ORIGINAL ARTICLE

Exercise pathophysiology and sildenafil effects in chronic thromboembolic pulmonary hypertension

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ABSTRACT

Objectives Symptoms in patients with chronic thromboembolic pulmonary hypertension (CTEPH) predominantly occur during exercise, while haemodynamic assessment is generally performed at rest. We hypothesised that exercise imaging of RV function would better explain exercise limitation and the acute effects of pulmonary vasodilator administration than resting measurements.

Methods Fourteen patients with CTEPH and seven healthy control subjects underwent cardiopulmonary testing to determine peak exercise oxygen consumption (VO_2peak) and ventilatory equivalent for carbon dioxide (VE/VCO_2) at the anaerobic threshold. Subsequently, cardiac MRI was performed at rest and during supine bicycle exercise with simultaneous invasive measurement of mean pulmonary arterial pressure (mPAP) before and after sildenafil.

Results During exercise, patients with CTEPH had a greater increase in the ratio of mPAP relative to cardiac output (CO) than controls (6.7 (5.1–8.7) vs 0.94 (0.86–1.8) mm Hg/L/min; p<0.001). Stroke volume index (SVi) and RVEF increased during exercise in controls, but not in patients with CTEPH (interaction p<0.001). Sildenafil decreased the mPAP/CO slope and increased SVi and RVEF in patients with CTEPH (p<0.05) but not in controls. In patients with CTEPH, RVEF reserve correlated moderately with VO_2peak (r=0.60; p=0.030) and VE/VCO_2 (r=−0.67; p=0.012). By contrast, neither VO_2peak nor VE/VCO_2 correlated with resting RVEF.

Conclusions Exercise measures of RV function explain much of the variance in the exercise capacity of patients with CTEPH while resting measures do not. Sildenafil increases SVi during exercise in patients with CTEPH, but not in healthy subjects.

INTRODUCTION

In patients with pulmonary hypertension (PH), RV function is the most important predictor of outcome.[1 2] Cardiac magnetic resonance (CMR) imaging studies have emphasised the predictive value of stroke volume index (SVi), RVEF and indexed RV end-diastolic and end-systolic volumes (EDVi and ESVi, respectively).[1] These assessments are performed while the patient is resting, but patients with PH typically develop symptoms with physical exertion. Evaluation of RV performance during exercise may better explain why some patients with PH have more impaired exercise capacity than others despite similar findings during investigations during resting.[3]

Despite this rationale for RV imaging during exercise, measurement of RV function during exercise is challenging. Recently, real-time CMR imaging has emerged as a promising technique for biventricular volume assessment during exercise with free breathing and without ECG gating.[4 5] Our group has developed a sequence for real-time CMR imaging during maximal exercise intensity and has validated its feasibility, accuracy and high reproducibility.[5] It has been demonstrated that patients with PH have an impaired SV response when cardiac imaging is performed immediately after exercise.[6 7] However, until the present day, no studies have evaluated RV performance during continuous exercise and free breathing in patients with chronic thromboembolic pulmonary hypertension (CTEPH).

Therefore, the aim of this study was to evaluate biventricular volumes with simultaneous invasive haemodynamic measurements during exercise in patients with CTEPH as compared with healthy controls. We sought to evaluate whether exercise RV performance would better explain exercise limitation than resting measures. Additionally, we investigated the mechanisms by which the pulmonary vasodilator, sildenafil, improves exercise capacity in patients with CTEPH, and whether non-invasive CMR measures of exercise RV performance are predictive of the improvement in exercise haemodynamics following administration of sildenafil.

METHODS

Subjects

Fourteen consecutive patients referred to our institution for the assessment and management of CTEPH were invited to participate in this study. All patients were recently diagnosed with CTEPH by pulmonary angiography and right heart catheterisation in accordance with contemporary guidelines.[8] None of the patients was on medical therapy with a pulmonary vasodilator. All 14 subjects volunteered to participate in the study.

A group of seven healthy control subjects volunteered to participate after responding to local advertisements. All respondents were healthy, with no history of cardiovascular disease or risk factors, and had a normal ECG and transthoracic echocardiogram.

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

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Study design

First, cardiopulmonary exercise testing (CPET) with continuous monitoring of expiratory gases was performed on an upright cycle ergometer (ER900 and Oxycon Alpha, Jaeger, Germany) using a continuous ramp protocol until exhaustion.[9] The anaerobic threshold was identified as the ventilatory equivalent for oxygen (VE/VO_2) nadir. Outcome measures included ventilatory equivalent for carbon dioxide (VE/VCO_2), VE/VO_2 and end-tidal CO_2 tension ($PETCO_2$) at the anaerobic threshold. Additionally, peak oxygen consumption (VO_2peak), maximal power output in Watts (Pmax), capillary to end-tidal CO_2 gradient ($P(c\text{-}ET)CO_2$), alveolar-arterial oxygen tension ($PA\text{-}aO_2$) difference and the ratio of dead-space to tidal volume (Vd/Vt) ratio were evaluated at maximum exercise.

