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ORIGINAL RESEARCH

Pulmonary Vascular and Right Ventricular Reserve in Patients With Normalized Resting Hemodynamics After Pulmonary Endarterectomy

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***Background*—**Patients with normalized mean pulmonary artery pressure (mPAP) after pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH) do not always regain normal exercise capacity. We evaluated right ventricular function, its interaction with both pulsatile and resistive afterload, and the effect of sildenafil during exercise in these patients.

***Methods and Results*—**Fourteen healthy controls, 15 CTEPH patients, and 7 patients with normalized resting mPAP (≤25 mm Hg) post-PEA underwent cardiopulmonary exercise testing, followed by cardiac magnetic resonance imaging with simultaneous invasive mPAP measurement during incremental supine cycling exercise. Peak oxygen consumption and peak heart rate were significantly reduced in post-PEA and CTEPH patients compared to controls. The mPAP–cardiac output slope was steeper in post-PEA patients than in controls and similar to CTEPH. Relative to controls, resting right ventricular ejection fraction was reduced in CTEPH, but not in post-PEA patients. In contrast, peak exercise right ventricular ejection fraction was reduced both in post-PEA and CTEPH patients. Exercise led to reduction of pulmonary arterial compliance in all groups. Nevertheless, resting pulmonary arterial compliance values in CTEPH and post-PEA patients were even lower than those in controls at peak exercise. In post-PEA patients, sildenafil did not affect resting hemodynamics nor right ventricular function, but decreased the mPAP/cardiac output slope and increased peak exercise right ventricular ejection fraction.

***Conclusions*—**Exercise intolerance in post-PEA patients is explained by abnormal pulmonary vascular reserve and chronotropic incompetence. The mPAP/cardiac output slope and pulmonary arterial compliance are sensitive measures demonstrating abnormal resistive and pulsatile pulmonary vascular function in post-PEA patients. These abnormalities are partially attenuated with sildenafil. **(*J Am Heart Assoc*. 2015;4:e001602 doi: 10.1161/JAHA.114.001602)**

Key Words: cardiac magnetic resonance imaging • chronic thromboembolic pulmonary hypertension • exercise • pulmonary arterial compliance • pulmonary vascular resistance • right ventricle

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious complication of pulmonary embolism, occurring in 0.1% to 4% of patients surviving an episode of acute pulmonary embolism.[1,2] Currently, pulmonary endarterectomy (PEA) is the only potentially curative treatment option resulting in improved functional status, hemodynamics, and overall survival.[3,4] Despite normalization of resting mean pulmonary artery pressures (mPAP) and pulmonary vascular resistance (PVR) after PEA,[5,6] abnormal increases in right ventricular (RV) afterload may be apparent during exercise and may explain the reduced exercise capacity that persists in many patients.[7]

Although RV afterload is often described as PVR, a more complete description is provided by incorporating measures of both resistive and pulsatile load. Pulmonary arterial compliance (C_{PA}) represents the distensibility of the pulmonary circulation, whereas PVR is the ratio of mean pressure to mean flow. It has been suggested that a reduction in C_{PA} during exercise is the strongest predictor of exercise limitation in post-PEA patients and indicative of an abnormal pulmonary vascular response to exercise.[7] However, the consequence of an increase in RV afterload during exercise on RV contractile reserve has not been quantified in post-PEA patients, despite RV function being the main predictor of

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outcome and exercise capacity in PH, irrespective of any change in PVR.[8] Recently, we validated a novel cardiac magnetic resonance (CMR) imaging technique that enables accurate and reproducible quantification of biventricular volumes during uninterrupted strenuous exercise and continued breathing.[9] This represents the ideal tool to investigate subtle RV dysfunction that may only become evident under the hemodynamic stress of exercise.[10]

The aim of this study was to evaluate RV afterload and RV function during exercise in patients with normalized resting mPAP after PEA. We compared post-PEA patients with healthy controls and CTEPH patients with the hypothesis that differences in pulmonary vascular and RV function would be more appreciable during exercise and may be associated with exercise intolerance in post-PEA patients. Furthermore, we sought to assess whether the relationship between PVR and C_{PA} remains constant during exercise in the different study populations and whether C_{PA} is a better predictor of exercise capacity than PVR or right ventricular ejection fraction (RVEF). Finally, we evaluated the effects of a single oral dose of the pulmonary vasodilator sildenafil on exercise hemodynamics and RV function in the post-PEA patients.

Methods

Subjects

Fourteen healthy subjects volunteered to participate after responding to local advertisements. All subjects were (1) healthy; (2) had no history of cardiovascular disease, symptoms, or risk factors; and (3) had a normal ECG and transthoracic echocardiogram. Given the constraints of recruiting healthy subjects for an invasive study protocol, we did not attempt to match age and gender in control subjects with the CTEPH and post-PEA patients. However, where appropriate, we included an analysis of the 7 oldest controls and 7 youngest CTEPH patients such that age and gender in the 3 comparison groups were similar.

The CTEPH group consisted of 15 consecutive patients with documented CTEPH who were referred to our institution for further investigation regarding suitability for PEA. Diagnosis of CTEPH was established in all patients by ventilation/perfusion scan, pulmonary angiography, and right heart catheterization in accordance with contemporary guidelines.[11] None of the patients were on medical therapy with a pulmonary vasodilator.

The group of post-PEA patients consisted of 7 patients in whom mPAP normalized (≤25 mm Hg) measured at least 6 months after PEA. Six of the post-PEA patients were also included in the CTEPH group prior to surgery. Patients with resting mPAP >25 mm Hg or pulmonary capillary wedge pressure (PCWP) >15 mm Hg after surgery were excluded.

The study protocol conformed to the Declaration of Helsinki and was approved by the local ethics committee. All patients provided informed consent.

Study Design

First, cardiopulmonary exercise testing was performed on an upright cycle ergometer (ER900 and Oxycon Alpha, Jaeger, Germany) using a continuous ramp protocol until exhaustion. Breath-by-breath analysis provided measures of oxygen consumption at peak exercise (VO_2 peak), maximal power output in watts (P_{max}), and the minute ventilation–carbon dioxide production relationship (VE/VCO_2 slope).

Twenty-four hours later, all subjects underwent exercise CMR with simultaneous invasive pressure measurement. Prior to exercise, a 7-Fr pulmonary artery catheter was inserted in the internal jugular vein and guided under fluoroscopy or pressure curve monitoring to the proximal right main pulmonary artery. A 20-gauge arterial catheter was placed in the radial artery. In the CMR suite, these catheters were attached to CMR-compatible pressure transducers that were connected to a PowerLab recording system (AD Instruments, Oxford, United Kingdom).

Patients underwent exercise CMR at rest and at 25%, 50%, and 66% of maximal power output in watts determined during the previous cardiopulmonary exercise testing. We have previously demonstrated that 66% of the maximal upright exercise power (in watts) corresponded to the maximal sustainable exercise intensity in a supine position.[9] Thus, these workloads will subsequently be referred to as rest, low-, moderate-, and peak-intensity exercise. During the exercise CMR protocol, pulmonary and systemic arterial pressures were continuously recorded by the pulmonary and radial artery catheters and analyzed off-line using LabChart v6.1.1 (AD Instruments). All pressure measurements were averaged over 10 consecutive cardiac cycles during unrestricted respiration.[12] In the post-PEA patients, exercise CMR was repeated 30 to 60 minutes after administration of a single oral dose of sildenafil. The same absolute workload was used during both the baseline and postsildenafil exercise evaluation.

