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Peripheral chemoresponsiveness during exercise in male athletes with exercise-induced arterial hypoxaemia

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Abstract

Exercise-induced arterial hypoxaemia (EIAH) is characterized by a decrease in arterial oxygen tension and/or saturation during whole-body exercise, which may in part result from inadequate alveolar ventilation. However, the role of peripheral chemoresponsiveness in the development of EIAH is not well established. We hypothesized that those with the most severe EIAH would have an attenuated ventilatory response to hyperoxia and hypercapnia during exercise. To evaluate this, on separate days, we measured ventilatory sensitivity to hyperoxia and separately hypercapnia at rest and during three different exercise intensities (25, 50% of $\dot{V}_{O_{2\max}}$ and ventilatory threshold ($\sim 67\%$ of $\dot{V}_{O_{2\max}}$)) in 12 males cyclists ($\dot{V}_{O_{2\max}} = 66.6 \pm 4.7 \text{ ml kg}^{-1} \text{ min}^{-1}$). Subjects were divided into two groups based on their end-exercise arterial oxygen saturation (ear oximetry, S_{pO_2}): a normal oxyhaemoglobin saturation group (NOS, $S_{pO_2} = 93.4 \pm 0.4\%$, $n = 5$) and a low oxyhaemoglobin saturation group (LOS, $S_{pO_2} = 89.9 \pm 0.9\%$, $n = 7$). There was no difference in $\dot{V}_{O_{2\max}}$ (66.4 ± 2.9 vs. $66.8 \pm 6.0 \text{ ml kg}^{-1} \text{ min}^{-1}$, respectively, $P = 0.9$), peak ventilation during maximal exercise (182 ± 15 vs. $197 \pm 32 \text{ l min}^{-1}$, respectively, $P = 0.36$) or ventilatory response to hyperoxia ($P = 0.98$) at any exercise intensity between NOS and LOS groups. However, those in the LOS group had a significantly lower ventilatory response to hypercapnia ($P = 0.004$, ($\eta^2 = 0.18$)). There was also a significant relationship between the mean hypercapnic response and end-exercise S_{pO_2} ($r = 0.75$, $P = 0.009$) but not between the mean hyperoxic response and end-exercise

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AUTHOR CONTRIBUTIONS

T.K.C., S.R.H. and D.C.M. designed the study. T.K.C. enrolled participants and conducted data collection. E.A.G., T.K.C., S.R.H., D.C.M. and P.B.D. analysed the data. All authors had complete access to all the study data, contributed to drafting and critically revising the manuscript. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

COMPETING INTERESTS

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

S_{pO_2} ($r = 0.21$, $P = 0.51$). A blunted hypercapnic ventilatory response may contribute to EIAH in highly trained men due to a failure to increase ventilation sufficiently to offset exercise-induced gas exchange impairments.

Keywords

carotid chemosensor; hypercapnia; hypoxia; ventilation

1 | INTRODUCTION

Throughout a range of exercise intensities, most healthy individuals are able to maintain their arterial oxygen tension (P_{aO_2}) near resting (~ 90 – 100 mmHg) levels. However, some well-trained endurance athletes are unable to maintain blood gas homeostasis during whole-body exercise. In these individuals P_{aO_2} will decrease (Dempsey, Hanson, & Henderson, 1984) and will consequently reduce arterial oxyhaemoglobin saturation and oxygen content, potentially limiting maximal oxygen uptake and exercise tolerance (Harms et al., 2000; Koskolou & McKenzie, 1994; Powers, Lawler, Dempsey, Dodd, & Landry, 1989). Altogether, the phenomenon is termed exercise-induced arterial hypoxaemia (EIAH) and occurs through a widening of the alveolar-to-arterial oxygen difference and/or relative alveolar hypoventilation (Dempsey & Wagner, 1999). The extent to which each contributes to EIAH is varied between individuals and not fully elucidated (Dempsey & Wagner, 1999).

In men, only those who have a relatively high maximal oxygen uptake $\dot{V}_{O_{2max}}$ have been shown to develop EIAH, and thus aerobic fitness appears to play a role in the development of EIAH. However, the range of end-exercise P_{aO_2} can be 30–40 mmHg or greater for subjects of similar aerobic fitness (Dominelli & Sheel, 2018; Stickland, Lindinger, Olfert, Heigenhauser, & Hopkins, 2013), and therefore additional factors clearly contribute to EIAH. One possible explanation is the (in)adequacy of compensatory hyperpnoea during exercise (Dempsey et al., 1984). Specifically, all individuals will develop a progressive widening of the alveolar-to-arterial gradient during exercise (Stickland et al., 2013). This gas exchange impairment is usually offset by increasing ventilation $\dot{V}_E$ which raises alveolar P_{O_2} and ensures arterial P_{O_2} remains near resting levels. However, this sufficient level of compensatory hyperpnoea does not occur in all individuals and is termed relative alveolar hypoventilation (Powers et al., 1992). For some subjects the relative alveolar hypoventilation is mechanical in origin (e.g. expiratory flow limitation; Dominelli et al., 2013; Johnson, Saupe, & Dempsey, 1992), while for others the blunted increase in $\dot{V}_E$ could be due to a depressed ventilatory drive from the peripheral chemosensors. Typically, the peripheral, rather than central, chemosensors are thought to be more important for EIAH because they respond more rapidly and widely to stimuli during dynamic exercise (Forster, Haouzi, & Dempsey, 2012). Previous work examining the relationship between ventilatory sensitivity at rest and EIAH in men has been equivocal (Guenette et al., 2004; Harms & Stager, 1995; Hopkins & McKenzie, 1989; Miyachi & Tabata, 1992). A limitation of the above-mentioned studies is that chemosensitivity was determined at rest; however, it is known that

chemosensitivity is enhanced during even mild exercise (Weil et al., 1972; Whipp & Pardy, 2011). For this reason, measurements of peripheral chemoresponsiveness during exercise may provide a better approximation of the influence of chemosensitivity on EIAH, but this has not been previously studied.