Approximately 24 h later, all subjects underwent exercise CMR during simultaneous invasive pressure measurement. Before exercise, a 7 Fr pulmonary artery catheter was inserted in the internal jugular vein and guided to the proximal right main pulmonary artery under fluoroscopy, while 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, UK). Mean right atrial (RA) pressure and pulmonary and systemic arterial pressures were continuously recorded during the exercise CMR protocol and analysed off-line using LabChart V.6.1.1 (AD Instruments). All pressure measurements were averaged over 10 consecutive cardiac cycles during unrestricted respiration.[10]

Patients underwent exercise CMR at rest and at 25%, 50% and 66% of the maximal power output (Pmax) as determined during the previous CPET. We have previously demonstrated that 66% of the maximal upright exercise power (in Watts) corresponded with the maximal sustainable exercise intensity in a supine position.[5] These workloads will subsequently be referred to as rest, low-intensity, moderate-intensity and peak-intensity exercise. Subjects were then given a single oral dose of 50 mg sildenafil and were allowed to rest for 30–60 min. Exercise CMR was repeated at low, moderate and peak-intensity exercise using the same wattages as during the baseline exercise CMR.

CMR equipment, image acquisition and analysis

Biventricular volumes were measured during supine cycling exercise and free breathing using a real-time CMR method that we previously described in detail and validated against invasive standards.[5] 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 five-element phased-array coil (Philips Medical Systems, Best, The Netherlands). Figure 1 illustrates the technique in a patient with CTEPH.

Using a software program (RightVol, Leuven, Belgium) developed in-house, LV and RV endocardial contours were manually traced on short-axis images with compensation for respiratory phase and with simultaneous reference to the horizontal long axis plane, thus enabling the analysers (GC and ALG) to confirm the position of the atrio-ventricular plane, as previously described.[5] Volumes were calculated by a summation of disks and indexed for body surface area. SVi was measured as the difference between LV EDVi and LV ESVi. In accordance with previous studies, SVi was determined from LV rather than RV volumes because patients with PH frequently develop tricuspid regurgitation, particularly during exercise, which may confound

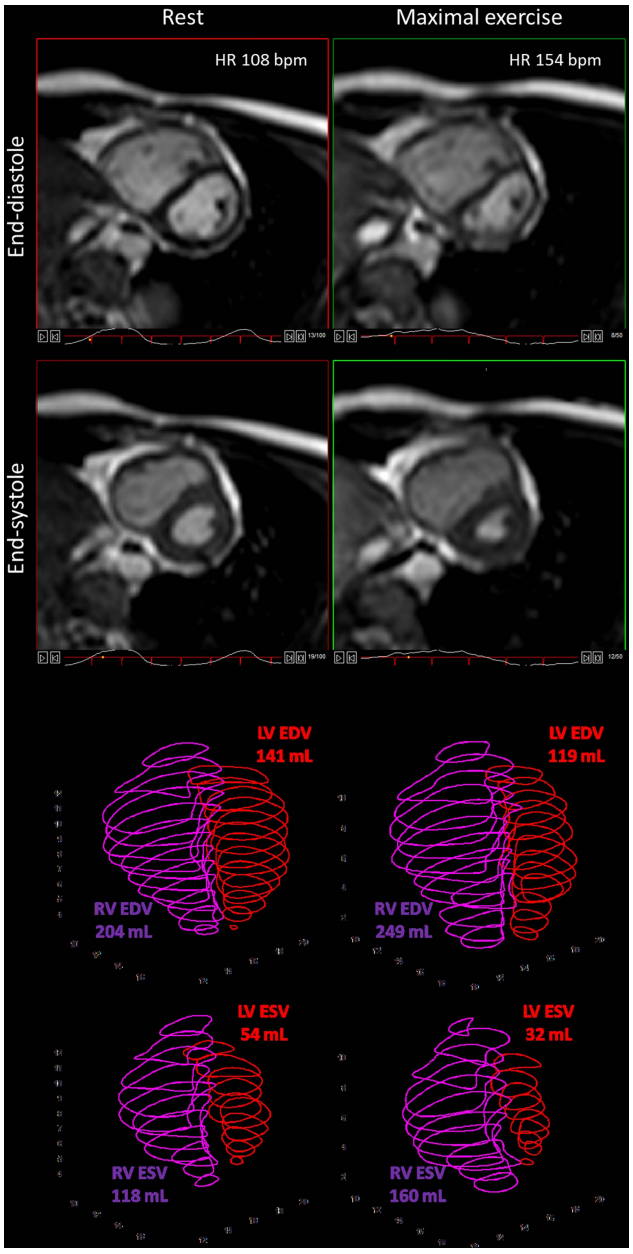

Figure 1 Illustration of biventricular volume changes during exercise in a patient with chronic thromboembolic pulmonary hypertension (CTEPH). The upper panels show a representative mid-ventricular slice at rest and during peak-intensity exercise. The lower panels show the 3D volume stack generated by the software after manual delineation of LV and RV endocardial borders at end-diastole (upper panels) and end-systole (bottom). During exercise, RV volumes become larger, whereas RV ejection remains unaltered. As a result, the LV becomes progressively underfilled and stroke volume augmentation is impaired. EDV, end-diastolic volume; ESV, end-systolic volume.

