Articles in PresS. J Appl Physiol (July 14, 2016). doi:10.1152/japplphysiol.00087.2016

Exercise Physiological Responses to Drug Treatments in Chronic Thromboembolic Pulmonary Hypertension

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ABSTRACT WORD COUNT: 201, TOTAL WORD COUNT: 2730

There were no sources of funding for this work.

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ABSTRACT:

We tested the hypothesis that patients with chronic thromboembolic pulmonary hypertension (CTEPH) deemed inoperable were more likely to respond to PAH drugs than those CTEPH deemed operable, using cardiopulmonary exercise testing (CPX). We analyzed CPX data of all CTEPH patients who were treated with PAH drugs and had undergone CPX testing pre- and post-treatment at a single Pulmonary Hypertension center between February 2009 and March 2013. Suitability for pulmonary endarterectomy (PEA) was decided at a PEA expert center. The inoperable group included 16 patients and the operable group 26 patients. There was no difference in demographics and baseline hemodynamics between the groups. Unlike the operable group, after drug treatment inoperable patients had a significantly higher peak VO_2 ($p<0.001$), workload ($p=0.002$) and oxygen pulse ($p<0.001$). In terms of gas exchange, there was an overall net trend towards improved VE/VCO_2 in the inoperable group, with an increased $PaCO_2$ ($p=0.01$), suggesting reduced hyperventilation. No changes were seen in the operable patients. In conclusion, treatment with PAH drug therapies reveals important pathophysiological differences between inoperable and operable CTEPH, with significant pulmonary vascular and cardiac responses in inoperable disease. Drug effects on exercise function seen in inoperable CTEPH cannot be translated to all forms of CTEPH.

Key words: chronic thromboembolic pulmonary hypertension; pulmonary arterial hypertension drug therapies; cardiopulmonary exercise testing.

NEW & NOTEWORTHY:

This is the first study using gas exchange on exercise to assess the response to PAH drug therapies in patients with chronic thromboembolic pulmonary hypertension. At the same time we are also comparing for the first time operable and inoperable chronic thromboembolic pulmonary hypertension patients.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease caused by obstruction of the pulmonary vasculature by organised chronic thromboemboli resulting in an increase in pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP), ultimately causing right ventricular failure (12). Moser and Braunwald originally proposed that small vessel arteriopathy akin to that seen in pulmonary arterial hypertension (PAH) may exist in the "open" vessels and not in the "closed" vessels unexposed to high pulmonary artery pressures, thus creating a two-compartment model (14). Histologic examination of biopsy and autopsy samples from patients with CTEPH have subsequently demonstrated features indistinguishable from PAH, including plexogenic lesions (13). Further studies have suggested that this process can occur distal to obstructed vessels (7, 11). The presence of this PAH-like pathology has led to the hypothesis that PAH-targeted therapies may be efficacious in CTEPH patients. Trials in inoperable CTEPH have demonstrated contradictory results regarding the response of patients' exercise capacity (6, 9, 17). Likewise, in CTEPH deemed operable, PAH drugs used as a bridge to PEA have shown different impact on patients' functional status (15, 16).

In the current study, we sought to assess the response of CTEPH patients who were deemed operable and inoperable to PAH drugs using cardiopulmonary exercise testing (CPX). Since inoperable CTEPH resembles PAH more than operable CTEPH, we hypothesized that inoperable patients might have a better response to PAH drugs.

METHODS

Patients

Consecutive patients attending a single specialist PH center between April 2008 and March 2013 were studied. We included patients who were diagnosed with CTEPH, started on PAH specific drugs and had attended at least two incremental CPX, one immediately prior to starting treatment and one

at their subsequent visit, usually between 3 and 6 months later. Patients were investigated according to a standard guideline-based protocol (5). CTEPH was defined in accordance with guidelines at the time by the presence of pre-capillary PH, whereby mPAP ≥ 25 mmHg, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and PVR > 2 Wood units in patients with multiple, chronic/organized occlusive thrombi in the elastic pulmonary arteries (5). In our center we routinely use both ventilation/perfusion (V/Q) scan and CT pulmonary angiogram to make the diagnosis of CTEPH. We excluded patients with severe lung disease identified clinically, on spirometry and on high-resolution CT scan, as in these patients PAH drugs are contraindicated (5).

