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EFFECTS OF EXERCISE-INDUCED ARTERIAL HYPOXAEMIA ON LIMB MUSCLE FATIGUE AND PERFORMANCE

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SUMMARY

1. Reductions in arterial O_2 saturation (–5% to –10% S_aO_2 below rest) occur over time during sustained heavy-intensity exercise in a normoxic environment, caused primarily by the effects of acid pH and increased temperature on the position of the HbO_2 dissociation curve.

2. We prevented the desaturation incurred during exercise at ~90% $\dot{V}O_{2\,MAX}$ via increased fraction of inspired O_2 (F_iO_2) (0.23 to 0.29) and showed that exercise time to exhaustion was increased.

3. We used supramaximal magnetic stimulation (1–100 Hz) of the femoral nerve to test for quadriceps fatigue. We used mildly hyperoxic inspirates (F_iO_2 0.23 to 0.29) to prevent O_2 desaturation. We then compared the amount of quadriceps fatigue incurred following cycling exercise at S_aO_2 91% vs 98% with each trial carried out at identical work rates and for equal durations.

4. Preventing the normal exercise-induced O_2 desaturation prevented about one-half the amount of exercise-induced quadriceps fatigue; plasma lactate and effort perception were also reduced. In a subset of less fit subjects who showed only minimal arterial hypoxaemia during sustained exercise (S_aO_2 ~95%), breathing a mildly hypoxic inspirate (F_iO_2 0.17; S_aO_2 ~88%) exacerbated the quadriceps fatigue.

5. We conclude that the normal exercise-induced O_2 desaturation during heavy-intensity endurance exercise contributes significantly to exercise performance limitation in part because of its effect on locomotor muscle fatigue.

Key words: central fatigue, force : frequency, quadriceps fatigue.

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EXERCISE-INDUCED ARTERIAL HYPOXAEMIA

Exercise-induced arterial hypoxaemia (EIAH) is defined as a reduction in arterial O_2 saturation (S_aO_2) and occurs for a variety of reasons. During short-term incremental exercise in some highly trained subjects, arterial partial pressure of O_2 (PO_2) may fall secondary to an excessively widened alveolar to arterial PO_2 difference and in the absence of significant hyperventilation.[1] If this EIAH is prevented (via increased fraction of inspired O_2 (F_iO_2)), $\dot{V}O_{2MAX}$ is increased.[2] During constant load, high-intensity cycling or running exercise sustained to the point of exhaustion, S_aO_2 falls progressively over time caused primarily by a time- (and intensity-) dependent metabolic acidosis and rising body temperature, which shifts the O_2 dissociation curve to the right (Fig. 1). In some highly fit subjects (especially during running exercise), a reduced PO_2 will also contribute to a reduced S_aO_2[3] (Fig. 2). Preventing this desaturation by adding small amounts of hyperoxic inspired gas mixtures (F_iO_2, 0.23–0.30) induces an increase in exercise time to exhaustion (Fig. 3). Furthermore, if the O_2 desaturation is exacerbated by acutely reducing F_iO_2 or ascending to high altitudes, exercise time to exhaustion is further reduced (Fig. 3).

We asked the fundamental question, 'Why does arterial hypoxaemia, either the 6–10% reduction in S_aO_2 induced by prolonged heavy exercise in a normoxic environment or the more severe O_2 desaturation encountered during prolonged heavy exercise at high altitudes, curtail performance time?' Is this curtailment strictly a result of reduced O_2 transport to working locomotor muscle leading to 'peripheral' end-organ fatigue? This peripheral fatigue effect is certainly a reasonable hypothesis given the evidence that hypoxaemia will reduce Ca^{2+} reuptake and release in the sarcoplasmic reticulum, thereby decreasing cross-bridge activation and force output.[4] This effect may occur through several mechanisms, including accumulation of lactate and hydrogen ions, inorganic phosphate and/or free radical production.[5] A recent study showed indirect myoelectric evidence of severe hypoxic effects on locomotor muscle fatigue during cycling.[6]

Alternatively, the long-held concept of a 'central governor' limiting motor recruitment of working muscle such that the function of vital organs is protected may explain exercise limitation in the presence of hypoxaemia.[7] Hence, this latter hypothesis would require reflex inhibition of central motor output to locomotor muscles in