CMR Equipment, Image Acquisition, and Analysis

Biventricular volumes were measured during supine cycling exercise using a real-time CMR method that we previously described in detail and have validated against invasive standards.[9] In brief, subjects performed supine exercise within the CMR bore using a cycle ergometer with adjustable electronic resistance (Lode, Groningen, The Netherlands). Images were acquired with a Philips Achieva 1.5 T CMR with a 5-element phased-array coil (Philips Medical Systems, Best, The Netherlands).

Using an in-house-developed software program (RightVol, Leuven, Belgium), LV and RV endocardial contours were manually traced on a stack of short-axis image slices with simultaneous reference to the horizontal long-axis plane, thus enabling the analyzers (G.C. and A.L.G.) to confirm the position of the atrioventricular plane. End-diastolic and end-systolic volumes (EDV and ESV) were calculated by a summation of disks. Stroke volume (SV) was measured as the difference between EDV and ESV. Cardiac output (CO) was measured as the product of SV and heart rate, while ejection fraction (EF) was calculated as SV/EDV. Total pulmonary resistance (tPVR) was defined as the ratio of mPAP to CO and total systemic vascular resistance as the ratio of mean systemic arterial pressure to CO. C_{PA} was calculated as the ratio of RVSV to pulmonary arterial pulse pressure. The time constant of the pulmonary circulation (RC time) was calculated as the product of tPVR (in mm Hg·s·mL^{-1}) and C_{PA}.

Statistics

Data were analyzed using IBM SPSS statistics 22 software. Descriptive data for continuous variables are presented as means±SD or as medians (25% and 75% percentile) when appropriate. Comparisons between groups were performed using 1way ANOVA and Bonferroni post-hoc test for multiple comparisons. The effects of sildenafil in the post-PEA group were assessed using a paired-samples *t* test. The biventricular volume response from rest to peak-intensity exercise was evaluated using a repeated-measures ANOVA with exercise intensity as within-subject effect and group (post-PEA patients versus controls versus CTEPH) as a between-subject effect. Individual mPAP-flow slope coefficients were derived from serial measurements of mPAP and CO during incremental exercise using linear regression analysis.[12] Differences in mPAP/CO slope coefficients between groups were compared using 1-way ANOVA.

Pearson correlation coefficients were used to assess the univariate relationships between C_{PA} and VO_2 peak. To demonstrate the relationship between tPVR and C_{PA}, a nonlinear curve was fitted according to the formula y=cte/x (hyperbola formula). The impact of exercise on the tPVR–C_{PA} relation was evaluated by a linear mixed model that included tPVR, condition (rest versus exercise), and their interaction as fixed effects. To account for the repeated nature of the data, an unstructured variance–covariance matrix was included in the model. Both C_{PA} and tPVR were log-transformed to obtain a linear association between the 2. To increase the certainty of correct assumptions given the number of tests performed in our experiments, a *P*-value <0.01 was considered significant.

Results

Clinical Characteristics

The clinical characteristics and cardiopulmonary exercise testing data are depicted in Table 1. CTEPH and post-PEA patients were older than the controls, whereas gender proportions were similar. Some of the CTEPH and post-PEA patients were receiving negative chronotropic medications that were withheld for 24 hours prior to testing. Nevertheless, peak heart rate was significantly lower in post-PEA and CTEPH patients compared to controls. Post-PEA patients were in lower New York Heart Association functional class than CTEPH patients, although their VO_2 peak was similar.

Central Hemodynamics and Biventricular Function

As demonstrated in Table 2, resting tPVR was lower in post-PEA patients than in CTEPH patients ($P<0.0001$) and tended to be higher than in controls ($P=0.059$). Resting C_{PA} was higher in controls than in post-PEA and CTEPH patients ($P<0.0001$) and correlated strongly with VO_2 peak (Figure 1A). Resting RVESV was larger, and RVEF lower in CTEPH patients relative to both controls and post-PEA patients ($P<0.0001$), the latter 2 groups having similar values. LVEDV and LVESV were smaller in CTEPH and post-PEA patients than in controls, whereas LVEF was similar in all groups.

As illustrated in Figure 2A, the slope of mPAP/CO plots was steeper in post-PEA patients relative to controls, but similar to CTEPH patients (4.7 [4.2–10.3] versus 1.0 [0.8–1.7] versus 6.7 [5.2–10.1] mm Hg/L per minute, respectively; $P<0.0001$). From rest to peak exercise, tPVR did not change significantly in healthy controls ($P=0.064$) and CTEPH patients ($P=0.960$), whereas it tended to increase in post-PEA patients ($P=0.018$; Figure 2B). In contrast, C_{PA} decreased in all subjects during exercise. The absolute exercise-induced reduction in C_{PA} correlated highly with VO_2 peak (Figure 1B). Overall, the exercise reduction in C_{PA} was greatest in controls (Figure 4A). However, peak exercise C_{PA} in control subjects still remained higher than the resting values in CTEPH and post-PEA patients ($P<0.01$). These significant differences in C_{PA} and mPAP/CO slope were preserved when the oldest control subjects were considered for an age-matched comparison (Table 3).

From rest to peak exercise, RVESV decreased in controls and increased in CTEPH and post-PEA patients ($P<0.0001$ for interaction between within-subject changes during exercise versus between-subject groups; Figure 2C). Similarly, RVEDV decreased in controls, whereas it increased in CTEPH and post-PEA patients ($P<0.0001$ for interaction). Therefore, contrary to resting measures, peak exercise RVEF was reduced both in CTEPH and in post-PEA patients relative to

Table 1. Clinical Characteristics

	Healthy Controls (n=14)	CTEPH (n=15)	Post-PEA (n=7)	*P* Value
Clinical				
Age, y	36±15	62±13*	62±12*	<0.0001
BSA, m^2	1.88±0.21	1.94±0.28	1.99±0.14	0.553
BMI, kg/m^2	24.2±5.2	28.2±5.4	29.8±5.6	0.048
Sex, M (F)	11 (3)	10 (5)	6 (1)	0.583
NYHA class				
I	–	1	3	0.040
II	–	4	3	0.448
III	–	10	1	0.022
IV	–	0	0	
Medications				
Pulmonary vasodilators	0	0	0	
Negative chronotropic drugs		5	4	0.290
β-Blockers	–	4	2	0.926
Amiodarone	–	1	2	0.163
Digoxin	–	1	1	0.563
Biochemical				
NTproBNP, ng/L	28 (5–41)	399 (232–1271)*	118 (66–343)	<0.0001
CPET				
VO_2 peak, $mL \cdot kg^{-1} \cdot min^{-1}$	34.4±8.0	13.0±3.3*	15.0±4.3*	<0.0001
VO_2 peak, % of predicted	94±24	55±17*	63±15*	<0.0001
Peak HR, bpm	174±18	126±19*	114±23*	<0.0001
Peak power, W	215±67	77±29*	91±37*	<0.0001
VE/VCO_2	0.026±0.005	0.043±0.006*	0.035±0.005	<0.0001

BMI indicates body mass index; BSA, body surface area; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; F, female; HR, heart rate; M, male; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; post-PEA, patients after pulmonary endarterectomy; VE/VCO_2, minute ventilation-carbon dioxide production relationship; VO_2, oxygen consumption; W, watts.

*$P<0.01$ vs healthy controls.

Data presented as mean±SD or median (25% and 75% percentile).

controls (both $P<0.0001$; Figure 2D). The changes in RVEF at rest and at near-maximal intensity exercise for all individual subjects are plotted in Figure 3. Between the patient groups, post-PEA patients had higher RVEF and smaller RVESV throughout exercise, respectively, than CTEPH patients (Table 2).