Treatment protocol

Patients were treated in line with a nationally-agreed policy, drawn up by the National Pulmonary Hypertension Service Physicians' Committee and National Health Service Specialized Commissioners (18). In line with this policy, PAH-targeted therapy was offered at diagnosis and prior to the assessment of operability in patients with WHO FC III/IV symptoms. Medical treatment was continued after assessment of operability either if patients were deemed inoperable or, if they were ultimately deemed operable, in an attempt to improve symptoms while on the waiting list. Treatment was offered as a choice to patients and not all opted to receive it. Patients were not offered treatment as an alternative to surgery and surgery was not delayed in order to assess the response to medical therapy. First line treatment was with a phosphodiesterase type 5 inhibitor (PDE5i); second line was with an endothelin receptor antagonist (ERA). Prostacyclins could not be used in line with national policy at the time.

Assessment of operability

All patients were referred to Papworth Hospital, the National PEA center, where an experienced, multidisciplinary CTEPH team adjudicated their operability. Decisions on operability in CTEPH were based mainly on the degree of pulmonary artery obstruction, as determined by imaging, and the

degree to which PVR, measured at right heart catheterisation, was in proportion to this, with the CTEPH team deciding whether the majority of the vascular resistance could be explained by obstructive disease which could be removed by endarterectomy surgery. In view of the association between high PVR and operative mortality most experienced PEA surgical centers agree that mortality risk with PEA increases when the PVR is > 1200 dynes.cm.s^{-5} (3).For patients with this degree of hemodynamic impairment, PEA was still offered as long as the patient had at least 6-7 occluded segments. The final decision was based on the ratio of risk and benefit for the individual patient. There are few absolute contraindications to PEA, although most clinicians agree that patients with severe parenchymal lung disease and very poor ventilation will not benefit from improved perfusion.

Cardiopulmonary exercise testing

CPX was performed on an upright cycle ergometer using a breath-by-breath system (Master Screen CPX; Jaeger; Hoechberg, Germany) according to the ATS/ACCP Statement on Cardiopulmonary Exercise Testing (2) and is presented in the supplementary material (Table 6). We compared data from CPX undertaken before starting therapy with the first available test post-treatment. The interval between pre-treatment CPX and cardiac catheterization was one day in the majority of our patients. All measurements were made by an experienced physiologist who was unaware of the operative status of the patient.

Statistical analysis

Continuous variables were expressed either as mean ± standard deviation or as median value (interquartile range), when they did not follow a normal distribution. Categorical variables were expressed as frequency and percentages. Paired Student's *t* test was applied to compare pre- and post-treatment CPX variables within the groups and unpaired for between groups comparisons. χ^2 test was used to assess differences in categorical values between groups. We performed a univariate

linear regression analysis of CPX variables and hemodynamic (independent variables) to examine their correlation with post/pre peak VO_2 ratio (dependent variable). All statistical analyses were performed using SPSS (version 20). The study was approved by the National Research Ethics Service Committee – London South East (13/LO/0695).

RESULTS

Patient characteristics

Between February 2009 and March 2013, 42 patients received PAH drug therapies and had pre- and post-drug CPX available for analysis. A further 17 patients who were started on therapy prior to surgery underwent surgery prior to repeat testing and were not included. A further five patients could not undergo testing due to inability to complete a test due to injuries, deterioration or administrative error. Of the 42 patients with paired CPX , 16 were deemed inoperable and 26 were deemed operable. The baseline characteristics of the two groups are shown in Table 1. There was no significant difference regarding their demographics, six-minute walk test distance or hemodynamics at baseline.

The median time interval between start of PAH therapy and post-treatment CPX was 6 (3, 7.5) months in the inoperable and 5.5 (4, 12) months in the operable group (p=0.23). In the inoperable group 11 patients (69 %) were treated with a PDE5i and 5 (31 %) with an ERA, while in the operable group 23 patients (88.5%) were prescribed PDE5i and 3 (11.5%) an ERA (p=0.09). The most common form of PDE5i was sildenafil 25 mg tid.