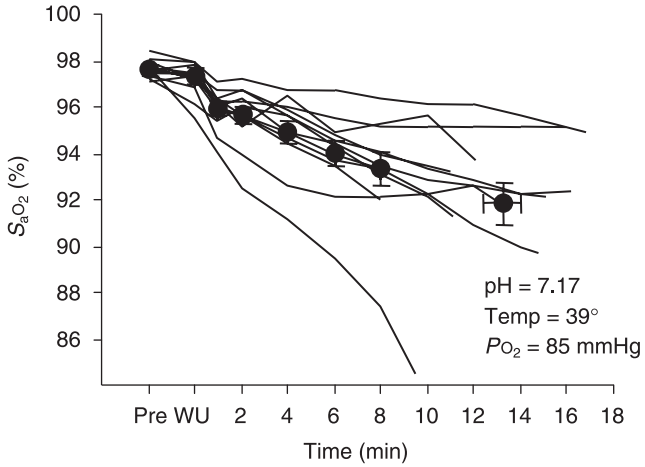

Fig. 1 Exercise-induced arterial hypoxaemia (EIAH) during heavy intensity, constant load cycling exercise in 11 fit young adult male cyclists (90% $\dot{V}O_{2max}$; F_iO_2, 0.21). The O_2 desaturation was caused primarily by a time-dependant metabolic acidosis (pH ~7.17) and rise in temperature (by ~ +2°C) as partial pressure of O_2 (PO_2) was 80–90 mmHg, temperature was 39°C.

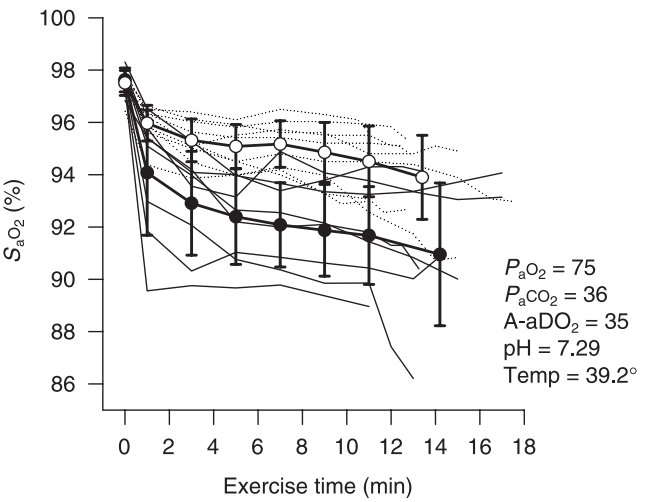

Fig. 2 Arterial O_2 saturation during constant-load, high-intensity treadmill running to exhaustion in 17 fit young women (fraction of inspired O_2 (F_iO_2) 0.21; 90% $\dot{V}O_{2max}$). Mean values are shown for those with a low partial pressure of O_2 (PO_2) (~75 mmHg) (closed circles) and those who maintained a high PO_2 (85–90 mmHg) (open circles) throughout. Dashed lines refer to subjects who did not show hypoxaemia during exercise (mean values, open symbols) and solid lines refer to those with hypoxaemia (closed symbols, mean values). The partial pressure of CO_2 (PCO_2) was higher and the alveolar to arterial PO_2 difference wider in the low PO_2 group. The time-dependent fall in S_aO_2 beyond the first 2 min of running was caused by the rise in temperature (+2.2°C) and fall in arterial pH (~7.25 pH) (after Wetter *et al.*[3]).

order to protect against impending failure of vital organs[7] and/or the occurrence of lung oedema.[8] Limiting the duration and/or magnitude of cerebral hypoxia in order to preserve cerebral aerobic metabolism may present yet another potential source of central inhibition of locomotor muscle recruitment. A recent study prevented EIAH during maximal rowing exercise and observed an increased oxygenation in the brain but no change in the muscle, thereby implying that changing S_aO_2 had little effect on muscle O_2 transport, *per se*.[9] Indeed, the classic studies of John Sutton, Jack Reeves and colleagues in Operation Everest II predicted a major role for non-peripheral factors in limiting exercise performance during the simulated ascent of Everest.[10,11]