At rest, the RC time (product of tPVR and C_{PA}) was lower in patients with CTEPH than in healthy controls ($P=0.005$; Figure 4B). At peak exercise, the RC time was similar between the different groups. Figure 5A depicts the inverse relationship between tPVR and C_{PA}, both at rest and peak exercise. At peak exercise, the tPVR–C_{PA} relation is shifted downward and to the left. Figure 5B shows a plot of log(tPVR) against log (C_{PA}) for all groups. The lines show the best fits for rest (green line) and peak exercise (red line). Linear mixed-model analysis showed a significant difference in the slopes of the lines ($P=0.002$). Thus, for each given value of tPVR, C_{PA} was lower during peak exercise than at rest and the difference was most profound in those subjects with the lowest tPVR and highest C_{PA} at rest (ie, healthy subjects).

Acute Effect of Sildenafil on Exercise Hemodynamics and RV Function in Post-PEA Patients

The administration of sildenafil did not affect hemodynamics or RV function in the post-PEA patients when measured at rest (Table 4). In contrast, exercise measures improved significantly following sildenafil. Sildenafil decreased the mPAP/CO slope and peak exercise tPVR (Figure 6), whereas peak exercise C_{PA} increased ($P=0.010$). This was associated with a reduction in RVESV and an increase in RVEF at peak

Table 2. Biventricular Function and Hemodynamics During Exercise CMR With Simultaneous Invasive Pressure Measurement

	Controls (n=14)	CTEPH (n=15)	Post-PEA (n=7)	*P* Value
HR, bpm				
Rest	66±7	78±12	82±14	0.004
Peak ex	149±11	120±20*	108±26*	<0.0001
mPAP, mm Hg				
Rest	10±3	44±10*	21±5*†	<0.0001
Peak ex	22±8	65±11*	38±4*†	<0.0001
PA pulse pressure, mm Hg				
Rest	10±3	52±11*	25±6*†	<0.0001
Peak ex	24±11	78±16*	48±10*†	<0.0001
PCWP, mm Hg				
Rest	–	10±3	9±2	0.902
Peak ex	–	–	–	–
mSAP, mm Hg				
Rest	93±14	93±13	84±17	0.351
Peak ex	114±15	115±22	97±13	0.302
LVEDV, mL				
Rest	162±44	112±27*	117±18	0.001
Peak ex	156±43	102±26*	129±20	0.001
RVEDV, mL				
Rest	161±47	177±46	128±18	0.059
Peak ex	148±43	200±43*	157±26	0.005
LVESV, mL				
Rest	68±24	44±16*	42±13	0.003
Peak ex	48±14	36±15	46±11	0.083
RVESV, mL				
Rest	69±26	114±37*	56±12†	<0.0001
Peak ex	42±15	132±35*	70±15†	<0.0001
LVSV, mL				
Rest	94±24	68±17*	75±8	0.002
Peak ex	108±32	66±21*	83±12	<0.0001
RVSV, mL				
Rest	92±24	63±15*	73±8	<0.0001
Peak ex	107±30	68±20*	87±14	0.001
LVEF, %				
Rest	58.8±5.7	61.3±9.1	64.5±6.2	0.258
Peak ex	69.2±4.4	64.5±12.5	64.8±4.6	0.316
RVEF, %				
Rest	58.3±5.5	36.2±6.4*	57.0±4.5†	<0.0001
Peak ex	72.2±5.0	34.0±8.2*	55.9±4.2*†	<0.0001
CO, L/min				
Rest	6.2±1.9	5.1±1.6	6.1±1.4	0.200
Peak ex	16.2±5.3	7.9±0.7*	9.5±3.8*	<0.0001

Continued

Table 2. Continued

	Controls (n=14)	CTEPH (n=15)	Post-PEA (n=7)	*P* Value
CI, L/min per m^2				
Rest	3.3±0.8	2.6±0.6	3.1±0.7	0.059
Peak ex	8.5±2.3	4.0±1.0*	4.7±1.7*	<0.0001
PVR, dynes·s·cm^{-5}				
Rest	–	584±182	160±67†	<0.0001
Peak ex	–	–	–	–
tPVR, dynes·s·cm^{-5}				
Rest	134±49	728±191*	287±105†	<0.0001
Peak ex	114±49	724±258*	364±124†	<0.0001
tPVR, wood units				
Rest	1.7±0.6	9.1±2.4*	3.6±1.2†	<0.0001
Peak ex	1.4±0.6	9.1±3.2*	4.6±1.6†	<0.0001
tSVR, dynes·s·cm^{-5}				
Rest	1310±477	1580±558	1160±374	0.148
Peak ex	617±200	1274±472*	922±409	0.001
C_{PA}, mL/mm Hg				
Rest	9.7±3.1	1.3±0.4*	3.1±0.6*	<0.0001
Peak ex	5.1±1.8	0.9±0.3*	1.9±0.3*	<0.0001
RC time, s				
Rest	0.89±0.25	0.65±0.11*	0.64±0.22	0.002
Peak ex	0.41±0.17	0.44±0.10	0.51±0.22	0.358

CI indicates cardiac index; CMR, cardiac magnetic resonance; CO, cardiac output; C_{PA}, pulmonary arterial compliance; CTEPH, chronic thromboembolic pulmonary hypertension; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; ex, exercise; HR, heart rate; LV, left ventricle; mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure; post-PEA, patients after pulmonary endarterectomy; PVR, pulmonary vascular resistance; RC, time constant; RV, right ventricle; SV, stroke volume; tPVR, total pulmonary vascular resistance; tSVR, total systemic vascular resistance.

*$P<0.01$ vs healthy controls.

†$P<0.01$ vs CTEPH.

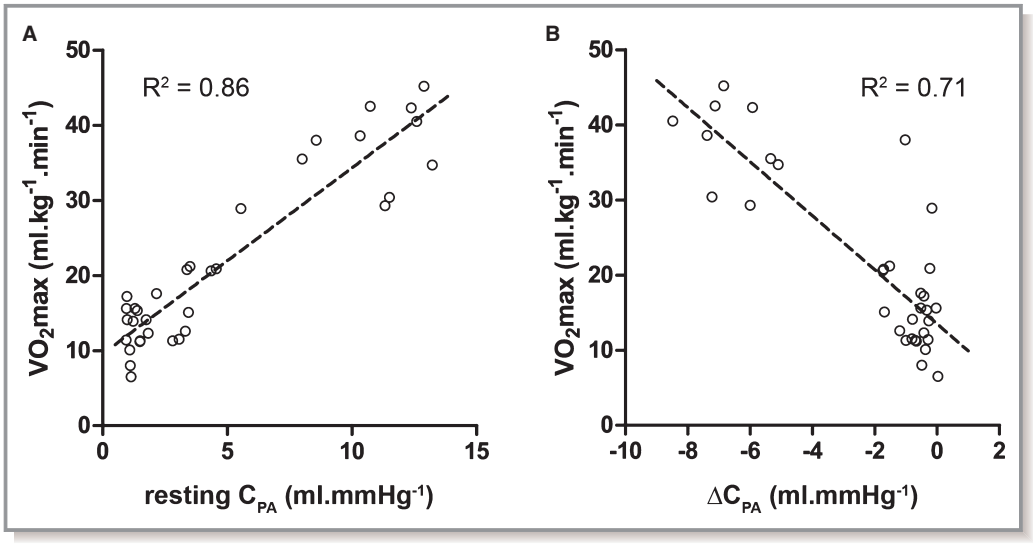

Figure 1. Correlation between (A) peak oxygen consumption (VO_2 peak) and pulmonary arterial compliance (C_{PA}) at rest and (B) between VO_2 peak and the change in C_{PA} from rest to peak exercise (ΔC_{PA}).