Exercise performance improves in inoperable, but not operable, patients with PAH therapies

InopCTEPH achieved a significantly higher peak VO_2 ($p<0.001$) and workload (p=0.002) after starting on treatment (Table 2), while there was no difference in opCTEPH (Table 3). There was also an increase in peak lactate (p=0.01) and O_2 pulse ($p<0.001$) in inopCTEPH, therefore to account for any difference in effort, we measured O_2 pulse at the same work rate (isowork O_2 pulse) in the pre- and

post-treatment test. We chose the peak work rate in either test, whichever was the lower, to capture the highest work rate available for analysis in both tests and showed that isowork O_2 pulse was higher post-treatment ($p < 0.001$) in inopCTEPH. $PaCO_2$ and physiologic dead space at peak exercise (V_D/V_{Tphys}) were significantly increased post-treatment in inopCTEPH (p=0.01 and 0.03 respectively), but the overall effect led to a trend towards greater ventilatory efficiency (VE/VCO_2 slope decreased, p=0.1) following treatment. No changes were noticed in the opCTEPH group after treatment. No differences were seen according to type of drug therapy used (data not shown). When patients treated with PDE5i alone were analyzed, improvements in peak VO_2, O_2 pulse, isowork O_2 pulse, peak workload and $PaCO_2$ remained significantly different in inopCTEPH (p=0.04, 0.03, 0.03, <0.001, 0.004 respectively), with no changes observed in opCTEPH.

PEA surgery improves physiological outcomes in operable CTEPH

Not all patients with opCTEPH received PEA surgery; one had co-morbid coronary artery disease and deemed too high-risk for surgical intervention, 8 refused surgery and one was on the waiting list. Those patients who did undergo surgery had significant improvements in functional class, six minute walk distance, hemodynamics and exercise performance (Tables 4 and 5).

DISCUSSION

This is the first study using gas exchange on exercise to assess the response to PAH drug therapies in patients with CTEPH, also comparing for the first time operable and inoperable CTEPH patients. This is an observational study based on a standardized departmental clinical treatment protocol. Not only do we show that inopCTEPH patients improve their peak exercise performance six months after starting on treatment, while the opCTEPH patients do not, but this is supported by significant, *effort-independent* changes, much less vulnerable to bias, in cardiopulmonary physiology in the inoperable group, while there are no such effects in the operable group. Following treatment in the inoperable group, gas exchange changed significantly with an increase in peak V_D/V_{Tphys} suggesting significant

pulmonary vascular effects of therapy and $PaCO_2$ rose in keeping with decreased hyperventilation, a feature associated with severity of heart failure. In all of these respects, operable CTEPH was starkly unaffected by drug therapies, and as expected showed significant improvements in hemodynamic and exercise physiology following PEA surgery.

The cardinal features of CTEPH on exercise are impaired oxygen delivery and ventilatory inefficiency (Fig 1A). Impaired oxygen delivery manifests as a reduced peak VO_2 and an early anerobic threshold as a result of a reduced stroke volume. Effective treatment in pulmonary hypertension would be expected to increase stroke volume through right ventricular afterload reduction and thus increase peak VO_2 and the VO_2 at anerobic threshold (Fig 1B). In support of this, in inopCTEPH we saw an increase in peak VO_2, a trend towards an increase in VO_2 at anerobic threshold and a significant increase in oxygen pulse, suggesting an increase in stroke volume (Table 2).

Ventilatory inefficiency results from a combination of increased V_D/V_{Tphys} due to pulmonary vasculopathy / vascular thrombotic occlusion and hypocapnia, as illustrated by the modified Bohr Equation:

$$^{VE}/_{VCO_2} = EqCO_2 = \frac{863}{PaCO2\ x\ (1-VD/VT)}$$

It is well-documented that patients with pulmonary hypertension develop hypocapnia as a result of hyperventilation due to increased chemosensitivity associated with heart failure and that this correlates with impairment of cardiac function as well as mortality (8). With effective reduction in right ventricular afterload by pulmonary vasodilators, we would expect an increase in $PaCO_2$ and thus an improvement in ventilatory inefficiency. This has not been demonstrated before except following PEA surgery, where $PaCO_2$ increased from 31 to 34 mmHg at 3 months (20), which is identical to our study. Here, we also show a significant increase in $PaCO_2$ to a similar degree in

227 inopCTEPH but not in opCTEPH following treatment with PAH therapies compatible with improved
228 cardiac function and a trend towards lower VE/VCO_2 (-8.5%) and $EqCO_2$ (-5.0%).

