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ABSTRACT

It is unknown whether hypoxemia, a hallmark of fibrotic interstitial lung disease (*f*-ILD), may impair cerebral oxygenation during exercise in these patients.

Twenty-seven patients [23 males, 72±8 years, lung diffusing capacity for carbon monoxide (DL_{CO})= 44±11% predicted] and 12 controls performed an incremental bicycle test. Prefrontal oxygenation [tissue saturation index (TSI)] was assessed by near-infrared spectroscopy.

Patients showed lower arterial O_2 saturation (SpO_2) and larger fall in cerebral TSI during exercise *vs* controls ($p<0.05$). However, changes (Δ) from rest to peak-exercise in SpO_2 (-2.2% to -26.9%) and TSI (1.4% to -16.6%) varied substantially among patients. In the 16 patients showing significant cerebral deoxygenation (Δ TSI ≥4% based on controls), SpO_2 decreased more (-12.6±6.7% *vs* -5.7±2.8%, $p=0.001$) and peak O_2 uptake was lower (68.3±19.2% *vs* 87.8±24.8% predicted, $p=0.03$) *vs* their 11 counterparts. In association with DL_{CO} and forced vital capacity, Δ cerebral TSI independently predicted peak O_2 uptake on multivariable regression analysis ($R^2=0.54$).

Exertional hypoxemia impairs cerebral oxygenation in a dose-dependent fashion in *f*-ILD. Future studies are warranted to investigate whether this potentially reversible abnormality play a contributory role in limiting exercise tolerance in these patients.

Abstract word count: 185

Keywords: exercise test; hypoxia; hypoxia, brain; pulmonary fibrosis; spectroscopy, near-infrared.

1. INTRODUCTION

Adequate oxygen (O_2) delivery to the brain during exercise is critically dependent on cerebral blood flow (CBF) and arterial O_2 content (CaO_2). (Smith and Ainslie, 2017) In healthy humans, impaired cerebral O_2 delivery has been related to the development of central fatigue i.e. a reduction in central motor output to the peripheral muscles. (Amann et al., 2007; Verges et al., 2012) The inhibition of the descending central drive is particularly relevant in the presence of severe hypoxemia (Amann et al., 2007) and may translate into increased perception of effort/fatigue upon exertion. (Amann et al., 2007; Millet et al., 2012) It follows that impaired cerebral oxygenation might contribute to poor exercise tolerance in chronic respiratory diseases associated with low CaO_2. (Goodall et al., 2014a)

In this context, fibrotic interstitial lung disease (*f*-ILD) constitutes a group of disorders in which profound exercise-related hypoxemia is a cardinal feature. (Du Plessis et al., 2018) Although exercise intolerance in *f*-ILD is characteristically multi-factorial [e.g. impaired pulmonary gas exchange, abnormalities in respiratory mechanics, cardio-circulatory abnormalities (Agusti et al., 1991; Faisal et al., 2016; Hansen and Wasserman, 1996)], the influence of severe hypoxemia on cerebral oxygenation during exercise in these patients is currently unknown. Several investigations previously showed that an impairment in cerebral oxygenation may contribute to a reduction in exercise tolerance in diverse chronic cardiorespiratory diseases. (Marillier et al., 2018b; Oliveira et al., 2016; Oliveira et al., 2012) Patients with *f*-

ILD may also present with limited ability of increasing cardiac output to compensate for a severely reduced CaO_2. Pulmonary micro-vasculopathy, hypoxia-induced pulmonary vasoconstriction and, as observed in some patients, overt pulmonary hypertension (Han et al., 2013; Patel et al., 2007) may hinder these compensatory haemodynamic adjustments aiming at preserving O_2 delivery under these conditions. Additionally, recent findings suggest a role for exertional hypoxemia towards reduced brain perfusion and atrophy in patients with idiopathic pulmonary fibrosis. (Hett, 2019) Collectively, these premises suggest a hitherto unexplored contributory role for cerebral hypoxia in decreasing *f*-ILD patients' tolerance to dynamic exercise.

We therefore aimed to: (i) investigate the effect of exercise-related hypoxemia on cerebral oxygenation in patients with *f*-ILD and, (ii) determine whether impairment in cerebral oxygenation, when present, is associated with poorer exercise tolerance in these patients. We hypothesized that (i) increased severity of exertional hypoxemia would be associated with poorer cerebral oxygenation in patients with *f*-ILD and, (ii) impaired cerebral oxygenation would be associated with poorer exercise tolerance in this patient population.

2. MATERIALS AND METHODS

2.1. Participants. Twenty-seven patients with well-established *f*-ILD (using clinical, physiological, high-resolution computed tomography and, in selected cases, histopathological criteria) were recruited from the Division of Respirology's ILD clinic

(Kingston, Canada) between November 2018 to February 2020 to participate in the present prospective study. Patients were considered for study inclusion if they did not experience any ILD exacerbation requiring oral corticosteroids within the previous 3 months. Twelve healthy controls, matched for age, sex and body-mass index, were recruited from a list of sedentary subjects who had previously participated in clinical studies in our Laboratory or via advertisement. Participants refrained from intense physical activity on the two days prior to the tests and were asked to abstain from drinking caffeinated beverages on test days. This study was approved by the Queen's University Research Ethics Board (DMED-2150-18). All participants gave their written informed consent prior to their participation in the study.

2.2. Resting procedures. Self-reported physical activity and dyspnea burden on daily activities were assessed with the Baecke Physcial Activity Questionnaire and the MRC dyspnea scale, respectively. (Baecke et al., 1982; Fletcher et al., 1959) Spirometry, static lung volumes and lung diffusing capacity for carbon monoxide (DL_{CO}) were performed using automated equipment (Vmax229d; SensorMedics, Yorba Linda, CA). Values were compared to those predicted by specific regression equations. (Quanjer et al., 2012; Quanjer et al., 1993; Stanojevic et al., 2017)

2.3. Incremental cardiopulmonary exercise test. Subjects exercised on a computer-controlled electronically-braked cycle ergometer (Ergoline 800s™; SensorMedics, Yorba Linda, CA) with breath-by-breath gas analysis and ECG measurement

(SensorMedicsVmax229d™ system). After a 3-min resting period, workload was increased by 5-15 W (according to patient's reported dyspnea burden) every 2 min until symptom limitation. Arterial O_2 saturation was measured continuously by earlobe pulse oximetry (SpO_2; Masimo Radical 7, Masimo Corp., Irvine, CA). Participants were not required to stop exercise based on SpO_2 readings. Dyspnea and leg discomfort scores (0-10 category-ratio Borg scale) (Borg, 1982) and dynamic inspiratory capacity were obtained in the last 30 seconds of each stage. Reference equations for peak work rate and O_2 uptake were the ones from Blackie and colleagues. (Blackie et al., 1989)