With the above as a background, the purpose of our study was to determine if differences in peripheral chemosensitivity during exercise explain the variability in the occurrence of EIAH in trained males. We hypothesized that a blunted chemoresponsiveness in response to elevations in arterial oxygen and decreases in carbon dioxide during exercise would be evident in those who developed the most severe EIAH.

2 | METHODS

2.1 | Ethical approval

The study was approved by the Institutional Review Board of the University of British Columbia Research Ethics Board (no. 12505), and adhered to the *Declaration of Helsinki*, except for registration in a database. All participants were informed of the experimental procedures, potential risks involved, and provided written informed consent.

2.2 | Participants

Thirty-six trained male cyclists were initially recruited. Participants were excluded if they had a history of pulmonary disease, did not meet normal spirometry values, or if they did not have a maximal oxygen uptake $\dot{V}_{O_{2\max}} \geq 5.0 \text{ l min}^{-1}$ or $60.0 \text{ ml kg}^{-1} \text{ min}^{-1}$. After excluding 24 subjects for the above reasons, a total of 12 completed all aspects of the study. Subjects were divided into two groups based on their end-exercise arterial oxygen saturation (measured via pulse oximetry, S_{pO_2}). Five subjects were placed in the normal oxyhaemoglobin saturation group (NOS, $S_{pO_2} \geq 93\%$) and seven subjects were placed in the low oxyhaemoglobin saturation group (LOS, $S_{pO_2} < 91\%$). The grouping was selected to be consistent with prior definitions of EIAH (Dempsey & Wagner, 1999) with the NOS group having absent or 'mild' EIAH and the LOS group being classified as 'moderate to severe' EIAH.

2.3 | Experimental overview

Testing took place over 5 days. The first day consisted of anthropometric measurements, resting pulmonary function tests and an incremental cycle test to exhaustion. The other four sessions consisted of two resting and two exercise trials for the hypercapnic and hyperoxic chemoresponse tests, which took place on different days with a minimum of 24 h separating the sessions. The order of all resting and exercise chemosensitivity testing (days 2–5) was randomized.

2.4 | Resting pulmonary function testing

Resting pulmonary function testing was assessed at the beginning of the first day using a metabolic cart (Medgraphics CPX/D, St Paul, MN). Each subject completed a series of trials in order to obtain reproducible measurements according to American Thoracic Society

standards (Miller et al., 2005). The following were measured to determine if the subjects would move onto the incremental exercise testing: forced vital capacity (FVC), force expired volume in 1 s (FEV_1), ratio of forced expired volume in 1 s to forced vital capacity (FEV_1/FVC), and peak expiratory flow (PEF). Each value had to exceed the lower limit of normal (Tan et al., 2011).

2.5 | Incremental exercise testing to determine $\dot{V}_{O_{2max}}$

Subjects completed an incremental exercise test to volitional exhaustion on an electronically braked ergometer (Mijnhardt, KEM-3, The Netherlands). The exercise protocol was used to determine if subjects met the inclusion criteria for $\dot{V}_{O_{2max}}$ as well as to determine subsequent workloads for the chemoresponse tests. Subjects utilized their own cycling pedals and shoes and adjusted the seat and handle-bar configuration. After a self-selected warm-up the work rate started at 0 W and increased 30 W min^{-1} until the subject was unable to continue the test or cadence fell below 30 rpm. Maximal oxygen uptake was determined with a customized metabolic cart that measured inspired gas flow (Vacumetrics no. 17159, Ventura, CA), expired oxygen (Applied Electrochemistry, N-22 M, Bastrop, TX) and carbon dioxide (Beckman, LB-2, Mississauga, Ontario) concentrations and interfaced with a personal computer. A 15 s epoch was averaged and used for determining $\dot{V}_{O_{2max}}$. Arterial oxygen saturation was measured with an ear oximeter (Hewlett-Packard, 47201A, Mississauga, Ontario) with the probe placed on the pinna. This oximeter has been shown to provide accurate measurements of arterial oxyhaemoglobin saturation at saturations above 65% (Rebuck, Chapman, & D'Urzo, 1983) even during exercise, and is superior to pulse oximetry in this regard (Douglas et al., 1979; Smyth, D'Urzo, Slutsky, Galko, & Rebuck, 1986). Prior to placement of the probe, a vasodilatory cream (Finalgon, Boehringer/Ingelheim, Germany) was applied to enhance perfusion. S_{pO_2} was recorded at 1 Hz and later smoothed using a 30 s moving mean to provide a better approximation of average arterial oxygen saturation and minimize any breath-to-breath fluctuations.

2.6 | Chemoresponse testing

Chemoresponse testing for the rest and exercise trials took place on different days with a minimum of 24 h separating a chemoresponse test and any exercise training completed by the subjects. The chemoresponse tests consisted of determining the ventilatory responses to brief periods of hypercapnia or hyperoxia (described below) both at rest and during exercise. The resting trials took place while the subject was in a supine position in order to ensure the subject was appropriately rested and not anticipating exercise. During the exercise trials, the subjects' exercise work rates were determined through least squares regression analysis of $\dot{V}_{O_2}$ and power output. These work rates were 25% of $\dot{V}_{O_{2max}}$ (very low power output, VLPO), 50% of $\dot{V}_{O_{2max}}$ (low power output, LPO), and oxygen uptake at ventilatory threshold $\dot{V}_{O_{2TH}}$ (moderate power output, MPO). The work rates were selected to minimize extraneous ventilatory stimuli (e.g. pH changes) and to ensure the subjects could complete multiple trials. Before any exercise testing, the subjects warmed up at 50% of their exercise work rate for 5–10 min.