229 Hyperventilation itself has been proposed to result in increased V_D/V_T (4), but in our study, V_D/V_{Tphys}
230 increased in inopCTEPH following treatment despite an increase in $PaCO_2$, suggesting a real increase
231 in ventilation-perfusion mismatch (Fig 1B). This will have offset the increase in $PaCO_2$ attenuating the
232 benefit on improving ventilatory inefficiency as seen from the modified Bohr equation. This is the
233 first time the impact of treatment on V_D/V_{Tphys} has been reported in CTEPH. We have not assessed
234 the mechanism of this worsening of V_D/V_{Tphys} since this would require the use of the multiple inert
235 gas elimination technique, but propose that this results from increased perfusion to low ventilation-
236 perfusion areas on lung. It has previously been suggested that any intervention which lowers
237 pulmonary vascular tone causes a deterioration in ventilation-perfusion relationships (1, 10)

238 The lack of any discernible change in any of the gas exchange parameters in opCTEPH compared
239 with inopCTEPH suggests that drug therapies are unmasking different pathophysiological
240 characteristics between the two phenotypes, perhaps with increased pulmonary vascular tone being
241 far less relevant in operable disease. It also further supports the view that PAH therapies have little
242 impact on opCTEPH with surgical intervention being the treatment of choice.

243 In previous trials with Sildenafil and Bosentan, improvement in hemodynamics has not been
244 matched by an improvement in six-minute walk test distance in patients with inopCTEPH and
245 persistent pulmonary hypertension post PEA surgery (9, 17). We previously hypothesised that the
246 worse ventilatory inefficiency during walking may account for the disconnection between
247 improvement in six-minute walk and hemodynamics, if patients are running out of breathing reserve
248 before cardiac reserve (19). Data from the CHEST-1 study of the soluble guanylate cyclase stimulator,
249 Riociguat, in inopCTEPH show no such disparity (6). The effects of Riociguat during CPX have not yet
250 been assessed in inopCTEPH. One explanation may be that it has a more favourable effect on
251 V_D/V_{Tphys} than other PAH therapies, translating hemodynamic benefits into improved exercise

function. An alternative explanation is that the study population was a purer population of distal disease due to better patient selection compared with previous studies. Operability in CTEPH is subjective and depends on the experience of the PEA surgeon(s) within the adjudication committee and ability to reach more distal segmental obstruction. With growing expertise, centers are operating on more distal disease, thus the definition of inoperability may be becoming more precise with time, with the result that patients deemed inoperable are more "PAH-like" and thus more likely to respond to medical therapies.

This study was not intended to evaluate PAH therapies in terms of efficacy, but was rather addressing a different question of how different disease phenotypes respond physiologically to drug intervention, akin to looking for potential responders and non-responders within a heterogeneous group of patients. Hence, we compare patients with their baseline, rather than perform any statistical analysis between groups. Although patients were not blinded to their treatment, we showed that effort-dependent measurements were tracked by changes in effort-independent measurements, supporting the validity of the peak data. Measures such as $PaCO_2$ and lactate are not open to bias. Peak VO_2 and oxygen pulse are reported directly by the exercise system software and V_D/V_{Tphys} is directly calculated from end-of-test data and cannot be manipulated. We also used a measure of isowork oxygen pulse to guard against an effort effect. The only measures open to user input in our study are VE/VCO_2 slope and the anerobic threshold, however, the physiologist making the measurements was unaware of operative status. We acknowledge that the open-label nature of the study could still have impacted on the absolute levels of effort-dependent change, such as peak VO_2 and work rate. Furthermore, the peak RER measures are lower than expected or a maximal cardiovascular test, suggesting that maximal capacity may not have been assessed. Thus, while we can state with confidence that the two subgroups of CTEPH respond differentially to treatment, the true magnitude of these two effort-dependent effects remains uncertain. To evaluate efficacy/magnitude is a different question and would have required a different design, including blinding and a placebo arm.

