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Cerebral and muscle deoxygenation, hypoxic ventilatory chemosensitivity and cerebrovascular responsiveness during incremental exercise

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ABSTRACT

To examine if cerebral (frontal cortex) and skeletal muscle (m. vastus lateralis) deoxygenation and cerebral blood flow velocity (V_{mean}) in the middle cerebral artery differentiated between normoxic and hypoxic (end-tidal P_{O_2} 71 mmHg) conditions, and if they were associated with hypoxic ventilatory chemosensitivity and cerebrovascular responsiveness, 8 men performed incremental cycling trials (30 W/min ramp) under normoxic (T1-N) and hypoxic (T1-H) conditions until volitional fatigue, or until arterial O_2 saturation decreased below 80%. The tests were repeated (T2-N; T2-H) on another day with supplemental O_2 (Sup-O_2) at the end of exercise. The V_{mean} response was similar in normoxia and hypoxia. In hypoxia compared to normoxia, cerebral deoxygenation (↑ deoxyhemoglobin concentration (Δ[HHb]) and ↓ tissue oxygenation index (TOI)) was greater at a given work rate. A strong hypoxic ventilatory chemosensitivity was associated with a rapid reduction of cerebral TOI ($r = 0.94$, $P < 0.001$). Muscle deoxygenation was similar in normoxia and hypoxia suggesting greater muscle blood flow in hypoxia compared to normoxia and thus the existence of control features that match muscle perfusion and O_2 delivery tightly with O_2 demand during exercise. Sup-O_2 reduced both cerebral and muscle deoxygenation, at least transiently.

1. Introduction

Numerous studies have been carried out to describe the changes in ventilation ($\dot{V}_E$), cerebral blood flow (CBF), or cerebral oxygenation that occurs in response to acute and chronic exposures to hypoxia. In acute hypoxia, CBF (Cohen et al., 1967) and CBF velocity (CBFv) (Jensen et al., 1996; Poulin et al., 1996; Kolb et al., 2004; Steinback and Poulin, 2008) increase to maintain O_2 delivery. However, despite an increase in CBF, reduction in regional cerebral oxygen saturation does occur in acute hypoxia, as has been seen after a night at 3459 m (Imray et al., 2003) and during an acute hypoxic ventilatory response (AHVR) (Kolb et al., 2004). In our recent study (Peltonen et al., 2007), cerebral tissue saturation declined from an average of 63 to 57% during an AHVR test while muscle saturation was maintained close to the initial normoxic level. Exercise, especially with superimposed arterial hypoxemia, may reduce cerebral oxygenation so that cerebral mitochondrial O_2 tension is no longer adequate to support cerebral metabolism and maintain motor function (Nybo and Rasmussen, 2007; Subudhi et al., 2007). Consistent with this, hyperoxic breathing has been reported to improve cerebral oxygenation and exercise performance during maximal exercise (Nielsen et al., 1999; Subudhi et al., 2008).

Proper function of the brain during exercise relies on a constant and adequate supply of blood flow and oxygen delivery. Cerebral blood flow increases as function of exercise intensity during exercise (Querido and Sheel, 2007) of mild to moderate intensity (Jorgensen et al., 1992). However, during intense whole body exercise CBF is reduced (Hellstrom et al., 1996; Gonzalez-Alonso et al., 2004) because CBF is highly sensitive to alterations in the partial pressures of O_2 (Pa_{O_2}) and CO_2 (Pa_{CO_2}) in the arterial blood and the hyperventilation associated with intense exercise lowers Pa_{CO_2} which results in a constriction of cerebral arterioles (Brugniaux et al., 2007; Querido and Sheel, 2007).

The magnitude of the initial changes in CBF in response to hypoxia depends not only upon the magnitude of the hypoxic exposure, but also individual cerebrovascular and ventilatory sensitivities to O_2 and CO_2 (Brugniaux et al., 2007). The chemosensitivity

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of the ventilatory response to lowered arterial O_2 tensions is monitored at rest with an AHVR test, while end-tidal CO_2 tension is clamped to isocapnia (Weil and Zwillich, 1976; Kolb et al., 2004; Peltonen et al., 2007). Blunted chemosensitivity has been observed in athletes with high aerobic capacity in comparison with normal controls, while experienced climbers show vigorous respiratory responses to hypoxia to maintain adequate oxygenation (Schoene, 1982). Although increased ventilation in hypoxia is beneficial in elevating arterial O_2 saturation (Gavin et al., 1998; Katayama et al., 2001), hyperventilation reduces Pa_{CO_2}, which increases cerebral vasoconstriction and reduces CBF (Ellingsen et al., 1987; Ainslie and Poulin, 2004). This may cause poorer oxygenation of the brain despite greater ventilation, likely because of a hypocapnia-induced decrease in CBF that more than offsets the increase in arterial O_2 saturation (Hornbein et al., 1989).

During acute hypoxia at rest, Ainslie and Poulin (2004) have shown the inter-individual variability in AHVR to be linked to the variability in CBF velocity as individuals with a high AHVR were found also to have high CBF velocity response to hypoxia. However, the integrative ventilatory, cerebrovascular and cardiovascular responses to hypoxia were strongly influenced by Pa_{CO_2}. During poikilocapnic hypoxia, a high AHVR blocked much of the acute hypoxic cerebral blood flow responses due to hypocapnia-induced cerebral vasoconstriction (Ainslie and Poulin, 2004).

In muscle, there is a progressive increase in muscle deoxygenation during incremental exercise (Bhambhani et al., 1998), but the effects of hypoxia have produced equivocal results as both similar (DeLorey et al., 2004b; Ainslie et al., 2007) and greater (Maehara et al., 1997; Subudhi et al., 2007) muscle deoxygenation have been reported in comparison with normoxia.