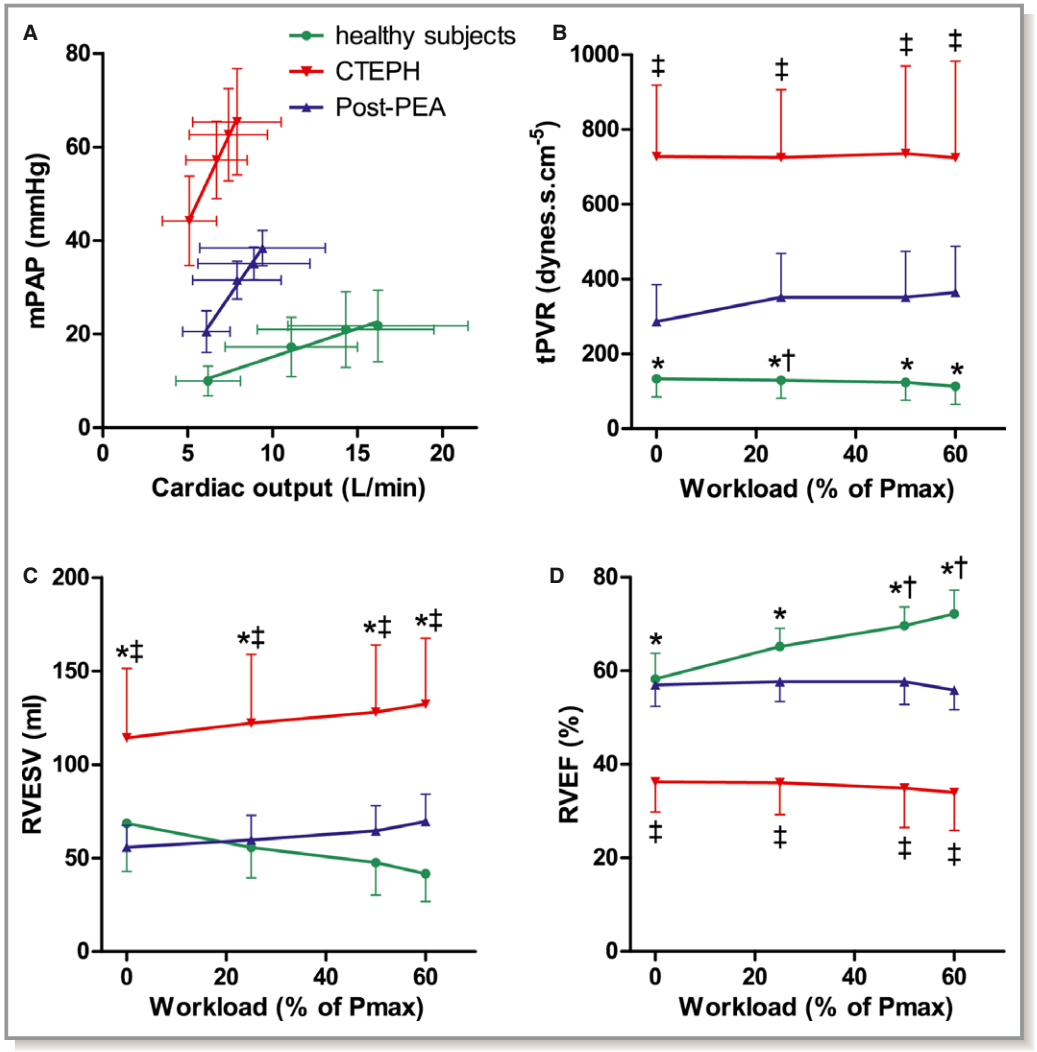

Figure 2. Pulmonary vascular and right ventricular reserve in healthy subjects, patients with chronic thromboembolic pulmonary hypertension (CTEPH), and patients after pulmonary endarterectomy (post-PEA). A, Relationship between mean pulmonary artery pressure (mPAP) and cardiac output during incremental exercise. Changes in (B) total pulmonary vascular resistance (tPVR), (C) right ventricular end-systolic volume (RVESV), and (D) RV ejection fraction (RVEF) from rest to peak exercise. At each exercise intensity, **P*<0.01 for difference between healthy controls and CTEPH patients, †*P*<0.01 for difference between healthy controls and post-PEA patients, and ‡*P*<0.01 for difference between CTEPH and post-PEA patients.

exercise (*P*<0.01), whereas peak exercise LVESV and LVEF were unchanged. The RC time remained constant before and after sildenafil (Figure 7).

Discussion

The present study documents significant exercise intolerance in post-PEA subjects despite a decrease of mPAP to near-normal values and normal RVEF at rest. Using novel exercise CMR combined with invasive PAP measures, this reduction in exercise capacity can be explained by (1) increased RV afterload during exercise, and (2) significant chronotropic impairment. Despite increased resistive and pulsatile RV afterload, post-PEA patients have an increase in SV from rest to peak exercise, in contrast to CTEPH. However, SV augmentation during exercise in post-PEA patients is associated with an increase in RV volumes as opposed to the observed reduction in healthy subjects. These hemodynamic abnormalities during exercise were partially reversible after administration of a single oral dose of sildenafil. Thus, exercise measures provide critical insights into the pathophysiological mechanisms underpinning exercise intolerance in post-PEA patients and raise clinical questions as to whether there may be a role for pulmonary vasodilators in further improving pulmonary vascular physiology and functional capacity.

Table 3. Comparison of Biventricular Function and Hemodynamics Between Age-Matched Controls, CTEPH, and Post-PEA Patients

	Controls (n=7)	CTEPH (n=7)	Post-PEA (n=7)	*P* Value
Age, y	48±11	58±16	62±12	0.14
HR, bpm				
Rest	64±6	80±17	82±14	0.030
Peak ex	148±12	112±23	108±26*	0.004
mPAP, mm Hg				
Rest	11±3	45±11*	21±5†	<0.0001
Peak ex	25±8	61±13*	38±4†	<0.0001
PA pulse pressure, mm Hg				
Rest	12±3	52±12*	25±6†	<0.0001
Peak ex	30±10	76±16*	48±10†	<0.0001
mSAP, mm Hg				
Rest	103±12	90±15	84±17	0.068
Peak ex	123±11	108±20	97±13	0.265
LVEDV, mL				
Rest	162±41	120±30	117±18	0.024
Peak ex	153±37	111±28	129±20	0.046
RVEDV, mL				
Rest	160±47	192±48	128±18	0.027
Peak ex	145±36	211±42*	157±26	0.006
LVESV, mL				
Rest	64±20	47±17	42±13	0.056
Peak ex	44±12	37±14	46±11	0.429
RVESV, mL				
Rest	65±23	124±45*	56±12†	0.001
Peak ex	37±13	138±43*	70±15†	<0.0001
LVSV, mL				
Rest	98±25	74±14	75±8	0.026
Peak ex	110±27	74±18	83±12	0.010
RVSV, mL				
Rest	94±26	68±12	73±8	0.020
Peak ex	108±26	73±16	87±14	0.011
LVEF, %				
Rest	60.8±5.7	62.0±5.5	64.5±6.2	0.487
Peak ex	71.6±3.5	67.1±6.5	64.8±4.6	0.060
RVEF, %				
Rest	59.7±6.2	36.6±8.2*	57.0±4.5†	<0.0001
Peak ex	75.0±4.8	35.7±9.8*	55.9±4.2*†	<0.0001
CO, L/min				
Rest	6.2±1.8	5.7±1.7	6.1±1.4	0.840
Peak ex	16.4±5.0	8.3±2.7*	9.5±3.8	0.002