2.7 | Chemoresponse trials

Two commercially available compressed gas mixtures were used in the chemoresponse testing (i) 13% CO₂, 21% O₂ and 66% N₂ for the hypercapnic peripheral chemoresponse and (ii) 100% O₂ for the hyperoxic chemoresponse. The hypercapnic response test was adapted from previous description and is intended to just stimulate peripheral chemosensors (McClean, Phillipson, Martinez, & Zamel, 1988). Thirteen per cent inspired CO₂ was utilized for testing after pilot testing determined it would raise end-tidal CO₂ by ~15–20 mmHg, which would provide a robust ventilatory response.

To eliminate errors in $\dot{V}_E$ calculations due to difference in inspired gas composition and density, a ‘bag-in-a-box’ technique was used (Figure 1). Briefly, the inspired side of the non-rebreathing valve was connected to the outlet port of a four-way valve. The three inlets of the four-way valve were connected to the bag-in-a-box system in the following manner: (i) a port that was continuous with the ~250 l air-tight box, (ii) a port that was continuous with a ~60 l Douglas bag inside the box filled with the hyperoxic mixture, and (iii) a port that was continuous with a ~60 l Douglas bag inside the box filled with the hypercapnic mixture. A fourth port on the box was connected to a pneumotach (Hans Rudolph no. 3800, Shawnee, KS). In this way, ventilation can be continuously measured despite changing inspire concentrations.

For both tests, 30 s of pre-stimulus data were collected before any gas administration. During the hypercapnic trials, the gas mixture was given for one breath through a four-way valve after the 30 s of pre-stimulus (e.g. baseline) data. Immediately after the single breath of the gas mixture, the subject was switched back to breathing room air. The entire trial lasted 60 s and there was a period of 3–5 min between the minimum of five repeated trials for each chemoresponse test. During the exercise tests, the subjects were cycling continuously for the full duration of the test. The determination of the subjects’ hypercapnic response was as follows. The control (pre-stimulus) $\dot{V}_I$ was the mean $\dot{V}_I$ of the five breaths prior to the stimulus breath. The response breath was defined as the highest single breath $\dot{V}_I$ recorded within 20 s of the gas mixture being administered. The control end-tidal CO₂ (P_{ETCO_2}) was the mean value during the 30 s pre-stimulus period and was used rather than five breaths to ensure a more representative average without errant breaths. The hypercapnic response was determined as the ratio of the difference between the control $\dot{V}_I$ and the response $\dot{V}_I$ and the difference between the control P_{ETCO_2} and the P_{ETCO_2} of the response breath. The reported response for the hypercapnic peripheral chemoresponse test for the subject was the mean of the five trials responses. There was no significant effect of order for any of the tests for either group ($P = 0.68$).

The hyperoxic tests were based on previous work investigating the hypoxic chemoreflex during exercise (Stockley, 1978). Hyperoxia was used to determine the peripheral chemosensors’ tonic contribution to ventilation (Prasad et al., 2020). We elected not to use hypoxia because of the potential to hinder oxygen delivery and the greater variability of the response compared to hyperoxia (Prasad et al., 2020). For the hyperoxic trials, the gas mixture (100% O₂) was given through a similar four-way valve. During the resting trials,

after the pre-stimulus rest breathing room air, subjects breathed the gas mixture for 20 s (approximately three breaths). During the exercise trials, the subjects breathed the hyperoxic gas for the same number of breaths they had in the resting trials. Once complete, the subjects breathed room air again. The determination of the subjects' hyperoxic response was as follows: the control $\dot{V}_I$ was the mean $\dot{V}_I$ over the 30 s, pre-stimulus period. After the hyperoxic breathing had started, $\dot{V}_I$ data were smoothed using a three breath moving average. The subjects' response was the ratio of the lowest three breaths' $\dot{V}_I$ value averaged across trials to the average control period $\dot{V}_I$ value.

2.8 | Statistical analysis

Student's *t* test was used to compare the normal and low saturation groups on descriptive characteristics. Repeated-measures ANOVA was used to compare the hypercapnic and hyperoxic peripheral chemoresponse between groups. Additionally, the hypercapnic chemosensitivity for all three exercise trials was averaged to a single value and the groups were compared with Student's *t* test. When significant *F* ratios were detected, a Tukey *post hoc* test was used to determine where the differences lay. Linear regression was performed to determine the association between the subject's mean exercise response for each of the two chemoresponse tests and the S_{pO_2} during maximal exercise. Statistical significance was set at $P < 0.05$, two tailed. Results are expressed as means $\pm$ standard deviation.

3 | RESULTS

Anthropometric and pulmonary function data are presented in Table 1; the groups were not significantly different for any variables except a greater peak expiratory flow in the low saturation group ($P = 0.05$). Maximal exercise and ventilatory threshold values are presented in Table 2. There was no significant difference in maximal $\dot{V}_{O_2}$ ($P = 0.90$), $\dot{V}_{CO_2}$ ($P = 0.99$), $\dot{V}_E$ ($P = 0.36$) and power output ($P = 0.78$) between the groups. There was also no significant relationship between $\dot{V}_{O_{2max}}$ and nadir S_{pO_2} when either all subjects were combined ($P = 0.67$) or analysed by group ($P = 0.43$ and $P = 0.30$ for LOS and NOS, respectively). The $\dot{V}_{O_{2TH}}$ was at a significantly higher fraction of $\dot{V}_{O_{2max}}$ in the LOS compared to the NOS group (63 ± 3 vs. $69 \pm 3\%$ of $\dot{V}_{O_{2max}}$, respectively, $P = 0.007$) and these subjects also had significantly higher average power output ($P = 0.007$).

