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Relating exercise-induced desaturation and gas-exchange in pulmonary artery hypertension

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ABSTRACT

We measured pulmonary gas exchange during six minute walk test (6MWT) in patients with idiopathic (IPAH) and congenital heart disease-related pulmonary hypertension (CHDPH), and determined the relationship between the degree of desaturation and changes in minute ventilation to carbon dioxide production ($\dot{V}_E\dot{V}CO_2$ and end-tidal partial pressure for carbon dioxide ($P_{et}CO_2$) in both groups. Fifty-two patients (IPAH, n = 28; CHDPH, n = 24) completed 6MWT with simultaneous pulmonary gas exchange. Whilst no significant difference in six minute walk distance was observed between groups (IPAH: 529 ± 89; CHDPH: 476 ± 119 m, p = 0.10), oxygen uptake, carbon dioxide production, and minute ventilation were higher in IPAH than CHDPH ($p < 0.01$). In addition, CHDPH desaturated to a greater extent than IPAH with a lower post-6MWT S_pO_2 (IPAH: 92.3 ± 7.9; CHDPH: 73.3 ± 14.9%, $p < 0.01$). The change in S_pO_2 correlated to the change in $\dot{V}_E/\dot{V}CO_2$ ($r = -0.44$, p = 0.02) and $P_{et}CO_2$ ($r = 0.49$, $p < 0.01$) for CHDPH, but not IPAH. The exercise-induced hypoxic stimulus during 6MWT in CHDPH may be associated with an enhanced ventilatory response.

1. Introduction

Pulmonary hypertension (PH) represents one of the most rapidly growing chronic disease populations in the world. By definition, the hallmark of PH is elevated pulmonary arterial pressures; that is, patients typically diagnosed with a mean pulmonary arterial pressure > 25 mmHg (Hoeper et al., 2013). Whilst there are a number of aetiologies, common symptoms include dyspnea at rest or during mild exercise, reduced exercise tolerance and, right ventricular dysfunction and premature death – particularly if the condition is left untreated (Tonelli et al., 2013). Whilst pharmacotherapy is a well-recognised treatment modality in the management of PH, most patients can remain symptomatic with a poor prognosis despite optimized therapeutic treatment (Tonelli et al., 2013).

Reduced exercise capacity, measured using a six minute walk test (6MWT) or cardiopulmonary exercise test (CPET), are associated with poorer prognosis and long-term outcomes in PH (Galie et al., 2015). We recently demonstrated that both idiopathic (IPAH) and congenital heart disease-related PH (CHDPH) patients have reduced six minute walk distance (6MWD), and that greater ventilatory inefficiency (elevated ventilation per unit carbon dioxide production - $\dot{V}_E/\dot{V}CO_2$) reflects more advanced disease, independent of exercise capacity (Morris et al., 2017). Indeed, previous studies have shown that alterations in $\dot{V}_E/\dot{V}CO_2$ and end-tidal partial pressure for carbon dioxide ($P_{et}CO_2$) during exercise are associated with PH disease severity and prognosis (Markowitz and Systrom, 2004; Oudiz et al., 2007; Oudiz et al., 2010). Moreover, there is now evidence that survival may be worse for patients that tend to desaturate to a greater extent during exercise (Manes et al., 2014). We reported that patients with CHDPH desaturated to a greater extent (approximately 3 fold) than those with IPAH during 6MWT despite obtaining a similar 6MWD (Morris et al., 2017). Given that hypoxia is known to result in increased firing of peripheral chemoreceptors (Prabhakar and Peng, 2004), which serve to stimulate a greater drive for breathing (Sun et al., 2001; Woods et al., 2011), it may be argued that patients with CHDPH would demonstrate greater alterations in $\dot{V}_E/\dot{V}CO_2$and $P_{et}CO_2$ compared to patients with IPAH during a 6MWT. Determining how these pulmonary gas exchange parameters are altered during 6MWT may be particularly important for clinicians when discerning between various aetiologies and severities of PH, and when other differential diagnoses are possibly being considered (Markowitz

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and Systrom, 2004).

Therefore, the purpose of this study was to measure pulmonary gas exchange during 6MWT in IPAH and CHDPH patients and to determine the relationship between the degree of desaturation and changes in $\dot{V}_E/\dot{V}CO_2$ and $P_{et}CO_2$ in both groups. We hypothesized that the level of desaturation would be correlated to the change in $\dot{V}_E/\dot{V}CO_2$ and $P_{et}CO_2$ in patients with CHDPH, but not in those with IPAH.