2.4. Near-infrared spectroscopy (NIRS). Left prefrontal cortex oxy- (HbO_2) and deoxyhemoglobin (HHb) concentration changes were measured throughout the testing sessions using a two-wavelength (690 and 830 nm), frequency-domain multidistance NIRS system (Imagent, ISS Inc., Champaign, IL). NIRS signal was assessed between Fp1 and F3 locations according to the international 10-20 EEG system with an interoptode distance of 2.0 to 3.5 cm. The cortical probe was secured to the skin with double-sided tape and maintained with a latex swim cap. HbO_2 and HHb are measured as differences from the initial rest period during the exercise test. Total haemoglobin concentration (HbTot) was calculated as the sum of HbO_2 and HHb. NIRS parameters reflect the dynamic balance between O_2 demand and supply in the tissue microcirculation: HbO_2 and HbTot are mostly sensitive to blood flow and O_2 delivery while HHb is closely associated with changes in venous O_2 content and therefore tissue O_2 extraction (Ferrari and Quaresima, 2012; Rolfe, 2000). Tissue saturation index (TSI) was calculated as the

ratio of HbO_2 over HbTot and is considered as a reliable estimate of change in tissue (de-)oxygenation status (Rooks et al., 2010).

2.5. Data analysis. Cardiorespiratory and NIRS data were averaged over the last 30 s of the resting period and over the last 30 s of each increment during exercise. Patients were categorized according to the presence of cerebral deoxygenation defined as a ≥ 4% drop in cerebral TSI during exercise. This 4% threshold was used to contrast *f*-ILD patients for cerebral deoxygenation as none of the 12 healthy subjects of similar sex, age and body-mass index (**Table 1**) showed a decrease above 3% (range: +7 to -3%) in cerebral TSI at the peak of incremental cycling in the present study.

2.6. Statistical analysis. All statistical procedures were performed on Statistica v.10 (Statsoft, Tulsa, OK, USA). Owing to the fact that the study's main outcome (cerebral oxygenation) has not been previously reported in fibrotic interstitial lung disease (*f*-ILD), we could not perform an "a priori" sample size calculation for the present study. Based on our sample size (N= 27 in patients with *f*-ILD, N= 12 in controls), α=0.05, and considering the results provided in the manuscript i.e. changes in cerebral TSI from rest to the peak of incremental cardiopulmonary exercise testing= -4.7 ± 4.2 % *vs* +1.7 ± 2.8% [mean difference (95% confidence intervals) = -6.4% (-9.1%; -3.7%); p<0.001] in patients with *f*-ILD and controls, respectively, the estimated post-hoc power of the present study was however 100%. For between-group comparisons, unpaired t-test or Mann-Whitney U test were used for continuous and discrete variables, respectively. χ^2 were used to

compare frequencies. SpO_2 and NIRS data collected throughout exercise were analyzed by using two-way [group (healthy controls *vs* patients with *f*-ILD showing *vs* showing no significant cerebral deoxygenation) × exercise time (rest, 20%, 40%, 60%, 80%, 100% of individual exercise duration)] ANOVA. Bonferroni post-hoc tests were applied to adjust *p*-value for multiple comparisons if ANOVA revealed a statistically significant main effect or interaction. Relationships between exercise-related hypoxemia [peak-exercise SpO_2 and changes in SpO_2 from rest to peak exercise (Δ SpO_2)] and cerebral oxygenation (Δ TSI from rest to peak exercise) and between cerebral oxygenation and exercise tolerance (peak O_2 uptake) in patients with *f*-ILD were evaluated by Pearson product-moment correlation and bivariate linear regression analysis. A stepwise backward multivariable regression analysis was performed to identify predictors of exercise tolerance in these patients. For all statistical analyses, a two-tailed alpha level of 0.05 was used as the cut-off for significance. Data are presented as mean ± SD or median [interquartile range] for continuous and discrete variables, respectively.

3. **RESULTS**

3.1. Participants' characteristics

Resting characteristics of healthy controls and patients with *f*-ILD are presented in **Table 1**. Healthy controls and patients with *f*-ILD had similar sex, age and body-mass index. Patients with *f*-ILD reported higher smoking history and daily dyspnea burden and lower physical activity compared to healthy controls (p<0.05). Lung volumes and DL_{CO} were lower in patients with *f*-ILD compared to controls (p<0.05). There was no

significant difference in anthropometric characteristics, smoking history, daily dyspnea burden, self-reported physical activity and pulmonary function between patients showing (n=16) or not (n=11) cerebral deoxygenation during exercise. In addition, the prevalence of idiopathic pulmonary fibrosis was similar in patients showing (12/16; 75%) or not (8/11; 73%) cerebral deoxygenation (p>0.05). Additional information regarding the clinical history and associated comorbidities of healthy controls and patients with *f*-ILD are provided in **Supplementary Table S1**.

3.2. Incremental cardiopulmonary exercise testing

Physiological and perceptual responses at the peak of incremental cardiopulmonary exercise testing in healthy controls and patients with *f*-ILD are presented in **Table 2**. In comparison to healthy controls, patients with *f*-ILD had lower peak work rate, peak O_2 uptake, heart rate (% predicted) and tidal volume and higher respiratory rate, ventilatory equivalent for carbon dioxide (CO_2) and ventilatory limitation (p<0.05). They presented with lower peak-exercise SpO_2 and end-tidal carbon dioxide pressure and larger Δ SpO_2 and Δ cerebral TSI than controls (p<0.05). Patients with *f*-ILD showing significant cerebral deoxygenation during exercise presented with larger exercise-related hypoxemia and lower peak O_2 uptake (% predicted) compared to other patients (p<0.05). Peak work rate and O_2 uptake were strongly associated (r=0.80; p<0.001) in our sample of participants. Despite exercising at lower absolute work rates, patients with *f*-ILD had greater scores of dyspnea throughout exercise in comparison to

controls (main effect of group, F = 12.3, p<0.001). Leg discomfort did not differ between groups (main effect of group, F = 1.4, p=0.25; **Figure 1**).

3.3. Effect of exercise-related hypoxemia on cerebral oxygenation in *f*-ILD

Δ HbO_2, Δ HHb and Δ HbTot as a function of exercise time during incremental cycling in healthy controls and patients with *f*-ILD are shown in **Figure 2**. Δ HbO_2 values were lower in patients with cerebral deoxygenation at 60% of exercise duration *vs* healthy controls and at 80 and 100% of exercise duration *vs* others (group × exercise time interaction, F = 6.0, p <0.001). Δ HHb values were greater in patients showing cerebral deoxygenation at 40% of exercise duration *vs* healthy controls and at 60, 80 and 100% of exercise duration *vs* others (group × exercise time interaction, F = 6.7, p <0.001). No difference was observed between groups for Δ HbTot (p >0.05). Δ SpO_2 and Δ cerebral TSI as a function of exercise time during incremental cycling in healthy controls and patients with *f*-ILD are shown in **Figure 3**. Δ SpO_2 was larger in patients showing cerebral deoxygenation at 40% of exercise duration *vs* healthy controls and at 60, 80 and 100% of exercise duration *vs* others; Δ SpO_2 at peak was also larger in patients showing no cerebral deoxygenation *vs* healthy controls (group × exercise time interaction, F = 7.3, p <0.001). Δ cerebral TSI at any exercise time was larger in patients showing cerebral deoxygenation *vs* others except at 20% for controls (group × exercise time interaction, F = 11.4, p<0.001). Δ cerebral TSI was significantly associated with peak-exercise SpO_2 (R^2=0.46, r=0.70; p<0.001) and Δ SpO_2 (R^2= 0.55, **Figure 4**) in patients with *f*-ILD.

