

## ORIGINAL ARTICLE

# Reduced haemodynamic coupling and exercise are associated with vascular stiffening in pulmonary arterial hypertension

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## ABSTRACT

**Objective** Inadequate right ventricular (RV) and pulmonary arterial (PA) functional responses to exercise are important yet poorly understood features of pulmonary arterial hypertension (PAH). This study combined invasive catheterisation with echocardiography to assess RV afterload, RV function and ventricular–vascular coupling in subjects with PAH.

**Methods** Twenty-six subjects with PAH were prospectively recruited to undergo right heart catheterisation and Doppler echocardiography at rest and during incremental exercise, and cardiac MRI at rest. Measurements at rest included basic haemodynamics, RV function and coupling efficiency ( $\eta$ ). Measurements during incremental exercise included pulmonary vascular resistance ( $Z_0$ ), characteristic impedance ( $Z_C$ , a measure of proximal PA stiffness) and proximal and distal PA compliance ( $C_{PA}$ ).

**Results** In patients with PAH, the proximal PAs were significantly stiffer at maximum exercise ( $Z_C = 2.31 \pm 0.38$  vs  $1.33 \pm 0.15$  WU $\times$ m<sup>2</sup> at rest;  $p=0.003$ ) and PA compliance was decreased ( $C_{PA} = 0.88 \pm 0.10$  vs  $1.32 \pm 0.17$  mL/mm Hg/m<sup>2</sup> at rest;  $p=0.0002$ ).  $Z_0$  did not change with exercise. As a result, the resistance–compliance (RC) time decreased with exercise ( $0.67 \pm 0.05$  vs  $1.00 \pm 0.07$  s at rest;  $p < 10^{-6}$ ). When patients were grouped according to resting coupling efficiency, those with poorer  $\eta$  exhibited stiffer proximal PAs at rest, a lower maximum exercise level, and more limited  $C_{PA}$  reduction at maximum exercise.

**Conclusions** In PAH, exercise causes proximal and distal PA stiffening, which combined with preserved  $Z_0$  results in decreased RC time with exercise. Stiff PAs at rest may also contribute to poor haemodynamic coupling, reflecting reduced pulmonary vascular reserve that contributes to limit the maximum exercise level tolerated.

## INTRODUCTION

Assessment of right ventricular (RV) and pulmonary arterial (PA) function is critical for monitoring disease progression and identifying successful treatment strategies in patients with pulmonary arterial hypertension (PAH). In particular, metrics of RV–PA haemodynamic coupling and PA compliance have demonstrated better prognostic value than traditional haemodynamic measurements used in the clinical setting, such as mean pulmonary arterial

pressure (mPAP) and pulmonary vascular resistance.<sup>1–4</sup> Furthermore, the response of the RV and pulmonary vasculature to exercise may be even more revealing.<sup>5–6</sup> However, changes in haemodynamic coupling efficiency and PA compliance with exercise have been underinvestigated, particularly in subjects with PAH.

In healthy subjects performing physical exercise, vascular resistance typically stays constant or decreases due to PA distension and recruitment of normally collapsed arteries.<sup>7</sup> The effect of exercise on resistance in patients with PAH has been inconsistent.<sup>8–10</sup> Furthermore, it is unclear how PA compliance changes during exercise.<sup>11–12</sup> The resistance–compliance characteristic time (RC time), which is constant under most conditions, decreases during exercise in healthy subjects, while the results for patients with PAH have not been definitive.<sup>12</sup> A more comprehensive measure of cardiopulmonary status is ventricular–vascular coupling efficiency.<sup>13</sup> Coupling efficiency at rest is decreased in patients with PAH,<sup>14–15</sup> and recent findings indicate that uncoupling occurs during exercise.<sup>16</sup> However, the associations of coupling efficiency at rest with vascular stiffness and maximum exercise level have not been investigated.

Here, a novel methodology was used to investigate the effect of exercise on RV afterload, including proximal PA stiffness (by characteristic impedance  $Z_C$ ), proximal and distal PA compliance (by  $C_{PA}$ ) and total pulmonary vascular resistance (tPVR) (by  $Z_0$ ), in subjects with PAH. Simultaneous PA pressure and flow measured with echocardiography during right heart catheterisation (RHC) and exercise were analysed. The hypothesis tested was that haemodynamic coupling efficiency at rest associates with proximal PA stiffness and maximum exercise level tolerated.

## METHODS

### Study population and design

Subjects with known or suspected PAH who were referred for clinical RHC at Northwestern Memorial Hospital or University of Wisconsin-Hospital were invited to participate. Inclusion criteria were subjects aged 18–80 with diagnosed or suspected PAH, including idiopathic PAH (IPAH), PAH associated with systemic sclerosis (SSc-PAH) or chronic thromboembolic pulmonary hypertension (CTEPH). Exclusion criteria



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included WHO functional class IV patients, recent syncope, contra-indication to either MRI or physical exercise.