Figure 2 depicts the individual mean subject responses and the group mean responses for the hyperoxic and hypercapnic trials during rest and over the three exercise levels. There was no significant difference between the groups in terms of the mean response to the hyperoxia (Figure 2b) ($P = 0.98$). There was little consistency in the individual hyperoxic responses across the different workloads and there was considerable overlap between groups (Figure 2a). Pre-hyperoxic $\dot{V}_E$ was not different between the low or normal S_{pO_2} groups at rest (12 ± 1 vs. 11.0 ± 1 l min⁻¹), 25% $\dot{V}_{O_2}$ (37 ± 4 vs. 36 ± 2 l min⁻¹), 50% $\dot{V}_{O_2}$ (67 ± 10 vs. 63 ± 5 l min⁻¹) (all $P > 0.05$). At $\dot{V}_{O_{2TH}}$ the low S_{pO_2} group had a significantly higher pre-hyperoxia $\dot{V}_E$ (103 ± 15 vs. 82 ± 2 l min⁻¹, $P = 0.01$), but the percentage decrease was not different

(Figure 2). Despite the pre-stimulus $\dot{V}_E$ being greater (103 ± 15 vs. $82 \pm 21 \text{ min}^{-1}$, $P = 0.01$) in the low S_{pO_2} group at ventilatory threshold, the absolute (17 ± 6 vs. $14 \pm 4 \text{ l min}^{-1}$, $P = 0.26$) and relative (Figure 2) decrease in $\dot{V}_E$ were not different.

The ventilatory response to hypercapnia was more consistent within a subject, with most subjects increasing the responsiveness as exercise intensity increased (Figure 2c) ($\eta^2 = 0.18$). As a group, the NOS subjects had a significantly greater ventilatory response to hypercapnia than the LOS group (Figure 2d). Specifically, there was a main effect of group and intensity for the hypercapnic response. There was no significant interaction in the hypercapnic response. When ventilatory response to hypercapnia for all three exercise trials was averaged and compared between the groups, the LOS group was significantly lower, with no differences in resting hypercapnic chemosensitivity. The S_{pO_2} immediately prior to each ventilatory test is presented in Table 3. There was no difference between groups except for the hypercapnic test performed during exercise at $\dot{V}_{O_{2TH}}$. Table 4 shows ventilatory variables immediately prior to and subsequent to the hypercapnic ventilatory response. For the rest, 25% and 50% trials, the absolute $\dot{V}_E$, P_{ETCO_2} , $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and workload were not different between groups. During the hypercapnic test at ventilatory threshold, the low S_{pO_2} group had a greater workload, $\dot{V}_E$ and $\dot{V}_{CO_2}$ and lower P_{ETCO_2} compared to the normal S_{pO_2} group. The differences in hypercapnic sensitivity were primarily due to differences in the change in $\dot{V}_E$ rather than the change in P_{ETCO_2} (Table 4). The exception being the hypercapnic tests at ventilatory threshold where the change in P_{ETCO_2} was greater in the low S_{pO_2} group.

Figure 3 displays the mean exercise response to the two chemoresponse tests plotted against the nadir S_{pO_2} during maximal exercise. There was no relationship between the hyperoxic response and S_{pO_2} (Figure 3a) ($r = 0.21$, $P = 0.51$). However, there was a significant relationship between the mean hypercapnic response and S_{pO_2} (Figure 3b) ($r = 0.72$, $P < 0.009$), such that those with a higher sensitivity to hypercapnia had the highest end exercise S_{pO_2} . There was also a significant relationship between maximal $\dot{V}_E$ and end-exercise S_{pO_2} in the LOS group ($r = 0.80$, $P = 0.03$).

4 | DISCUSSION

4.1 | Major findings

We tested the hypothesis that aerobically trained male athletes who develop the most severe EIAH would also have the lowest peripheral chemoresponsiveness during exercise. The major findings presented in this paper are threefold. First, the group with a lower S_{pO_2} during maximal exercise was less responsive to hypercapnia during exercise than those that maintained a higher S_{pO_2} during exercise. Second, there were no differences between groups in the ventilatory response to hyperoxia. The lack of response to the hyperoxia suggests the tonic activity from oxygen sensing is not related to the development of EIAH. Third, there

was a significant linear relationship between the nadir S_{pO_2} during maximal exercise and the mean hypercapnic ventilatory response but not hyperoxic response. The significant relationship between nadir S_{pO_2} and hypercapnic sensitivity supports the notion that hypercapnic sensitivity may explain some of the variability in end-exercise S_{pO_2} observed in our study. Overall, our findings suggest that peripheral chemoresponsiveness to hypercapnia may contribute to the development of EIAH in aerobically trained men exercising at sea-level.

4.2 | Carbon dioxide and oxygen sensing during exercise

We found that those who better maintained S_{pO_2} during exercise had a significantly greater hypercapnic ventilatory response (Figure 2c,d). Our findings agree with those of others who also demonstrated a significant relationship between hypercapnic sensitivity and exercise saturation (Harms & Stager, 1995; Miyachi & Tabata, 1992). Interestingly, however, the previous two studies determined their hypercapnic sensitivity at rest and extrapolated their results to exercise. If we only compared hypercapnic sensitivity at rest we would not have found any differences between the groups ($P = 0.62$). Indeed, it can be appreciated that exercise increased the sensitivity to hypercapnia in both of our groups and the increase appeared more pronounced in those with a normal S_{pO_2} (Figure 2d). Specifically, if we combine each subject's three exercise intensity chemosensitivity trials into a single mean value and then compare the groups, we find the low S_{pO_2} group's hypercapnic sensitivity to be significantly lower during exercise ($P < 0.001$) but not different at rest. If one group had a lower S_{pO_2} prior to the hypercapnic test, this could impact the magnitude of the response. However, while the low S_{pO_2} groups did have a significantly lower S_{pO_2} prior to the hypercapnic ventilatory test at ventilatory threshold (Table 3), the difference in hypercapnic response was already apparent at the lowest exercise intensity (Figure 2d). It would also be expected that a lower S_{pO_2} would also augment the CO_2 response. As such we surmise that the blunted hypercapnic response in the low S_{pO_2} group was present before a significant difference in S_{pO_2} existed and this may have actually attenuated our findings.

