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Hypocapnia during hypoxic exercise and its impact on cerebral oxygenation, ventilation and maximal whole body O_2 uptake

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ABSTRACT

With hypoxic exposure ventilation is elevated through the hypoxic ventilatory response. We tested the hypothesis that the resulting hypocapnia reduces maximal exercise capacity by decreasing (i) cerebral blood flow and oxygenation and (ii) the ventilatory drive.

Eight subjects performed two incremental exercise tests at 3454 m altitude in a blinded manner. In one trial end-tidal P_{CO_2} (PET_{CO_2}) was clamped to 40 mmHg by CO_2-supplementation. Mean blood flow velocity in the middle cerebral artery ($MCAv_{mean}$) was determined by trans-cranial Doppler sonography and cerebral oxygenation by near infra-red spectroscopy.

Without CO_2-supplementation, PET_{CO_2} decreased to 30 ± 3 mmHg ($P < 0.0001$ vs isocapnic trial). Although CO_2-supplementation increased $MCAv_{mean}$ by $17 \pm 14\%$ ($P < 0.0001$) and attenuated the decrease in cerebral oxygenation ($-4.7 \pm 0.9\%$ vs $-5.4 \pm 0.9\%$; $P = 0.002$) this did not affect maximal O_2-uptake. Clamping PET_{CO_2} increased ventilation during submaximal but not during maximal exercise ($P = 0.99$).

We conclude that although hypocapnia promotes a decrease in $MCAv_{mean}$ and cerebral oxygenation, this does not limit maximal O_2-uptake. Furthermore, hypocapnia does not restrict ventilation during maximal hypoxic exercise.

1. Introduction

Hypoxia reduces maximal O_2-uptake ($\dot{V}_{O_2\,max}$) by affecting each step of the O_2 transport cascade (Calbet and Lundby, 2009). At the pulmonary level hypoxia decreases the pressure gradient across the alveolar-capillary membrane limiting diffusive O_2 transport (Wagner et al., 1987). This becomes particularly critical during exercise as the elevated cardiac output shortens pulmonary capillary transit time (Hopkins et al., 1996). The alveolar-arterial P_{O_2} difference widens with increasing intensities and the concomitant decrease in arterial O_2 saturation (Sa_{O_2}) eventually limits $\dot{V}_{O_2\,max}$ (Bebout et al., 1989; Calbet and Lundby, 2009). This is to some extent counteracted by the hypoxic ventilatory response which is activated by stimulation of the peripheral chemoreceptors and elevates pulmonary ventilation ($\dot{V}_E$) at rest and during exercise (Klausen et al., 1970; Lahiri et al., 1972). This partially restores alveolar P_{O_2} and diffusive O_2 transport (Calbet and Lundby, 2009). Concurrently, the hypoxic ventilatory response reduces arterial P_{CO_2} (Pa_{CO_2}) (Sutton et al., 1988) which further increases Sa_{O_2} by shifting the oxyhemoglobin dissociation curve to the left (Bohr et al., 1904). Despite this positive effect on oxygenation, however, hypoxic ventilatory response induced hypocapnia could negatively affect $\dot{V}_{O_2\,max}$ by other mechanisms.

First, hypocapnia may impair $\dot{V}_{O_2\,max}$ by a mechanism related to cerebral blood flow (CBF). Fatigue originating from the central nervous system is referred to as central fatigue and may be promoted by an insufficient O_2 delivery to the brain (Amann and Calbet, 2008; Rasmussen et al., 2010). With exercise CBF generally increases up to intensities of 60–80% of maximal capacity where after it plateaus (Querido and Sheel, 2007) or decreases toward or below resting values (Moraine et al., 1993; Hellström et al., 1996). Since CBF is reduced in parallel with Pa_{CO_2} as arterial P_{O_2} remains constant (Ide et al., 2003), the reduction in CBF during exercise has been attributed to hypocapnia (Poulin et al., 2002; Rasmussen et al., 2006; Bhambhani et al., 2007). Accordingly, blunted CBF combined with low arterial O_2-content in hypoxia causes brain de-oxygenation and may promote central fatigue (Imray et al., 2005; Rasmussen et al., 2006; Subudhi et al., 2009). This hypothesis was recently tested by Subudhi et al. (2011) by providing inspiratory CO_2 supplementation during exercise in hypobaric hypoxia

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corresponding to 4875 m altitude. This intervention increased CBF and cerebral oxygenation but, contrary to their hypothesis, reduced maximal exercise capacity. We speculated that these intriguing findings might be explained by the severe degree of hypoxia that was applied. There is indeed evidence that, for submaximal exercise, cerebral de-oxygenation only becomes a limiting factor when Sa_{O_2} falls below 82% (Amann and Calbet, 2008). However, maximal exercise capacity at altitudes >4000 m is crucially reduced by a decrease in maximal cardiac output (Calbet et al., 2003) and peripheral limitations (Lundby et al., 2008; Robach et al., 2008) which may together have overruled a potential benefit from an increased cerebral oxygenation. We therefore aimed to investigate whether the recent findings of Subudhi et al. (2011) could be confirmed at an altitude that is <4000 m, yet still in a range where effects of cerebral de-oxygenation on exercise performance have been observed previously (Goodall et al., 2012).