2. Methods

The data presented in this article were collected as part of a larger study describing pulmonary gas exchange measurements during 6MWT, and how these parameters were related to the severity of PH (Morris et al., 2017). However, the current article addresses a different question and we repeat only the methods and data essential to the novel findings presented here.

2.1. Participants

A total of 52 individuals; 36 men and 16 women attending a tertiary PH referral center were included in this study. Participants were categorized into two sub-groups according to their diagnoses: idiopathic (IPAH, n = 28) and congenital heart disease-related PH (CHDPH, n = 24). In addition, each participant was assigned a New York Heart Association Functional Classification (NYHA FC I, II, III or IV) by their attending physician. Prior to all testing, the study purpose and experimental protocols were disclosed, and all participants provided informed consent. The experimental procedures were reviewed and approved by the Metro North Hospital and Health Service, Human Research Ethics Committee, The Prince Charles Hospital (HREC/14/QPCH/47), and complies with the guidelines set out in the Declaration of Helsinki.

2.2. Experimental design

All participants underwent a 6MWT, which was performed in accordance with standard guidelines (ATS statement, 2002). Pulmonary gas exchange was measured using indirect calorimetry (Metamax, Cortex BXB, Lepzig, Germany) throughout the 6MWT. At each minute of the 6MWT, the severity of dyspnea was determined using a 0–10 scale of breathlessness.

2.3. Pulmonary gas exchange

During the 6MWT, each participant breathed through a mask (Hans Rudolph, Kansas City, USA) for the collection and analysis of expired gases. The metabolic system was calibrated for volume and expired concentrations of oxygen and carbon dioxide prior to each test. Minute-by-minute measurements of oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}_E$), $\dot{V}_E/\dot{V}CO_2$, $P_{et}CO_2$, and oxygen saturation (S_pO_2) were recorded. Oxygen pulse ($\dot{V}O_2$/heart rate) was also calculated.

2.4. Echocardiography

As a part of standard clinical protocol, all participants underwent echocardiographic evaluation of cardiac function on the same day as their 6MWT. Two-dimensional (2-D) and pulsed-wave Doppler echocardiography were performed using a Vivid 7 ultrasound system (GE Healthcare, Milwaukee, WI, USA) equipped with a 4 MHz matrix-array transducer (M3S cardiac transducer; GE Healthcare, Milwaukee, WI, USA). Echocardiography was performed in accordance with the guidelines published by the American Society of Echocardiography (Lang et al., 2015). Right ventricular systolic pressure (RVSP) was determined from tricuspid regurgitation, and right ventricular systolic function was determined by assessing the tricuspid annular plane systolic excursion (TAPSE).

2.5. Statistical analysis

Statistical analysis was performed using SPSS 22.0 (SPSS Inc, Chicago, IL, USA). Between-group participant characteristics, 6MWD, and cardiovascular measures were assessed using independent samples *t*-tests. A two-way mixed analysis of variance with repeated-measures for time (pre- vs post-6MWT) was performed to examine whether pulmonary gas exchange measures differed between groups (IPAH and CHDPH). Pair-wise comparisons using Bonferroni adjustments were applied when a significant main effect was detected. Linear regression analyses were performed to compare the change in S_pO_2 to the change in $P_{et}CO_2$, $\dot{V}_E/\dot{V}CO_2$, and $\dot{V}_E$ during the 6MWT. Statistical significance was accepted at $p < 0.05$. All data are presented as mean ± standard deviation.

3. Results

3.1. Participant characteristics

There were no differences in age, height, weight, and BMI between groups ($p > 0.05$), and participants were either NYHA FC II or III with a similar proportion of each functional classification in both aetiology sub-groups (Table 1). Additionally, mean RVSP, TAPSE, and left ventricular ejection fraction were similar between each sub-group ($p > 0.05$).

3.2. 6MWD and cardiovascular measurements

6MWD and end-exercise cardiovascular measurements for both groups are displayed in Table 2. There were no differences in 6MWD, heart rate (when expressed as an absolute value and % predicted), or breathlessness between groups ($p > 0.05$); however, CHDPH demonstrated a lower O_2 pulse and six minute walk work compared to IPAH (both $p < 0.01$).