The differences in hypercapnic sensitivity were primarily driven by change in $\dot{V}_E$ rather than P_{ETCO_2} , the exception being at ventilatory threshold. Previous work has indicated that aerobic training may attenuate ventilatory sensitivity to CO_2 at rest, but not necessarily exercise (McConnell & Semple, 1996; Miyamura, Yamashina, & Honda, 1976), yet similar to the hypoxic response, longitudinal studies (albeit in rats) failed to show this effect (Hughson, 1980). However, whether CO_2 sensitivity changes acutely with trained subjects is equivocal, with some finding an increase (McConnell & Semple, 1996) and others no effect (Miyamura et al., 1976). The discrepancy is most likely due to the variability between subjects and potentially artefacts from the employed techniques (Duffin, Bechbache, Goode, & Chung, 1980) but also potentially genetic aspects (Saunders, Leeder, & Rebuck, 1976). A different example of potential blunting of the CO_2 reactivity with training comes from breath-hold divers (Bain, Drvis, Dujic, MacLeod, & Ainslie, 2018). Although not always

consistent, it has been shown that those who competitively train for static breath-hold have a reduced CO₂ sensitivity (Bain et al., 2018). The reduced CO₂ sensitivity would be advantageous in this case as it would potentially prolong the 'easy' time of the breath-hold. While the mechanism responsible for this blunted CO₂ reactivity is unknown, it is possible that our LOS group could also have a similar adaptation. Overall, our data suggest that in highly trained men, ventilatory sensitivity to CO₂ during exercise plays a role in the development of EIAH.

It has long been known that acute hyperoxia has a depressant effect on ventilation (Dejours, 1962; Downes & Lambertsen, 1966; Dripps & Comroe, 1947) and this response is augmented during exercise (Stockley, 1978). The lowered ventilation occurs because the hyperoxic gas removes the tonic activity arising from oxygen sensing. As such, the decrease in ventilation with hyperoxia is related to the contribution of oxygen sensing to sustain ventilation. Indeed, we found that ventilation decreased between ~7 and 32% when subjects inspired several breaths of 100% O₂ (Figure 2a). However, we found that the low and normal S_{pO_2} groups were not different in terms of their hyperoxic response at rest and any exercise intensity (Figure 2a,b). Moreover, there was little consistency between groups and exercise had a variable effect modulating the response. Given our groups were determined based on end-exercise S_{pO_2} and the depressive effect of hyperoxia on ventilation is more pronounced if the subject is hypoxic prior to O₂ administration, the S_{pO_2} immediately prior to hyperoxia could explain our results. However, there was no difference in S_{pO_2} between the groups immediately prior to hyperoxia administration at rest or during exercise (Table 2). A similar S_{pO_2} between groups would be expected at rest, but the lack of difference during exercise was surprising. Most likely, although EIAH is observed during submaximal exercise, it is most common at maximal exercise. Our classification of groups was also based on the S_{pO_2} at maximal exercise. Furthermore, there was a trend towards a difference in S_{pO_2} , but it did not reach statistical significance.

When testing the contribution of oxygen sensing at the opposite end of the spectrum, the extent to which hypoxic sensitivity impacts EIAH is also equivocal. Some have found that the hypoxic ventilatory response is not related to S_{pO_2} during exercise (Guenette et al., 2004; Hopkins & McKenzie, 1989); conversely others have shown relationship (Harms & Stager, 1995). The question becomes, why is there considerable variation in the results? Aerobic fitness is one possibility as some have shown that $\dot{V}_{O_{2max}}$ is negatively correlated with the hypoxic ventilatory response (Byrne-Quinn, Weil, Sodal, Filley, & Grover, 1971; Guenette et al., 2004). Yet, others do not report a relationship between $\dot{V}_{O_{2max}}$ and hypoxic ventilatory response (Sheel et al., 2006). And an acute sea-level aerobic training programme does not appear to alter hypoxic ventilatory sensitivity (Levine et al., 1992). Most likely, the discrepancies regarding the impact of fitness and hypoxic ventilatory responsiveness are from the high intra- and between-subject variability with the test (Teppema & Dahan, 2010). A further source of variability is that most of the previous work investigated the hypoxic ventilatory response at rest, rather than during exercise, which is thought to augment the

response (Weil et al., 1972). Genetic differences have also been shown to impact both hypoxic and hypercapnic chemoresponsiveness (Weil, 2003), with the hypoxic ventilatory response being similar in twins when exercise training was accounted for (Leitch, 1976).