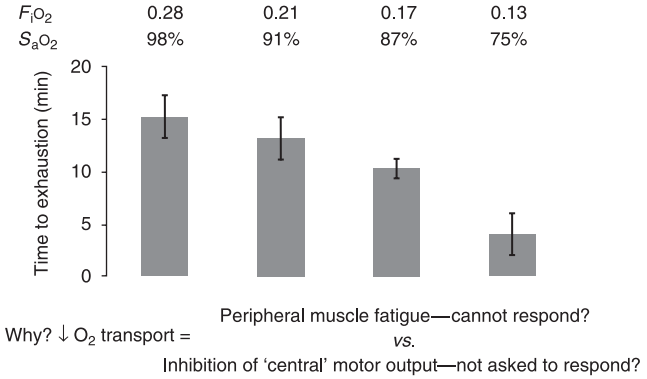

Fig. 3 Effects of exercise-induced arterial hypoxaemia (EIAH) on time to exhaustion at a fixed, high-intensity work rate (90% $\dot{V}O_{2max}$, 300 watts). Note in a normoxic environment with an end – exercise, arterial O_2 saturation that averaged 91% (Fig. 2) time to exhaustion was about 13 min. Preventing this reduction in O_2 saturation (S_aO_2) (via fraction of inspired O_2 (F_iO_2) 0.23 to 0.29) allowed the subjects to exercise at least 16% longer, whereas reducing F_iO_2 below normoxic levels caused moderate (at F_iO_2 0.17 and 87% S_aO_2) and then marked (at F_iO_2 0.13 and 75% S_aO_2) reductions in exercise time to exhaustion.

General methods

Eleven above average aerobic fitness subjects were studied ($\dot{V}O_{2max}$ = 44–69 mL/kg per min, ages 19–33 years). We used supramaximal magnetic stimulation of the femoral nerve before and after cycling exercise to determine if indeed locomotor muscle fatigue, *per se*, was induced by changing levels of arterial oxygenation during high-intensity exercise in normoxic and in hypoxic environments. This procedure consisted of paired, supramaximal stimuli delivered over a range of frequencies (1–100 Hz), achieved by varying the duration of the interstimulus interval. The quadriceps force output in response to supramaximal nerve stimulation was shown to be highly reproducible (coefficient of variation < 6%) both within and between days. Evoked potentials in response to nerve stimulation were measured from the quadriceps muscle electromyogram (EMG); their magnitude remained unchanged from baseline to postexercise conditions, ensuring that the motor input to the muscle was supramaximal and equal before and after the cycling exercise. Superimposition of a supramaximal twitch on a maximum voluntary quadriceps contraction produced an average force output that averaged 7% of the potentiated twitch value at rest, indicating that subjects did not fully activate their quadriceps via voluntary effort.

EXPERIMENT A: PREVENTING EXERCISE-INDUCED ARTERIAL HYPOXAEMIA IN A NORMOXIC ENVIRONMENT

Subjects cycled at a fixed workload at an intensity that averaged 90% of their peak maximal work rate, until they could no longer maintain a target pedalling frequency. Arterial blood was obtained periodically, and magnetic stimulation was applied at baseline and at