3.3. Pulmonary gas exchange

There was a significant increase in $\dot{V}O_2$ (Fig. 1, Panel A), $\dot{V}CO_2$(Fig. 1, Panel B), and $\dot{V}_E$ (Fig. 1, Panel C) for both sub-groups (all $p < 0.01$); however, these measures were higher in IPAH than CHDPH at the end of the 6MWT (all $p < 0.01$). In addition, whilst CHDPH commenced the 6MWT with a lower S_pO_2 compared to IPAH ($p < 0.05$) (Fig. 1, Panel D), CHDPH desaturated to a greater extent than IPAH during 6MWT with a lower post-6MWT S_PO_2 ($p < 0.01$).

For CHDPH, there was a significant association between the change

Table 1
Participant characteristics.

	IPAH (n = 28)	CHDPH (n = 24)
Age (yr)	46 ± 15	41 ± 14
Height (m)	1.7 ± 0.1	1.6 ± 0.1
Weight (kg)	77 ± 18	61 ± 11*
BMI (kg/m^2)	27 ± 5	23 ± 4
Male/female	17/11	19/5
NYHA FC (II/III)	19/9	18/6
RVSP (mmHg)	79 ± 25	86 ± 23
TAPSE (mm)	20 ± 4	16 ± 4
LVEF (%)	64 ± 6	61 ± 10
Mono	7	16
Dual	12	5
Triple	9	13

Data are mean ± SD. IPAH: idiopathic pulmonary arterial hypertension participants; CHDPH: congenital heart disease-related pulmonary hypertension participants; BMI: body mass index; NYHA FC; New York Heart Association Functional Class; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; LVEF: left ventricular ejection fraction.

* Significantly different between groups, $p < 0.05$.

Table 2
End-exercise cardiovascular measurements.

	IPAH (n = 28)	CHDPH (n = 24)
Six minute walk distance (m)	529 ± 89	476 ± 119
Six minute walk work (kg/m)	40839 ± 12156	29098 ± 8473*
Heart rate (beats/min)	139 ± 23	125 ± 27
Heart rate (% predicted)	80 ± 12	72 ± 17
Breathlessness (0-10)	3.4 ± 1.4	3.4 ± 1.7
O_2 pulse (ml/beat)	8.0 ± 2.7	6.1 ± 1.7*

Data are mean ± SD. IPAH: idiopathic pulmonary arterial hypertension participants; CHDPH: congenital heart disease-related pulmonary hypertension participants.

* Significantly different between groups, $p < 0.05$.

in S_pO_2 and the change in $P_{et}CO_2$ (Fig. 2, Panel A) and $\dot{V}_E/\dot{V}CO_2$ (Fig. 2, Panel B) during the 6MWT. There was no significant relationship between the change in S_pO_2 and the change in $\dot{V}_E$ (Fig. 2, Panel C) during 6MWT. For the IPAH group, the change in S_pO_2 was not significantly associated with changes in $P_{et}CO_2$ (Fig. 2, Panel D), $\dot{V}_E/\dot{V}CO_2$ (Fig. 2, Panel E), and $\dot{V}_E$ (Fig. 2, Panel F) during the 6MWT.

4. Discussion

This is the first study to examine the relationship between the degree of desaturation and changes in $\dot{V}_E/\dot{V}CO_2$ and $P_{et}CO_2$ during 6MWT in IPAH and CHDPH patients. The findings of the present study showed that CHDPH patients had a lower $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}_E$during 6MWT than IPAH, and that CHDPH patients also desaturated to a greater extent with a lower end-exercise S_pO_2 compared to IPAH. In accordance with our hypothesis, the degree of desaturation was significantly associated with changes in $\dot{V}_E/\dot{V}CO_2$ and $P_{et}CO_2$ for CHDPH patients during 6MWT, but not in those with IPAH.

Only a few studies to date have examined pulmonary gas exchange responses during 6MWT in patients with PH. Specifically, Deboeck et al (2005) assessed pulmonary gas exchange responses in PH patients during 6MWT and more recently, Mainguy et al (Mainguy et al., 2014) assessed pulmonary gas exchange responses in PH patients to a range of different exercise tests including 6MWT, incremental exercise test, incremental shuttle walk test and endurance shuttle walk test. Notably, the patients included in both of these studies were of mixed aetiologies (i.e., idiopathic, connective tissue disease, congenital, portal hypertension and fenfluramine-related PH). Whilst the sub-groups of patients were not examined independently, both of these studies reported similar 6MWD and end-exercise $\dot{V}O_2$ values to that described in our previous work which measured gas exchange responses during 6MWT in PH patients (Morris et al., 2017), as well as that demonstrated in the current study.

