Published in final edited form as:

Respir Physiol Neurobiol. 2009 April 30; 166(2): 125–128. doi:10.1016/j.resp.2009.02.013.

Effect of ventilation on cerebral oxygenation during exercise: Insights from canonical correlation

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Abstract

We tested hypothesis that cerebral deoxygenation near maximal exercise intensity is mediated by hyperventilation, via hypocapnia-induced reductions in cerebral blood flow, by utilizing canonical correlation analysis (CCA) to determine the relative influence of cardiopulmonary changes on cerebral oxygenation, as assessed by near infrared spectroscopy (NIRS). Twenty-three subjects performed incremental exercise tests under normoxic and hypoxic conditions. Changes in ventilation ($\dot{V}_E$) were strongly correlated with end-tidal CO_2 (PET_{CO_2}) and NIRS after the respiratory compensation point (RCP) ($r^2 > 0.97$). However, in contrast to our expectations, CBF velocity (CBFv) shared the least amount of variance with NIRS measurements ($r^2 < 0.56$) and the reduction in CBFv was not accompanied by a reduction in cerebral blood volume. These results demonstrate that while cerebral deoxygenation was associated with hyperventilation, it was not solely explained by hypocapnia-induced reductions in CBFv. CCA revealed that a relative increase in the venous contribution to NIRS explained a larger amount of variation in cerebral oxygenation than reductions CBFv.

Keywords

hypoxia; near infrared spectroscopy; cerebral blood flow; transcranial Doppler

1. Introduction

Reductions in regional cerebral oxygenation during high intensity aerobic exercise may limit performance, particularly at high altitude (Amann et al. 2007; Subudhi et al. 2007; Subudhi et al. 2008). The mechanisms responsible for reduced regional cerebral oxygenation are unknown, but have been theorized to stem from hypocapnia-induced cerebral vasoconstriction subsequent to hyperventilation (Bhambhani et al. 2007; Querido et al. 2007; Thomas et al. 2008). Support for this theory is based on a series of bivariate relationships which show that during high intensity exercise, a disproportionate increase in pulmonary ventilation ($\dot{V}_E$) relative to metabolic production CO_2 decreases arterial partial pressure of CO_2 (Pa_{CO_2}).

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Decreased Pa_{CO_2} leads to vasoconstriction of cerebral vessels which in turn reduces cerebral blood flow (CBF) and oxygenation. While these relationships demonstrate a linkage between hyperventilation and cerebral deoxygenation, they do not describe the relative influence that each step has on cerebral oxygenation.

Canonical Correlation Analysis (CCA) is a statistical method which analyzes relationships between multiple predictor and criterion variables, as opposed to multiple regression which evaluates multiple predictors against a single criterion (Sherry et al. 2005). CCA is well suited for physiological investigations since multiple variables are logically grouped to describe an overall effect on an organ system (e.g. individual spirometry measurements are grouped to assess overall pulmonary function). CCA is a particularly promising tool for analyzing cerebral oxygenation data obtained via near infrared spectroscopy (NIRS), because the criterion oxygenation measurement is a function of concurrent changes in oxygenated, deoxygenated and total hemoglobin concentrations (O_2Hb , HHb and THb). Moreover, CCA offers an advantage over multiple bivariate analyses because it yields ‘cross loading’ terms which explain the relative influence that each predictor has on an overall criterion value while controlling for Type I error.

In this study, we illustrate how CCA was used to test the hypothesis that hyperventilation influences cerebral oxygenation via hypocapnia-induced cerebral vasodilation in normoxic and hypoxic conditions. We hope that this work will inspire others to consider the use of CCA in physiological studies.

2. Methods

2.1 Subjects

Athletic subjects were recruited from the local community as part of a larger study investigating acute mountain sickness. All participants provided informed consent conforming to the Declaration of Helsinki and underwent physical examinations to assess general health prior to participation.

Exercise protocol

Subjects performed two randomized and blinded incremental exercise trials in a hypobaric chamber under normoxic ($\text{PB} = 610 \text{ mmHg}$; $\text{PI}_{\text{O}_2} = 118 \text{ mmHg}$) and hypoxic conditions ($\text{PB} = 425 \text{ mmHg}$; $\text{PI}_{\text{O}_2} = 79 \text{ mmHg}$) with 30 min of rest between. After reaching the first target pressure, 15 min were taken to instrument the subject. Resting data were collected for 2 min prior to a 5-min warm up period at 50W. Workrate was then increased continuously (25W/min) until subjects could not maintain 60 rpm (W_{max}). Cool-down exercise was performed at 50W for 5 min before chamber pressure was adjusted and the protocol was repeated.