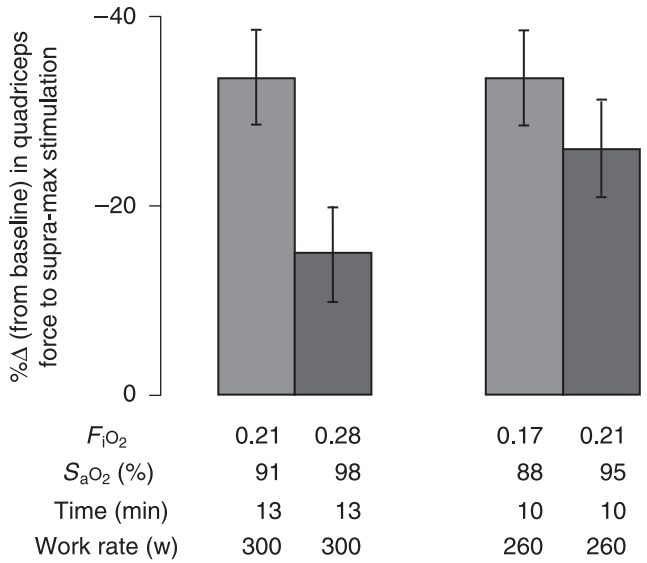

Fig. 4 Cycling exercise to exhaustion in normoxia caused a reduction in force output of the quadriceps in response to supramaximal femoral nerve stimulation, which averaged one-third below baseline. When the hypoxaemia was prevented (F_iO_2 0.27) and the exercise carried out for an identical time and work rate as at F_iO_2 of 0.21, quadriceps fatigue was reduced by more than 50%. When exercise-induced arterial hypoxaemia (EIAH) was made greater by mild environmental hypoxia (fraction of inspired O_2 (F_iO_2) 0.17), quadriceps fatigue was enhanced.

intervals from 2.5 to 70 min following exercise. Then the subjects returned and repeated the experiment only with supplemental inspired O_2 (F_iO_2 0.23–0.29) added in amounts that were just sufficient to prevent EIAH, i.e. S_aO_2 was maintained at resting levels (~98%). On this second day, subjects exercised at power outputs and for durations that were identical to those under control (F_iO_2 0.21) conditions. Thus, the only difference between the two exercise conditions was the S_aO_2, i.e. 91% compared with 98%.

The key fatigue findings are summarized in Fig. 4. Note that exercise in normoxia, which caused a progressive desaturation to 91% S_aO_2 (range = 87–93%), resulted in a reduction of force output immediately following exercise at all stimulation frequencies (1–100 Hz) that averaged 33% below baseline and returned gradually to baseline levels over 70 min of recovery. When the EIAH was prevented and S_aO_2 held at resting levels, the reduction in force output was still significant but only about one-half of which occurred under control conditions in the presence of EIAH. Thus, the prevention of EIAH, *per se* significantly reduced the amount of quadriceps fatigue induced by the exercise. It also significantly lowered the absolute level and rate of rise of arterial blood lactate concentration over the final half of the exercise and reduced the rate of rise of effort perception for both limb discomfort and dyspnoea (data not shown). Finally, using the twitch stimulation superimposed on the maximum voluntary contraction, we observed that voluntary activation of the quadriceps was reduced from 93% during the pre-exercise resting baseline to 85% following exercise in normoxia; and when desaturation was prevented, voluntary activation fell less than half this amount (93% at baseline to 90% immediate postexercise).

These findings demonstrate that the arterial O_2 desaturation that normally accompanies heavy-intensity sustained exercise in a normoxic environment contributes significantly to locomotor muscle fatigue. In turn, we think it reasonable to conclude that the lessening of local muscle fatigue with the prevention of O_2 desaturation contributes to an enhancement of exercise performance. Nevertheless, we cannot claim a true cause–effect relationship because we are unable to determine how these data obtained during supramaximal nerve stimulation in recovery translate precisely into the subjects' capability for sustaining a given (likely submaximal) power output during the preceding exercise.

Although these data clearly implicate a significant effect of reduced O_2 transport on locomotor muscle fatigue and on exercise performance, they do not rule out an effect of O_2 desaturation on reducing motor output to the locomotor muscles during exercise, i.e. 'central fatigue'.[12] Indeed, the finding that exercise significantly reduced voluntary activation of the quadriceps and that this was largely relieved by preventing O_2 desaturation indirectly implicates a contribution from 'central fatigue' to hypoxaemic effects on exercise limitation. A major outstanding problem with interpretation of these tests is whether the change in force output with the superimposed twitch, as conducted in the resting subject during recovery, truly represents 'central inhibition' of the volitional force produced during the preceding rhythmic exercise task. To date, there is no direct evidence – pro or con – of an effect of arterial hypoxaemia on reflex inhibition of central motor output to locomotor muscles during exercise. Certainly, the reduced rates of rise of effort perceptions during exercise when EIAH was prevented might also have contributed to exercise performance limitation and may be classified as 'central' fatigue (or 'symptom limited'). However, as much of the cause of enhanced effort perceptions in the presence of hypoxaemia likely originated from intensified sensory feedback input from fatiguing, acidic muscles, then this type of 'central' fatigue is causally linked to 'peripheral' fatigue.