4.3 | Role of chemoresponsiveness in EIAH

The cause of EIAH is multifaceted and most likely variable between individuals (Dempsey & Wagner, 1999). Of the mechanisms responsible for EIAH, the role of ventilation perfusion inequality and diffusion limitation is better understood, with most individuals developing ventilation perfusion inequality, but those who develop EIAH showing a greater extent of diffusion limitation of oxygen transport (Hopkins, 2007; Hopkins, McKenzie, Schoene, Glenny, & Robertson, 1994; Hopkins et al., 1998; Schaffartzik et al., 1992; Stickland et al., 2013; Torre-Bueno, Wagner, Saltzman, Gale, & Moon, 1985; Wagner et al., 1986). In contrast, the impact of relative alveolar hypoventilation on EIAH is variable between individuals and/or groups (i.e. males vs. females) (Dominelli & Sheel, 2018). Relative alveolar hypoventilation can broadly be divided into the mechanical ability to generate ventilation and the integrated neural drive to breathe. Mechanical constraints to ventilation contribute to EIAH in some populations, but are rarely (if ever) the exclusive cause (Dominelli et al., 2013). Our current study investigated if there were differences in peripheral chemoreceptor sensitivity between those who develop mild *versus* severe EIAH. In theory, reduced chemosensitivity would lead to lower ventilation or minimal compensatory hyperpnoea. The lack of a brisk compensatory hyperpnoea response would result in alveolar P_{O_2} not being raised to a sufficient level to offset the underlying gas exchange impairment (i.e. increasing $A-aD_{O_2}$). During intense or near maximal exercise, a blunted ventilatory response would be especially problematic as the $A-aD_{O_2}$ is typically greatest and other factors (i.e. low pH) would reduce haemoglobin's affinity for oxygen (i.e. 'right shift'). However, at maximal exercise, there was no significant difference in $\dot{V}_E$ between our groups (Table 2). While it appears the LOS group is trending towards a greater $\dot{V}_E$, this is from a single subject with an extraordinary $\dot{V}_E$ ($>230 \text{ l min}^{-1}$) and $\dot{V}_{CO_2}$ ($>7.0 \text{ l min}^{-1}$). Nonetheless, despite the similar $\dot{V}_E$, the LOS group most likely had greater ventilatory stimuli. That is, the lower S_{pO_2} is either from a lower P_{aO_2} , or a greater 'right shift' in the oxyhaemoglobin dissociation curve (e.g. lower pH, greater temperature) or some combination. All of the above factors will independently stimulate ventilation, and thus we would have expected the LOS group to have a higher $\dot{V}_E$. That $\dot{V}_E$ values are similar despite a lower S_{pO_2} would suggest the LOS group has a diminished ventilatory sensitivity.

EIAH is most often reported during near maximal or maximal exercise intensities (Dempsey & Wagner, 1999) and this leads to the development of the 'demand *versus* capacity' theory (Dempsey, 1986). However, it is now recognized that EIAH often occurs during submaximal exercise intensities and the 'demand *versus* capacity' theory cannot explain that occurrence (Dempsey, Amann, Harms, & Wetter, 2012; Dominelli & Sheel, 2018). Participants who have a lower P_{aO_2} during submaximal intensities are more prone to desaturation during more maximal exercise due to shifting of the oxygen dissociation curve as they are already on the

steeper aspect. This may predispose those subjects to more severe EIAH as exercise progresses.

4.4 | Methodological considerations

There are methodological considerations that merit comment. First, chemoresponsiveness was measured at three discrete power levels: very low, low and moderate power out, corresponding to oxygen uptakes of 25, 50% of maximal oxygen uptake and ventilatory threshold, respectively. As such, no measurements were taken during very heavy or maximal exercise, where EIAH is most severe (Dominelli & Sheel, 2018; Stickland et al., 2013). Rather, we elected to test these submaximal workloads to minimize known extraneous ventilatory stimuli. For example, at the workloads investigated, we expected core temperature and pH (both of which would augment ventilation) to be relatively stable and not dramatically increase or decrease, thereby minimizing additional ventilatory confounds. Furthermore, at supra-threshold exercise intensities, and especially maximal exercise, ventilation continues to increase despite no change in workload, and thus no steady state is observed. For example, determining the hypercapnic ventilatory response at near maximal intensities would be extremely difficult because the increased $\dot{V}_E$ due to hypercapnia would be contaminated by the typical constant rise in $\dot{V}_E$.

Second, we assessed haemoglobin saturation, and subsequently determined EIAH, with an ear oximeter rather than direct arterial blood gas measurements. While obtaining temperature-corrected arterial blood gases is obligatory for the assessment of pulmonary gas exchange efficiency, the intention of our study was to relate the degree of oxyhaemoglobin desaturation to chemoresponsiveness. As detailed above in 'Methods', the pulse oximeter we employed utilized multiple bandwidths and has been shown to be superior to other devices. We acknowledge, however, that we are unable to determine if the reductions in S_{pO_2} are the results of a lowered arterial oxygen tension or decreased affinity of haemoglobin for oxygen (i.e. rightward shift of the oxygen dissociation curve).

Third, the current study only investigated male athletes. Females also develop EIAH, but there is no consensus as to whether females develop EIAH more often and to a greater degree than men (Dominelli et al., 2013; Harms et al., 1998; Hopkins et al., 2000; Olfert et al., 2004). Part of the variability may also revolve around female sex hormones, which are known to influence resting ventilation but appear to have minimal effect during exercise (MacNutt, De Souza, Tomczak, Homer, & Sheel, 2012). However, the previous study made chemosensitivity measures during rest and as our results support, the response is likely enhanced with exercise. Similar to our current results, though, others have shown the peripheral chemoresponsiveness to oxygen did not influence end-exercise S_{pO_2} in females (Guenette et al., 2004). The question as to whether women with EIAH also have a blunted hypercapnic ventilatory response awaits experimental testing.

Fourth, while the end-exercise S_{pO_2} values were different between groups, we did not obtain haemoglobin levels and are unable to determine arterial oxygen content. However, our groups were relatively homogeneous with subjects being aerobically trained with similar

maximal oxygen uptakes, and as such we expect minimal variability in terms of haemoglobin levels. It should be acknowledged that our sample size was relatively small. As such, it is possible that, by chance, some of our subjects may have had a specific response to the stimulus that is not representative of a greater population. Finally, we recognize that chemosensation is multifaceted and interactive between the peripheral and central chemosensors and sensitive to a multitude of agents (Blain, Smith, Henderson, & Dempsey, 2010). As such, we are unable to isolate a specific sensor (e.g. isolating the carotid body) role in our results. Rather, we sought to determine the integrative response to ventilatory chemical stimuli in exercising men.