The study included simultaneous RHC and echocardiography at rest as well as during one or more stages of incremental exercise. MRI at rest was performed within 2 weeks of the RHC. All study procedures are summarised in [table 1](#), which includes the number of subjects who completed each test and the primary endpoints for each test. All patients gave written informed consent. The study was compliant with the Health Insurance Portability and Accountability Act (HIPAA) and approved by the institutional review boards of both institutions.

### Cardiac catheterisation

The RHC procedure was identical at the two sites. Participants underwent recording of invasive haemodynamics using a fluid-filled, 6F PA catheter (Edwards Lifesciences, Irvine, California, USA) and a properly zeroed pressure transducer. Systolic, diastolic and mean PA pressure (sPAP, dPAP and mPAP, respectively) and pulmonary capillary wedge pressure (PCWP) were measured. Pulmonary artery pulse pressure (PAPP) was calculated as systolic minus diastolic PA pressure. All haemodynamic pressure measurements were made at end-expiration. Cardiac output (CO) was calculated using thermodilution (average of three measurements) and indexed to body surface area (BSA) to calculate cardiac index (CI). Haemodynamic assessment also included RV stroke volume index (RV-SVI=CI/HR), total pulmonary vascular resistance (tPVR=mPAP/CO), total pulmonary vascular resistance index (tPVRI=mPAP/CI), and PA compliance (CPA=RV-SVI/PAPP).

Pressure measurements at rest were repeated using a high-fidelity solid-state micromanometer-tipped catheter with either a custom 6F dual-sensor unit or a 3.5F single-sensor unit (Millar Instruments, Houston, Texas, USA), operating at 1 kHz. Prior to each catheterisation, the pressure readout from the solid-state sensor was calibrated using a Veri-Cal pressure transducer tester (Utah Medical Products, Midvale, Utah, USA).

### Exercise protocol and echocardiography

Subjects performed exercise on a bicycle ergometer (Medical Positioning, Kansas City, Missouri, USA) mounted on the catheterisation table. Starting from rest (0 W), the workload was gradually increased every 2–4 min by increments of 15 W until a maximum was achieved per subject exhaustion under careful supervision of a physician. PA pressure was recorded at the end of each stage of exercise. Transthoracic Doppler echocardiography (Vivid 7 or Vivid E9, GE Healthcare, Waukesha, Wisconsin, USA) was used to measure blood velocity in the RV outflow tract, as previously

described.<sup>17</sup> In addition, echocardiography was used to measure pulse wave Doppler early mitral inflow (E) velocity at the mitral valve leaflet tips, tissue Doppler early diastolic (e') velocity at the lateral mitral annulus and RV outflow tract diameter. Tracings of PA pressure, pulse wave Doppler profile of flow through the RV outflow tract, and ECG signals were synchronised using a dedicated haemodynamic analysis workstation (Cardiovascular Engineering, Norwood, Massachusetts, USA).

### Magnetic resonance imaging

Cardiac MRI was performed at Northwestern Memorial Hospital on a 1.5 T scanner (Avanto/Espre, Siemens Medical Systems, Erlangen, Germany) and at UW-Hospital, on a 3.0 T scanner (MR750, GE Healthcare). RV volume was assessed from ECG-gated, cine-balanced, steady-state, free-precession, axial images. Cycle-averaged areas were calculated for the length of the RV for 20 time frames using OsiriX Imaging Software (revision 6.5, Pixmeo, Bernex, Switzerland). Areas were then combined into a single RV volume for each time point. From the resulting RV volume waveform and BSA, end-diastolic volume index (RV-EDVI), end-systolic volume index (RV-ESVI), stroke volume index (RV-SVI=RV-EDVI–RV-ESVI) and ejection fraction (RV-EF=RV-SVI/RV-EDVI) were calculated.

### Analysis of pulmonary vascular characteristics

[Figure 1A](#) summarises data collection and analytical methods used to assess pulmonary vascular function at rest and exercise. Synchronised PA pressure (from RHC) and flow (from echocardiography) were used to calculate  $Z_0$ , which is a measure of tPVR, and  $Z_C$ , which is a measure of proximal PA stiffness.

Pulmonary vascular impedance was calculated using frequency-domain analysis as the ratio of PA pressure to flow moduli,<sup>18</sup> and normalised by BSA.  $Z_0$  was taken as the zero-frequency value of the pulmonary vascular impedance modulus, whereas  $Z_C$  was computed averaging the fourth through tenth harmonic.  $C_{PA}$  was assessed as the ratio of RV-SVI (estimated from echocardiography) to PAPP. The RC time was assessed as the product of  $C_{PA}$  and  $Z_0$ . Left atrial pressure (LAP) was estimated from echocardiography as

$$LAP = 1.9 + 1.24E/e' \quad (1)$$

as reported previously<sup>19</sup> and recently confirmed to be moderately accurate in patients with PAH.<sup>20</sup>