Continued

Table 3. Continued

	Controls (n=7)	CTEPH (n=7)	Post-PEA (n=7)	*P* Value
CI, L/min per m^2				
Rest	3.2±0.8	2.8±0.8	3.1±0.7	0.624
Peak ex	8.5±2.4	4.1±1.3*	4.7±1.7*	0.001
tPVR, dynes·s·cm^{-5}				
Rest	157±57	669±230*	287±105†	<0.0001
Peak ex	127±57	651±289*	364±124†	<0.0001
tPVR, wood units				
Rest	2.0±0.7	8.4±2.9*	3.6±1.2†	<0.0001
Peak ex	1.6±0.7	8.1±3.6*	4.6±1.6†	<0.0001
tSVR, dynes·s·cm^{-5}				
Rest	1475±572	1327±284	1160±374	0.405
Peak ex	660±228	1109±283	922±409	0.102
C_{PA}, mL/mm Hg				
Rest	8.5±3.6	1.4±0.4*	3.1±0.6*	<0.0001
Peak ex	3.9±0.9	1.0±0.3*	1.9±0.3*	<0.0001
RC time, s				
Rest	0.88±0.18	0.64±0.14	0.64±0.22	0.031
Peak ex	0.37±0.20	0.45±0.12	0.51±0.22	0.358

CI indicates cardiac index; CO, cardiac output; C_{PA}, pulmonary arterial compliance; CTEPH, chronic thromboembolic pulmonary hypertension; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; ex, exercise; HR, heart rate; LV, left ventricle; mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; PA, pulmonary arterial; post-PEA, patients after pulmonary endarterectomy; RC, time constant; RV, right ventricle; SV, stroke volume; tPVR, total pulmonary vascular resistance; tSVR, total systemic vascular resistance.

*P<0.01 vs healthy controls.

†P<0.01 vs CTEPH.

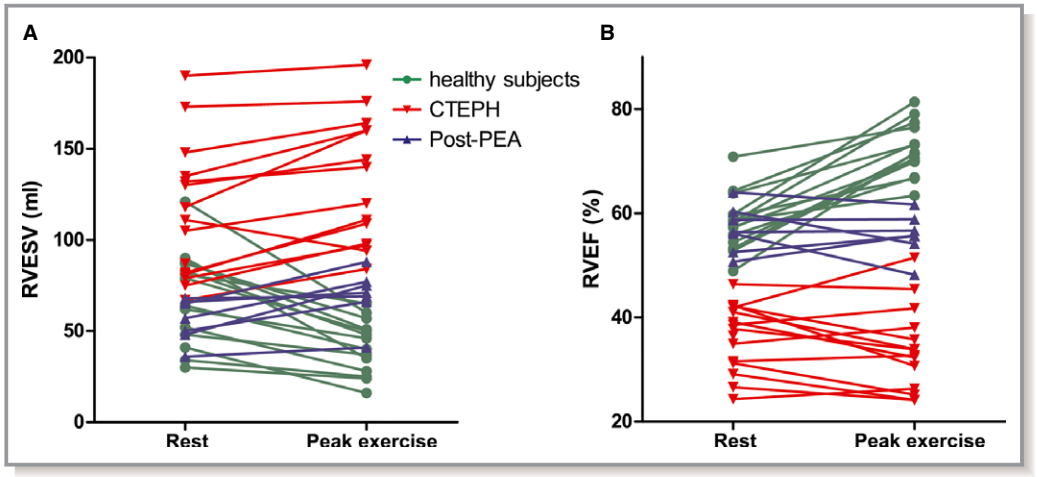

Figure 3. Individual changes in right ventricular end-systolic volume (RVESV) and ejection fraction (RVEF) from rest to peak exercise. A, RVESV decreases from rest to peak exercise in all healthy subjects (green lines and symbols), whereas an increase is seen in post-PEA patients (blue lines) and CTEPH patients (red lines). B, All healthy subjects demonstrate an increase in RVEF during exercise as opposed to CTEPH and post-PEA patients. CTEPH indicates chronic thromboembolic pulmonary hypertension; post-PEA, patients after pulmonary endarterectomy.

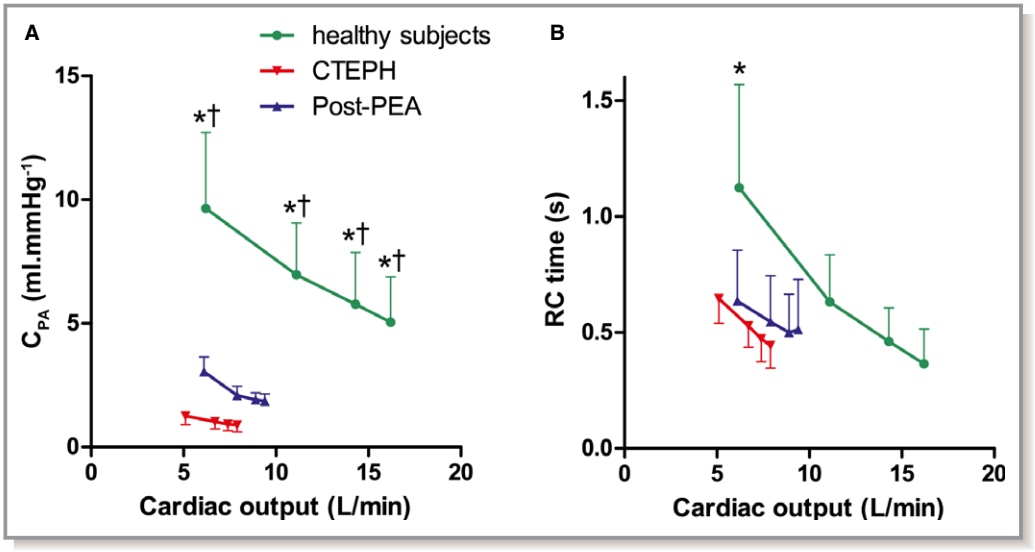

Figure 4. Effect of exercise on pulmonary arterial compliance (C_{PA}). A, C_{PA} decreases in all groups with increasing cardiac output. Although C_{PA} decreases during exercise even in healthy subjects, C_{PA} is significantly lower at rest and throughout exercise in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and patients after pulmonary endarterectomy (post-PEA). B, Mean resistance-compliance product (RC time) for each subgroup relative to cardiac output. The RC time is lower at rest in CTEPH patients and post-PEA patients relative to healthy subjects and decreases in all groups during exercise. At each exercise intensity, *P<0.01 for difference between healthy controls and CTEPH and †P<0.01 for difference between healthy controls and post-PEA patients.