the assessment of effective RVSV.[11] Cardiac index (CI) was measured as the product of SVi and heart rate (HR). EF was calculated as (EDV−ESV)/EDV. Total pulmonary resistance (tPVR) was defined as the ratio of mean pulmonary artery pressure (mPAP) to cardiac output (CO, product of SV and HR), and total systemic vascular resistance (tSVR) was calculated as the ratio of mean systemic arterial pressure (mSAP) to CO. Exercise reserve was derived as the difference between rest and peak exercise volume or haemodynamic measures.[12]

Blood samples

At rest and during peak exercise, before and after administration of sildenafil, arterial and central venous blood samples were collected and analysed for oxygen saturation (SaO_2, $ScvO_2$), oxygen tension (PaO_2, $PcvO_2$), and carbon dioxide tension ($PaCO_2$, $PcvCO_2$) using an automated blood gas analyser (ABL 700, Radiometer; Copenhagen, Denmark). Arterial-central venous differences in oxygen content ($C(a\text{-}cv)O_2$) and VO_2 at rest and at peak exercise were calculated according to the Fick principle from CMR-derived CO, arterial and central venous oxygen saturations and haemoglobin. Blood samples were further analysed for creatinine, haemoglobin and N-terminal pro-brain natriuretic peptide (NT-proBNP).

Statistical analysis

Data were analysed using IBM SPSS statistics V.22 software. Descriptive data for continuous variables are presented as means ±SEM or as medians (25% and 75%) when appropriate. Categorical data was compared using the Fisher's exact test. Comparisons between groups for continuous variables were performed using unpaired two-sample t tests or the Mann–Whitney test, as appropriate. The biventricular volume response from rest to peak-intensity exercise in patients with CTEPH versus control subjects was compared using a repeated measures analysis of variance with exercise intensity and sildenafil as within-subject effects and group (patients vs controls) as a between-subject effect. The relationships between CO and mPAP and mSAP, respectively, were determined using linear regression analysis. Analysis of group effects with repeated exercise measures was performed by comparing mean slope coefficients from individual linear regressions. Pearson correlation coefficients were used to evaluate the univariate relationships between resting and exercise measures of biventricular function and CPET parameters.

To determine the sample sizes, the following estimates were used. In a recent study using exercise CMR, we demonstrated that healthy subjects had a 12±11 increase in SVi from rest to maximal exercise.[5] According to our hypothesis, we predicted that SVi will not change (0% increase) during exercise in patients with CTEPH. Using these assumptions, a sample size of n=7 was calculated to provide 80% power in detecting impaired SVi augmentation during exercise in the CTEPH group (α=5%, 1-β=80%, n=7). A p value <0.05 was considered statistically significant.

RESULTS

The clinical characteristics of patients with CTEPH and control subjects are presented in table 1 and, as expected, measures of exercise capacity were reduced in patients with CTEPH relative to control subjects. The results of the resting and peak exercise haemodynamic and blood gas measurements before and after sildenafil administration are displayed in table 2. As expected, patients with CTEPH had higher resting mPAP and tPVR and lower SVi and CI than control subjects. These haemodynamic abnormalities became more prominent during peak exercise.

Table 1 Clinical characteristics

	Healthy controls (n=7)	CTEPH (n=14)	p Value
Age, years	51±2	61±4	0.065
Male sex, %	71	71	1.000
Weight, kg	78±7	84±5	0.535
BMI, kg/m^2	25.8±2.1	28.2±1.5	0.360
BSA, m^2	1.92±0.08	1.96±0.07	0.745
NYHA functional class, n			
I	–	1	–
II	–	4	–
III	–	9	–
IV	–	0	–
NTproBNP, ng/L	39 (37–56)	537 (239–1428)	0.001
Hb, g/dL	13.4±0.3	15.0±0.3	0.005
Creatinine, mg/dL	0.78±0.03	0.85±0.05	0.265
6MWD, m	–	359±42	–
CPET parameters			
Peak power output, W	221±27	78±8	0.001
Peak heart rate, bpm	170±7	126±6	<0.001
VO_2peak, mL/kg/min	34.4±4.3	13.2±1.1	0.002
Vd/Vt, %	26±1	45±2	<0.001
PA-aO_2, mm Hg	29±6	62±4	<0.001
P(c-ET)CO_2, mm Hg	0.33±1.2	7.4±0.8	<0.001
VE/VO_2 at AT	24.2±0.5	42.2±1.9	<0.001
VE/VCO_2 at AT	24.9±0.5	48.3±2.2	<0.001
$PETCO_2$ at AT, mm Hg	42.8±1.2	23.3±1.1	<0.001

Data presented as mean±SE or median (25% and 75% percentile); p values from Fisher's exact test, unpaired two-sample t tests or Mann–Whitney test were appropriate.
AT, anaerobic threshold; BMI, Body Mass Index; BSA, body surface area; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; Hb, haemoglobin; 6MWD, 6 min walking distance; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; P(c-ET)CO_2, capillary to end-tidal carbon dioxide gradient; PA-aO_2, alveolar-arterial oxygen tension difference; $PETCO_2$, end-tidal carbon dioxide tension; Vd/VT, ratio of dead-space to tidal volume; VE/VCO_2, ventilatory equivalent of carbon dioxide; VE/VO_2, ventilatory equivalent of oxygen; VO_2peak, peak oxygen consumption.