### Analysis of cardiac contractility and RV–PA coupling

Cycle-averaged RV pressures (from RHC) were obtained from 15 to 25 beats to eliminate variability due to breathing and analysed using custom LabVIEW routines (National Instruments, Austin, Texas, USA). RV pressure and volume waveforms were synchronised into a single pressure–volume loop ([figure 1B](#)), from which maximum isovolumic pressure ( $P_{max}$ ), stroke work (RV-SW), end-systolic elastance ( $E_{es}$ ) and arterial elastance ( $E_a$ ) were computed using a single-beat method.<sup>21</sup> Coupling efficiency was computed as  $\eta = E_{es}/E_a$ , as well as using a volume-only method (RV-SV/RV-ESV, more commonly referred to as SV/ESV) and a pressure-only method ( $P_{max}/mPAP-1$ ).<sup>1</sup>

### Statistical analysis

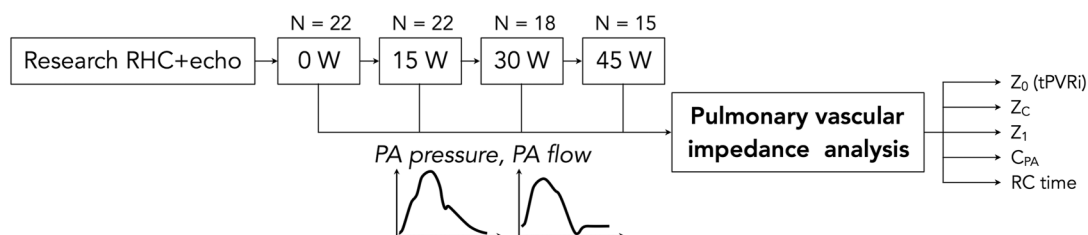
All results are presented as mean±SE, unless indicated otherwise. The comparison between haemodynamics at rest and at maximum exercise was performed using a Student's t-test. The association between haemodynamics and incremental exercise level was analysed using a linear mixed-effect model with

**Table 1** Summary of the tests performed in this study

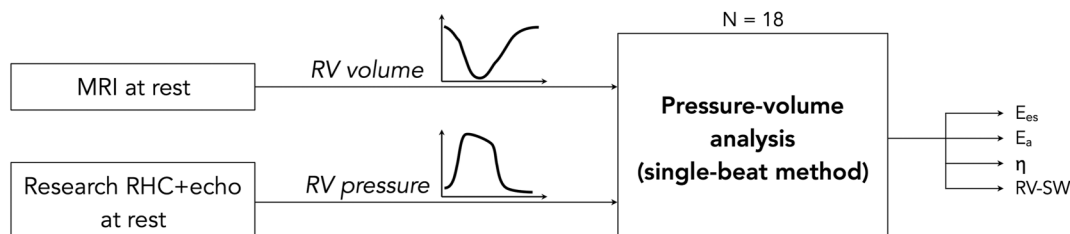
Test	n	Primary endpoints
Clinical RHC		
Rest (0 W)	26	Baseline haemodynamics
Research RHC+echo		
Rest (0 W)	22	RV pressure, PA pressure, PA flow, LAP
15 W	22	PA pressure, PA flow, LAP
30 W	18	PA pressure, PA flow, LAP
45 W	15	PA pressure, PA flow, LAP
MRI		
Rest (0 W)	18	RV volume, EDV, ESV, SV, EF, SV/ESV

RV pressure, PA pressure, PA flow and RV volume data were collected as time-dependent waveforms, averaged over multiple heartbeats.  
EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LAP, left atrial pressure; PA, pulmonary artery; RHC, right heart catheterisation; RV, right ventricle; SV, stroke volume.

### A Analysis of pulmonary vascular characteristics



### B Analysis of cardiac contractility and RV-PA coupling



**Figure 1** Data analysis flow chart. (A) Pulmonary vascular impedance analysis was performed using pulmonary arterial (PA) pressure data from right heart catheterisation (RHC) and PA flow data from echocardiography, at rest and each exercise level. Not every subject was able to exercise up to 45 W, so the group size decreased with increasing exercise intensity. A frequency-domain analysis of the pressure–flow data was performed. Endpoints included various metrics of impedance, PA compliance and resistance–compliance (RC) time. (B) Pressure–volume loop analysis was performed at rest using right ventricular (RV) pressure data from RHC and RV volume data from MRI. A single-beat method was used for this analysis. Endpoints included  $E_{es}$ ,  $E_a$  and  $\eta$ . SW, stroke work.

repeated measures. Tukey's honestly significant difference test was used as a post hoc test of significance.

Comparisons between the low- $\eta$  group ( $\eta$  below the median value) and high- $\eta$  group ( $\eta$  above the median value) were performed using an unpaired t-test. Correlations between variables were investigated using Pearson's correlation coefficient. The correlation between mPAP and CI was obtained for pooled data after performing Poon's adjustment for individual variability.<sup>22</sup>

## RESULTS

Data were obtained from a study group of 26 patients. After accounting for patients who either declined MRI or had incomplete haemodynamic data, 22 patient datasets were usable for pulmonary vascular analysis at exercise, and 18 patient datasets were usable for cardiac contractility and RV–PA coupling analysis at rest. The demographics for the 26 patients included in the study are summarised in [table 2](#). One of the subjects included in this study had severe tricuspid regurgitation.

