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Effects of Exercise and Vasodilators on Cerebral Tissue Oxygenation in Pulmonary Hypertension

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Abstract
Background Arterial and thromboembolic pulmonary hypertension (PH) lead to arterial hypoxaemia.
Objective To investigate whether cerebral tissue oxygenation (CTO) in patients with PH is reduced and whether this is associated with reduced exercise tolerance.
Methods 16 patients with PH (mean pulmonary arterial pressure ≥25 mmHg, 14 arterial, 2 chronic thromboembolic) and 15 controls underwent right heart catheterisation with monitoring of CTO at rest, during maximal bicycle exercise and during inhalation of oxygen and NO. The 6 min walk distance (6MWD) was measured.
Results Median CTO in PH-patients at rest was 62 % (quartiles 53; 71), during exercise 60 % (53; 65); corresponding values in controls were 65 % (73; 73) (P = NS) and 68 % (66; 70) ($p = .013$ vs. PH). Inhalation of NO and oxygen improved CTO in PH. In multivariate regression analysis CTO at maximal exercise predicted the work load achieved when controlled for age, pulmonary vascular resistance and mixed venous oxygen saturation ($R^2 = .419$, $p < .000$); in addition, the 6MWD was predicted by CTO (adjusted $R^2 = .511$, $p < .000$).
Conclusion In PH-patients but not in controls CTO decreased during exercise. Since CTO was an independent predictor of the work load achieved and the 6MWD cerebral hypoxia may contribute to exercise limitation in PH. Clinicaltrials.gov: NCT01463514.

Keywords Pulmonary hypertension · Exercise · Cerebral tissue oxygenation

Abbreviation

CTEPH	Chronic thromboembolic pulmonary hypertension
CtHb	Cerebral total haemoglobin
CTO	Cerebral tissue oxygenation
mPAP	Mean pulmonary artery pressure
NIRS	Near infrared spectroscopy
NO	Nitric oxide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
QMtHb	Quadriceps muscle total haemoglobin
QMTO	Quadriceps muscle tissue oxygenation

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RHC	Right heart catheter
6MWD	6 minute walk distance
SpO2	Peripheral oxygen saturation
SmvO2	Mixed venous oxygen saturation

Introduction

Precapillary pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) $\geq$25 mmHg along with a pulmonary artery wedge pressure $\leq$15 mmHg [1]. PH is associated with various diseases and leads to progressive functional impairment, reduced quality of life and premature death. In the absence of lung diseases, the two major groups of PH are pulmonary arterial hypertension (PAH), including idiopathic and associated forms, and chronic thromboembolic PH (CTEPH) [1, 2].

With progressing disease, patients develop increasing hypoxaemia due to reduced cardiac output resulting in a low mixed venous oxygen saturation, ventilation perfusion mismatch and a decreased pulmonary capillary bed [3]. As a consequence, tissue oxygenation may decrease and impair important physiological functions including those of the brain and the muscles [4, 5]. However, whether cerebral and muscle tissue oxygenation are reduced at rest and during exercise has not been rigorously studied in PH-patients. The aim of the current study was therefore to investigate the patterns of cerebral (CTO) and quadriceps muscle oxygenation (QMTO) using non-invasive near infrared spectroscopy (NIRS) along with pulse oximetry in PH-patients at rest and during maximal exercise, and in response to inhalation of oxygen and nitric oxide (NO). We hypothesized that cerebral and muscle tissue oxygenations in PH would be reduced in association with impaired exercise tolerance, and could be improved by oxygen or inhaled NO.

Methods

Study Design

Patients with PH and controls without PH undergoing right heart catheterisation (RHC) had hemodynamic and NIRS evaluations at rest breathing either room air, oxygen or NO, all applied in random order with the patients blinded to respective treatments, and thereafter during supine bicycle exercise.

Patients

From October 2011 to March 2013, all patients (>18y) of both genders scheduled for RHC due to unexplained dyspnoea and suspected PH were eligible upon written informed consent. Patients were excluded if they had significant comorbidity e.g. left heart disease with a pulmonary capillary wedge pressure $\geq$15 mmHg, active psychiatric or neurologic disease, lung disease (forced expiratory volume in 1'' and vital capacity <70 % predicted), renal dysfunction or other relevant comorbidity.