Biventricular function and haemodynamics during exercise in patients with CTEPH versus control subjects

The pattern of biventricular volume changes during exercise differed between patients with CTEPH and control subjects (figure 2). In control subjects, LVEDVi and RVEDVi did not change from rest to peak-intensity exercise, while LVESVi and RVESVi decreased (both p<0.01), and LVEF and RVEF increased (both p<0.01). By contrast, in patients with CTEPH, it was seen that RVEDVi and RVESVi increased with incremental exercise intensity (both p<0.001), whereas LVEDVi and LVESVi decreased (both p<0.05). Therefore, while LVEF tended to increase (p=0.094), RVEF remained unchanged during exercise in patients with CTEPH (p=0.213).

In control subjects, SVi increased during low-intensity exercise (p=0.002) and then remained unchanged during moderate and peak-intensity exercise (figure 3A). By contrast, in patients with CTEPH, SVi did not increase during exercise (p<0.001 for interaction between SVi response to exercise and group). Compared with control subjects, patients with CTEPH had a greater increase in HR per watt (1.0±0.1 vs 0.7±0.1 bpm/W; p=0.020), whereas HR reserve was significantly reduced (55±8 vs 143±12%; p<0.001), suggesting chronotropic incompetence.

As demonstrated in figure 3B, patients with CTEPH had a greater mPAP/CO slope than control subjects (6.7 (5.1–8.7) vs 0.94 (0.86–1.8) mm Hg/L/min; p<0.001). Furthermore, while tPVR tended to decrease during exercise in control subjects (p=0.107), no change in tPVR occurred in patients with CTEPH (p=0.967). By contrast, tSVR decreased in both groups during exercise (p<0.01; table 2).

Table 2 Changes in gas exchange parameters, biventricular function and haemodynamics from rest to peak exercise before and after sildenafil administration

	Controls (n=7)			CTEPH (n=14)		
	Pre-sildenafil	Post-sildenafil	p Value	Pre-sildenafil	Post-sildenafil	p Value
Heart rate, bpm						
Rest	61±3	78±4	0.002	79±3*	82±3	0.152
Peak exercise	147±4†	153±7†	0.186	122±5†*	118±5†*	0.038
LVEF, %						
Rest	60.7±2.1	65.6±2.6	0.072	61.0±2.5	63.5±2.2	0.004
Peak exercise	69.6±1.6†	73.0±1.7†	0.044	64.1±3.6	67.4±3.2†	0.006
RVEF, %						
Rest	59.1±2.3	62.5±3.3	0.268	36.2±1.8*	40.1±1.9*	<0.001
Peak exercise	73.2±1.9†	75.3±3.2†	0.436	34.8±2.2*	40.0±3.0*	0.002
SVi, mL/m^2						
Rest	53±5	50±5	0.370	35±2*	37±2*	0.036
Peak exercise	59±6	57±6	0.462	34±3*	39±3*	0.009
CI, L/min m^2						
Rest	3.1±0.3	3.7±0.2	0.019	2.7±0.2	2.9±0.2*	0.006
Peak exercise	8.7±1.1†	8.8±1.2†	0.692	4.1±0.3†*	4.5±0.2†*	0.021
mSAP, mm Hg						
Rest	101±5	91±5	0.058	94±4	83±3	0.001
Peak exercise	125±3†	118±4†	0.062	117±6†	105±5†	0.001
mPAP, mm Hg						
Rest	11±1	8±1	0.012	45±3*	38±2*	<0.001
Peak exercise	24±3†	19±1†	0.026	64±3.0†*	54±3.0†*	<0.001
RA pressure, mm Hg						
Rest	–	–		8±2	6±2	0.044
Peak exercise	–	–		19±3†	14±4†	0.017
tPVR dyne/s/cm^5						
Rest	154±23	97±11	0.012	727±53*	553±41*	<0.001
Peak exercise	126±22	95±11	0.105	688±63*	527±53*	<0.001
tSVR, dyne/s/cm^5						
Rest	1483±217	1072±108	0.012	1565±154	1227±104	<0.001
Peak exercise	661±86†	639±114†	0.641	1271±136†*	1031±109†*	0.001
tPVR/tSVR ratio						
Rest	0.11±0.01	0.09±0.01	0.094	0.48±0.03*	0.47±0.03*	0.130
Peak exercise	0.20±0.02†	0.16±0.01†	0.037	0.59±0.04†*	0.53±0.03†*	0.019
PaO_2, mm Hg						
Rest	102±7	85±6	0.078	71±6*	56±3*	0.001
Peak exercise	90±6	95±7	0.294	65±6*	56±3*	0.037
$PaCO_2$, mm Hg						
Rest	36±2	37±1	0.541	33±1	33±1*	0.529
Peak exercise	37±1	33±2†	0.053	29±1†*	31±1†	0.020
$ScvO_2$,%						
Rest	73±2	74±1	0.669	65±2*	62±2*	0.057
Peak exercise	43±6†	41±5†	0.201	38±3†	41±3†	0.083
C(a-cv)O_2, mL O_2/100 mL						
Rest	4.8±0.4	4.4±0.2	0.169	6.3±0.4*	6.0±0.3*	0.434
Peak exercise	10.8±1.0†	11.3±0.9†	0.303	11.3±0.6†	10.2±0.6†	0.003