### Effect of exercise on haemodynamics

Haemodynamic data obtained at rest and during exercise are summarised in [table 3](#). All measured and calculated parameters increased with exercise except LAP, tPVR, tPVRI and RV-SVI. During RHC, patients were able to perform exercise up to a maximum workload of  $46.7 \pm 3.5$  W, on average.

At increasing levels of exercise, increases in mean pressure (mPAP) and mean flow (CI) were correlated. When data were normalised using Poon's adjustment, the slope of the mPAP–CI curve was  $8.70$  mm Hg/(L/min/m<sup>2</sup>), and the intercept was  $18.98$  mm Hg ( $R^2=0.764$ ,  $p<0.05$ ), as reported in [figure 2](#). While  $Z_0$  did not change with exercise ([figure 3A](#)),  $Z_c$  and  $C_{PA}$  changed significantly: from resting conditions to 45 W,  $Z_c$  was nearly doubled ([figure 3B](#)), whereas  $C_{PA}$  decreased by about 21% ([figure 3C](#)). The RC time was  $1.00 \pm 0.07$  s at rest, and progressively decreased with exercise ([figure 3D](#)). Online supplementary figure S1 shows a comparison between  $Z_c$  from frequency-domain analysis (as reported in this study) and time-domain analysis.

**Table 2** Demographic data of the 26 patients included in the study group

Variable	n	All subjects Mean $\pm$ SD	All subjects range
Age (years)	26	55.7 $\pm$ 10.6	36–78
Female (%)	15	58	
BSA (m <sup>2</sup> )	26	1.90 $\pm$ 0.28	1.46–2.70
Diagnosis (%)			
IPAH	7	27	
SSc-PAH	13	50	
CTEPH	6	23	
WHO class (%)			
I	1	4	
II	11	42	
III	14	54	
PAH medications (%)			
Sildenafil	11	42	
Ambrisentan	4	15	
Treprostinil	6	23	
Tadalafil	3	12	
Bosentan	1	4	
Flolan	1	4	
No treatment*	11	42	

\*Patients who were not on pulmonary vasodilator therapy presented for RHC for the initial diagnosis of PAH.

BSA, body surface area; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; RHC, right heart catheterisation; PAH, pulmonary arterial hypertension; SSc-PAH, pulmonary arterial hypertension associated with systemic sclerosis.

### Reduced resting coupling efficiency is associated with decreased maximum exercise level

Haemodynamic coupling efficiency  $\eta$  at rest was assessed in the 18 patients who completed an MRI scan. This dataset was split in two groups, using the median of  $\eta$  as the threshold value. The maximum exercise level tolerated was compared between

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**Table 3** Haemodynamic parameters measured at rest and maximum exercise level

Variable	n	Rest	Maximum exercise	p Value
Workload	22	–	45.7±3.9	–
RHC+echo	22			
sPAP (mm Hg)		65.6±4.6	88.0±5.9*	<0.001
dPAP (mm Hg)		29.8±2.8	37.4±3.0*	0.0012
mPAP (mm Hg)		43.6±3.3	58.8±3.8*	<0.001
PAPP (mm Hg)		35.9±2.9	51.2±4.1*	<0.001
LAP (mm Hg)		11.1±0.8	12.2±1.3	0.238
HR (bpm)		80.2±2.7	111.8±2.8*	<0.001
CO (L/min)		5.86±0.34	8.41±0.80*	<0.001
CI (L/min/m <sup>2</sup> )		3.02±0.16	4.28±0.35*	<0.001
tPVR (WU)		7.91±0.74	8.17±0.83	0.668
tPVRI (WU×m <sup>2</sup> )		15.3±1.4	15.8±1.6	0.689
C <sub>PA</sub> (mL/mm Hg/m <sup>2</sup> )		1.32±0.17	0.88±0.10*	0.0019
RC time (s)		1.00±0.07	0.67±0.05*	<0.001
RV-SVI (mL/m <sup>2</sup> )		38.0±1.9	39.1±3.5	0.659
Z <sub>i</sub> index (WU×m <sup>2</sup> )		3.57±0.38	4.63±0.57*	0.0047
Z <sub>c</sub> index (WU×m <sup>2</sup> )		1.33±0.15	2.31±0.38*	0.026
MRI	18			
RV-ESVI (mL/m <sup>2</sup> )		75.8±8.9	NA†	–
RV-EDVI (mL/m <sup>2</sup> )		106.1±8.8	NA†	–
RV-EF		0.32±0.03	NA†	–
RHC+MRI	18			
RV-SW (mL/mm Hg)		2398±296	NA†	–
E <sub>es</sub> (mm Hg/mL)		0.89±0.13	NA†	–
E <sub>a</sub> (mm Hg/mL)		1.36±0.25	NA†	–
SV/ESV		0.53±0.09	NA†	–
P <sub>max</sub> /mPAP–1		1.46±0.16	NA†	–

Values are expressed as mean±SE. \*p<0.05.