The study was approved by the institutional ethics committee and registered (Clinicaltrials.gov, NCT01463514).

Assessments

Demographics and medical history were noted and physical examination performed. The 6 min walk distance (6MWD) was measured [6].

Right Heart Catheterization

A Swan-Ganz catheter (Swan Ganz CCOmbo V, 8F, Edwards Lifesciences, Irvine, CA 92614, USA) was placed in the pulmonary artery via the right jugular vein. The transducer was placed at 60 % of the back-sternum distance at the presumptive level of the right atrium and zeroed to atmospheric pressure. The following parameters were recorded: heart rate (HR), mean arterial and pulmonary artery pressure (mPAP), pulmonary artery wedge pressure and right atrial pressure. The cardiac output was continuously measured by thermodilution (Vigilance II, Edwards Lifesciences, Irvine CA 92614, USA), and the mixed venous oxygen saturation ($SmvO_2$) was assessed. The mean pressures were calculated as 2x diastolic and 1x systolic PAP/3. Systemic and pulmonary vascular resistance (PVR) were calculated. Selected variables were indexed to body surface area.

Blood Analysis and Oximetry

Arterial and mixed venous blood gases were immediately analysed at baseline and after 100 % oxygen administration (ABL 90 Flex-blood analyzer, Radiometer GmbH). Pulse oximetry was continuously monitored.

Cerebral and Muscle Tissue Oxygenation by NIRS

CTO and QMTO were recorded by NIRS along with changes in cerebral and muscle total haemoglobin concentration (CtHb, MtHb) at a sampling rate of 1/6 Hz (INVOS, Somanetics Corporation, Troy, Michigan, USA). Two optic sensors (optodes) were placed on the left and right forehead above the frontal sinus and at both thighs at the ventral mid-level of the quadriceps muscles.

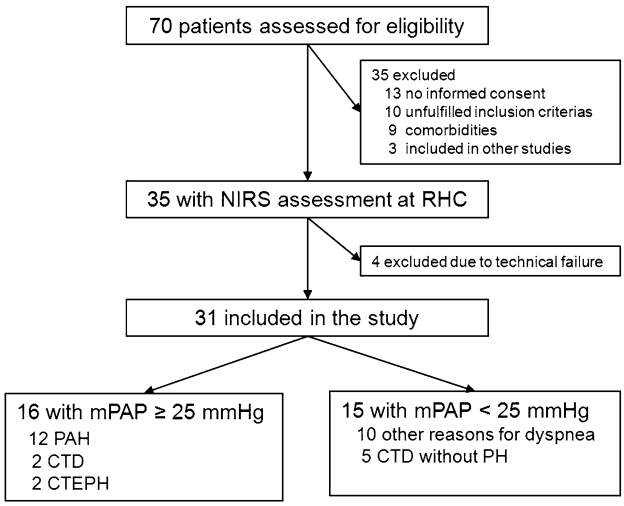

Fig. 1 The flow of patients scheduled for right heart catheterisation and included or excluded to the study is shown. *NIRS* near infrared spectrometry, *RHC* right heart catheter, *mPAP* mean pulmonary arterial pressure, *CTD* connective tissue disease

Interventions During Right Heart Catheterization and Randomization

The following inhalative interventions were performed over 10 min each in a randomized order with the patients blinded to the corresponding treatment. A wash-out period of 10 min separated each application. For randomization, patients had to draw a sequence number from an envelope. After another 10 min of rest, patients performed supine progressive cycle test (TheraVital, Medica Medizintechnick GmbH, Germany) starting with 10 Watts followed by an increase of 10 Watt every 3 min to exhaustion.