Similar to our previous work (Morris et al., 2017), the difference in exercise capacity between sub-groups was highlighted by pulmonary gas exchange measurements, whereby a significantly lower $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}_E$ was observed in CHDPH patients compared to IPAH. While both groups demonstrated a similar 6MWD, patients with CHDPH performed less work during the 6MWT than those with IPAH. This was evidenced by CHDPH demonstrating a lower six minute walk work than IPAH patients. These findings, as well as the findings of previous studies (Deboeck et al., 2005; Mainguy et al., 2014; Morris et al., 2017), suggest that the addition of pulmonary gas exchange measurements to a 6MWT may improve the sensitivity of the test in discerning between various aetiologies and severities of PH.

Patients with PH typically exhibit elevated $\dot{V}_E/\dot{V}CO_2$ accompanied

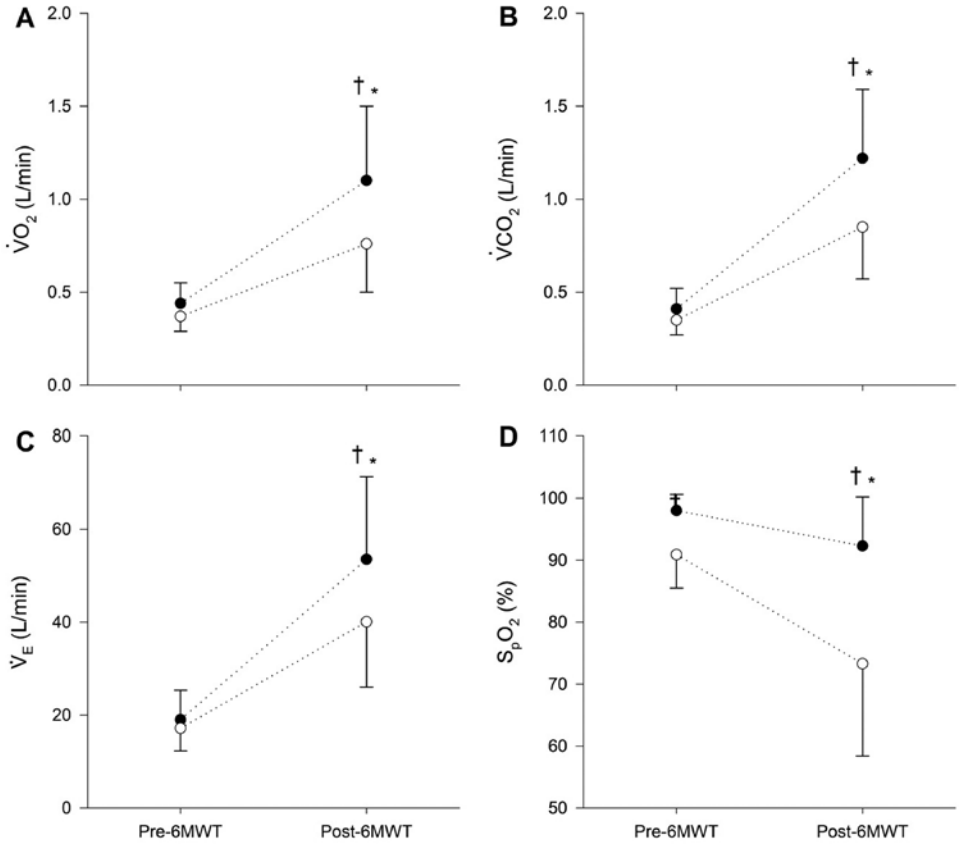

Fig. 1. $\dot{V}O_2$ (Panel A), $\dot{V}CO_2$ (Panel B), $\dot{V}_E$(Panel C), and S_pO_2 (Panel D) measured pre- and post-6MWT for patients with IPAH (closed circles) and CHDPH (open circles). IPAH: idiopathic pulmonary arterial hypertension participants; CHDPH: congenital heart disease-related pulmonary hypertension participants; $\dot{V}O_2$: rate of oxygen consumption; $\dot{V}CO_2$: rate of carbon dioxide production; $\dot{V}_E$: minute ventilation; S_pO_2: oxygen saturation. Data are mean ± SD. †Significantly different between groups, $p < 0.05$; *Significantly different from Pre-6MWT, $p < 0.05$.