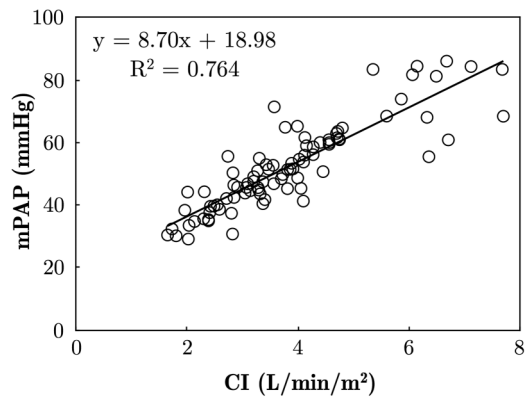
†MRI was only performed at rest so MRI-based calculations are only available at rest. CI, cardiac index; CO, cardiac output; C<sub>PA</sub>, PA compliance; dPAP, diastolic pulmonary artery pressure; EDVI, end-systolic volume index; EF, ejection fraction; ESV, end-systolic volume; ESVI, end-systolic volume index; HR, heart rate; LAP, left atrial pressure; mPAP, mean pulmonary arterial pressure; PAPP, pulmonary artery pulse pressure; P<sub>max</sub>, maximum isovolumic pressure; RC, resistance–compliance; RHC, right heart catheterisation; RV, right ventricular; sPAP, systolic pulmonary artery pressure; SV, stroke volume; SVI, stroke volume index; SW, stroke work; tPVR, total pulmonary vascular resistance; tPVRI, total pulmonary vascular resistance index.

low- $\eta$  ( $\eta=0.49\pm0.04$ ) and high- $\eta$  patients ( $\eta=1.06\pm0.15$ ). As reported in [table 4](#), patients with lower  $\eta$  had a significantly lower tolerance to exercise. In fact, low- $\eta$  patients were able to exercise up to  $40.0\pm5.6$  W, compared with a  $56.7\pm4.2$  W for the high- $\eta$  patients ( $p<0.05$ ). For comparison, the analysis was repeated for haemodynamics typically assessed in the clinical setting (HR, CI, mPAP, PAPP, Z<sub>0</sub>), and for non-invasive coupling efficiency (SV/ESV). None of the metrics considered was significantly associated with the maximum exercise level tolerated ([table 4](#)).

The slope of the mPAP–CI curve, after Poon's adjustment, was 12.10 mm Hg/(L/min/m<sup>2</sup>), and the intercept was 17.54 mm Hg for the low- $\eta$  patients ( $R^2=0.769$ ,  $p<0.05$ ). For the high- $\eta$  patients, the slope was 9.19 mm Hg/(L/min/m<sup>2</sup>), and the intercept was 13.25 mm Hg ( $R^2=0.833$ ,  $p<0.05$ ). The difference in slope between the two groups was not significant.

### Patients with reduced resting coupling efficiency exhibit increased arterial stiffness at rest and stiffening with exercise

The resting values of typically measured clinical haemodynamics and metrics of RV and PA function were compared between patients with low resting  $\eta$  and high resting  $\eta$ . This analysis



**Figure 2** Mean pulmonary arterial pressure (mPAP)–flow relationship during incremental exercise. Pooled data include all patients who completed the exercise protocol, and were adjusted for individual variability following Poon's method.<sup>22</sup> Pearce's linear correlation ( $R^2=0.764$ ) is superimposed on the individual data points. CI, cardiac index.

included subjects who completed both MRI and research RHC at rest (N=15). The two groups had similar RV contractility ( $E_{es}$ ) and no significant difference in  $E_a$  ( $1.82\pm0.47$  vs  $0.88\pm0.20$  mm Hg/mL,  $p=0.106$ ) but a lower resting  $\eta$  was associated with reduced C<sub>PA</sub> at rest ( $0.80\pm0.06$  vs  $1.88\pm0.34$  mL/mm Hg,  $p<0.05$ ), increased mPAP at rest ( $49.2\pm4.0$  vs  $36.9\pm3.5$  mm Hg,  $p<0.05$ ) and increased PAPP at rest ( $46.5\pm1.6$  vs  $27.1\pm5.0$  mm Hg,  $p<0.05$ ) ([table 5](#)). The RC time at rest was significantly decreased in low- $\eta$  patients ( $0.85\pm0.06$  vs  $1.17\pm0.13$  s,  $p<0.05$ ). Resting RV volumes were not different between low- $\eta$  and high- $\eta$ , but RV-SW at rest was significantly nearly doubled in low- $\eta$  patients ( $p<0.05$ ).