p Values from repeated measures ANOVA for difference between pre-sildenafil and post-sildenafil, and for rest vs peak exercise; †p<0.05 for difference vs rest; *p<0.05 for difference vs healthy control subjects by unpaired two-sample t test.
ANOVA, analysis of variance; C(a-cv)O_2, arterial-central venous oxygen content difference; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; RA, right atrial pressure; $ScvO_2$, central venous oxygen tension; SVi, indexed stroke volume; tPVR, total pulmonary vascular resistance; tSVR, total systemic vascular resistance.

Correlations between RV functional reserve and CPET parameters in patients with CTEPH

No associations were found between resting RVEF or LVEF and any of the CPET parameters. By contrast, as illustrated in figure 4, RVEF reserve correlated moderately with VO_2peak (r=0.60; p=0.030) and VE/VCO_2 (r=−0.69; p=0.009). Similarly, RVEF reserve correlated moderately with VE/VO_2 (r=−0.67; p=0.012) and $PETCO_2$ (r=0.76; p=0.002), but not with P(A-a)O_2, P(c-ET)CO_2 or VD/VT (r=0.063, r=−0.097 and r=−0.279, respectively).

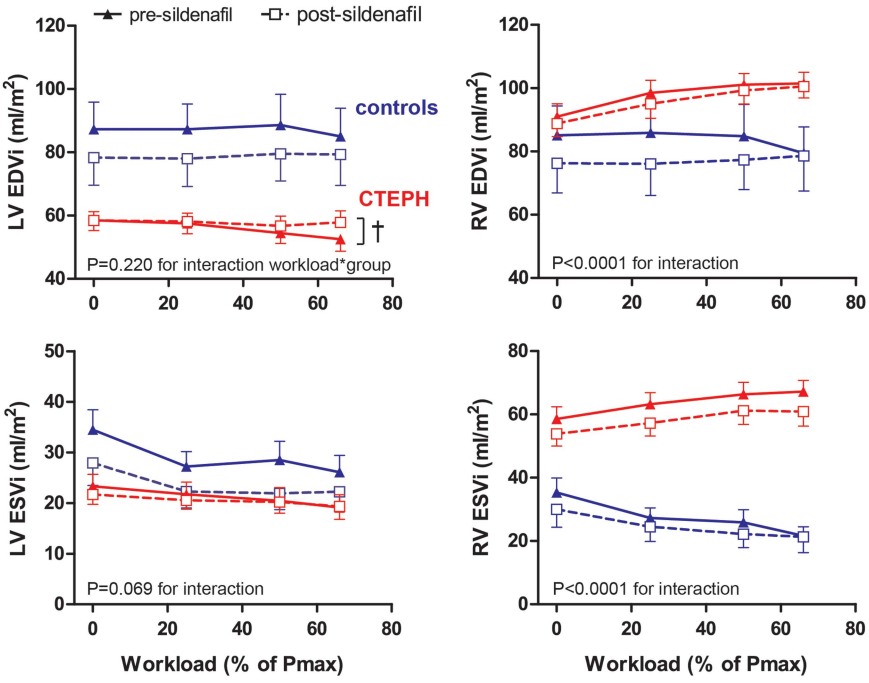

Figure 2 Comparison of biventricular volume changes during incremental exercise in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and healthy control subjects before and after sildenafil. Workloads are presented as a percentage of maximum power output (Pmax) determined during previous cardiopulmonary exercise testing. p Values are shown for the interaction between group (patients vs controls) and exercise-intensity using repeated measures analysis of variance. †Denotes significant interaction ($p<0.05$) between volume response to exercise presildenafil vs postsildenafil administration. Data are presented as means and SEM at each time point. EDVi, indexed end-diastolic volume; ESVi, indexed end-systolic volume.

Effects of sildenafil on biventricular function and haemodynamics

Administration of sildenafil had a different effect on biventricular volumes in control subjects versus patients with CTEPH (figure 2). In control subjects, sildenafil consistently decreased LVEDVi, LVESVi and RVEDVi during resting and exercise (mean differences -8 ± 1, -5 ± 2 and -7 ± 2 mL/m^2, respectively; all $p<0.05$), while RVESVi remained unchanged. Therefore, while LVEF slightly increased, RVEF was not affected by sildenafil (table 2). In patients with CTEPH, LVEDVi decreased during exercise in the baseline setting, but remained constant following administration of sildenafil. Changes in RVEDVi during exercise were similar to pre-sildenafil and post-sildenafil administration. More impressively, sildenafil decreased RVESVi (mean difference -6 ± 2 mL/m^2; $p=0.004$) during resting and exercise, but did not affect LVESVi. As a result, sildenafil increased both LVEF and RVEF during resting and exercise in patients with CTEPH (table 2).