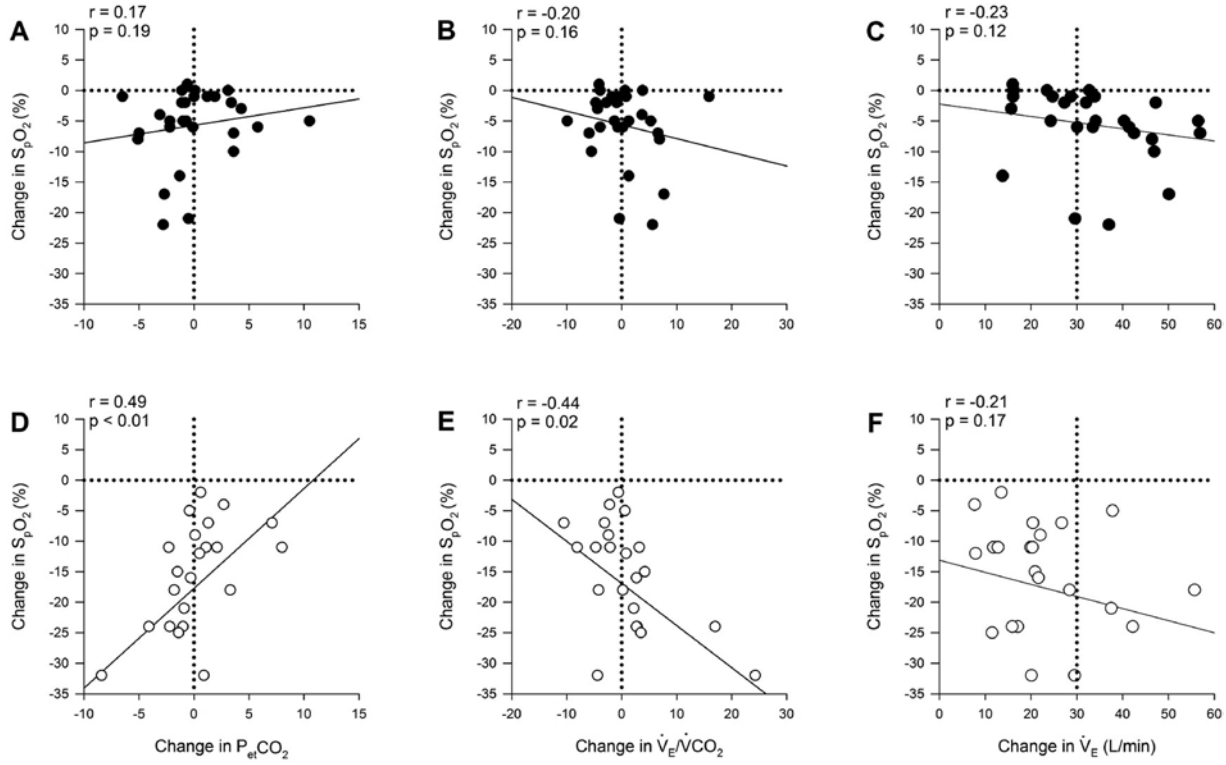

Fig. 2. Correlation plots comparing the change in $P_{et}CO_2$ (Panels A and D), the change in $\dot{V}_E/\dot{V}CO_2$ (Panels B and E), and the change in $\dot{V}_E$ (Panels C and F) against the change in S_pO_2 during 6MWT for patients with IPAH (closed circles) and CHDPH (open circles). IPAH: idiopathic pulmonary arterial hypertension participants; CHDPH: congenital heart disease-related pulmonary hypertension participants; $P_{et}CO_2$: end-tidal partial pressure for carbon dioxide; $\dot{V}_E$: minute ventilation; S_pO_2: oxygen saturation.