2.2 Cerebral oxygenation

A continuous wave NIRS (Oxymon MK III, Artinis Medical Systems, The Netherlands) was used to monitor cerebral oxygenation throughout the chamber session, as previously described (Subudhi et al. 2007). NIRS transmitters and detectors were spaced 40 to 50mm apart, depending on individual head geometry, just above the supra-orbital ridge and were tightly strapped with a custom made headset. Tissue absorbance measurements of two NIR light sources (780 and 850 nm) were used to calculate O_2Hb and HHb concentrations (in μM) using the modified Beer-Lambert law and a path-length factor of 5.93. Total Hb (THb) was calculated as the sum of O_2Hb and HHb and used as an indicator of cerebral blood volume (CBV). All values were expressed as changes from the rest period prior to warm up, arbitrarily defined as 0 μM . Data were recorded at 125Hz and averaged in 5 sec windows prior to analysis. Transcranial Doppler (DWL Multi Dop T2, Germany) was used to measure cerebral blood

flow velocity of the left middle cerebral artery (MCA). The custom NIRS headset was modified to hold a 2-MHz Doppler probe over the left temporal window to insonate the MCA and record the maximal velocity envelope at 125Hz. Time averaged mean velocity (CBFv) was calculated beat-by-beat and reported as % change from rest.

2.3 Cardiopulmonary measurements

Minute ventilation (VE) and mix expired gases were analyzed via a metabolic measurement system (TrueMax 2400 analyzer, Parvomedics, USA). Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were calculated in 15 sec increments using the Haldane transformation. End tidal O_2 and CO_2 were sampled at the mouth with a separate analyzer (O_2 Cap, Oxigraf, USA). Subjects cycled in an aerodynamic position (Velotron, Racermate, Seattle, WA) which allowed fingertip oxygen saturation (SpO_2) measurements from the left middle and ring finger (Nellcor, N-200 oximeter, USA; Criticare, 503 oximeter, USA). The average of both SpO_2 readings was used for analysis. Mean arterial blood pressure (MABP) was measured continuously from the left index finger (Nexfin HD, BMEye BV, The Netherlands). Analog signals from all instruments were converted to digital format (Powerlab, ADInstruments, Colorado Springs) and merged into one datafile with a sampling rate of 200Hz for offline analysis.

2.4 Analyses

For each individual, data were divided into 100 bins based on maximal power output (1 to 100% W_{max}). A two-segmental piecewise linear regression identified the downward inflection point in PET_{CO_2} (Sigmaplot 10.0, Systat Software). This downward inflection point represents hyperventilation in response to exercise intensity and is known as the respiratory compensation point (RCP). Repeated measures ANOVAs were run to evaluate differences across workrate (rest, RCP, 100% W_{max}) at each PB (610 and 425 mmHg). A canonical correlation analysis (CCA) determined relationships between cardiopulmonary and cerebral oxygenation measurements before and after the RCP. The CCA grouped individual predictors and criteria to calculate overall predictor and overall criterion variable. The canonical correlation was the bivariate correlation between these two overall variables. In this study, MABP, VE, SpO_2 , PET_{CO_2} and CBFv were considered predictors of the CCA derived index of cerebral oxygenation (COX), calculated from concurrent changes in O_2Hb , HHb and THb. To study the individual influence of each cardiopulmonary variable on COX, the cross loadings derived from the CCA were analyzed. Cross loadings represented the bivariate correlations between individual predictors and COX. Statistical significance was evaluated using the multivariate Wilks Lambda statistic to control for type I error at the $P < 0.05$ level.

3. Results

3.1 Subjects

Data from 23 subjects (21 males, 2 females) were used for analysis. Subjects were 28.6 ± 7.9 years of age 181.7 ± 8.0 cm tall, and weighed 73.7 ± 10.0 kg.

3.2 Normoxia

$\dot{V}O_{2-max}$ was 3.49 ± 0.76 L/min and W_{max} was 305 ± 52 W. The average RCP occurred at 199 ± 47 W or $65 \pm 11\%$ of W_{max} (Figure 1). Prior to the RCP, changes in VE, PET_{CO_2} , CBFv, and NIRS variables (O_2Hb , HHb and THb) were highly correlated ($r^2 > 0.62$); however, after the RCP, $PET_{CO_2} - CBFv$ and CBFv - NIRS variables correlations were reduced ($r^2 < 0.29$). The CCA ($r_{CCA} > 0.99$; Wilks Lambda < 0.05) showed that VE and PET_{CO_2} were strongly associated with COX throughout exercise ($r^2 > 0.62$), yet changes in CBFv explained the least amount of variance after the RCP ($r^2 < 0.23$) (Table 1).

