	0.609–0.856	20	67	74
PCWP mean (mmHg)	0.771	0.635–0.867	32	82	57
$PCWP_{resp}$ mean (mmHg)	0.693	0.548–0.808	33	42	86
PCWP V wave (mmHg)	0.756	0.616–0.857	44	79	68
PA mean (mmHg)	0.749	0.604–0.853	48	69	75
PA $mean_{resp}$ (mmHg)	0.741	0.600–0.845	44	64	75
Resting left heart function					
LV e' velocity (cm/s)	0.492	0.342–0.643	—	—	—
LV s' velocity (cm/s)	0.558	0.371–0.729	—	—	—
Left ventricular ejection fraction (%)	0.590	0.434–0.730	—	—	—
LA reservoir strain (%) (*n* = 57/61)	0.664	0.512–0.789	15.4	42	92
LA compliance (%/mmHg) (*n* = 57/61)	0.713	0.563–0.828	0.72	52	96
Resting right heart function and RV-PA coupling					
RV FAC (%) (*n* = 55/61)	0.714	0.558–0.831	48	66	77
TAPSE (mm) (*n* = 58/61)	0.640	0.488–0.768	—	—	—
RV s' (cm/s)	0.731	0.588–0.836	9	58	78
RV FAC/mPAP (%/mmHg) (*n* = 55/61)	0.767	0.620–0.869	1.75	76	69
TAPSE/mPAP (mm/mmHg) (*n* = 58/61)	0.791	0.648–0.886	0.61	80	75
RV's/mPAP ($cm \cdot s^{-1}$/mmHg)	0.835	0.707–0.914	0.27	64	100
Exercise right heart function and RV-PA coupling					
RV FAC (%) (*n* = 50/60)	0.680	0.515–0.809	52	59	74
TAPSE (mm) (*n* = 51/61)	0.678	0.511–0.810	17	52	83
RV s' (cm/s) (*n* = 54/61)	0.694	0.534–0.817	10.5	63	83
RV FAC/mPAP (%/mmHg) (*n* = 50/61)	0.763	0.606–0.870	0.95	54	87
TAPSE/mPAP (mm/mmHg) (*n* = 51/61)	0.805	0.651–0.902	0.37	73	88
RV s'/mPAP ($cm \cdot s^{-1}$/mmHg) (*n* = 54/61)	0.797	0.649–0.893	0.19	59	92

Optimal cut points are based on Youden's index.
AUC, area under the receiver operating characteristic curve; $Ca_{O2} - Cv_{O2}$, arterial-venous O2 content difference; Ea, elastance; FAC, fractional area change; f_b, respiratory rate; LV, left ventricular; PCWP, pulmonary capillary wedge pressure; $PCWP_{resp}$, average pressure throughout respiration; PVR, pulmonary vascular resistance; Qp, pulmonary flow/cardiac output; RA, right atrial; RV, right ventricular; s', systolic tissue Doppler velocity; Sens, sensitivity; SMD, standardized mean difference; Spec, specificity; TAPSE, tricuspid annular plane systolic excursion; V_D/V_T, dead space fraction; V_E, minute ventilation; V_E/VCO_2, ventilatory efficiency; V_T, tidal volume.

higher NT-proBNP and RV pressures, revealing that some may have been undertreated for HF. The focus of this study was on RV function and RV-PA coupling, and while LV function was assessed at rest, it was not evaluated during exercise. Although mitral and tricuspid regurgitation was similar between groups at rest, we did not assess exertional changes in valvular function. Cut points derived for prediction of lung water during exercise in this study require external validation in independent samples. Lung ultrasound may be performed in 1–28 chest regions.[18,19] Because of the time constraints for imaging during exercise and the inability to scan the right thorax in the invasive laboratory, lung ultrasound was performed in two regions on the left chest. This may have reduced the sensitivity of our assessment for EVLW, and it is possible that some of the $HFpEF_{LW-}$ group might have displayed B-lines if more regions of the thorax were imaged. However, B-lines are 50% more likely to develop in the left lung during exercise as compared to the right, and the two regions imaged in this study (anterior and mid-axillary) represent the 'wet spaces' most likely to display B-lines during supine exercise.[18,48] Scali *et al.*[48] recently demonstrated that examinations during exercise including four regions (two per lung) provided equivalent information on lung congestion to the full 28 region assessment.

Conclusions

Over half of stable outpatients with HFpEF develop increases in interstitial lung water during exercise, even at low levels of exertion. The acute development of lung congestion in HFpEF is correlated with increases in pulmonary capillary hydrostatic pressures and systemic venous hypertension that is associated with impairments in RV-PA coupling. Further study is required to better delineate the treatment for and mechanisms causing lung congestion during exercise in HFpEF.



Take home figure Development of extravascular lung water associated with both increased pulmonary capillary wedge pressure leading to fluid filtration, as well as increased right atrial and central venous pressure potentially impeding lymphatic lung water drainage.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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