3.4. Effect of impaired cerebral oxygenation on exercise tolerance in *f*-ILD

Peak O_2 uptake (% predicted) was significantly associated with Δ cerebral TSI (R^2=0.26, **Figure 5**) and Δ SpO_2 (R^2=0.11, r=0.38; *p*=0.047) in patients with *f*-ILD. On the other hand, peak work rate (% predicted) was not significantly associated with Δ cerebral TSI (*p*=0.71). On a multivariable regression analysis, Δ cerebral TSI, DL_{CO} and forced vital capacity (% predicted), independently predicted peak O_2 uptake (% predicted) (**Table 3**).

4. DISCUSSION

The present study is the first to investigate the influence of hypoxemia on cerebral oxygenation during physical exertion and its consequences on exercise tolerance in patients with *f*-ILD. We found that i) exertional hypoxemia was associated with impaired cerebral oxygenation in a dose-dependent fashion in patients with *f*-ILD and, ii) impairment in cerebral oxygenation was an independent predictor of poor exercise tolerance in this patient population. These findings indicate that profound exercise-related hypoxemia, a cardinal feature of *f*-ILD, may impair cerebral oxygenation, which, in turn, may contribute to decreasing exercise tolerance in these patients. The latter assertion, however, requires further investigation in interventional studies offering measurements of central fatigue.

4.1. Influence of hypoxemia on cerebral oxygenation during exercise

Impaired cerebral oxygenation is a consistent finding in healthy individuals exercising in hypoxia or at high altitude. (Marillier et al., 2020b; Rupp and Perrey, 2009; Subudhi et al., 2009) Although some studies reported an increase in CBF (Goodall et al., 2014b; Rasmussen et al., 2010; Subudhi et al., 2009) to compensate for a reduced CaO_2, cerebral O_2 delivery and oxygenation during exercise in hypoxia were found to be reduced (Goodall et al., 2012; Goodall et al., 2014b). This reduction in cerebral O_2 delivery may hold particularly true at high intensity of exercise in hypoxia and potentially constitute a signal to limit exercise capacity under such conditions (Vogiatzis et al., 2011). In chronic cardiorespiratory diseases, exercise-related hypoxemia has also been related to a poorer cerebral oxygenation. (Oliveira et al., 2016; Oliveira et al., 2012) For instance, diverging patterns of cerebral oxygenation were observed in patients with chronic obstructive pulmonary disease with or without exercise-induced O_2 desaturation in response to incremental cycling. (Oliveira et al., 2012) The severity of exertional hypoxemia in *f*-ILD, however, finds no parallel in respiratory medicine. (Du Plessis et al., 2018) A major advantage of the present study is the large variability in the extent of exercise-related hypoxemia experienced by patients with *f*-ILD to explore its effect on cerebral oxygenation (**Figure 3** and **4**). In fact, we found that exercise-related hypoxemia on its own explained ~50% of the variance in cerebral oxygenation on exertion (**Figure 4**). In this context, the remaining inter-individual variability in cerebral deoxygenation during exercise might be explained by other factors such as changes in CBF or cerebral metabolism. (Smith and Ainslie, 2017) Our data rather suggest that impairment in cerebral oxygenation in *f*-ILD may mostly be secondary to a low CaO_2 (i.e. an altered

balance between HbO_2 and HHb) rather than impaired CBF since similar HbTot (a surrogate of CBF) kinetics were observed during exercise in our 3 groups (**Figure 2**). Further studies providing comprehensive measurement of cerebral hemodynamics in *f*-ILD are yet warranted to confirm this assumption.

Patients with *f*-ILD presenting with mild to moderately-severe exercise-related hypoxemia (peak-exercise SpO_2= 85-94% (Dempsey and Wagner, 1999)) had preserved cerebral oxygenation in two thirds of cases (**Figure 4**). Different compensatory mechanisms aiming at preserving cerebral oxygenation under low levels of CaO_2 may have been brought into play. (Smith and Ainslie, 2017) Arterial blood gases (CO_2 in particular) have a major influence on CBF during exercise. (Smith and Ainslie, 2017) CBF increases as arterial partial pressure of O_2 falls below 60 mmHg (Ogoh et al., 2013) (SpO_2 ~90% (Madan, 2017)). In fact, a 0.5-2.5% increase in CBF typically occurs for each % reduction in SpO_2. (Hoiland et al., 2016) Milder decline in SpO_2, leading to a lesser increase in hypoxia-induced hyperventilation, may also prevent large drop in arterial partial pressure of CO_2. (Hoiland et al., 2018) This may help maintain greater CBF as any reduction of 1 mmHg in CO_2 levels has been associated with a 1-3% decrease in brain perfusion. (Willie et al., 2014) In the present study, we found no difference in end-tidal carbon dioxide pressure during exercise in patients showing significant cerebral deoxygenation and their counterparts (**Table 2**) and no association between end-tidal carbon dioxide pressure and Δ TSI or HbTot (an index of CBF) at peak exercise (data not shown). It is noteworthy that, however, end-tidal carbon dioxide pressure may poorly reflect arterial partial pressure of CO_2 in this population due to significant ventilation-

perfusion mismatch. In patients in whom exercise-related hypoxemia further intensified (peak-exercise SpO_2 <85%), cerebral oxygenation was systemically compromised (**Figure 4**). Oxygen therapy is commonly prescribed for patients with *f*-ILD although there is currently limited evidence supporting its clinical benefits (Khor et al., 2017); this may hold particularly true in case of isolated exertional hypoxemia (Johannson et al., 2017). Interestingly, exertional SpO_2 <85% coincides with a recent experts' consensus in which this threshold was established to recommend supplemental O_2 therapy in these patients with *f*-ILD. (Lim et al., 2019) Supplemental O_2 therapy may, therefore, be prescribed not only to help alleviate symptoms (e.g. dyspnea or cough) and functional impairment attributable to hypoxemia as proposed in this document (Lim et al., 2019) but also to preserve O_2 delivery to the organ the most in need: the brain.