Data Analysis and Statistics

Hemodynamic and NIRS measures were averaged over the last minute of baseline and each intervention (room air, oxygen and nitric oxide) and over the final minute of maximal exercise. Mean NIRS data from the left and right body sites are reported. The CtHb and QMtHb were calculated as the sum of oxygenated plus deoxygenated haemoglobin concentration and given in arbitrary units. The main outcome was the CTO, secondary outcomes were the QMTO, arterial oxygen saturation and hemodynamic variables.

As most data were not normally distributed, they were summarized by medians (quartiles). Differences between and within groups (PH-patients vs. controls) were calculated using the Mann–Whitney *U* test and the Wilcoxon matched pair test, respectively. Pearson correlation and multivariate regression analyses were used to evaluate associations of CTO with several physiological and clinical outcomes. A p value $< .05$ was considered statistically significant.

Results

Patients

The patient flow is illustrated in Fig. 1. The analysis includes data from 16 patients (11 females) diagnosed with

Table 1 Characteristics for PH-patients and controls

	Patients (mPAP ≥ 25 mmHg)	Controls (mPAP < 25 mmHg)
Number of participants	16 (11 females)	15 (10 females)
Age (year)	66 (49, 70)	51 (43, 66)
BMI, kg/m^2	29 (24, 32)	25 (22, 29)
NYHA Class (I, II, III, IV)	1 (6 %), 2 (13 %), 9 (56 %), 4 (25 %)	3 (20 %), 6 (40 %), 3 (20 %), 3 (20 %)
6 min walk distance (m)	452 (342, 503)*	520 (510, 591)
Work load during supine cycling (Watt)	30 (20; 40)*	50 (40; 60)
Classification, n (%)		
PH-patients mPAP ≥ 25 mmHg		
Pulmonary arterial hypertension	14 (87.5 %)	NA
Idiopathic	12 (75 %)	
Connective tissue disease	2 (12.5 %)	NA
Chronic thromboembolic	2 (12.5 %)	
Controls mPAP < 25 mmHg		
Connective tissue disease without PH	NA	5 (33 %)
Other reasons for dyspnoea		
(Lung- or heart diseases without PH, deconditioning)	NA	10 (67 %)

Medians (quartiles) or number (%).

PH pulmonary hypertension, *BMI* body mass index, *NYHA* New York Heart Association functional class, *U* Units, *mPAP* mean pulmonary artery pressure

* $p < .05$ vs. controls.

Table 2 Measurements at rest and during supine maximal bicycle exercise in patients with PH and controls

	Rest			Maximal exercise		
	PH	Controls	$p^{\#}$	PH	Controls	$p^{\#}$
Pulmonary hemodynamics and blood oxygenation						
Heart rate (1/min)	85	72	.022	101*	110*	.787
	(69, 92)	(62, 75)		(95, 121)	(99, 122)	
Mean arterial pressure (mmHg)	96	91	.128	122*	103*	.029
	(89, 106)	(78, 98)		(112, 129)	(91, 120)	
Mean pulmonary artery pressure (mmHg)	37	18	.000	54*	29*	.000
	(32, 48)	(17, 20)		(51, 65)	(23, 34)	
Cardiac index (l/min)	3.2	3.2	.711	3.5*	4.7*	.031
	(2.6, 3.6)	(2.7, 3.8)		(3.0, 4.1)	(3.9, 5.1)	
Pulmonary vascular resistance (WU)	4.9	1.2	.000	6.3*	1.5*	.000
	(2.7, 6.4)	(0.9, 1.5)		(4.6, 8.0)	(1.2, 2.5)	
Arterial oxygen saturation (%)	89	95	.001	88	96	.000
	(83, 94)	(94, 96)		(76, 92)	(94, 98)	
Mixed venous oxygen saturation (%)	63	72	.027	35*	45*	.002
	(58, 71)	(68, 74)		(26, 38)	(38, 54)	
Near infrared spectroscopy						
Cerebral tissue oxygenation (%)	62	65	.213	60	68	.010
	(53, 71)	(63, 73)		(53, 65)	(66, 70)	
Cerebral total haemoglobin (unit)	23	22	.470	27*	24	.782
	(20, 28)	(19, 26)		(21, 30)	(21, 32)	
Quadriceps tissue oxygenation (%)	79	78	.446	72*	78	.251
	(68, 82)	(76, 87)		(58, 81)	(69, 83)	
Quadriceps total haemoglobin (unit)	21	21	.800	21	19	.553
	(19, 21)	(19, 22)		(16, 24)	(16, 26)	