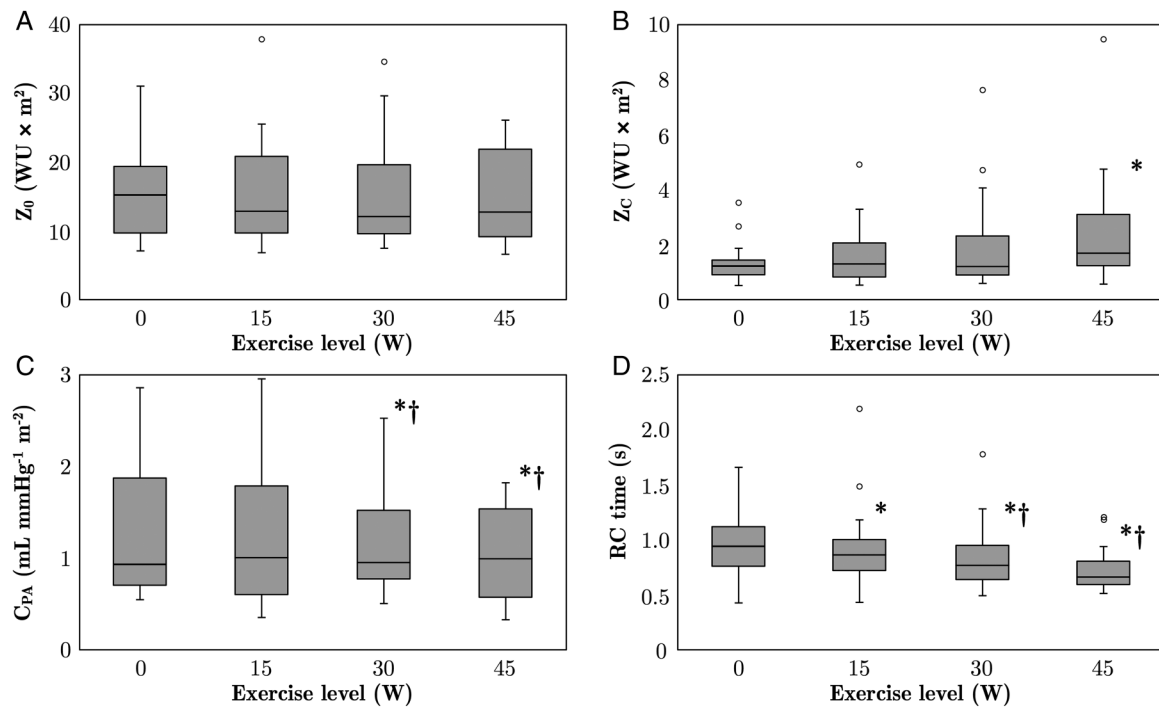
A positive linear correlation was found between  $\eta$  and C<sub>PA</sub> at rest ( $R^2=0.733$ ,  $p<0.05$ ). In addition,  $\eta$  at rest was negatively correlated with the change in C<sub>PA</sub> between 0 and 30 W ( $R^2=0.646$ ,  $p<0.05$ ), that is, patients with lower resting  $\eta$  experienced a smaller decrease in PA compliance with exercise.

## DISCUSSION

This study sought to investigate the effect of exercise on PA stiffness in patients with PAH as well as the association of haemodynamic coupling efficiency at rest with exercise ability. One major result was that exercise induced stiffening of pulmonary arteries with no change in vascular resistance. Also, significant associations between coupling efficiency at rest and PA stiffness and maximum exercise level tolerated were demonstrated for the first time.

This is the first study to measure pulmonary vascular impedance in patients with PAH during exercise. As a consequence, the findings of increased proximal PA stiffness, quantified by Z<sub>c</sub>, and decreased proximal and distal compliance, quantified by C<sub>PA</sub>, with exercise in patients with PAH, are novel. These results are consistent with a recent report that exercise reduces compliance in both controls and patients with CTEPH.<sup>12</sup> Since Z<sub>0</sub> was preserved in the current study, meaning that an increase in CO was associated with an increase in mPAP, PA stiffening with exercise may be the result of (1) strain-stiffening of the proximal PAs due to the increase in mPAP, (2) exercise-induced sympathetic vasoconstriction due to the increase in CO or (3) a combination of these mechanisms.

In the current study, the RC time decreased significantly with exercise and the RC time at rest was significantly lower in low- $\eta$



**Figure 3** Effect of incremental exercise on measures of right ventricular afterload. (A) Pulmonary vascular resistance ( $Z_0$ ) did not change from rest to 45 W exercise, likely reflecting that in patients with pulmonary arterial hypertension the pulmonary vasculature is already fully recruited and distended at rest. (B) Characteristic impedance ( $Z_c$ ) increased significantly from rest to 45 W. The exercise-induced increase in  $Z_c$  is consistent with arterial strain-stiffening and vasoconstriction mechanisms, also observed in healthy subjects at incremental exercise.<sup>12</sup> (C) Pulmonary arterial (PA) compliance ( $C_{PA}$ , normalised by body surface area) progressively decreased with exercise, consistent with the increase in  $Z_c$ . (D) The resistance–compliance (RC) characteristic time progressively decreased from rest to 45 W exercise. The resting RC time is consistent with observations in healthy controls.<sup>12</sup> The values obtained in this study are generally larger than in other studies in which pulmonary vascular resistance (PVR) instead of total PVR was used to calculate the RC time.<sup>23–26</sup> Data at the four exercise levels were obtained from 22 subjects (0 and 15 W), 18 subjects (30 W) and 15 subjects (45 W). \* $p < 0.05$ , compared with rest (0 W); † $p < 0.05$ , compared with 15 W.