4.2. Physiological consequences of impaired cerebral oxygenation

In the present study, patients with *f*-ILD showing significant cerebral deoxygenation during exercise (a priori defined as a ≥ 4% drop in cerebral TSI based on our sample of healthy matched controls) presented with greater exercise-related hypoxemia and poorer tolerance to physical exertion (peak O_2 uptake % predicted) compared to other patients (**Table 2**). In fact, larger cerebral deoxygenation was independently associated with a lower tolerance to exercise in our population (**Table 3**). Interestingly, exercise-related hypoxemia was not identified as an independent predictor of exercise tolerance:

monitoring cerebral oxygenation, in addition to systemic oxygenation, may therefore be of particular interest in a clinical setting in *f*-ILD.

In patients with *f*-ILD showing mild to moderately-severe exertional hypoxemia, an impairment of the descending motor drive to the exercising muscles, the so-called central fatigue (Verges et al., 2012), may have arisen from a heightened stimulation of peripheral muscles' afferences (Amann et al., 2009): poorer O_2 delivery to the working muscles, due to a low CaO_2, has been associated with disturbance in muscle metabolic milieu (Allen et al., 2008). However, in the context of severe hypoxemia, a marked reduction in cerebral oxygenation may promote an impairment of the descending motor drive independently of muscle afferences during exercise. (Goodall et al., 2014a) It follows that impaired cerebral oxygenation, and, consequently, central fatigue are typically considered as major contributors to exercise limitation when SpO_2 ≤75%. (Goodall et al., 2014a; Verges et al., 2012) Interestingly, almost 50% of *f*-ILD patients showing significant cerebral deoxygenation presented with peak-exercise SpO_2 ≤80%. While alterations in respiratory mechanics and cardio-circulatory abnormalities typically assume a prominent role in impeding exercise tolerance in patients with *f*-ILD (Agusti et al., 1991; Faisal et al., 2016; Hansen and Wasserman, 1996), the intensified severity of cerebral hypoxia may have been a pivotal mechanism in this subset of patients. Yet, this assumption remains to be confirmed since, for instance, supplemental O_2 (fraction of inspired O_2= 1.0) or heliox prolonged endurance time in patients with chronic obstructive pulmonary disease despite similar cerebral cortex O_2 delivery compared to room air, suggesting that an improvement in cerebral cortex O_2 availability

does not hold a contributing role in enhancing exercise capacity in these patients (Vogiatzis et al., 2013). Of note, chronic hypoxemia has been related to a lower supraspinal motor drive objectively assessed with neurostimulation techniques and, consequently, poorer exercise performance in other respiratory disorders. (Alexandre et al., 2016; Marillier et al., 2018a)

Beyond its contribution to exercise intolerance, repeated bouts of cerebral hypoxia during daily life physical activity might have additional deleterious physiological consequences in *f*-ILD. Recurrent exposure to cerebral hypoxia, in combination with an increased prevalence of atherosclerosis observed in elderly individuals (Uryga and Bennett, 2016) might enhance the risk of ischemic stroke in *f*-ILD. In fact, intermittent hypoxia (hypothetically experienced if alternating phases of exercise and rest) has been shown to increase the occurrence of stroke due to endothelial dysfunction. (Beaudin et al., 2017) It is also conceivable that long-term exposure to cerebral hypoxia might lead to negative cognitive outcomes in patients with *f*-ILD. For instance, chronic exposure to intermittent hypoxia secondary to upper airway obstruction in sleep apnea has been related to brain structural alterations. (Rosenzweig et al., 2015) These structural impairments may illustrate cognitive disorders (memory, attention, learning and executive function (Bucks et al., 2017)) typically observed in these patients. (Rosenzweig et al., 2015) Seminal findings have recently suggested a role for exertional hypoxemia towards reduced brain perfusion and atrophy in patients with idiopathic pulmonary fibrosis. (Hett, 2019) Yet, the implication of these results in terms of cerebrovascular events and cognitive outcomes remains to be investigated in *f*-ILD.

4.3. Limitations and perspectives

NIRS is only suitable for investigating cerebral hemodynamics in structures that are not deeper than approximately 2–3 cm below the surface of the brain (Perrey, 2008). It also allows the investigation of restricted brain areas (e.g. prefrontal cortex). However, this cerebral region may be of particular interest: the role of the prefrontal cortex in exercise tolerance and termination has been recently emphasized (Robertson and Marino, 2016). In fact, the prefrontal cortex is involved in motivational and decision-making processes and may act as a relay station in the central fatigue related network regulating central command through peripheral feedback (Perrey, 2015). Moreover, assessing this brain area may be of further interest due to its implication in different cognitive processes (i.e. executive function, attention and memory) (Miller and Cohen, 2001). Comprehensive measurement of CBF (e.g. using transcranial Doppler) and the influence of arterial blood gases on brain perfusion would provide additional insights into cerebral hemodynamics during exercise in patients with *f*-ILD. Patients with respiratory disorders typically avoid strenuous physical activity (Guthrie et al., 2001), which might dampen the translation of our results in daily life. Yet, larger exercise-induced hypoxemia (owing to a larger muscle mass and, therefore, greater O_2 extraction) is usually found in response to walking compared to cycling. This might translate into larger cerebral deoxygenation in patients with *f*-ILD. Although exercise-induced hypoxemia has been shown to impair muscle oxygenation and exacerbate peripheral muscle fatigue in patients with *f*-ILD (Marillier et al., 2020a), our assumptions relating

impaired cerebral oxygenation to the subsequent development of central fatigue are of inferential nature. Future research using neurostimulation techniques to objectively assess central/supraspinal mechanisms of fatigue (e.g. transcranial magnetic stimulation (Marillier et al., 2017)) and intervention (e.g. O_2 supplementation) in this population would help confirm this hypothesis. Such investigations may help identify patients in whom impaired cerebral O_2 delivery assume a prominent role in exercise limitation due to exaggerated neuromuscular fatigue.

4.4. Conclusion

The present study innovates by investigating the influence of exertional hypoxemia on cerebral oxygenation and its consequences on exercise tolerance in patients with *f*-ILD. Our main findings indicate that exertional hypoxemia does impair cerebral oxygenation in a dose-dependent fashion in these patients, being independently related to exercise capacity. Reversing cerebral hypoxia with O_2 supplementation may have positive effects on patients' disablement beyond those expected from lower ventilation and dyspnea, an issue that deserves further investigation.

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Table 1. Resting characteristics of healthy controls and patients with *f*-ILD. Patients were categorized by the presence (+) or not (-) of cerebral deoxygenation during incremental cardiopulmonary exercise testing.