Medians (quartiles). *PH* precapillary pulmonary hypertension defined as mean pulmonary artery pressure ≥25 mmHg with a pulmonary artery wedge pressure <15 mmHg

$^{\#}$ p for comparisons between groups; * $p < .05$ compared with rest within group. *WU* Wood units

PH (mPAP ≥ 25 mmHg, 12 idiopathic PAH, 2 associated with connective tissue disease, 2 CTEPH), and from 15 non-PH controls (mPAP < 25 mmHg), 5 scleroderma-patients without PH, 10 patients with other causes of dyspnea: deconditioning, lung and heart diseases without PH. Baseline characteristics are listed in Table 1.

Baseline Measurements and Response to Exercise

According to the selection criteria, we found highly significant differences in baseline mPAP between PH and controls (Tables 1, 2). Patients with PH had a higher heart rate and PVR and a lower SpO_2 and $SmvO_2$. The resting room air baseline CTO, QMTO, CtHb and QMtHb were similar in patients and controls (Table 2; Fig. 2).

During maximal exercise, there was a significantly higher mPAP and PVR along with a lower cardiac index and a lower SpO_2 and $SmvO_2$ in PH-patients compared with controls (Table 2; Fig. 2). As CTO in PH-patients tended to fall during exercise, but increased in controls the values of CTO during maximal exercise were significantly lower in patients than in controls. The CtHb was similar in both groups with exercise; however, it increased significantly from baseline in PH-patients at maximal exercise. QMTO decreased with exercise in PH-patients but not in controls. The QMtHb remained unchanged.

CTO at rest was negatively correlated with age ($R = -.498$, $p = .004$), NYHA functional class ($R = -.469$, $p = .008$) and PVR ($R = -.418$, $p = .019$). CTO at rest was positively correlated with the SpO_2 ($R = .376$, $p = .037$), $SmvO_2$ ($R = .670$, $p < .000$), the maximal work load in watt achieved ($R = .616$, $p < .000$) and the 6MWD ($R = .715$, $p < .000$, Fig. 3a), whereas QMTO did not correlate with the 6MWD ($R = .323$, $p = .094$, Fig. 3b). CTO at maximal exercise was negatively correlated with the PVR ($R = -.660$, $p < .000$) and positively correlated with the 6MWD ($R = .713$, $p < .000$) and maximal workload achieved ($R = .662$, $p < .000$). In a multiple regression model including age, CTO, $SmvO_2$ and PVR, the resting CTO was the best independent predictor