To our knowledge, there are no published studies at the present that link both cerebral and muscle tissue deoxygenation status to ventilatory and cerebrovascular responsiveness during exercise in normoxia and acute hypoxia. Therefore, the purpose of the present study was to examine (i) the extent of cerebral and muscle tissue deoxygenation during exercise in normoxia and acute hypoxia and their relationship with ventilatory chemosensitivity and cerebrovascular responsiveness, (ii) the association between hypoxic ventilatory chemosensitivity and cerebrovascular responsiveness during exercise and at rest (Peltonen et al., 2007), and (iii) whether hyperoxic breathing (i.e., supplemental O_2) in the latter stages of incremental exercise improves only cerebral (Nielsen et al., 1999) or both cerebral and muscle oxygenation (Subudhi et al., 2008). We hypothesized that (i) a high cerebrovascular responsiveness to hypoxia would be beneficial in maintaining cerebral oxygenation during exercise, while high hypoxic ventilatory chemosensitivity would be detrimental due to a hypocapnia-induced reduction in CBFv; (ii) a strong correlation would exist between ventilatory and cerebrovascular sensitivity during exercise and at rest; (iii) a rapid change from normoxia or hypoxia to hyperoxia should improve especially cerebral oxygenation, as previously suggested (Nielsen et al., 1999; Subudhi et al., 2008).

2. Materials and methods

2.1. Subjects

Eight healthy males (185 ± 5 cm, 79 ± 3 kg, 28 ± 5 years) volunteered and gave written, informed consent to participate in the study. This is the same subject group for whom we reported data of hypoxic ventilatory chemosensitivity and cerebrovascular responsiveness at rest (Peltonen et al., 2007). The study was approved by The University of Western Ontario Health Sciences Research Ethics Board and conformed to the Declaration of Helsinki. All subjects were physically active, ranging from recreational exercisers to competitive cyclists. The subjects were medically screened (including ultrasound study of the heart and the carotid arteries, and a standard 12-lead ECG at rest) and had no history of cardiovascular, respiratory, or musculoskeletal diseases and were free of medication.

2.2. Experimental sequence and exercise protocol

All participants completed four different exercise protocols. They reported to the laboratory three to four hours after a meal, and after abstaining from caffeine or alcohol ingestion for at least 24 h and physical exercise for at least 12 h. The subjects performed ramp incremental (RI) protocols on a cycle ergometer in normoxia (T1-N) and hypoxia (T1-H) on separate days (3–30 days between the tests) in a randomized order. In the normoxic room air condition, the test was initiated with a 2 min rest (end-tidal P_{O_2} (PET_{O_2}), 104 ± 8 mmHg) while the subject sat relaxed on a cycle ergometer. The subject began with 10 min baseline cycling at 20 W, after which the RI exercise protocol was initiated (30 W min^{-1}) and the subject continued exercise until volitional fatigue. In the hypoxic condition, the test was initiated with 2 min rest while breathing normoxic room air (PET_{O_2}, 107 ± 10 mmHg). Subjects then began baseline cycling at 20 W, and after 5 min, the subject began hypoxic breathing (PET_{O_2} clamped to 71 mmHg) and the subject continued exercising at 20 W for an additional 5 min followed by the RI protocol (30 W min^{-1}) to volitional fatigue. On average, the target PET_{O_2} was achieved with P_{IO_2} of 118 ± 5 mmHg, equivalent to ~2500 m above sea level. To ensure the well-being of the subjects, exercise was terminated if arterial O_2 saturation (Sp_{O_2}%) fell below 80% for 15 s. The hypoxic exercise was monitored by a physician and included an electrocardiogram (12-lead ECG).

The tests were repeated (T2-N, T2-H) on separate days (3–30 days between the tests), but in each case the increment in work rate (WR) was stopped and held at 30 W below the peak WR achieved in T1 ($WR_{pk\text{-}T1}$) while supplemental O_2 (Sup-O_2) (PET_{O_2} clamped to 158 mmHg) was initiated. After 1 min, the WR was increased and held at $WR_{pk\text{-}T1}$ and the subject continued to exercise until volitional fatigue while still breathing Sup-O_2. If the subject did not fatigue after 10 min cycling at WR_{pk}, the test was terminated. Calculation of total work (W_{tot}) during the test was based on the ratio 1 W s^{-1} = 1 J.

A dynamic end-tidal forcing technique was used to clamp PET_{O_2} at a desired level and to change O_2 concentrations rapidly. Accurate control of the end-tidal gases was achieved with a computer-controlled fast gas mixing system as previously described (Poulin et al., 1993; Peltonen et al., 2007). Briefly, the controlling computer generated the inspired partial pressures of O_2 and N_2 by comparison of the measured end-tidal values with the desired values and adjusted the gas mixture for the next inspiration as needed.

2.3. Measurements of cardiorespiratory responses

Heart rate (fH) was continuously monitored by ECG and Sp_{O_2}% by pulse oximetry (Nonin 8600, Nonin Medical, Inc., Plymouth, MN, USA) from the earlobe. Ventilation ($\dot{V}_E$) and alveolar gas exchange including end-tidal partial pressures for O_2 and CO_2 were measured breath-by-breath throughout the test protocol. The subjects breathed through a mouthpiece connected to a low-deadspace (90 ml) low-resistance turbine (Alpha Technologies VMM 110, Aliso Viejo, CA, USA) for measurement of inspiratory and expiratory volumes and flow. The turbine was calibrated before each test by using a syringe of known volume (3.01 L, Hans Rudolph Inc., Kansas City, MO, USA). A pneumotachograph attached between the volume turbine and a 50-mm diameter inspiratory mixing chamber was used to record breathing phase for the microcomputer controlling the dynamic gas forcing system. Inspired and expired gases were sam-