		***f*-ILD**		
	Controls (n=12)	**All patients (n=27)**	**(-) Cerebral deoxygenation (n=11)**	**(+) Cerebral deoxygenation (n=16)**
Sex	9 ♂ / 3 ♀	23 ♂ / 4 ♀	10 ♂ / 1 ♀	13 ♂ / 3 ♀
Age (years)	73.3 ± 8.9	71.6 ± 8.1	74.6 ± 7.1	69.6 ± 8.4
BMI ($kg \cdot m^{-2}$)	27.3 ± 3.2	28.3 ± 3.5	28.7 ± 3.9	28.0 ± 3.3
Smoking history ($pack \cdot year^{-1}$)	2 ± 4	21 ± 18 *	23 ± 21	19 ± 16
Questionnaires				
MRC	1.0 [0.0]	2.0 [1.0] *	2.0 [1.0]	3.0 [2.0]
Baecke	7.9 [1.1]	7.3 [1.6] *	6.6 [1.9]	7.3 [1.3]
Pulmonary function				
FEV_1 (% pred)	99.1 ± 16.6	73.6 ± 15.5 *	78.7 ± 16.9	70.1 ± 14.0
FVC (% pred)	107.1 ± 13.9	75.9 ± 20.2 *	79.6 ± 22.5	73.4 ± 18.8
FEV_1/FVC (%)	71.0 ± 7.2	75.6 ± 10.2	76.5 ± 9.4	74.9 ± 10.9
TLC (% pred)	98.5 ± 11.2	65.3 ± 15.0 *	67.6 ± 15.0	63.6 ± 15.3
RV (% pred)	87.3 ± 20.8	49.5 ± 15.1 *	50.4 ± 9.6	48.9 ± 18.2
FRC (% pred)	90.1 ± 15.1	61.2 ± 16.4 *	60.7 ± 17.2	61.5 ± 16.4
IC (% pred)	108.4 ± 18.4	79.1 ± 20.9 *	86.7 ± 19.6	73.9 ± 20.8
DL_{CO} (% pred)	91.7 ± 16.9	43.5 ± 10.7 *	47.8 ± 10.0	40.5 ± 10.5

Data are mean ± SD or median [interquartile range]. BMI: body mass index; DL_{CO}: lung diffusing capacity for carbon monoxide; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; FVC: forced vital capacity; IC: inspiratory capacity; *f*-ILD: fibrotic interstitial lung disease; MRC: Medical Research Council; RV: residual volume; TLC: total lung capacity. * $p<0.05$: patients with *f*-ILD *vs* healthy controls.

Table 2. Physiological and perceptual responses of healthy controls and patients with *f*-ILD at the peak of cardiopulmonary exercise testing. Patients were categorized by the presence (+) or not (-) of cerebral deoxygenation during cardiopulmonary exercise testing.

		***f*-ILD**		
	Controls (n=12)	**All patients (n=27)**	**(-) Cerebral deoxygenation (n=11)**	**(+) Cerebral deoxygenation (n=16)**
Power/Metabolic/cardiovascular				
Work rate (W)	109.8 ± 20.7	75.3 ± 22.7 *	82.1 ± 16.0	70.6 ± 25.8
Work rate (% pred)	80.6 ± 21.4	53.9 ± 13.8 *	56.4 ± 10.7	52.1 ± 15.7
VO_2 (mL·kg·min^{-1})	21.5 ± 4.1	14.9 ± 3.6 *	15.9 ± 3.1	14.3 ± 3.9
VO_2 (% pred)	110.0 ± 30.8	76.3 ± 23.3 *	87.8 ± 24.8	68.3 ± 19.2 †
HR (bpm)	137.6 ± 16.7	125.1 ± 19.5	128.3 ± 20.4	123.0 ± 19.3
HR (% pred)	94.0 ± 11.8	84.3 ± 12.7 *	88.2 ± 14.0	81.6 ± 11.3
Ventilatory				
V_E (L)	67.0 ± 17.1	61.8 ± 16.0	64.0 ± 18.2	60.3 ± 14.8
V_E/VCO_2	33.0 ± 4.3	43.2 ± 7.8 *	41.2 ± 6.5	44.6 ± 8.5
V_T/IC (%)	72.2 ± 13.6	85.2 ± 15.7 *	83.6 ± 13.1	86.4 ± 17.5
V_E/MVV (%)	71.6 ± 22.4	87.4 ± 22.2 *	84.7 ± 24.0	89.2 ± 21.4
V_T (L)	2.07 ± 0.42	1.54 ± 0.43 *	1.69 ± 0.40	1.44 ± 0.44
RR (breaths·min^{-1})	32.9 ± 5.5	41.8 ± 10.9 *	39.3 ± 12.4	43.6 ± 9.7
Pulmonary gas exchange				
SpO_2 (%)	97.3 ± 0.6	85.2 ± 7.7 *	90.4 ± 3.0	81.7 ± 8.0 †
Δ SpO_2 (%)	-0.3 ± 1.0	-9.8 ± 6.4 *	-5.7 ± 2.8	-12.6 ± 6.7 †
$P_{ET}CO_2$ (mmHg)	35.1 ± 3.9	30.8 ± 4.1 *	31.2 ± 4.7	30.5 ± 3.8
Cerebral oxygenation				
Δ TSI (%)	1.7 ± 2.8	-4.7 ± 4.2 *	-0.8 ± 1.4	-7.4 ± 3.3 †
Symptoms				
Dyspnea/work rate	0.034 [0.018]	0.057 [0.031] *	0.054 [0.009]	0.063 [0.045]
Leg discomfort/work rate	0.045 [0.026]	0.058 [0.040]	0.068 [0.035]	0.048 [0.046]

Data are mean ± SD or median [interquartile range]. HR: heart rate; IC: inspiratory capacity; *f*-ILD: fibrotic interstitial lung disease; MVV: maximal voluntary ventilation; $P_{ET}CO_2$: end-tidal carbon dioxide pressure; RR: respiratory rate; SpO_2: oxygen saturation by

pulse oximetry; Δ SpO_2: difference between peak and resting oxygen saturation values; VCO_2: carbon dioxide output; V_E: minute ventilation; V_E/VCO_2: ventilatory equivalent for CO_2; VO_2: oxygen uptake; V_T: tidal volume; Δ TSI: difference between peak and resting values in cerebral tissue saturation index. ***** $p<0.05$: patients with *f*-ILD *vs* healthy controls. **†** $p<0.05$: patients with *f*-ILD showing *vs* showing no cerebral deoxygenation.

Table 3. Stepwise backward multivariable regression analysis to predict exercise tolerance (peak O_2 uptake, % predicted) in patients with fibrotic interstitial lung disease.

Independent predictors	B	95% confidence interval	*p*	Adjusted R^2
DL_{CO} (% predicted)	0.804	0.149–1.459	0.018	0.538
Δ TSI (%)	1.916	0.297–3.534	0.022	
FVC (% predicted)	0.385	0.039–0.732	0.031	
Constant	21.048	-15.139–57.234		

In addition to lung diffusing capacity for carbon monoxide (DL_{CO}), difference between peak and resting values in cerebral tissue saturation index (Δ TSI) and forced vital capacity (FVC), variables initially considered in the multivariable model were: total lung capacity (% predicted), inspiratory capacity (% predicted), peak exercise O_2 saturation by pulse oximetry (SpO_2, %), difference between peak and resting values in SpO_2 (Δ SpO_2, %), peak exercise tidal volume/inspiratory capacity and minute ventilation/maximal voluntary ventilation ratios and ventilatory equivalent for carbon dioxide nadir.