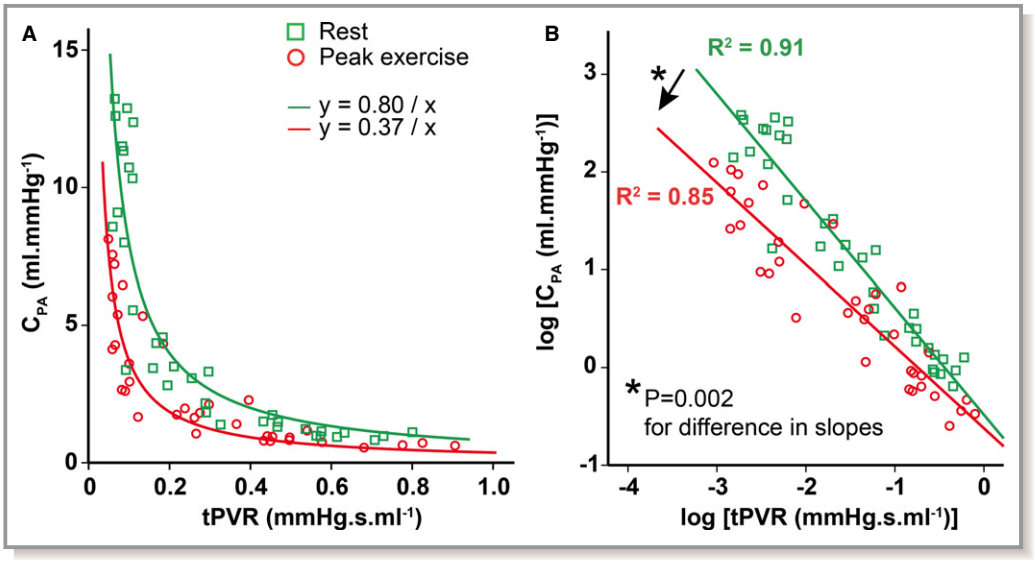

Figure 5. Effect of exercise on the pulmonary vascular resistance-compliance relationship (tPVR–C_{PA}). A, tPVR–C_{PA} for each subject is plotted at rest and at peak exercise (66% of maximal power during cardiopulmonary exercise testing). B, Plot of log(tPVR) against log(C_{PA}) for healthy subjects, patients with chronic thromboembolic pulmonary hypertension (CTEPH), and patients after pulmonary endarterectomy (post-PEA). Best-fit lines are shown for rest (green line, R^2=0.91) and peak exercise (red line, R^2=0.85). Linear mixed-model analysis showed a significant difference in the slopes of the lines as depicted by the arrow (*P=0.002).

Exercise Evaluation Facilitates Recognition of Subtle Pulmonary Vascular Disease

For patients with CTEPH, PEA is the "gold standard" procedure and currently the only potentially "curative" treatment option.[13] After successful PEA, most patients have a sustained improvement of functional status, hemodynamics, RV function,[3] and overall survival.[4] Nevertheless, despite a normalization of mPAP and/or PVR, exercise capacity does not return to normal in a significant

Table 4. Comparison of Biventricular Function and Hemodynamics Before and After Sildenafil in Post-PEA Patients

	Post-PEA (n=7)		
	Baseline	Sildenafil	*P* Value
HR, bpm			
Rest	82±14	86±9	0.759
Peak ex	108±26	112±23	0.929
mPAP, mm Hg			
Rest	21±5	18±4	0.117
Peak ex	38±4	30±2	<0.0001
PA pulse pressure, mm Hg			
Rest	25±6	21±5	0.035
Peak ex	48±10	42±10	<0.0001
mSAP, mm Hg			
Rest	84±17	86±8	0.383
Peak ex	97±13	105±9	0.010
LVEDV, mL			
Rest	117±18	113±17	0.671
Peak ex	129±20	130±22	0.804
RVEDV, mL			
Rest	128±18	130±23	0.301
Peak ex	157±26	146±29	0.051
LVESV, mL			
Rest	42±13	39±10	0.913
Peak ex	46±11	40±11	0.177
RVESV, mL			
Rest	56±12	57±14	0.055
Peak ex	70±15	56±12	0.007
LVSV, mL			
Rest	75±8	74±11	0.784
Peak ex	83±12	90±13	0.153
RVSV, mL			
Rest	73±8	73±14	0.617
Peak ex	87±14	90±18	0.390
LVEF, %			
Rest	64.5±6.2	65.7±6.0	0.971
Peak ex	64.8±4.6	69.9±4.2	0.099
RVEF, %			
Rest	57.0±4.5	56.4±5.8	0.577
Peak ex	55.9±4.2	61.9±1.2	0.007
CO, L/min			
Rest	6.1±1.4	6.4±1.6	0.500
Peak ex	9.5±0.9	10.3±3.5	0.391

Continued

Table 4. Continued

	Post-PEA (n=7)		
	Baseline	Sildenafil	*P* Value
CI, L/min per m^2			
Rest	3.1±0.7	3.1±0.8	0.529
Peak ex	4.7±1.7	5.1±1.6	0.398
tPVR, dynes·s·cm^{-5}			
Rest	287±105	247±90	0.086
Peak ex	364±124	252±84	0.003
tSVR, dynes·s·cm^{-5}			
Rest	1160±374	1166±383	0.270
Peak ex	922±409	887±295	0.024
C_{PA}, mL/mm Hg			
Rest	3.1±0.6	3.6±1.2	0.128
Peak ex	1.9±0.3	2.2±0.5	0.010
RC time, s			
Rest	0.64±0.22	0.63±0.21	0.700
Peak ex	0.51±0.22	0.41±0.14	0.039

CI indicates cardiac index; CO, cardiac output; C_{PA}, pulmonary arterial compliance; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; ex, exercise; HR, heart rate; LV, left ventricle; mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; PA, pulmonary arterial; post-PEA, patients after pulmonary endarterectomy; RC, time constant; RV, right ventricle; SV, stroke volume; tPVR, total pulmonary vascular resistance; tSVR, total systemic vascular resistance.

proportion of patients after PEA.[5,6] This may be explained by a degree of residual thrombi in subsegmental pulmonary arteries and/or distal arteriopathy, thereby decreasing pulmonary vascular reserve although resting PVR is in the normal range. In these patients, the detection of abnormal pulmonary vascular reserve during exercise is important as it provides pathophysiological insights into the mechanisms limiting exercise capacity after PEA.[7] It also provides measures that can be used to assess whether early surgical and pharmacological interventions may improve exercise hemodynamics, functional capacity, and prognosis.

Despite the rationale for exercise evaluation, the definition of a clear-cut threshold for a normal pulmonary vascular response to exercise has been a source of debate, given that healthy individuals frequently exceed the proposed cut-off value of mPAP=30 mm Hg during exercise, especially trained athletes and those aged >50 years.[14–16] Indeed, due to the near linear relationship between mPAP and CO, highly trained athletes can attain considerably higher mPAP at peak exercise compared to nonathletes, as they are able to achieve higher COs.[15,16] Thus, pulmonary artery pressures should be considered relative to workload and/or CO. Currently, based on multiple invasive and noninvasive studies, it has been suggested that a mPAP/CO slope of >3 mm Hg/L per minute represents an abnormal pulmonary vascular response to exercise.[12] Accordingly, the pulmonary vascular response of the post-PEA patients in our study can be considered abnormal, despite their resting mPAP and PVR being below the threshold of persistent postoperative PH.[17]

A second mechanism that contributed substantially to the impaired CO augmentation and exercise intolerance in the post-PEA patients was an attenuated heart rate response. The observed chronotropic incompetence may have been compounded by the recent use of negative chronotropic medications in some patients but may also reflect the disease process. In patients with pulmonary arterial hypertension, chronotropic incompetence has been associated with RV myocardial β-adrenoreceptor downregulation in proportion to the physiologic severity of disease.[18,19] However, the degree of chronotropic incompetence did not improve following PEA despite a clear reduction of resting pulmonary vascular hemodynamics. It is possible that the remaining chronotropic impairment in post-PEA patients reflects the persisting RV pressure overload and functional impairment during exercise. Another putative mechanism may be that chronic right atrial stretch due to longstanding RV pressure overload prior to PEA-induced electrical and structural remodeling of the right atrium and sinus node,[20,21] which might not be fully reversible after PEA.