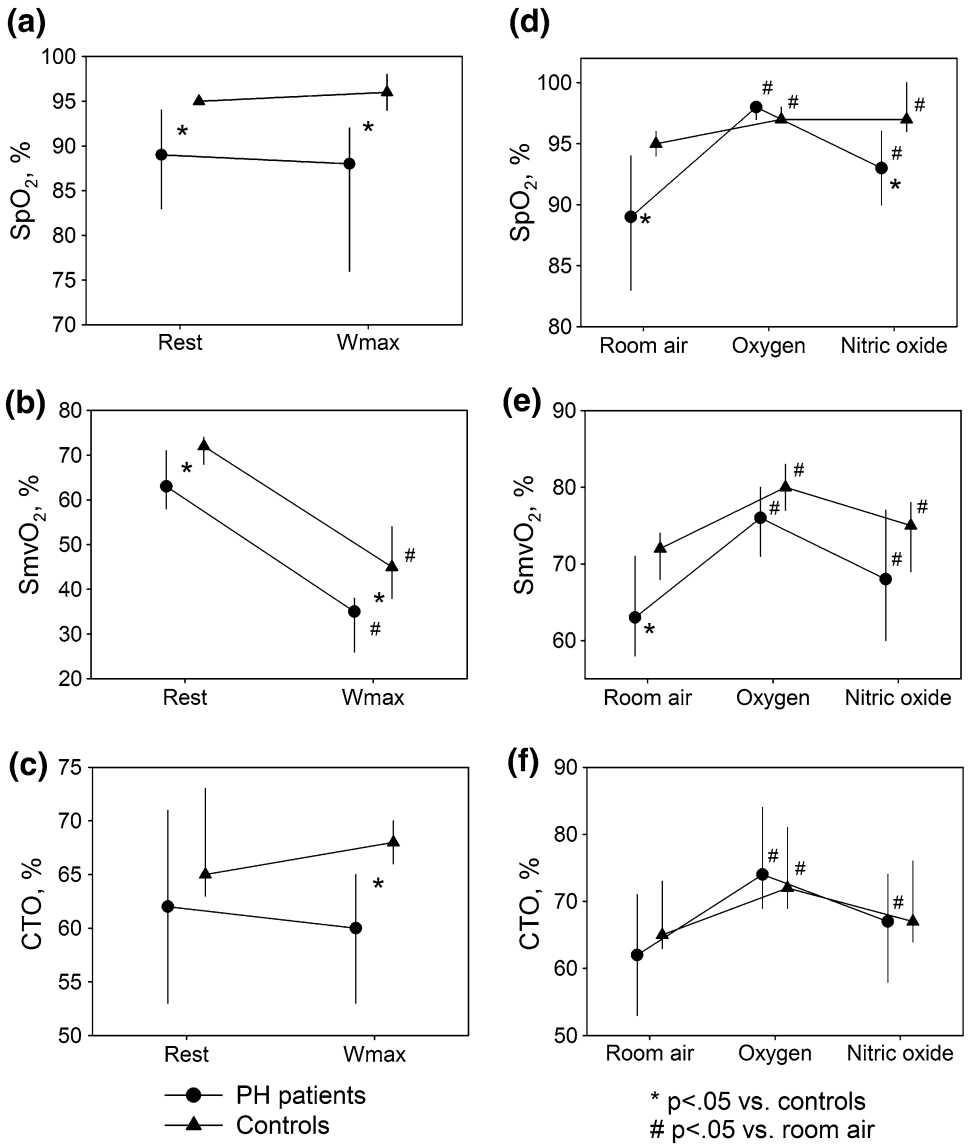

Fig. 2 Arterial oxygen saturation (%), mixed venous saturation (%) and cerebral tissue oxygenation (%) are shown for patients with pulmonary hypertension (PH-patients) and controls without PH during supine rest (baseline, breathing room air) and during bicycle exercise (*left panels* **a** to **c**) and during 100 % oxygen breathing and NO inhalation (*right panels*, **d** to **f**). $^{\#}p < .05$ compared with respective baseline. $^{*}p < .05$ between PH-patients and controls

of the 6MWD (adjusted $R^2 = .511$, $p < .000$). If the same model was applied with the QMTO instead of the CTO, the QMTO did not predict the 6MWD ($p = .773$). In the multiple regression model, CTO at maximal exercise was an independent predictor of the work load in watt achieved (adjusted $R^2 = .419$, $p < .000$) and the 6MWD (adjusted $R^2 = .489$, $p < .000$) in respective models including for age, $SmvO_2$ and the PVR. If the same models were applied with the QMTO instead of the CTO at maximal exercise, the QMTO at maximal exercise did neither predict the 6MWD ($p = .716$) nor the maximal work load achieved ($p = .160$).

Effect of Oxygen and Nitric Oxide

Compared to room air breathing at rest (see values in Table 2), inhalation of 100 % oxygen led to significant decreases in heart rate and mPAP along with significant increases in SpO_2, $SmvO_2$, CTO and QMTO in PH-patients and controls. The decrease in mPAP and the increases in SpO_2, $SmvO_2$, CTO and QMTO were greater in PH compared with controls, resulting in similar oxygenation variables in both groups (Table 3; Fig. 2). CtHb under oxygen was higher in PH-patients compared with controls, the QMtHb was similar.