Figure 3B depicts the reduction of the mPAP/CO slope in patients with CTEPH (-3.2 ± 1.2 mm Hg/L/min; $p=0.020$) versus no change in control subjects ($p=0.422$) following administration of sildenafil. Sildenafil decreased tPVR during resting and exercise, both in patients with CTEPH and control subjects (table 2). However, the reduction in tPVR was associated with an increase in SVi in the CTEPH group but not in control subjects (interaction group × sildenafil $p<0.001$; figure 3). In patients with CTEPH, the reduction in tPVR during peak exercise after sildenafil administration correlated highly with the increase in peak exercise SVi ($r=-0.80$; $p=0.001$) and RVEF ($r=-0.65$; $p=0.016$; figure 5). Furthermore, the increase in SVi with sildenafil was greater during peak exercise than at rest (5 ± 2 vs 1 ± 1 mL/m^2; $p=0.024$).

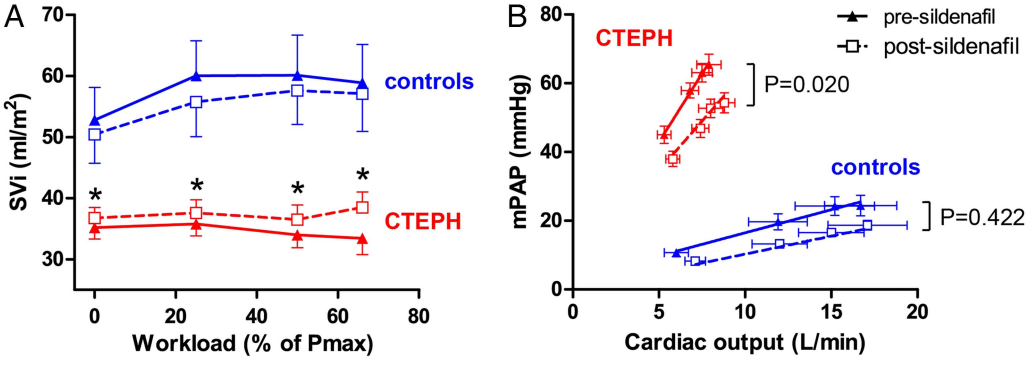

Figure 3 Stroke volume index (SVi) and pulmonary vascular reserve in patients with chronic thromboembolic pulmonary hypertension (CTEPH) versus healthy control subjects before and after sildenafil administration. (A) SVi response from rest to peak-intensity exercise in patients with CTEPH versus control subjects before (solid lines) and after sildenafil (dashed lines) administration. Asterisks denote significant differences between pre-sildenafil and post-sildenafil within each cohort by paired sample t test. Workloads are presented as a percentage of maximum power output (Pmax) determined during previous cardiopulmonary exercise testing. (B) Linear mean pulmonary artery pressure (mPAP)-flow relationships based on averages of serial measurements of mPAP and cardiac output (CO) during incremental exercise before (solid lines) and after (dashed lines) sildenafil. Error bars denote SEM. p Values are given for differences in mPAP/CO slope between pre-sildenafil and post-sildenafil administration using a paired sample t test.