FIGURE LEGENDS

Figure 1. Scores of dyspnea (panel a) and leg discomfort (panel b) as a function of exercise time during incremental cycling in healthy controls and patients with fibrotic interstitial lung disease (*f*-ILD) who presented (+) or not (-) with significant cerebral deoxygenation.

Data are mean ± SD and are slightly shifted at each exercise time to avoid overlap. ***** $p<0.05$: both groups of patients with *f*-ILD *vs* healthy controls (main effect of group).

Exercise times (i.e. 20% to 100% of exercise duration) correspond to an absolute work rate of (mean ± SD) 24 ± 8, 44 ± 9, 65 ± 14, 86 ± 17 and 110 ± 21 W in controls, 15 ± 0, 32 ± 7, 50 ± 12, 67 ± 14 and 82 ± 16 W in patients with no significant cerebral deoxygenation and 15 ± 6, 29 ± 11, 44 ± 16, 58 ± 20 and 71 ± 26 W in those presenting with significant cerebral deoxygenation, respectively.

Figure 2. Changes in (Δ) prefrontal cortex oxy- (HbO_2, panel a), deoxy- (HHb, panel b) and total (HbTot, panel c) hemoglobin concentration as a function of exercise time during incremental cycling in healthy controls and patients with fibrotic interstitial lung disease (*f*-ILD) who presented (+) or not (-) with significant cerebral deoxygenation.

Data are mean ± SD and are slightly shifted at each exercise time to avoid overlap. ***** $p<0.05$: patients with *f*-ILD *vs* healthy controls; **†** $p<0.05$: patients with *f*-ILD showing *vs* showing no cerebral deoxygenation for Δ HbO_2, HHb or HbTot at a specific exercise time.

Exercise times (i.e. 20% to 100% of exercise duration) correspond to an absolute work rate of (mean ± SD) 24 ± 8, 44 ± 9, 65 ± 14, 86 ± 17 and 110 ± 21 W in controls, 15 ± 0, 32 ± 7, 50 ± 12, 67 ± 14 and 82 ± 16 W in patients with no significant cerebral deoxygenation and 15 ± 6, 29 ± 11, 44 ± 16, 58 ± 20 and 71 ± 26 W in those presenting with significant cerebral deoxygenation, respectively.

Figure 3. Changes in (Δ) oxygen saturation by pulse oximetry (SpO_2) and cerebral tissue saturation (TSI) as a function of exercise time during incremental cycling in healthy controls and patients with fibrotic interstitial lung disease (*f*-ILD) who presented (+) or not (-) with significant cerebral deoxygenation.

Data are mean ± SD and are slightly shifted at each exercise time to avoid overlap. Dashed line indicates the threshold for cerebral deoxygenation defined as a ≥ 4% drop in cerebral TSI during exercise. ***** $p<0.05$: patients with *f*-ILD *vs* healthy controls; **†** $p<0.05$: patients with *f*-ILD showing *vs* showing no cerebral deoxygenation for Δ SpO_2 or Δ TSI at a specific exercise time.

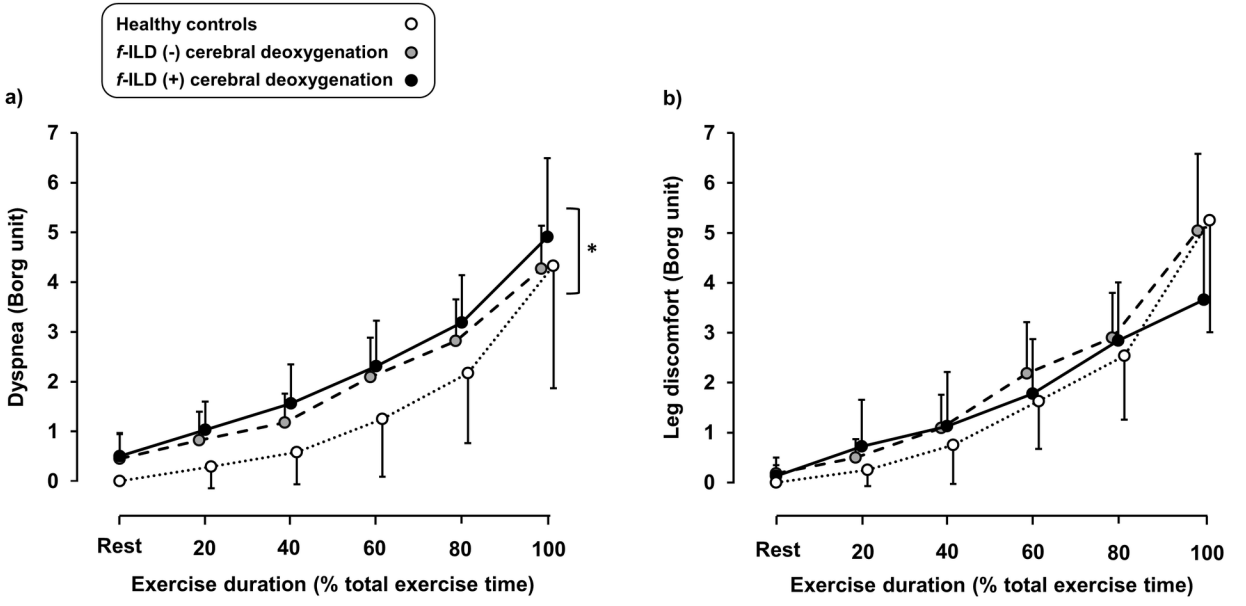
Exercise times (i.e. 20% to 100% of exercise duration) correspond to an absolute work rate of (mean ± SD) 24 ± 8, 44 ± 9, 65 ± 14, 86 ± 17 and 110 ± 21 W in controls, 15 ± 0, 32 ± 7, 50 ± 12, 67 ± 14 and 82 ± 16 W in patients with no significant cerebral deoxygenation and 15 ± 6, 29 ± 11, 44 ± 16, 58 ± 20 and 71 ± 26 W in those presenting with significant cerebral deoxygenation, respectively.