A greater proportion of patients received PDE5i than ERA, although no differences in response were noted according to drug treatment and the findings were unchanged when analyzing only those who received PDE5i. We nonetheless chose to include both therapy classes since neither is currently licensed and both have been shown to cause a reduction in pulmonary vascular resistance by similar amounts in inopCTEPH (9, 17). We have not evaluated the effect of Riociguat.

CONCLUSIONS

We have demonstrated that the responses to PDE5i/ERA in 'inoperable' and 'operable' CTEPH are different suggesting that these two forms of CTEPH demonstrate distinct pathophysiological features. These therapies produce significant alterations in cardiac function and gas exchange in patients deemed inoperable; however the treatments used in our cohort are not licensed for use in CTEPH as they have not shown efficacy in phase III clinical trials. This study shows the value of CPX in unravelling the reasons behind exercise limitation and eliciting differences in pathophysiology between CTEPH subtypes. We illustrate the importance of an expert CTEPH team in determining operability, since this will lead to the best outcome for patients. Finally, with the advent of new drugs shown to be effective in inoperable CTEPH (6) our study reinforces the recommendation of PEA as the treatment of choice for patients with operable CTEPH.

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356 **Table 1**.Baseline characteristics

	Inoperable (n=16)	**Operable (n=26)**	**p-value**
Age (yrs)	61 ± 17	61 ± 15	0.82
Sex (female)	9 (56 %)	15 (58 %)	0.75
WHO FC			0.82
II	0 (0 %)	1 (4 %)	
III	15 (94 %)	24 (92 %)	
IV	1 (6 %)	1 (4 %)	
6MWT distance (m)	313 ± 103	274 ± 122	0.31
mPAP (mmHg)	47 ± 11	47 ± 12	0.95
PAWP (mmHg)	12 ± 3	12 ± 3	0.89
LVEDP (mmHg)	11 ±4	12 ± 4	0.66
mRAP (mmHg)	10 ± 4	10 ± 4	0.82
RVEDP (mmHg)	11 ± 5	11 ± 4	0.71
Cardiac index (L/min/m^2)	2.1 ± 0.7	2.2 ± 0.6	0.60
PVR (Wood units)	11 ± 7	10 ± 6	0.59

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358 Data are presented as n (%) or mean values ± standard deviation.

359 mPAP= mean pulmonary artery pressure, mRAP= mean right atrial pressure, LVEDP= left
360 ventricular end-diastolic pressure, RVEDP= right ventricular end-diastolic pressure, PAWP=
361 pulmonary artery wedge pressure, PVR= pulmonary vascular resistance, WHO-FC= World
362 Health Organization functional class, 6MWT= six minute walk test

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364 **Table 2.** Comparison of cardiopulmonary exercise variables pre- and post-PAH therapy in the

365 deemed as inoperable CTEPH group.

Inoperable patients (n=16)	**Pre-treatment**	**Post-treatment**	**p-value**
VO_2 at anerobic threshold	717 ± 238	752 ± 211	0.19
Peak VO_2 (ml/kg/min)	11.7 ± 2.6	12.9 ± 2.5	**<0.001**
Respiratory exchange ratio	1.04 ± 0.09	1.05 ± 0.09	0.70
Lactate (mmol/L)	4.4 ± 1.7	5.3 ± 1.9	**0.01**
Heart rate reserve (bpm)	22 ± 15	21 ± 14	0.48
VE/VCO_2	55 ± 13	50 ± 10	0.12
$EqVCO_2$	50 ± 9	48 ± 6	0.19
O_2 pulse (ml/beat)	6.4 ± 2.4	7.1 ± 2.2	**<0.001**
Isowork O_2 pulse (ml/ beat)	6.4 ± 2.4	6.9 ± 2.4	**0.008**
V_D/V_{Tphys} (%)	41 ± 5	46 ± 3	**0.03**
Workload(W)	56 ± 29	66 ± 32	**0.002**
Workload (%)	53 ± 17	60 ± 19	**0.02**

Breathing reserve (L/min)	25 ± 20	24 ± 21	0.68
Tidal Volume (litres)	1.7 ± 0.7	1.7 ± 0.6	0.85
Breathing frequency (breaths/min)	33 ± 8	34 ± 8	0.20
$PaCO_2$(mmHg)	31 ± 4	33 ± 3	**0.01**

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368 Data are presented as mean values ± standard deviation.