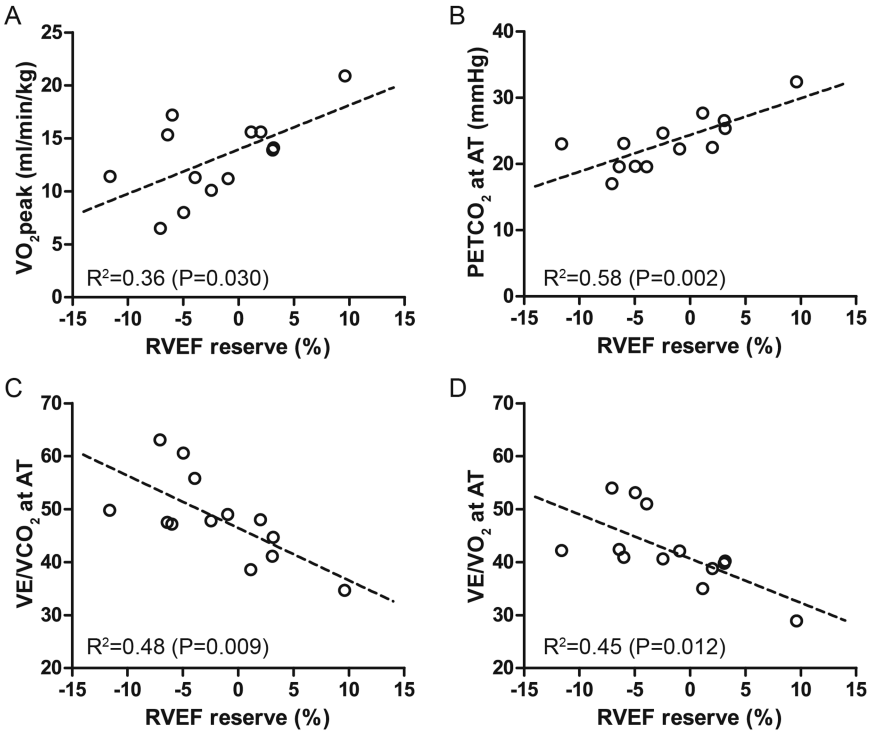

Figure 4 Correlations between RV functional reserve and measures of exercise capacity and ventilatory efficiency. The exercise-induced change in RVEF (RVEF reserve) correlated with (A) peak oxygen consumption (VO_2peak) and with (B) end-tidal carbon dioxide tension ($PETCO_2$), (C) ventilatory equivalent of carbon dioxide (VE/VCO_2) and (D) ventilatory equivalent of oxygen (VE/VO_2) at anaerobic threshold (AT).

Blood gas changes during exercise before and after sildenafil administration

Table 2 depicts the values of the arterial and central venous blood gas analysis at rest and at peak exercise before and after sildenafil administration. In the patients with CTEPH, sildenafil was associated with a reduction in PaO_2 during rest. During exercise, sildenafil was again associated with a reduction in PaO_2 but, additionally, was associated with an attenuated reduction in $ScvO_2$ ($p=0.016$ for interaction) resulting in a reduction in $C(a\text{-}cv)O_2$ as compared with the pre-sildenafil setting (see online supplementary figure).

DISCUSSION

In this study, we used simultaneous gold-standard invasive pressure and CMR-derived ventricular volume measurements during incremental exercise to comprehensively describe exercise physiology and limitation in patients with CTEPH relative to healthy subjects. Our findings extend previous studies which have typically assessed RV performance immediately after, but not during exercise. Moreover, we found that exercise rather than resting measures of RV function are associated with exercise capacity and ventilatory inefficiency. Furthermore, we provide new insights into the mechanisms by which the pulmonary vasodilator sildenafil improves exercise RV performance and SVi in patients with CTEPH, but not in healthy control subjects. Importantly, the increase in peak exercise RV performance after sildenafil correlated with the reduction in peak exercise tPVR, suggesting that exercise CMR may be used as a non-invasive modality to evaluate the effect of novel therapies on exercise haemodynamics and RV function.

Importance of RV functional reserve to explain exercise limitation in patients with CTEPH

Patients with CTEPH typically have an increased ventilatory drive, which is associated with an increase in VE/VCO_2 in proportion to the physiological severity of the disease.[13 14] Potential mechanisms for this inefficient ventilation include both an increased physiological dead space and an augmentation of the central drive to ventilation, that is, increased chemosensitivity.[15] In keeping with the latter, we found that both $PETCO_2$ and $PaCO_2$ were significantly lower in the CTEPH cohort compared with healthy controls, suggesting increased chemosensitivity.

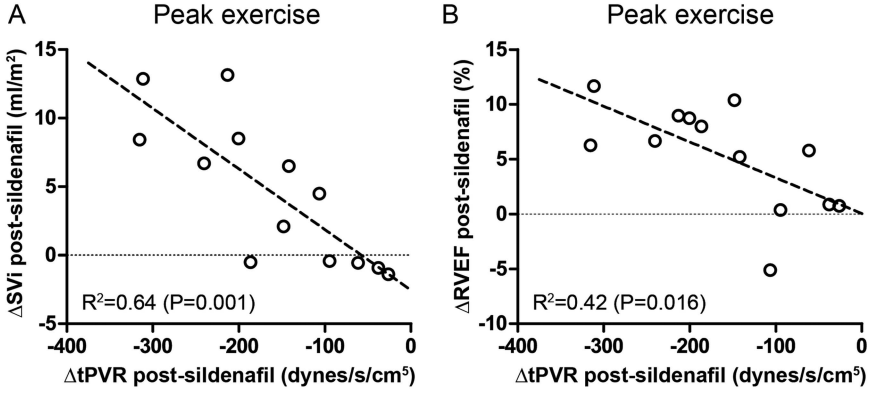

Figure 5 Correlations between peak exercise RV performance and pulmonary vascular resistance following sildenafil. The change in peak exercise total pulmonary vascular resistance (ΔtPVR) after sildenafil correlated highly with changes in (A) peak exercise stroke volume index (ΔSVi) and (B) peak exercise RVEF (ΔRVEF).

Interestingly, RV functional reserve during exercise correlated with $PETCO_2$ and $PaCO_2$, but not with parameters suggestive of increased physiological dead space ($P(A\text{-}a)O_2$, $P(c\text{-}ET)CO_2$ and V_D/V_T). Furthermore, we found that exercise measures of RV function were associated with exercise capacity and ventilatory inefficiency, while resting measures were not.