**Table 4** Association of basic haemodynamics and coupling efficiency with maximum exercise level tolerated

Variable	$W_{max}$ (W)			p Value
	Median	Below median	Above median	
HR (bpm)	80.0	51.0±4.6	42.7±5.6	0.284
CI (L/min/m <sup>2</sup> )	3.05	43.8±6.0	49.1±4.6	0.491
mPAP (mm Hg)	38.8	45.0±5.2	47.7±5.7	0.726
PAPP (mm Hg)	41.0	49.6±4.9	42.0±5.8	0.327
$Z_0$ (WU×m <sup>2</sup> )	6.93	50.0±4.6	42.3±6.0	0.316
$\eta$	0.68	40.0±5.6	56.7±4.2*	0.029
SV/ESV	0.40	46.7±5.8	50.0±5.6	0.685

$W_{max}$  values are expressed as mean±SE. \* $p < 0.05$ .

Data for basic haemodynamics (HR, CI, mPAP, PAPP,  $Z_0$ ) include all patients who completed the research RHC (N=22); data for coupling efficiency (both  $\eta$  and SV/ESV) include all patients who completed the resting MRI (N=18).

CI, cardiac index; ESV, end-systolic volume; HR, heart rate; mPAP, mean pulmonary arterial pressure; PAPP, pulmonary artery pulse pressure; RHC, right heart catheterisation; SV, stroke volume;  $W_{max}$ , maximum exercise level tolerated.

patients. The RC time is approximately constant in a wide range of conditions, both in healthy controls and PAH subjects.<sup>23–26</sup> Based on the assumption of a constant RC time, earlier reports postulated a limited contribution of proximal PA stiffness to pulmonary vascular compliance.<sup>27</sup> However, considering the current results as well as other reports that the RC time constant indeed may not always be constant,<sup>12 26 28 29</sup> the role of proximal PA stiffening in PAH progression deserves further investigation, in particular under stress conditions.

The other major finding of the current study was the associations of coupling efficiency at rest with maximum exercise level, resting  $C_{PA}$ , and  $C_{PA}$  decrease during exercise. Reduced coupling efficiency has been documented in patients with PAH.<sup>14 15</sup> The prognostic value of resting coupling efficiency has been demonstrated.<sup>1</sup> The current study further suggests that high resting  $\eta$  predicts the ability to accommodate an increase in CO during exercise. In fact, high- $\eta$  patients with PAH have better (ie, higher)  $C_{PA}$  at rest than low- $\eta$  patients, and during exercise they can reduce  $C_{PA}$  to a greater extent. These results suggest that patients who had PAH with more efficient haemodynamic coupling also have a greater pulmonary vascular reserve, which can be used to haemodynamic advantage when CO increases, resulting in improved tolerance to exercise compared with low- $\eta$  patients. These findings are consistent with the comparison between exercise-induced  $C_{PA}$  reduction in patients with CTEPH and healthy controls.<sup>12</sup> In contrast with basic haemodynamics typically assessed clinically, resting coupling efficiency showed a significant association with exercise tolerance. This result indicates that the main reason why patients with PAH become progressively unable to tolerate exercise is the decline in the efficiency in the haemodynamic interaction between ventricle and vasculature, rather than either ventricular or vascular function impairment alone. Assessing resting  $\eta$  from MRI and RHC data may have an important clinical value. Simultaneous MRI and invasive RV pressure recordings is an attractive approach, although not yet clinically viable.<sup>30</sup>

The separation between high- $\eta$  and low- $\eta$  patients with PAH revealed a number of significant differences between the two groups, which may be analogous to differences between healthy

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**Table 5** Comparison of resting haemodynamics and RV and PA function between patients with low resting coupling efficiency (below median value) and patients with high resting coupling efficiency (above median value)

Variable	Low resting coupling efficiency (N=8)	High resting coupling efficiency (N=7)	p Value
HR (bpm)	75.8±4.4	78.3±4.0	0.679
mPAP (mm Hg)	49.2±4.0	36.9±3.5*	0.040
PAPP (mm Hg)	46.5±1.6	27.1±5.0*	0.002
CI (L/min/m <sup>2</sup> )	2.81±0.28	3.21±0.31	0.362
Z <sub>0</sub> (WU×m <sup>2</sup> )	9.17±1.07	6.30±1.07	0.083
Z <sub>1</sub> (WU×m <sup>2</sup> )	4.60±0.50	2.74±0.74	0.052
Z <sub>c</sub> (WU×m <sup>2</sup> )	0.65±0.11	0.59±0.06	0.648
C <sub>PA</sub> (mL/mm Hg/m <sup>2</sup> )	0.80±0.06	1.88±0.34*	0.005
RC time (s)	0.85±0.06	1.17±0.13*	0.039
RV-ESVI (mL/m <sup>2</sup> )	90.9±7.2	73.2±16.7	0.327
RV-EDVI (mL/m <sup>2</sup> )	122.0±7.9	103.2±15.3	0.277
RV-EF	0.25±0.04	0.33±0.05	0.230
RV-SW (mL×mm Hg)	3206±451	1759±238*	0.018
E <sub>es</sub> (mm Hg/mL)	0.87±0.25	0.88±0.15	0.975
E <sub>a</sub> (mm Hg/mL)	1.82±0.47	0.88±0.20	0.106
SV/ESV	0.37±0.08	0.52±0.10	0.218
P <sub>max</sub> /mPAP-1	1.53±0.28	1.45±0.24	0.837

Values are expressed as mean±SE. \*p<0.05.