5 | CONCLUSIONS

We examined the effects of hypercapnia and hyperoxia on chemoresponsiveness during exercise in highly trained men who develop EIAH. Our main finding was that the subjects with the lower S_{pO_2} during exercise had the lowest sensitivity to hypercapnia during exercise. Yet we found no relationship between sensitivity to hyperoxia and S_{pO_2} . Our findings suggest that chemoreceptor sensitivity to CO_2 might play a role in the development of EIAH in aerobically trained men and could partially explain the variability in the occurrence and severity of EIAH.

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New Findings

- **What is the central question of this study?**

Do highly trained male endurance athletes who develop exercise-induced arterial hypoxaemia (EIAH) demonstrate reduced peripheral chemoresponsiveness during exercise?

- **What is the main finding and its importance?**

Those with the lowest arterial saturation during exercise have a smaller ventilatory response to hypercapnia during exercise. There was no significant relationship between the hyperoxic ventilatory response and EIAH. The findings suggest that peripheral chemoresponsiveness to hypercapnia during exercise could play a role in the development of EIAH. The findings improve our understanding of the mechanisms that contribute to EIAH.

FIGURE 1. Schematic representation of the chemosensitivity testing apparatus (a) along with a timeline for the hypercapnic (b) and hyperoxic (c) chemosensitivity trials. PT, pneumotachograph

FIGURE 2.

Individual mean subject responses (a,c), and the group mean responses (b,d) for the hypercapnic and hyperoxic trials for rest and over the three exercise levels. Data in (a,c) are presented as the mean for each subject for each trial. There were no significant effects for the hyperoxic response. There was a main effect of saturation and exercise intensity for the hypercapnic response. There were no significant interactions for the hypercapnic response. LPO, low power output; MPO, moderate power output; VLPO, very low power output.

*Significant main effect of saturation $P < 0.05$

FIGURE 3.

The relationship between end exercise oxyhaemoglobin saturation and chemoresponsiveness. (a) The hyperoxic response trials; (b) the hypercapnic response trials. Data are the mean exercise response of each subject over the three exercise levels plotted against the subjects' nadir oxyhaemoglobin saturation during the maximal exercise test. Nadir S_{pO_2} , lowest oxygen saturation of arterial haemoglobin

TABLE 1

Anthropometric and pulmonary values

Measurement	Group (n = 12)	NOS (n = 5)	LOS (n = 7)
Anthropometric			
Age (years)	27 ± 7	25 ± 5	28 ± 8
Height (cm)	182 ± 6	185 ± 5	180 ± 6
Mass (kg)	76.6 ± 6	78 ± 3	74 ± 7
BMI (kgm ⁻²)	23.0 ± 1.3	20.0 ± 0.6	23.1 ± 1.7
BSA (m ²)	1.98 ± 0.1	2.03 ± 0.06	1.94 ± 0.12
Pulmonary			
FVC (l)	6.1 ± 0.8	6.6 ± 0.6	5.8 ± 0.8
%Pred.	106 ± 9	107 ± 4	104 ± 12
FEV ₁ (l)	4.7 ± 0.7	5.0 ± 0.65	4.5 ± 0.7
%Pred.	97 ± 6	97 ± 6	98 ± 7
FEV ₁ /FVC	0.77 ± 0.08	0.75 ± 0.06	0.79 ± 0.1
%Pred.	83 ± 1	83 ± 1	83 ± 1
PEF (l s ⁻¹)	10.5 ± 1.6	9.5 ± 1.2	11.3 ± 1.4 *
%Pred.	122 ± 18	107 ± 11	132 ± 14
MVV (l min ⁻¹)	194 ± 21	188 ± 27	197 ± 16
%Pred.	104 ± 12	97 ± 11	110 ± 10

Values are means ± SD.

* Significantly different from the NOS group, $P < 0.05$.

BMI, body mass index; BSA, body surface area; FEV₁, force expired volume in 1 s; FVC, forced vital capacity; LOS, low oxyhaemoglobin saturation; MVV, maximal voluntary ventilation; NOS, normal oxyhaemoglobin saturation; PEF, peak expiratory flow; Pred., predicted.

TABLE 2

Maximal and ventilatory threshold exercise values

Measurement	Group (n = 12)	NOS (n = 5)	LOS (n = 7)
Maximal			
$\dot{V}_{O2\max}$ (l min ⁻¹)	5.08 ± 0.32	5.24 ± 0.34	4.96 ± 0.26
$\dot{V}_{O2\max}$ (ml kg ⁻¹ min ⁻¹)	66.6 ± 4.7	66.4 ± 2.9	66.8 ± 6.0
%Pred.	146 ± 10	143 ± 3	148 ± 13
$\dot{V}_{CO2}$ (l min ⁻¹)	5.98 ± 0.46	5.98 ± 0.42	5.98 ± 0.52
RER	1.17 ± 0.08	1.14 ± 0.05	1.2 ± 0.08
$\dot{V}_E$ (l min ⁻¹)	190 ± 27	182 ± 15	197 ± 32
$\dot{V}_E/\dot{V}_{O2}$	37.4 ± 4.9	34.6 ± 1.9	39.4 ± 5.4
$\dot{V}_E/\dot{V}_{CO2}$	31.8 ± 3.4	30.4 ± 1.2	32.8 ± 4.2
Heart rate (bpm)	188 ± 11	191 ± 6	186 ± 13
Peak power (W)	456 ± 27	453 ± 23	458 ± 31
Nadir S_{pO2} (%)	91.4 ± 2.0	93.4 ± 0.4	89.9 ± 0.9*
Ventilatory threshold			
$\dot{V}_{O2}$ (l min ⁻¹)	3.29 ± 0.12	3.31 ± 0.11	3.26 ± 0.14
$\dot{V}_{O2}$ (ml kg ⁻¹ min ⁻¹)	44.3 ± 4.2	42 ± 1.8	46.0 ± 4.7
$\dot{V}_{O2}/\dot{V}_{O2\max}$	67 ± 4	63 ± 3	69 ± 3*
$\dot{V}_{CO2}$ (l min ⁻¹)	3.11 ± 0.22	3.04 ± 0.13	3.17 ± 0.27
RER	0.92 ± 0.05	0.92 ± 0.03	0.93 ± 0.06
$\dot{V}_E$ (l min ⁻¹)	87 ± 12	81 ± 12	90 ± 11
$\dot{V}_E/\dot{V}_{O2}$	25.7 ± 3.3	24.5 ± 3.8	26.5 ± 2.9
$\dot{V}_E/\dot{V}_{CO2}$	27.8 ± 3.5	26.8 ± 4.5	28.5 ± 2.8
Heart rate (bpm)	155 ± 13	154 ± 13	155 ± 14
Power (W)	283 ± 29	259 ± 9	300 ± 26*