by a decreased $P_{et}CO_2$ during exercise, and often at rest. Indeed, previous studies have shown that alterations in $\dot{V}_E/\dot{V}CO_2$ and $P_{et}CO_2$ during exercise are associated with PH disease severity and prognosis (Markowitz and Systrom, 2004; Oudiz et al., 2007, 2010). While the exact mechanisms of abnormal ventilatory function remain unclear, several possible interacting mechanisms have been proposed. These include increased pulmonary vascular resistance, resulting in right ventricular (RV) dysfunction and a blunted cardiac output during exercise (Sun et al., 2001; van de Veerdonk et al., 2011). RV dysfunction is characterised by increased RV end-diastolic and end-systolic volumes during exercise, which would eventually result in left ventricular dysfunction. Furthermore, it must be noted that exercise results in an increased right-to-left shunting, which would also facilitate a larger desaturation in these patients (Sun et al., 2002). Consequently, active skeletal muscles become hypo-perfused causing an early onset of lactic acidosis and a subsequent increase in non-metabolic CO_2 production. The subsequent increase in non-metabolic CO_2 may lead to an increased drive to breathe, and a subsequent increase in $\dot{V}_E/\dot{V}CO_2$ (Paolillo et al., 2012). Consistent with this suggested mechanism is that an early production of metabolic by-products in active skeletal muscle has been shown to play an important role in an increase in $\dot{V}_E/\dot{V}CO_2$ in patients with chronic heart failure (Olson et al., 2010). In a classic study, Olsen et al (Olson et al., 2013) blocked the activity group III and IV afferent fibres supplying the ergoreceptors/metaboreceptors in heart failure patients during submaximal exercise and reported a significant reduction in $\dot{V}_E/\dot{V}CO_2$. As such, these authors concluded that the increased activity from the ergoreceptors/metaboreceptors during exercise results in an increased afferent input to the respiratory control centre, leading to an increased drive to breathe.

In addition to the increase in non-metabolic CO_2 production, it is likely that peripheral chemoreceptors may be stimulated secondary to exercise-induced arterial hypoxaemia (Prabhakar and Peng, 2004). Of note, CHDPH patients desaturated to a greater extent during 6MWT than IPAH in the present study. Indeed, the observed degree of desaturation in CHDPH in the present study could result in an increased activity of peripheral chemoreceptors, which would serve to stimulate a greater drive for breathing in this sub-group of PH patients (Sun et al., 2001; Woods et al., 2011). Consistent with this suggestion is that the greater degree of desaturation during the 6MWT was related to the increased ventilatory drive in patients with CHDPH, whereby the reduction in S_pO_2 was strongly correlated to the increase in $\dot{V}_E/\dot{V}CO_2$ and decrease in $P_{et}CO_2$. Therefore, these findings suggest that the exercise-induced hypoxaemic stimulus may be related to an enhanced ventilatory response in CHDPH patients. It must be acknowledged, however, that whilst the underlying mechanism for arterial hypoxaemia remains unclear, a ventilation-perfusion mismatch, a shortened red blood cell transit time through the restricted pulmonary vascular bed, and a reduced diffusion capacity have previously been proposed (Steenhuis et al., 2000). Furthermore, the degree of desaturation was not related to the change in V_E in both groups. Hence it may be argued that examining V_E for a fixed CO_2 production during the 6MWT is a more effective way of assessing the increased ventilatory response in these patients.

5. Considerations

Right heart catheter data was not obtained for all participants at the time when their first 6MWT was conducted. As a result, RVSP – derived using echocardiography – was used as a surrogate for invasive pulmonary arterial pressures. All echocardiography data were reported by the same cardiologist for all participants. Furthermore, PH is a condition of significant heterogeneity and we have only examined limited sub-groups of a cohort of Group I patients. It is possible that other sub-groups of PH patients may have different pulmonary gas exchange responses during a 6MWT; however, this is beyond the scope of the current study. Future studies should examine this notion directly.

6. Conclusions

The current experiment represents the only study to date to have examined the relationship between the degree of desaturation and changes in $\dot{V}_E/\dot{V}CO_2$ and $P_{et}CO_2$ during 6MWT in IPAH and CHDPH patients attending a tertiary PH referral centre. Our findings demonstrate that the degree of desaturation was strongly correlated with the change in $\dot{V}_E/\dot{V}CO_2$ and $P_{et}CO_2$ for CHDPH patients. We propose that the exercise-induced hypoxic stimulus may be associated with an enhanced ventilatory response in CHDPH patients, but not in those with IPAH.

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Disclosures

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