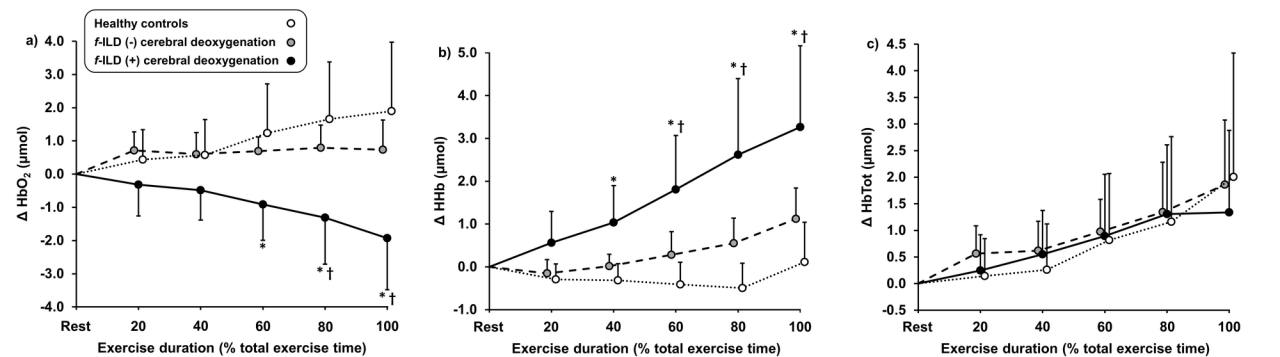
Figure 4. Relationship between changes from rest to peak exercise (Δ) in cerebral tissue saturation index and Δ O_2 saturation by pulse oximetry (Δ SpO_2) in patients with fibrotic interstitial lung disease who presented (+) or not (-) with significant cerebral deoxygenation.

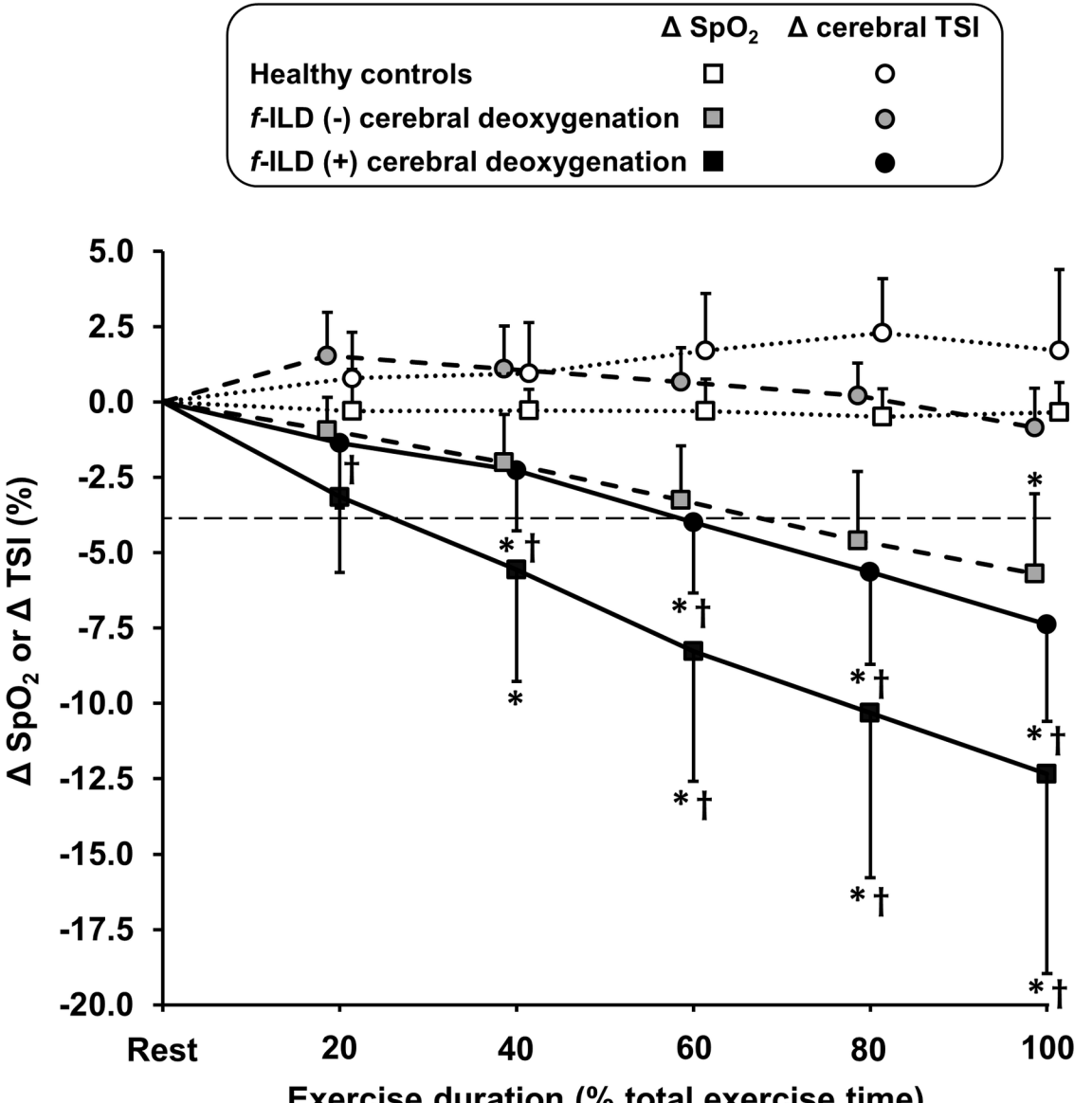
Dashed line indicates the threshold for cerebral deoxygenation defined as a ≥ 4% drop in cerebral tissue saturation index during exercise.

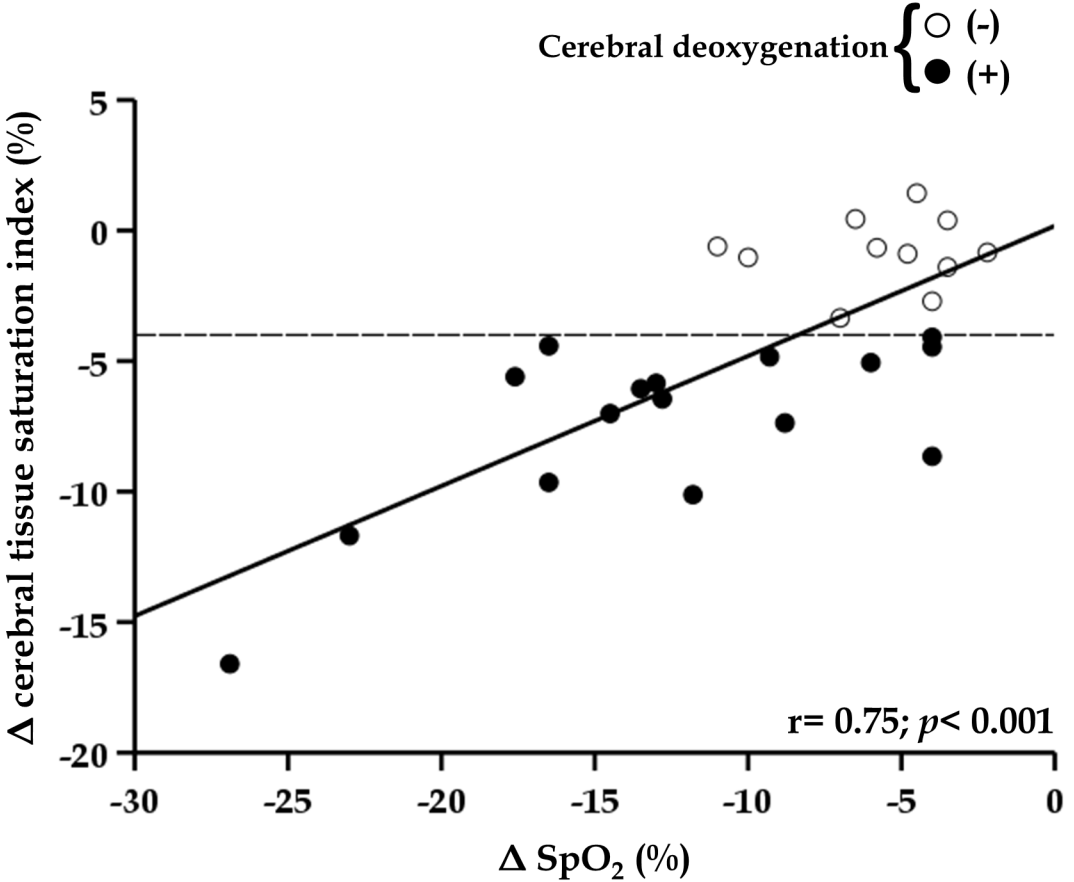
Figure 5. Relationship between changes from rest to peak exercise (Δ) in cerebral tissue saturation index and exercise tolerance (peak O_2 uptake, % predicted) in patients with fibrotic interstitial lung disease who presented (+) or not (-) with significant cerebral deoxygenation.

