SUMMARY

1. Reductions in arterial O₂ saturation (∼5% to ∼10% S_aO₂ 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 HbO₂ dissociation curve.

2. We prevented the desaturation incurred during exercise at ∼90% VO₂-max via increased fraction of inspired O₂ (F_iO₂) (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 inspirate (F_iO₂ 0.23 to 0.29) to prevent O₂ desaturation. We then compared the amount of quadriceps fatigue incurred following cycling exercise at S_aO₂ 91% vs 98% with each trial carried out at identical work rates and for equal durations.

4. Preventing the normal exercise-induced O₂ 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_aO₂ ∼95%), breathing a mildly hypoxic inspirate (F_iO₂ 0.17; S_aO₂ ∼88%) exacerbated the quadriceps fatigue.

5. We conclude that the normal exercise-induced O₂ 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.

EXERCISE-INDUCED ARTERIAL HYPOXIA

Exercise-induced arterial hypoxaemia (EIAH) is defined as a reduction in arterial O₂ saturation (S_aO₂) and occurs for a variety of reasons. During short-term incremental exercise in some highly trained subjects, arterial partial pressure of O₂ (P_aO₂) may fall secondary to an excessively widened alveolar to arterial O₂ difference and in the absence of significant hyperventilation. If this EIAH is prevented (via increased fraction of inspired O₂ (F_iO₂)), VO₂-max is increased. During constant load, high-intensity cycling or running exercise sustained to the point of exhaustion, S_aO₂ falls progressively over time caused primarily by a time- (and intensity-) dependent metabolic acidosis and rising body temperature, which shifts the O₂ dissociation curve to the right (Fig. 1). In some highly fit subjects (especially during running exercise), a reduced P_aO₂ will also contribute to a reduced S_aO₂ (Fig. 2). Preventing this desaturation by adding small amounts of hyperoxic inspired gas mixtures (F_iO₂ 0.23–0.30) induces an increase in exercise time to exhaustion (Fig. 3). Furthermore, if the O₂ desaturation is exacerbated by acutely reducing F_iO₂ 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_aO₂ induced by prolonged heavy exercise in a normoxic environment or the more severe O₂ desaturation encountered during prolonged heavy exercise at high altitudes, curtail performance time?’ Is this curtailment strictly a result of reduced O₂ 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 Ca²⁺ reuptake and release in the sarcoplasmic reticulum, thereby decreasing cross-bridge activation and force output. This effect may occur through several mechanisms, including accumulation of lactate and hydrogen ions, inorganic phosphate and/or free radical production. A recent study showed indirect myoelectric evidence of severe hypoxic effects on locomotor muscle fatigue during cycling.

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. Hence, this latter hypothesis would require reflex inhibition of central motor output to locomotor muscles in...
order to protect against impending failure of vital organs and/or the occurrence of lung oedema. 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. 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.

**General methods**

Eleven above average aerobic fitness subjects were studied (VO\(_{max}\) = 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 HYPOXÆMIA 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...
Hypoxia and limb fatigue

393

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 (FIO2 0.27) and the exercise carried out for an identical time and work rate as at FIO2 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 O2 (FIO2) 0.17), quadriceps fatigue was enhanced.

The key fatigue findings are summarized in Fig. 4. Note that exercise in normoxia, which caused a progressive desaturation to 91% SAO2 (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 SAO2 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 O2 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 O2 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 O2 transport on locomotor muscle fatigue and on exercise performance, they do not rule out an effect of O2 desaturation on reducing motor output to the locomotor muscles during exercise, i.e. ‘central fatigue’. Indeed, the finding that exercise significantly reduced voluntary activation of the quadriceps and that this was largely relieved by preventing O2 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 HYPOXAEDEA

This experiment was conducted in those subjects who experienced minimal O2 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 FIO2 of 0.17 reduced the mean exercise SAO2 to 88% and significantly increased the amount of quadriceps fatigue by 20–25% over that observed at FIO2 0.21 (SAO2, 95%) (Fig. 4). Furthermore, the moderate reductions in SAO2 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 SAO2 in a mildly hypoxic environment was linked to performance limitation by means of O2 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 O2 transport, which in turn would reduce muscle capillary PO2 and mitochondrial PO2. Because the work rates in our study required a VO2 close to VO2max, preventing the O2 desaturation also raised mean VO2 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.
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 O2 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 O2 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.

ACKNOWLEDGEMENTS

The original research reported in this manuscript was supported by NHLBI and the American Heart Association.

REFERENCES