These observations are consistent with recent data showing that evaluation during exercise using CPET enables identification of CTEPH in patients with suspected PH but normal resting echocardiography.[16] This is clinically relevant as an explanation for why some patients have severe symptoms but relatively modest impairment on resting measures of pulmonary vascular haemodynamics and RV function. Among our study patients, impaired RV functional reserve during exercise provided a far better explanation for the disparity between symptoms and resting investigations. Thus, pulmonary vascular reserve and RV functional reserve should be incorporated when evaluating patients with symptoms on exertion. In clinical practice, this is usually accomplished using exercise echocardiography. RV functional reserve can be measured using parameters, such as RV fractional area change[17] or tricuspid annular plane systolic excursion,[18] while pulmonary vascular reserve can be assessed using Doppler interrogation of the transtricuspid regurgitation jet.[17–19] However, assessment of RV performance with echocardiography is often challenging due to its complex geometry, its retrosternal position and poor acoustic windows. In these cases, exercise CMR may be an exciting imaging modality to evaluate exercise RV performance. We demonstrate that exercise CMR is feasible even in this population of seriously ill patients and that measurement of RV functional reserve can be obtained during intense exercise in all subjects regardless of body habitus and without the need to perform breath-holds.

Acute effects of sildenafil on cardiac haemodynamics

Although fixed thrombotic obstructions are the hallmark of CTEPH, several studies have demonstrated acute haemodynamic improvements following administration of sildenafil.[20–22] It has been postulated that these acute changes with sildenafil in CTEPH are due to its vasodilating effect on the non-obliterated pulmonary vasculature.[20 21] In this study, we demonstrate that the reduction in RV afterload following sildenafil administration increases the performance of the pressure-overloaded RV, which is associated with increased filling of the under-filled LV and an increase in SVi. Contrary to the modest increase that occurred while at rest, the magnitude of SVi improvement during peak exercise was far greater with sildenafil and may be considered a clinically relevant change in patients with PH.[23]

It is important to note that the purpose of this study was to evaluate the acute response of sildenafil on exercise haemodynamics, which by itself cannot be used to demonstrate its long-term efficacy. Nevertheless, it is known that acute pulmonary vascular reactivity is a predictor of long-term survival and response to surgery in patients with CTEPH undergoing pulmonary endarterectomy. We show that the improvement in peak exercise RVEF and SVi correlates highly with the reduction in exercise tPVR. This may suggest that exercise CMR may be used as a non-invasive modality to evaluate the acute effects of pulmonary vasodilators on exercise haemodynamics. Moreover, the evaluation of RV performance during exercise may represent a promising surrogate measure for future phase 2 clinical studies investigating interventions for PH. It has been suggested that RV contractile reserve may be more important than resting haemodynamic measurements for determining best therapy and prognosis among patients with PH.[24] Also, deterioration of RV function after initiation of PH-specific therapy can occur irrespective of changes in PVR and is associated with a poor outcome. In our current study, we describe an exciting novel methodology which may enable future therapies to be tested in this rare condition in an affordable manner.

Limitations

First, the comprehensive procedures undertaken in this study and the constraints of recruiting healthy subjects for an invasive study protocol limited the sample size. However, the established accuracy of exercise CMR measures enabled us to evaluate meaningful haemodynamic differences within this modest-sized cohort. Second, the control subjects had a better exercise capacity than the patients with CTEPH. However, determination of workloads was standardised for both groups as a percentage of Pmax obtained during CPET. Moreover, for both groups, changes in LV function served as an 'internal reference' for those of the RV. Hence, while LV functional changes during exercise mirrored those of the RV in control subjects, a significantly different pattern for both ventricles was observed in patients with CTEPH. Finally, because of technical considerations initially, RA pressure measures were not included in the haemodynamic assessment and, therefore, only available in the last eight patients with CTEPH.

CONCLUSIONS

Exercise measures of RV function explain much of the variance in the exercise capacity of patients with CTEPH while resting measures do not. During exercise, RV afterload increases disproportionately in patients with CTEPH resulting in a marked reduction in RVEF and SV reserve. This effect can be partially reversed with sildenafil.

Key messages

What is already known on this subject?

Some patients with chronic thromboembolic pulmonary hypertension (CTEPH) have worse capacity for exercise than others, despite similar resting haemodynamics and RV function.

What might this study add?

As compared with measures performed at rest, quantification of RV function performed during exercise provides a substantially better explanation for exercise limitation.

The increase in stroke volume following sildenafil administration in patients with CTEPH is greater during exercise than at rest.

The increase in exercise RVEF and stroke volume after sildenafil correlates strongly with reductions in pulmonary vascular resistance during exercise.

How might this impact on clinical practice?

Exercise measures of RV function should be incorporated when evaluating patients with symptoms on exertion.

Exercise cardiac MRI may be used as a non-invasive modality to evaluate the effect of novel pulmonary hypertension therapies on exercise haemodynamics and RV function.

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Heart

Exercise pathophysiology and sildenafil effects in chronic thromboembolic pulmonary hypertension

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