Compared to air breathing at rest (see values in Table 2), inhalation of NO led to a significant decrease in mPAP along with a significant increase in SpO_2, $SmvO_2$ and QMTO in both, patients and controls (Table 3). NO significantly decreased heart rate and increased CTO in PH-patients only. The increase in QTMO with NO was higher in PH-patients compared with controls.

The increase in CTO with oxygen breathing was correlated with the decrease in mPAP ($R = -.452$, $p = .011$)

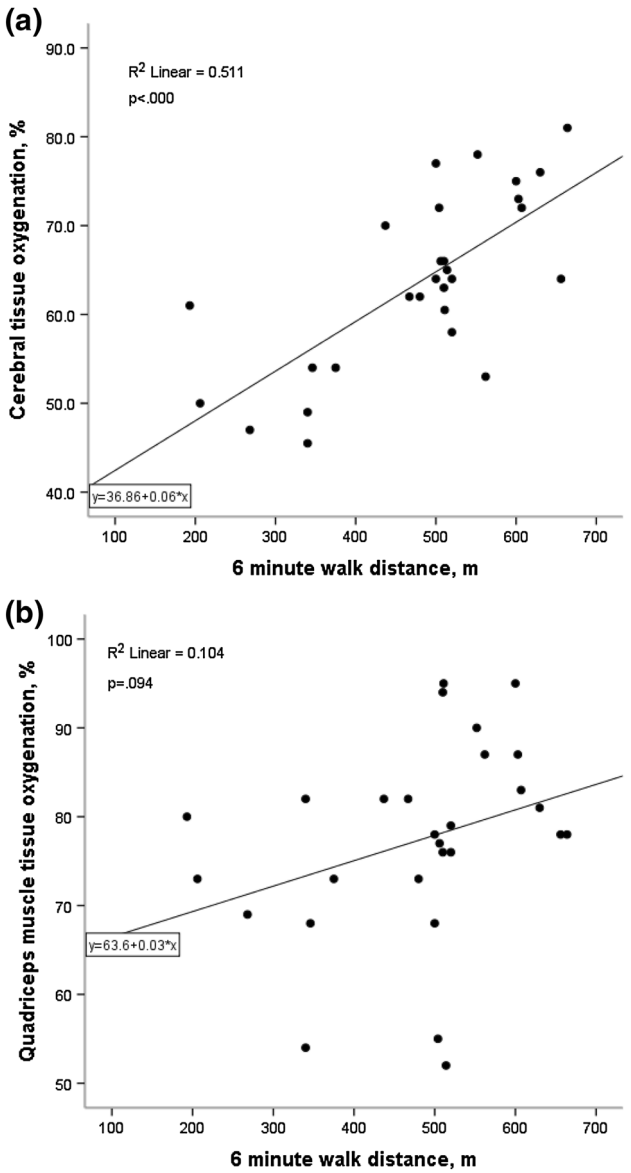

Fig. 3 **a** The significant correlation of the cerebral tissue oxygenation with the 6 min walk distance is shown. The correlation remained highly significant in models including age, mixed venous oxygen saturation and vascular resistance. **b** The lack of correlation of the quadriceps muscle oxygenation with the 6 min walk distance is shown

and the increase in SpO_2 and $SmvO_2$ ($R = .695$, $p < .000$ and $R = .483$, $p = .006$, respectively). Regression analysis revealed that this increase in CTO with oxygen breathing was significantly correlated with the decrease in mPAP ($p = .011$) even when controlled for age.

Under nitric oxide breathing, we found a negative correlation between CTO and PVR ($R = -.391$, $p = .033$) and a positive correlation between CTO and $SmvO_2$ ($R = .482$, $p = .007$). The increase in CTO under NO significantly correlated with the increase in $SmvO_2$ ($R = .400$, $p = .028$).