Values are mean ± SD. Values for $\dot{V}_{O2\max}$ predicated from equation.

* Significantly different from the NOS group, $P < 0.05$.

LOS, low oxyhaemoglobin saturation; Nadir S_{pO2} , lowest oxygen saturation of arterial haemoglobin; NOS, normal oxyhaemoglobin saturation;

$\dot{V}_{O2\max}$, maximal rate of oxygen uptake; Pred., predicted.

TABLE 3

Oxyhaemoglobin saturation immediately prior to each ventilatory response test

	Rest	25s% $\dot{V}_{O_{2\max}}$	50% $\dot{V}_{O_{2\max}}$	$\dot{V}_{O_{2TH}}$
Hyperoxia				
LOS	97.7 ± 0.9	97.3 ± 0.5	96.1 ± 0.8	95.6 ± 1.1
NOS	97.8 ± 0.8	97.6 ± 0.7	96.4 ± 0.6	96.3 ± 0.8
Hypercapnia				
LOS	97.7 ± 0.9	97.4 ± 0.7	96.9 ± 1.1	95.2 ± 0.9 [*]
NOS	97.5 ± 1.2	97.1 ± 0.4	96.2 ± 0.7	96.3 ± 0.1

Values are means ± SD.

^{*}Significantly different from the NOS group, $P < 0.05$.

LOS, low oxyhaemoglobin saturation; NOS, normal oxyhaemoglobin saturation. $\dot{V}_{O_{2\max}}$, maximal oxygen uptake; $\dot{V}_{O_{2TH}}$, oxygen uptake at ventilatory threshold.

TABLE 4

Ventilatory variables during hypercapnic ventilatory tests; $\dot{V}_E$, P_{ETCO_2} , $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ represent the average prior to the hypercapnic breath

	Rest	25% $\dot{V}_{O_{2max}}$			50% $\dot{V}_{O_{2max}}$			$\dot{V}_{O_2TH}$	<i>P</i>		
	LOS	NOS	LOS	NOS	LOS	NOS	LOS	NOS	Intensity	S_{pO_2}	Inter
$\dot{V}_E$ (l min ⁻¹)	12 ± 2	11 ± 1	33 ± 3	35 ± 1	63 ± 10	62 ± 5	97 ± 12	79 ± 5*	<0.001	.121	<0.001
$\Delta\dot{V}_E$ (l min ⁻¹)	4 ± 3	4 ± 2	9 ± 1	16 ± 3	16 ± 2	22 ± 7	18 ± 4	21 ± 4	<0.001	0.05	0.193
P_{ETCO_2} (mmHg)	44 ± 2	45 ± 1	46 ± 2	46 ± 1	48 ± 3	48 ± 1	45 ± 2	49 ± 2*	<0.001	0.209	0.028
ΔP_{ETCO_2} (mmHg)	7 ± 2	6 ± 2	14 ± 2	14 ± 2	19 ± 3	18 ± 3	22 ± 3	17 ± 4*	<0.001	0.281	0.03
$\dot{V}_{O_2}$ (l min ⁻¹)	0.3 ± 0.1	0.3 ± 0.0	1.3 ± 0.1	1.4 ± 0.1	2.4 ± 0.2	2.6 ± 0.2	3.3 ± 0.3	3.3 ± 0.1	<0.001	0.092	0.161
$\dot{V}_{CO_2}$ (l min ⁻¹)	0.26 ± 0.1	0.26 ± 0.02	1.1 ± 0.1	1.2 ± 0.1	2.3 ± 0.2	2.4 ± 0.2	3.3 ± 0.3	3.1 ± 0.2*	<0.001	0.928	0.049
Workload (W)	0 ± 0	0 ± 0	70 ± 12	77 ± 13	194 ± 20	197 ± 11	279 ± 36	232 ± 11*	<0.001	0.222	<0.001

All values are means ± SD.

* Significantly different from low arterial saturation (LOS) group, $P < 0.05$.

Inter, interaction; LOS, low oxyhaemoglobin saturation; NOS, normal oxyhaemoglobin saturation; P_{ETCO_2} , end-tidal carbon dioxide tension; ΔP_{ETCO_2} , change in end-tidal carbon dioxide tension after hypercapnic breath; S_{pO_2} , oxyhaemoglobin saturation; $\dot{V}_E$, minute ventilation; $\Delta\dot{V}_E$, change in minute ventilation after hypercapnic breath; $\dot{V}_{CO_2}$, carbon dioxide production; $\dot{V}_{O_2}$, oxygen uptake; $\dot{V}_{O_2TH}$, oxygen uptake at ventilatory threshold.