A second mechanism by which hypocapnia may impair $\dot{V}_{O_2\,max}$ in hypoxia is attenuation of the ventilatory drive (Dempsey, 1976) as this effect could amplify the hypoxemia during maximal exercise. At sea level, inspiratory CO_2 supplementation elevates maximal exercise $\dot{V}_E$ in young subjects (Babb, 1997), suggesting an inhibitory effect of hypocapnia rather than a mechanical limitation. Since the mechanical constraints associated with ventilation may be reduced in hypobaric hypoxia (Mognoni et al., 1982) while at the same time hypocapnia is more pronounced (Sutton et al., 1988), we speculated the blunting effect of hypocapnia on $\dot{V}_E$ to persist or become more pronounced than at sea level.

In summary, the aim of the present study was to investigate the impact of hypocapnia on exercise at 3454 m altitude. We hypothesized that clamping PET_{CO_2} to 40 mmHg would increase (i) CBF and cerebral oxygenation and (ii) $\dot{V}_E$ during exercise. We further expected one of these mechanisms or a combination hereof to increase $\dot{V}_{O_2\,max}$.

2. Methods

2.1. Subjects

Eight healthy subjects were recruited (5 males: 28 ± 1 years, 77 ± 10 kg, 182 ± 5 cm, and 3 females: 27 ± 1 years, 47 ± 5 kg, 163 ± 5 cm). The study was conducted at the Jungfraujoch Research Station (3454 m) in the Swiss Alps. It was approved by the local ethical committee (EK-2011-N-21) in accordance with the declaration of Helsinki. Prior to the start of the experiments, informed oral and written consents were obtained.

2.2. Protocol

Subjects were transported by train to the Jungfraujoch on the evening prior to the experiments and spent the night at the research station. The following day they performed two incremental exercise tests to exhaustion on an electronically braked bicycle ergometer (Monark 839E, Varberg, Sweden) breathing either ambient air (hypocapnic trial) or CO_2-enriched air (isocapnic trial). In the latter the inspired CO_2 fraction was continuously adjusted (Altitrainer, SMTEC, Nyon, Switzerland) to clamp PET_{CO_2} at 40 mmHg. The order of the trials was randomized and subjects, but not the investigators, were blinded. The trials were separated by at least 4 h where subjects had a snack and beverage.

Both exercise trials followed the same protocol starting with a warm-up period of 10 min at 100 W (males) or at 80 W (females). Thereafter the workload was increased every minute by 25 or 20 W, respectively, until exhaustion. Verbal encouragement was given in the end of all trials. Maximal workloads completed in the exercise tests were calculated as $W_{max} = W_{compl} + W_{increm} \times (t/60)$ with W_{compl} being the last completed workload, W_{increm} the workload increment per exercise step and t the number of seconds in the not completed workload.

2.3. Cerebral blood flow and cerebral oxygenation

The mean blood flow velocity in the middle cerebral artery ($MCAv_{mean}$) was determined as an estimate of CBF by insonating through the temporal window by trans-cranial Doppler sonography (2 MHz probe, Multi-Box, DWL, Singen, Germany; ST3 Digital, Spencer Technologies, Northbrough, USA). This approach is based on the assumption that the diameter of the MCA does not change during the measurement which we did not confirm experimentally. However, since an influence of Pa_{CO_2} on the MCA diameter has previously been excluded (Serrador et al., 2000) we were confident that the changes observed in $MCAv_{mean}$ reflected those in CBF. After the lowest signal to noise ratio was obtained the insonation probe was fastened to a headband and secured with adhesive sonography gel.

To assess cerebral oxygenation we used near infra-red spectroscopy (NIRS, NIRO-200, Hamamatsu, Japan), which exploits spatial resolution to attenuate the influence from superficial tissues. Although this technique is still affected by skin blood flow and cerebrospinal fluid (Yoshitani et al., 2007; Sørensen et al., 2012) it may detect changes in cerebral oxygenation during hypoxemia (Sørensen et al., 2012). We did not expect any differences between hemispheres, therefore the sensor was applied ipsilaterally to the Doppler probe. The sensor was placed high on the forehead to avoid influence from the frontal and saggital sinus.

2.4. Ventilatory variables

Subjects wore a mask covering nose and mouth for complete breath collection (Hans Rudolf, Kansas City, USA). The ventilatory exercise response was measured breath-by-breath by a spirometer (Cosmed Quark CPET, Rome, Italy). After the test, the highest average value for $\dot{V}_{O_2}$ calculated over 30 breaths was adopted as $\dot{V}_{O_2\,max}$. Pa_{CO_2} was calculated from tidal volume and end-tidal P_{CO_2} according to Jones et al. (1979). A pulse oximeter (LifeSense, Nonin Medical Inc., Plymouth, USA) was applied to the subjects' fingertip to determine Sa_{O_2} and heart rate (fH) was measured by a monitor belt (Polar Electro, Kempele, Finland).

2.5. Statistical analysis

Data were analyzed by two-way ANOVA on repeated measurements and given as mean with SEM. The statistical significance level was set to $P < 0.05$. The analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, USA).

3. Results

3.1. PET_{CO_2} and Pa_{CO_2}

In the isocapnic trial PET_{CO_2} was clamped to 40 ± 1 mmHg throughout the whole test (Fig. 1A). In the hypocapnic trial PET_{CO_2} decreased from 35 ± 1 mmHg ($P < 0.0001$ vs isocapnic trial) to 30 ± 3 during maximal exercise ($P < 0.0001$). Similarly, Pa_{CO_2} decreased in parallel with PET_{CO_2} in the hypocapnic trial but remained close to 40 mmHg in the isocapnic trial ($P < 0.0001$).

3.2. Exercise capacity

Clamping of PET_{CO_2} had no effect on $\dot{V}_{O_2\,max}$ which was 3.3 ± 1.0 l min^{-1} in the hypocapnic and 3.2 ± 1.0 l min^{-1} in the