CI, cardiac index; C<sub>PA</sub>, PA compliance; E<sub>a</sub>, effective arterial elastance, EDVI, end-systolic volume index; E<sub>es</sub>, end-systolic elastance; EF, ejection fraction; ESV, end-systolic volume; ESVI, end-systolic volume index; HR, heart rate; mPAP, mean pulmonary arterial pressure; PAPP, pulmonary artery pulse pressure; P<sub>max</sub>, maximum isovolumic pressure; RC, resistance-compliance; RV, right ventricular; SV, stroke volume; SW, stroke work.

subjects and patients with PAH. For instance, the association between reduced  $\eta$  and limited exercise capacity has been observed previously in a comparison between healthy subjects and patients with PAH.<sup>16</sup> Also, the mPAP–CI curve was about 32% steeper for patients with low- $\eta$  compared with high- $\eta$  in our study, although this difference was not significant, which is consistent with an increase in mPAP–CI slope in patients with pulmonary vascular disease compared with those without.<sup>10 12</sup>

The comprehensive approach to evaluation of cardiopulmonary performance used in this study (RHC and echocardiography during exercise) is viable for research, but it is unlikely to be used clinically. The clinical significance of this study is that pulmonary vascular haemodynamic reserve is an important contributor to exercise intolerance in PAH, based on the relationships found between PA stiffening and ventricular–vascular coupling efficiency at rest and during exercise. Importantly, prior to this study it was unclear whether proximal PAs stiffen during exercise independent of changes in resistance.

These results may help guide the clinical adoption of exercise testing protocols, which have been increasingly recommended to monitor PAH progression.<sup>5</sup> Exercise testing protocols generally include measures of PA resistance only (PVR, mPAP–CI curves). This study suggests that the response to exercise of proximal PAs may also need to be monitored, ideally non-invasively using stress echocardiography.

### Study limitations

The number of patients included was limited due to the complex, invasive protocol; therefore, the clinical implications of these results should be confirmed in larger studies. Also, this study did not include a disease-free group. PAH was due to different causes in this study, and the size of the subtype groups

was insufficient to investigate this effect. Similarly, sex differences were not investigated. Fifteen patients were on pulmonary vasodilator treatment at the time of this study. These medications may affect cardiopulmonary function and response to exercise; however, an analysis of the data at rest and maximum exercise did not indicate any difference (data not shown).

PCWP could not be measured during exercise. Instead, PCWP was estimated using echocardiography, which may have limited accuracy. Because of the short time available at each exercise increment, the exercise echocardiography protocol was limited to the measurements required for the pulmonary vascular impedance analysis.

### CONCLUSIONS

In patients with PAH, exercise-induced stiffening of pulmonary arteries aggravates RV afterload. PA stiffening was unrelated to changes in resistance, resulting in a progressive decrease in the RC time with exercise. Patients with less efficient haemodynamic coupling at rest exhibited a reduced pulmonary vascular reserve, which likely limited the maximum exercise level tolerated. The results of this comprehensive approach to evaluating cardiopulmonary performance may shed light on mechanical mechanisms of PAH progression and exercise tolerance, which in turn may lead to better, less invasive prognostic indicators. In addition, therapeutic strategies targeting the efficiency of haemodynamic coupling may be beneficial to exercise tolerance in patients with PAH and improve quality of life.

### Key messages

#### What is already known on this subject?

Right ventricular afterload, including pulmonary artery (PA) stiffness, and haemodynamic coupling are major determinants of outcome in patients with pulmonary arterial hypertension. Inability to exercise is also a critical factor, but the association of haemodynamic coupling with PA stiffness and maximum exercise level tolerated has not been investigated.

#### What might this study add?

In patients with pulmonary arterial hypertension, physical exercise exacerbated right ventricular afterload via pulmonary artery stiffening and sustained vascular resistance, which decreased the time constant of the pulmonary circulation. Poorer haemodynamic coupling was associated with reduced pulmonary vascular reserve, which may limit the ability to exercise.

#### How might this impact on clinical practice?

Assessment of haemodynamic coupling and vascular stiffness at exercise provides a more comprehensive evaluation of cardiopulmonary performance in pulmonary arterial hypertension, which furthers our understanding of the impact of pulmonary artery (PA) stiffening on right ventricular (RV) function. This new knowledge may lead to less invasive correlates of RV–PA uncoupling that will permit easy translation to clinical practice.

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**Heart**

## Reduced haemodynamic coupling and exercise are associated with vascular stiffening in pulmonary arterial hypertension

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