369 CTEPH= chronic thromboembolic pulmonary hypertension, $EqVCO_2$= equivalence of carbon dioxide,

370 $PaCO_2$= partial carbon dioxide arterial pressure, PAH= pulmonary arterial hypertension, VCO_2=

371 carbon dioxide production, V_D/V_{Tphys}= physiologic dead space, VE= ventilation, VO_2= oxygen

372 consumption.

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374 **Table 3.**Comparison of cardiopulmonary exercise variables pre- and post-PAH therapy in the deemed

375 as operable CTEPH group.

Operable patients (n=26)	**Pre-treatment**	**Post-treatment**	**p-value**
VO_2 at anerobic threshold	774 ± 260	760 ± 237	0.80
Peak VO_2 (ml/kg/min)	12.4 ± 3.0	12.6 ± 3.2	0.52
Respiratory exchange ratio	1.01 ± 0.08	0.99 ± 0.07	0.14
Lactate (mmol/L)	4.8 ± 1.8	4.4 ± 1.8	0.71
Heart rate reserve (bpm)	31 ± 18	30 ± 20	0.78
VE/VCO_2	57 ± 18	56 ± 16	0.68
$EqVCO_2$	50 ± 13	49 ± 10	0.91
O_2 pulse (ml/beat)	7.5 ± 2.1	7.6 ± 2.0	0.70
V_D/V_{Tphys} (%)	48 ± 7	47 ± 8	0.91
Workload (W)	61 ± 26	64 ± 31	0.12
Workload (%)	59 ± 26	61 ± 26	0.24
Breathing reserve (L/min)	20 ± 17	23 ± 15	0.37
Tidal Volume (litres)	1.6 ± 0.5	1.7 ± 0.6	0.36
Breathing frequency (breaths/min)	37 ± 7	36 ± 7	0.36
$PaCO_2$ (mmHg)	31 ± 6	30 ± 6	0.27

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Data are presented as mean values ± standard deviation.

CTEPH= chronic thromboembolic pulmonary hypertension, $EqVCO_2$= equivalence of carbon dioxide, $PaCO_2$= partial carbon dioxide arterial pressure, PAH= pulmonary arterial hypertension, VCO_2= carbon dioxide production, V_D/V_{Tphys}= physiologic dead space, VE= ventilation, VO_2= oxygen consumption.

Table 4.Hemodynamics pre- and post-PEA in 15 CTEPH patients deemed operable at 3 months.

Patients post-PEA (n=15)	**Pre-PEA**	**Post-PEA**	**p-value**
WHO FC			<0.001
I	0 (0 %)	4 (27 %)	
II	0 (0 %)	10 (67 %)	
III	14 (93 %)	1 (6 %)	
IV	1 (7 %)	0 (0%)	
6MWT distance (m)	290 ± 109	366 ± 86	0.04
mPAP (mmHg)	47 ± 13	26 ± 7	<0.001
PAWP (mmHg)	13 ± 3	10 ± 2	0.02
mRAP (mmHg)	11 ± 4	7 ± 2	0.006
RVEDP (mmHg)	11 ± 5	9 ± 3	0.13
Cardiac index (L/min/m^2)	2.1 ± 0.5	2.4 ± 0.4	0.07
PVR (Wood units)	11 ± 6	4 ± 2	0.006

Data are presented as n (%) or mean values ± standard deviation.

mPAP= mean pulmonary artery pressure, mRAP= mean right atrial pressure, LVEDP= left ventricular end-diastolic pressure, RVEDP= right ventricular end-diastolic pressure, PAWP= pulmonary artery wedge pressure, PEA=pulmonary endarterectomy, PVR= pulmonary vascular resistance, WHO-FC= World Health Organization functional class, 6MWT= six minute walk test

403 **Table 5.**Comparison of cardiopulmonary exercise variables pre- and post-PEA in 14 CTEPH patients