3.3 Hypoxia

Absolute $\dot{V}O_2$ -max (2.74 ± 0.60 L/m), Wmax (256 ± 38 W) and RCP (171 ± 26 W) were 21.5 %, 16.2% and 14.1% lower than normoxia ($P < 0.01$), yet the RCP occurred at a similar relative work rate (66 ± 8 % of hypoxia Wmax; $P = 0.89$ vs. normoxia). Prior to the RCP changes in $\dot{V}E$ were highly correlated with changes in O_2Hb ($r^2 = 0.93$) and HHb ($r^2 = 0.85$) while after the RCP PET_{CO_2} ($r^2 = 0.84$) and $\dot{V}E$ ($r^2 = 0.84$) shared the most variance with cerebral oxygenation. After the RCP the correlation between $CBFv$ and NIRS increased ($r^2 = 0.18$ to 0.56), but was only moderately strong. The CCA ($r_c > 0.99$; Wilks Lambda < 0.05) showed that changes in COX were more closely related to changes in PET_{CO_2} and $\dot{V}E$ than $CBFv$ (Table 1).

4. Discussion

We used CCA to test the hypothesis that hyperventilation influences cerebral oxygenation via hypocapnia-induced cerebral vasodilation under both normoxic and hypoxic conditions. Although hyperventilation resulted in concurrent decreases in PET_{CO_2} , $CBFv$ and COX, results of the CCA caused us to reject the hypothesis. Our rationale for rejecting the hypothesis based on CCA is discussed below.

The strong canonical correlations between grouped cardiopulmonary and cerebral oxygenation variables indicate that the model was successful ($r_c^2 > 0.99$). To assess the relative influence of each cardiopulmonary variable on the overall measurement of cerebral oxygenation (COX) we evaluated the cross loading terms (Table 1). Specifically, if COX was mediated by a reduction in CBF then we would have expected to see strong cross loading between $CBFv$ – COX. This was not the case. $CBFv$ shared the least amount of variance with COX, showing that factors other than reduced $CBFv$ explain decreased cerebral oxygenation near maximal exertion. In fact, bivariate analyses obtained with CCA showed that reductions in $CBFv$ were associated with increased THb ($r = -0.69$, $P < 0.01$), an estimation of regional CBV. This paradoxical finding was the result of an increased HHb contribution to the overall NIRS signal, suggesting that an increase in the relative proportion of venous blood in the cerebral volume illuminated by NIRS provides a more accurate measure of NIRS evaluated cerebral deoxygenation during high intensity exercise. We propose that simultaneous increases in HHb and THb may be due to a reduction in cerebral venous outflow (Stolz et al. 2009), leading to venous pooling at exercise intensities above the RCP. Future research should thus be directed towards supporting or refuting this hypothesis..

4.1 Conclusion

CCA provided a statistical tool to analyze complex interactions between multiple variables while controlling for type I error. We have demonstrated how results can provide new insights on the mechanisms responsible for cerebral deoxygenation during exercise and propose that additional physiological understanding may be gained by applying CCA to other questions.

Acknowledgements

The authors express their gratitude to Brittany Miramon and Matthew Granger for their managerial and technical assistance during data collection. This project was funded in part by National Heart, Lung and Blood Institute Grant HL-070362

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Figure 1. $\dot{V}_E$, $P_{ET}CO_2$, CBFv and NIRS responses during exhaustive incremental exercise relative to 100% W_{max} in normoxia and hypoxia (N=23). Dashed lines represent segmental regressions of $P_{ET}CO_2$, with vertical gray lines marking RCPs.

Table 1

Cross loadings between observed predictor variables with synthetic cerebral oxygenation (O₂Hb, HHb and THb) variable before and after the respiratory compensation point (RCP).

		Cerebral oxygenation	
		Normoxia	Hypoxia
BEFORE RCP	PET _{CO₂}	0.788	0.334
	VE	0.988	−0.992
	CBF _v	0.962	−0.883
	MABP	0.942	−0.883
	SpO ₂	−0.953	0.965
AFTER RCP	PET _{CO₂}	−0.985	0.989
	VE	0.987	−0.992
	CBF _v	−0.475	0.751
	MABP	0.913	−0.787
	SpO ₂	−0.988	0.444