EXPERIMENT B: EFFECT OF HYPOXIC-INDUCED MODERATE HYPOXAEMIA

This experiment was conducted in those subjects who experienced minimal O_2 desaturation (~95%) during the exercise in normoxia. A similar design was used as in experiment A, in that the effect on quadriceps fatigue was compared following exercise of identical work rates and durations. In these subjects, an F_iO_2 of 0.17 reduced the mean exercise S_aO_2 to 88% and significantly increased the amount of quadriceps fatigue by 20–25% over that observed at F_iO_2 0.21 (S_aO_2 95%) (Fig. 4). Furthermore, the moderate reductions in S_aO_2 below 90% increased the rate of rise of blood lactate and effort perceptions during the exercise. So again, as with the prevention of EIAH in a normoxic environment, the further-reduced S_aO_2 in a mildly hypoxic environment was linked to performance limitation by means of O_2 transport-induced reductions in the force output of the locomotor muscles in response to supramaximal motor nerve stimulation.

We propose that the effects of EIAH on locomotor muscle (peripheral) fatigue mechanisms were caused by reductions in muscle O_2 transport, which in turn would reduce muscle capillary PO_2 and mitochondrial PO_2. Because the work rates in our study required a VO_2 very close to $\dot{V}O_{2max}$, preventing the O_2 desaturation also raised mean VO_2 about 5% (at end exercise). Thus, subjects were exercising at a slightly lower relative work intensity, which would account for at least some of the reduction in lactate production and fatigue.

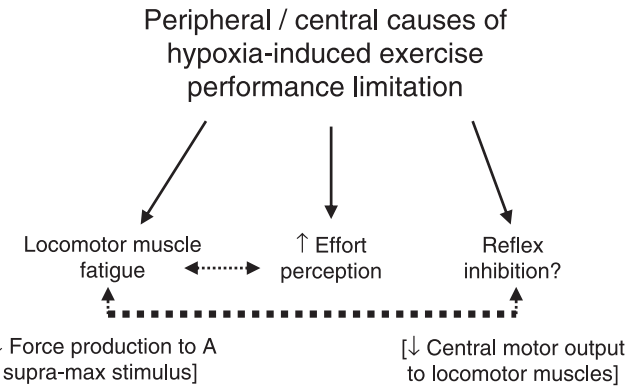

Fig. 5 Schematic diagram of the 'peripheral' and 'central' fatigue influences on hypoxaemic-induced limitations to exercise performance. We found peripheral locomotor muscle fatigue to be induced by all levels of arterial hypoxaemia studied, including the exercise-induced arterial hypoxaemia (EIAH), which occurs during heavy sustained exercise in normoxia. Indirect evidence also implicates 'central' fatigue contributions – especially in severe environmental hypoxia-induced arterial hypoxaemia.

SUMMARY

The schematic diagram in Fig. 5 outlines the various types of contributions to curtailment of performance experienced in the presence of arterial hypoxaemia. Listed are peripheral muscle fatigue secondary to reduced O_2 transport to muscle and two types of 'central' factors, namely conscious effort perception and reflex inhibition, which might limit performance by reducing motor output to the working locomotor muscles. Our results show that for both levels of hypoxaemia, its effect on limiting performance time was consistently associated with significant peripheral (i.e. locomotor muscle) fatigue. We especially emphasize that even in a normoxic (i.e. sea level) environment, the 6–10% arterial O_2 desaturation that is normally produced during heavy-intensity, sustained exercise in healthy subjects is sufficient to significantly exacerbate locomotor muscle fatigue. An additional contribution to exercise limitation occurs from the two types of 'central' influences inhibiting motor output to the limb muscles during exercise. One of these 'central' factors, i.e. conscious effort perception, is strongly influenced by peripheral muscle fatigue, *per se*. The other, 'reflex' inhibition has not been measured directly during whole-body exercise. A significant contribution from one or more of these 'central' influences is likely to be present during exercise at all levels of arterial hypoxaemia. It is also likely that the relative contributions of these 'peripheral' and 'central' mechanisms – and their interactive effects – to exercise performance will depend on the exercise intensity, severity of hypoxaemia and even the fitness of the subject.

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