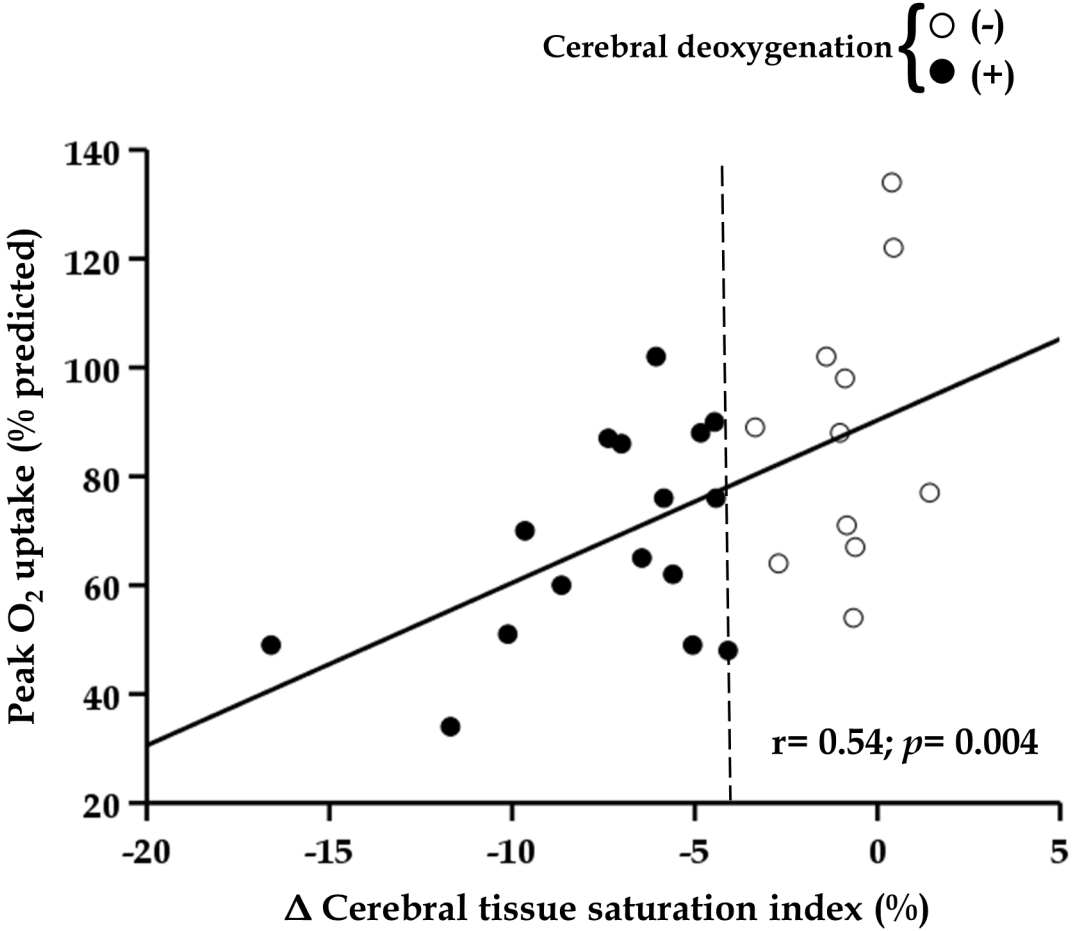
Dashed line indicates the threshold for cerebral deoxygenation defined as a ≥ 4% drop in cerebral tissue saturation index during exercise.


Healthy controls
f-ILD (-) cerebral deoxygenation
f-ILD (+) cerebral deoxygenation
a)
Dyspnea (Borg unit)
0
1
2
3
4
5
6
7
*
Rest
20
40
60
80
100
Exercise duration (% total exercise time)
b)
Leg discomfort (Borg unit)
0
1
2
3
4
5
6
7
Rest
20
40
60
80
100
Exercise duration (% total exercise time)


a)
Healthy controls
f-ILD (-) cerebral deoxygenation
f-ILD (+) cerebral deoxygenation
Δ HbO2 (μmol)
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
-4.0
*
*†
*†
Rest
20
40
60
80
100
Exercise duration (% total exercise time)
b)
Δ HHb (μmol)
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
*
*†
*†
*†
Rest
20
40
60
80
100
Exercise duration (% total exercise time)
c)
Δ HbTot (μmol)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Rest
20
40
60
80
100
Exercise duration (% total exercise time)


Δ SpO2
Δ cerebral TSI
Healthy controls
f-ILD (-) cerebral deoxygenation
f-ILD (+) cerebral deoxygenation
5.0
2.5
0.0
-2.5
-5.0
-7.5
-10.0
-12.5
-15.0
-17.5
-20.0
Δ SpO2 or Δ TSI (%)
Rest
20
40
60
80
100
Exercise duration (% total exercise time)


Cerebral deoxygenation
(-)
(+)
Δ cerebral tissue saturation index (%)
5
0
-5
-10
-15
-20
-30
-25
-20
-15
-10
-5
0
Δ SpO2 (%)
r= 0.75; p< 0.001


Cerebral deoxygenation
(-)
(+)
140
120
100
80
60
40
20
Peak O_2 uptake (% predicted)
-20
-15
-10
-5
0
5
Δ Cerebral tissue saturation index (%)
r= 0.54; p= 0.004