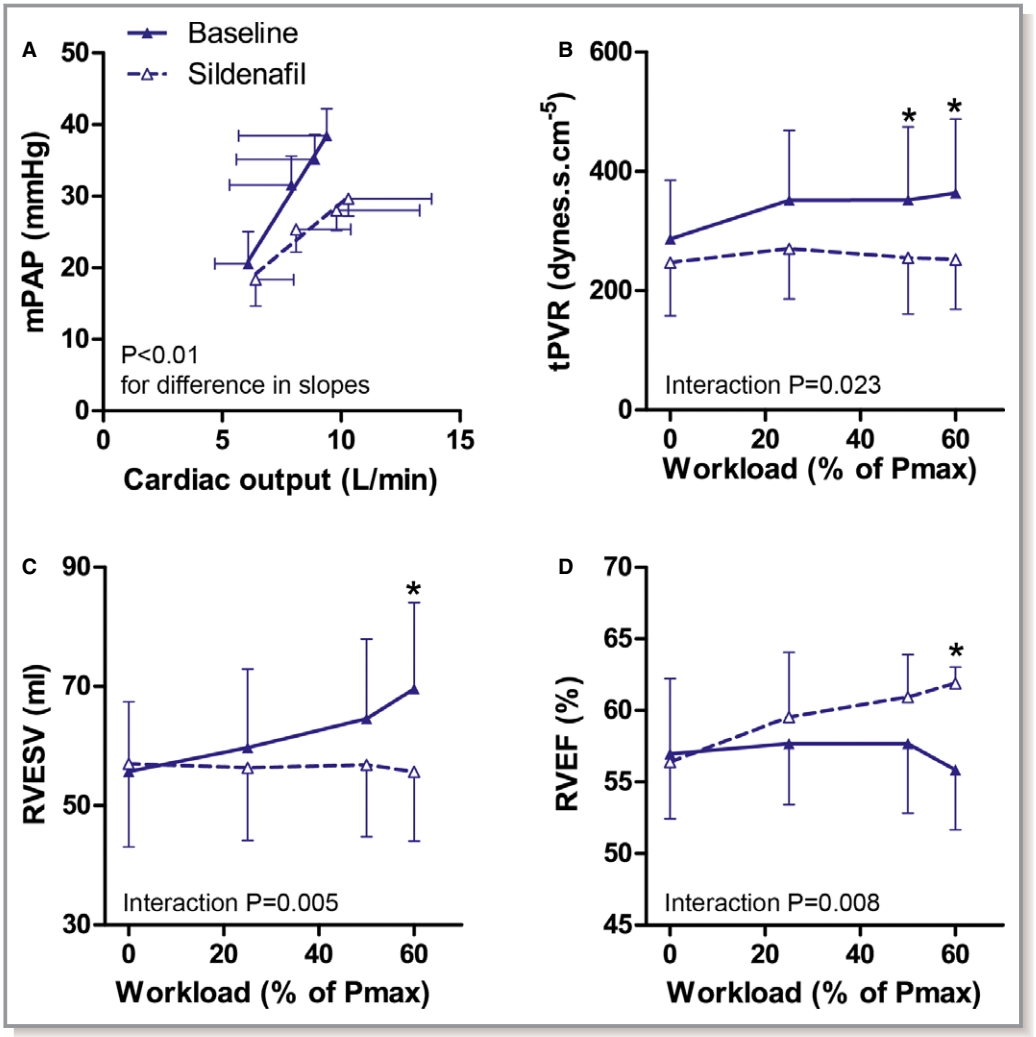

Figure 6. Sildenafil increases pulmonary vascular and right ventricular reserve in patients after pulmonary endarterectomy (post-PEA). A, Relationship between mean pulmonary artery pressure (mPAP) and cardiac output (CO) before and after sildenafil. Changes in (B) total pulmonary vascular resistance (tPVR), (C) right ventricular end-systolic volume (RVESV), and (D) RV ejection fraction (RVEF) from rest to peak exercise. Values are shown for the interaction between sildenafil administration and exercise intensity as within-subjects effects. At each exercise intensity, **P*<0.01 for the difference between baseline and sildenafil.

Response of the Right Ventricle to Increased Afterload During Exercise

In this study, we also evaluated the impact of an abnormal exercise-induced increase in RV afterload on RV performance itself. This is important because RV function is the primary determinant of exercise capacity and outcome in PH, irrespective of changes in PVR.[8] When evaluated at rest, CO and RV performance were indistinguishable between post-PEA patients and controls, indicating that RV contractility was sufficiently preserved to maintain optimal coupling between the RV and the pulmonary circulation at rest. Imaging during exercise enables quantification of RV contractile reserve as the change in RVEF or SV from rest to maximal exercise.[22]

We observed that the post-PEA patients had a similar increase in SV from rest to peak exercise compared to healthy subjects, suggesting that RV contractile reserve was preserved. However, the mechanisms by which the RV generated the increased SV during exercise were significantly different between post-PEA patients and healthy subjects. In healthy subjects, SV augmentation is mainly achieved by a decrease in ESV, reflecting contractile reserve, whereas EDV remains relatively unchanged or decreases slightly at near-maximal exercise due to reduced filling times.[9] In contrast, the exercise-induced increase in SV in the post-PEA patients was achieved by concomitant increases in RV EDV and ESV. Thus, RVEF did not increase during exercise (Figures 2 and 3). This suggests that, although global RV performance is preserved, the RV becomes more dependent upon

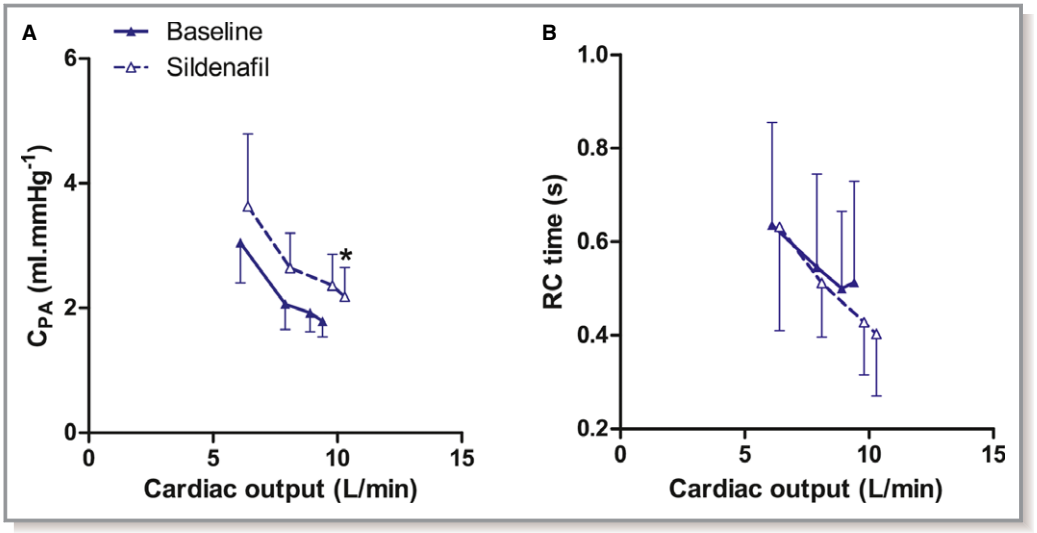

Figure 7. Effect of sildenafil on pulmonary arterial compliance (C_{PA}) and mean resistance–compliance product (RC time) in patients after pulmonary endarterectomy. Changes in (A) C_{PA} and (B) RC time from rest to peak exercise before and after sildenafil. At each exercise intensity, **P*=0.01 for the difference between baseline and sildenafil.