404 deemed operable

Patients post-PEA (n=14)	**Pre-PEA**	**Post-PEA**	**p-value**
VO_2 at anerobic threshold	733 ± 111	865 ± 172	**0.04**
Peak VO_2 (ml/kg/min)	12.4 ± 2.7	15.6 ± 4.5	**0.008**
Respiratory exchange ratio	1.04 ± 0.08	1.04 ± 0.10	0.40
Lactate (mmol/L)	5.3 ± 2.0	6.4 ± 2.4	0.28
Heart rate reserve (%) **Heart rate reserve (bpm)**	16 ± 11 28 ± 20	16 ± 14 29 ± 25	0.99 0.89
VE/VCO_2	58 ± 20	41 ± 6	**0.005**
$EqVCO_2$	50 ± 15	40 ± 6	**0.01**
O_2 pulse (ml/beat)	6.9 ± 1.2	8.9 ± 2	**<0.001**
Isowork O_2 pulse (ml/ beat)	6.9 ± 1.2	8.3 ± 1.9	**0.001**
V_D/V_{Tphys} (%)	47 ± 7	37 ± 6	**0.002**
Workload(W)	61 ± 19	80 ± 33	**0.01**
Workload (%)	59 ± 27	72 ± 25	**0.004**

Breathing reserve (L/min)	15 ± 16	19 ± 12	0.46
Tidal volume (litres)	1.6 ± 0.5	1.6 ± 0.5	0.92
Breathing frequency (breaths/minute)	38 ± 7	36 ± 6	0.37
$PaCO_2$(mmHg)	31 ± 7	34 ± 5	**0.04**

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409 Data are presented as mean values ± standard deviation.

410 CTEPH= chronic thromboembolic pulmonary hypertension, EqVCO_2= equivalence of carbon dioxide,

411 $PaCO_2$= partial carbon dioxide arterial pressure, PAH= pulmonary arterial hypertension, PEA=

412 pulmonary endarterectomy, VCO_2= carbon dioxide production, V_D/V_{Tphys}= physiologic dead space,

413 VE= ventilation VO_2= oxygen consumption.

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Table 6. Cardiopulmonary exercise protocol and equations

Cardiopulmonary exercise test protocol

Each test was performed in three stages: three minutes of rest, three minutes of unloaded pedaling and a progressive ramp increase in workload to maximum exercise, with the ramp rate estimated to result in a work phase of 8 to 12 minutes. Patients either wore a face mask or breathed via a mouth-piece wearing a nose-clip.

Systemic blood pressure was measured with a sphygmomanometer, finger oxygen saturation was measured with a pulse oximeter, and a 12-lead electrocardiogram was continuously recorded. Breath-by-breath measurements included oxygen uptake (VO_2), carbon dioxide production (VCO_2), and ventilation (VE).

An arterial blood sample was drawn just after termination of exercise for measurement of arterial partial pressure of O_2 (PaO_2), arterial partial pressure of CO_2 ($PaCO_2$) and lactate level.

The best estimate of anerobic threshold (AT) was calculated manually using a combination of the V-slope method and ventilatory equivalents for oxygen. VE/VCO_2 slope was obtained by linear regression analysis of the relation between VE and VCO_2 during exercise prior to the respiratory compensation point. The ventilatory equivalent for VCO_2 ($EqVCO_2$) was measured at its lowest value over a 30-second average, reflecting the highest degree of ventilatory efficiency for each patient.

Equations

- Breathing reserve (BR) was calculated as:

$$MVV - Peak\ Ventilation$$

where MVV is maximal voluntary ventilation and was calculated as 35 × FEV_1.

- Heart rate reserve (HRR) was defined:

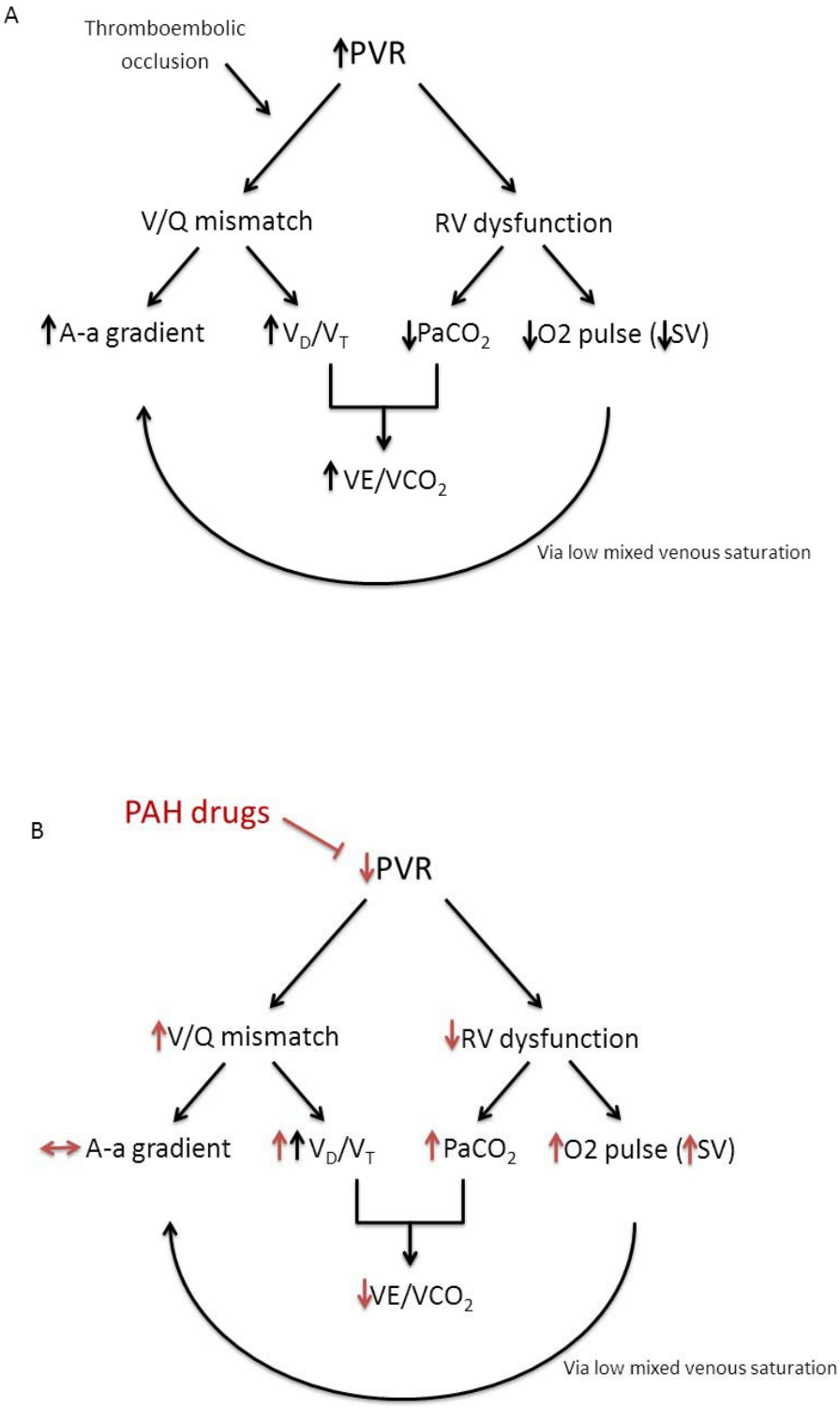
Maximum predicted heart rate – maximum heart rate

- Physiologic dead space (V_D/V_{Tphys}) was measured using the Bohr equation:

$$V_D/V_{Tphys} = \frac{PaCO2 - PeCO2}{PaCO2}$$

where $PeCO_2$ is the measured mixed expired partial pressure of CO_2.

Figure 1. Pathophysiological mechanisms in CTEPH and the effect of PAH therapy



A-a gradient= alveolar- arterial gradient, CTEPH= chronic thromboembolic pulmonary hypertension, $EqVCO_2$= equivalence of carbon dioxide, $PaCO_2$= partial carbon dioxide arterial pressure, PAH= pulmonary arterial hypertension, PVR= pulmonary vascular resistance, RV= right ventricular, VCO_2= carbon dioxide production, V_D/V_{Tphys}= physiologic dead space, VE= ventilation, VO_2= oxygen consumption, V/Q mismatch= ventilation/perfusion mismatch.