Discussion

The purpose of this study was to evaluate cerebral, muscle and arterial oxygenation in PH-patients at rest and in response to exercise and inhalation of oxygen and NO in comparison to controls without PH. Our data confirm the hypothesis that exercise was associated with a significantly lower CTO in PH-patients compared with controls. Oxygen breathing improved CTO in both patients and controls but to a greater degree in PH-patients. Nitric oxide increased CTO in PH-patients but not in controls. Since multiple regression analysis indicated that CTO in PH-patients was an independent predictor of the maximal work load achieved and the 6MWD, our data suggest that exercise performance of PH-patients is not only limited by the impaired pulmonary circulation but also by the associated reduction in cerebral oxygenation.

With progressing disease, precapillary PH is associated with a decreased arterial and mixed venous oxygenation mainly due to a decreased cardiac output, a diminished pulmonary capillary bed, ventilation perfusion mismatch and intrapulmonary shunts may additionally play a role [3, 7]. Hypoxaemia in PH is even more pronounced during exercise and sleep and these conditions might result in profound tissue hypoxia [8–10]. For the first time, we used NIRS to non-invasively and simultaneously monitor oxygenation of the brain and of exercising muscles of patients with and without PH in order to better understand the mechanisms of exercise limitation in PH and to evaluate the effects of oxygen and NO in affected patients [4, 5, 11].

In our study, CTO at rest and maximal exercise was an independent predictor of exercise performance, even in multivariate models adjusted for known limiting factors such as age, PVR and $SmvO_2$, whereas QMTO was not (Fig. 3). These findings are interesting and might suggest that a decreasing CTO with progressive disease may reduce motor neuron activation and thereby add to the limited exercise performance of PH-patients [5, 12]. We found that the CTO was significantly lower in PH compared to controls during exercise (Table 2). If one bears in mind that our controls were not healthy controls but rather patients with dyspnoea of various aetiologies other than PH [1], we expect that the difference in CTO between the current PH-patients and healthy controls would be even more pronounced. Studies have shown that in healthy subjects, CTO remains constant during low- and middle intensity exercise, whereas it falls in very hard exercise [5, 11, 13]. Training in healthy subjects is associated with smaller decrease in CTO during exercise [5, 13, 14]; whether the improvement in the 6MWD experienced by certain PH-patients with exercise training is related to improvements in CTO has not been studied. In patients with cardiorespiratory diseases, CTO during exercise was mostly lowered or unchanged, in line with our findings [15]. Thus,

Table 3 Effect of inhaled oxygen and nitric oxide in patients with pulmonary hypertension and controls

	Oxygen			Nitric oxide		
	PH	Controls	$p^{\#}$	PH	Controls	$p^{\#}$
Pulmonary hemodynamics and blood oxygenation						
Heart rate (1/min)	79*	66*	.020	78*	69	.053
	(67, 85)	(61, 72)		(67, 87)	(63, 75)	
Mean arterial pressure (mmHg)	98	91	.173	99	95	.383
	(89, 104)	(79, 99)		(87, 109)	(85, 102)	
Mean pulmonary artery pressure (mmHg)	31*	15*	.000	35*	15*	.000
	(26, 43)	(14, 17)		(27, 45)	(14, 18)	
Cardiac index (l/min)	3.0	2.9	.905	3.1	3.1	.546
	(2.5, 3.2)	(2.5, 3.8)		(2.6, 3.7)	(2.7, 4.0)	
Pulmonary vascular resistance (WU)	3.6*	0.9	.000	3.9	0.9	.000
	(2.9, 5.0)	(0.7, 1.4)		(2.3, 5.1)	(0.7, 1.3)	
Arterial oxygen saturation (%)	98*	97*	.767	93*	97*	.000
	(97, 98)	(97, 98)		(90, 96)	(96, 100)	
Mixed venous oxygen saturation (%)	76*	80*	.138	68*	75*	.104
	(71, 80)	(77, 83)		(60, 77)	(69, 78)	
Near infrared spectroscopy						
Cerebral tissue oxygenation (%)	74*	72*	.635	67*	67	.505
	(69, 84)	(69, 81)		(58, 74)	(64, 76)	
Cerebral total haemoglobin (unit)	25	19	.031	22	20	.429
	(21, 30)	(17, 25)		(19, 28)	(16, 24)	
Quadriceps tissue oxygenation (%)	86*	84*	.797	81*	81*	.588
	(77, 89)	(82, 93)		(74, 86)	(76, 88)	
Quadriceps total haemoglobin (unit)	20	20	.632	21*	21	.472
	(20, 24)	(19, 22)		(20, 25)	(20, 22)	