Frank–Starling recoil to meet its output requirements in post-PEA patients. A recent study in patients with long-term pulmonary arterial hypertension and a clinically stable profile demonstrated that preserved CO may mask RV failure progression, and that changes in RV volumes may be sensitive parameters to predict ultimate deterioration, even at the time of clinical stability.[23] Therefore, evaluation of RV volumes and RVEF during exercise may be clinically important to detect early RV failure development.

Pulmonary Arterial Compliance Decreases During Exercise

Resistance does not adequately describe afterload when considering the pulsatile nature of the circulation. C_{PA} represents the ability of the pulmonary circulation to stretch in response to an applied pressure, and its inverse relationship with PVR means that small increases in PVR are associated with large decreases in C_{PA}, thereby making it an important marker of early pulmonary vascular disease.[24,25] Previous studies have demonstrated that the product of C_{PA} and PVR remains constant over time and suggested that a pathologic hemodynamic response to exercise is characterized by an increase in PVR together with a decrease in C_{PA}.[7,24] However, Tedford et al showed that the coupling between C_{PA} and PVR can change during exercise in patients with left-sided heart disease because of an increase in PCWP.[26] More recently, MacKenzie Ross et al showed that it is not only an increase in PCWP that can change the product of PVR and C_{PA}, but also that proximal CTEPH and PEA surgery are able to alter this relationship.[27]

In this study, we extend these findings by demonstrating that in healthy subjects, both tPVR and C_{PA} decrease during exercise. Therefore, the product of tPVR and C_{PA} does not remain fixed from rest to exercise in healthy subjects, but C_{PA} becomes lower for any given value of tPVR (Figures 4 and 5). The reduction of C_{PA} during exercise can be explained by passive distention of the pulmonary vascular vessels with increasing CO such that the vessels become stiffer (less compliant) as their diameter increases.[28] Exercise-associated sympathetic nervous system stimulation may be another mechanism to explain the decrease in C_{PA} during exercise in healthy subjects.[29,30] Indeed, it has been shown in normal dogs that sympathetic nervous system activation may increase characteristic impedance without significantly changing PVR.[30]

Intriguingly, the reduction in RC time during exercise was most profound in the control subjects, indicating that the relative increase in pulsatile load during exercise is greater in healthy individuals than in CTEPH and post-PEA patients. However, the greater reduction in RC time is a simple consequence of the fact that the compliance and resistance of the pulmonary vasculature were far better in healthy subjects at baseline. As explained above, at maximal exercise there is a convergence whereby the pulmonary circulation became “stiff”. In healthy subjects this occurred at very high COs when the vascular resistance was low, whereas in the CTEPH patients this point was reached with only very modest increase in CO and no reduction in PVR. Another mechanism that may have contributed to the proportionately greater reduction in C_{PA} in healthy controls may be the higher exercise-induced increase in heart rate. It has been shown for

both the systemic and the pulmonary circulation that an increase in heart rate is associated with a reduction in arterial compliance.[31,32] Thus, the change in C_{PA} during exercise per se cannot be used to distinguish between a normal and abnormal pulmonary vascular reserve. Nevertheless, whereas controls demonstrated the greatest reductions in C_{PA} during exercise, peak exercise values still remained higher than the resting values in CTEPH and post-PEA patients. Moreover, despite the relatively greater contribution of pulsatile load, the total RV load remained much lower in the healthy subjects as reflected by the lower peak exercise mPAP and tPVR.

Effects of Sildenafil on Exercise Hemodynamics in Post-PEA Patients

Our study extends current understanding of the pathophysiology of exercise intolerance in post-PEA patients with potential therapeutic implications. Skoro-Sajer et al demonstrated that up to 77.7% of CTEPH patients have some degree of pulmonary vascular reactivity during nitric oxide administration prior to PEA, indicating distal vasoconstriction, and that a decrease in mPAP >10% predicts immediate postoperative PVR decrease and better long-term outcome after PEA.[33] Our current results indicate that even after successful PEA some residual pulmonary vasoconstriction remains present, which can be partially reversed after administration of a pulmonary vasodilator. Importantly, the beneficial effects of sildenafil were measurable during exercise, but not at rest. It is yet to be determined whether the short-term improvements in exercise hemodynamics and RV function following sildenafil administration translate to improved clinical outcomes with long-term pulmonary vasodilators. Our study provides a rationale for investigating the efficacy of post-PEA pulmonary vasodilator therapy and suggests that exercise metrics should be included in the outcome measures.

Limitations

This is the largest series to include invasive pulmonary artery measures in CTEPH patients and healthy controls. Recruiting healthy controls for such a study is challenging and is seldom attempted. In this context, we felt that the very small but potentially serious potential for adverse events in performing PCWP measurements during exercise was unacceptable, so PCWP was only measured at rest in the CTEPH and post-PEA patients and no PCWP measurements were obtained in controls. Therefore, we could not assess the degree to which PCWP influenced the changes in C_{PA} and PVR observed during exercise. Although PCWP can increase to as high as 30 mm Hg in exercising athletes,[34] increases in PCWP only become significant at very high COs,[35] whereas we observed a reduction in C_{PA} even during low-intensity exercise.

Secondly, given the constraints of recruiting healthy subjects for an invasive study protocol and the low community prevalence of CTEPH, we did not attempt to match the control, CTEPH, and post-PEA cohorts for age. Nevertheless, the RV pressure–volume response to exercise remained significantly different between control subjects and post-PEA patients when only the oldest controls, matched for age, were considered in a subanalysis (Table 3). Also, the small sample size may have increased the probability of type II statistical errors due to lack of power, whereas the use of multiple comparisons increased the chances of type I errors. We have addressed the latter concern by increasing the significance level required for rejecting the null hypothesis to $P<0.01$. The established accuracy of exercise CMR measures enabled us to evaluate meaningful hemodynamic differences within this modest-sized cohort with high levels of statistical significance. Lastly, the use of a fluid-filled catheter to calculate pulse pressure can be problematic due to catheter ringing, particularly in healthy subjects where small changes in pulse pressure can lead to significant differences in compliance.[36] High-fidelity micromanometer-tipped catheters would have provided more precise pressure measures but are unable to be used in the CMR environment.

Conclusions

Despite normalized hemodynamics at rest, post-PEA patients have significant exercise intolerance, which is explained by abnormal pulmonary vascular reserve and chronotropic incompetence. The mPAP/CO slope and C_{PA} are sensitive measures of resistive and pulsatile pulmonary vascular function, which correlate strongly with exercise capacity. Sildenafil partially attenuates abnormalities in post-PEA hemodynamics, providing rationale for studies investigating the efficacy of chronic pulmonary vasodilator therapy in this group.

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Disclosures

Claessen, La Gerche, Dymarkowski, Claus, and Heidbuchel have none. Delcroix served as investigator, speaker, consultant, or steering committee member for Actelion, Bayer, Eli Lilly, GlaxoSmithKline, Pfizer, and United Therapeutics, and received research grants from Actelion, GlaxoSmithKline, and Pfizer.

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