Data given as median (IQR). *PH* precapillary pulmonary hypertension defined as mean pulmonary artery pressure ≥25 mmHg with a pulmonary artery wedge pressure <15 mmHg.

$^{\#}$ p for comparison between groups; * $p < .05$ compared within groups with respective room air resting values are listed in Table 2

cerebral oxygenation might be a limiting factor for maximal exercise performance [16], which is supported by our results. Studies have shown that age influences regional CTO and that older subjects may recruit other areas of the brain to complete cognitive tasks [17]. In our collective, age correlated with CTO, however, age did not significantly add information in models including CTO at rest and exercise, blood oxygenation or pulmonary haemodynamics in order to predict exercise capacity. Thus, CTO was the best predictor of exercise performance and even a better predictor compared with age, blood oxygenation and haemodynamics (Fig. 3). An improved CTO under hyperoxia was associated with increased exercise capacity in healthy untrained men [18] and in patients with terminal lung diseases [15]. Hyperoxia given to healthy subjects at the point of exhaustion during cycling at hypoxic condition led to continuation of exercise at higher power outputs and the authors concluded that the limiting factor to endurance exercise performance was not the contractile muscle dysfunction but rather the central motor drive to active muscle [19].

In our PH collective, exercise was associated not only with a reduced CTO, but also reduced QMTO. Inadequate O_2 delivery to the skeletal muscle relative to O_2 demands potentially influences the response profile of muscle O_2 extraction and impairs the intramyocytic metabolic machinery leading to increased muscle fatigability and reduced exercise tolerance in PH [4, 20]. In addition to skeletal, also respiratory muscles might suffer from reduced tissue oxygenation and herewith contribute to exercise limitation in PH [21]. However, in our collective, QMTO at rest or maximal exercise was not correlated with the work load achieved during cycling nor the 6MWD. Thus, CTO decline might more be a limiting factor in our PH-patients and not the decline in QMTO.

Another focus of our study was to get insight into acute CTO response to vasodilator therapies. We demonstrated for the first time in PH-patients that the pulmonary vasodilators oxygen and inhaled NO both significantly increased CTO and QMTO along with improved pulmonary hemodynamics and arterial oxygenation (Table 3). Since cardiac index and

systemic blood pressure did not change with oxygen or with NO inhalation in PH-patients, the improvement in CTO with these therapeutics seems to be related to the improved arterial oxygen saturation and oxygen delivery to the brain. In controls, inhalation of NO did not improve CTO, consistent with the lack of hemodynamic changes. Our results in PH-patients are in line with studies in preterm new-born lambs in which administration of iloprost and inhaled NO improved pulmonary hemodynamics and prevented CTO dips [22]. Moreover, in human infants post-operative after cardiac surgery intravenous sildenafil showed a significant increase in CTO underpinning the relevance of improvements in pulmonary circulation for cerebral oxygenation in conditions with PH [23].

In summary, in this first study investigating CTO in PH-patients compared to controls, we found that exercise resulted in a significantly lower CTO in patients compared with controls. Since CTO was correlated independently with the 6MWD in multiple regression models corrected for age and other markers of disease severity these findings may indicate that a reduced cerebral oxygenation may contribute to exercise limitation in PH-patients. Supplemental oxygen increased CTO to a significantly greater extent in PH-patients compared with controls. Inhaled nitric oxide improved CTO in PH-patients but not in controls with normal PVR. Whether long-term vasodilator or oxygen therapy would persistently improve CTO in PH-patients and potentially increase exercise capacity remains to be determined.

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Conflict of interest None of the authors has any financial disclosures in relation to this manuscript.

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