

Relationship Between Ventilatory Threshold and Cerebral Blood Flow During Maximal Exercise in Humans

Thomas P. Olson, Jennifer Tracy and Donald R. Dengel*

University of Minnesota, 1900 University Avenue S.E., 110 Cooke Hall, Minneapolis, MN 55455, USA

Abstract: *Background:* This work studied the relationship between changes in cerebral blood flow velocity (CBFV) through the middle cerebral artery (MCA) with non-invasive ventilatory threshold (VT) measurements determined by gas-exchange during upright maximal cycle ergometry.

Methods: Fourteen (M=8, F=6) healthy, young (23.1 ± 3.9 yr) participants volunteered for this study and performed a cycle ergometer protocol to maximal exertion. The CBFV was monitored continuously through the MCA by transcranial Doppler ultrasound and was assessed at rest, VT, and at maximal exertion (VO_{2max}). Ventilatory threshold was assessed using three common methods: 1) V-slope, 2) nadir of the ventilatory equivalent for carbon dioxide production (V_E/VCO_2), and 3) maximal partial pressure of carbon dioxide ($P_{ET}CO_2$).

Results: Analysis of variance demonstrated significant ($p < 0.001$) main effects for CBFV, volume of oxygen consumed (VO_2), volume of carbon dioxide produced (VCO_2), and $P_{ET}CO_2$. Bonferroni post hoc analysis demonstrated an increase in CBFV from rest to a peak CBFV ($p < 0.01$) with a decrease from peak CBFV to VO_{2max} ($p < 0.01$). Stepwise linear regression suggest the only predictor of a reduction in CBFV during maximal exercise is the nadir of V_E/VCO_2 ($p < 0.01$).

Conclusion: These data demonstrate an increase in CBFV during dynamic upright exercise up to approximately 78% VO_{2max} after which CBFV decreases significantly to VO_{2max} . This decrease in CBFV was closely related to common non-invasive measures of ventilatory threshold suggesting a close relationship between cerebral blood flow and the threshold for ventilatory compensation.

Keywords: Ventilation, cerebrovascular circulation, middle cerebral artery, exercise.

INTRODUCTION

Transcranial Doppler ultrasonography (TCD) is a imaging technique enabling clinicians and researchers to non-invasively insonate cerebral arteries and monitor changes in cerebral blood flow velocity (CBFV). The response of cerebral blood flow to dynamic exercise has demonstrated mixed results. Early work demonstrated either no change [1, 2] or a decrease [3, 4] in cerebral blood flow; however, more recent work has shown an increase [5-7] of cerebral blood flow in response to exercise. The lack of agreement on the exact changes in cerebral blood flow which take place during exercise may be due to methodological differences between the studies.

Despite the controversy related to the direction of cerebral blood flow during exercise, the TCD technique, used to measure CBFV through the middle cerebral artery (MCA) has established results consistent with the widely used ^{133}Xe clearance method, which is indicative of changes in global cerebral blood flow. Jorgensen and colleagues [8] conducted an elaborate study demonstrating significant increases of 25-30% in both CBFV of the MCA using TCD and global cerebral blood flow using the ^{133}Xe -clearance method during supine cycle ergometry. Hellstrom *et al.* [9] found similar

results for CBFV in the MCA also using the TCD technique. These authors report an increase in CBFV of approximately 30% during submaximal supine exercise with a drop to approximately 15% above baseline during maximal exertion.

It has been suggested that alterations in CBFV may be a direct reflection of changes in carbon dioxide tension, independent of neurohumoral or arterial pressure changes [10, 11]. Utilizing a re-breathe technique at rest, Ide and colleagues [10] have demonstrated a close relationship between partial pressure of end-tidal carbon dioxide tension ($P_{ET}CO_2$) and CBFV within a wide hypo – hypercapnic range. These authors suggest that changes which occur in CBFV are likely a result of alterations in arterial carbon dioxide content. Because of this close relationship at rest, it is reasonable to hypothesize that the considerable physiologic changes which occur in carbon dioxide tension at or around the ventilatory threshold (VT) during exercise will result in alterations in cerebral blood flow. It has yet to be determined, however, whether the changes in CBFV that occur during upright maximal cycle ergometry up to and beyond the VT are related to the physiologic changes in carbon dioxide tension.

The present study was conducted to evaluate the relationship between the ventilatory threshold and alterations in CBFV through the MCA elicited by graded maximal cycle ergometry in the upright position in young, healthy adults by means of TCD. We hypothesized that the often demonstrated decline in CBFV prior to maximal exertion is closely associated with the decline in $P_{ET}CO_2$ which occurs at and beyond

*Address correspondence to this author at the University of Minnesota, 1900 University Avenue S.E., 110 Cooke Hall, Minneapolis, MN 55455, USA; Tel: 612-626-9701; Fax: 612-625-8867; E-mail: dengel001@umn.edu

the ventilatory threshold during dynamic exercise. The ability to non-invasively determine the point at which the CBFV declines during heavy exercise may have important implications in the exercise prescription strategy for various healthy and chronic disease populations.

METHODS

Study Population

Fourteen (Male=8, Female=6) healthy (BMI=23.5 ± 2.0 kg/m²), adult (23.7 ± 4.1 y) participants were recruited from the Minneapolis / St. Paul community and volunteered to participate in this study. All participants gave written informed consent after being provided a description of study requirements and successful screening for participation in exercise *via* the Physical Activity Readiness Questionnaire (PAR-Q) (ACSM, 1998). The study protocol was approved by the University of Minnesota Institutional Review Board and Human Subjects Committee; all procedures followed institutional and Health Insurance Portability and Accountability Guidelines Act (HIPAA) guidelines.

Study Protocol

Participants fasted for twelve hours and completed testing in the morning at the University of Minnesota's Laboratory of Physiological Hygiene. Upon arrival to the laboratory for testing the participants rested quietly for 10 minutes to acclimate to the climate controlled laboratory conditions. Immediately following this period while seated on the cycle ergometer and prior to beginning the exercise protocol, resting data was collected for 3 minutes. Cycle exercise was performed on an electrically braked stationary cycle ergometer (Dimeq ERG 401, Berlin, Germany) in the upright position. The cycle exercise consisted of a stepwise protocol starting at 50 watts and increased 25 watts every 2 minutes until volitional fatigue. Participants were verbally encouraged to continue the exercise protocol to maximal exertion which was determined by meeting 3 of the 4 primary criteria as outlined by the American College of Sports Medicine [12].

Ventilatory and Gas Exchange Measurements

All ventilatory and gas exchange data were collected continuously at rest and throughout the exercise protocol using a standard metabolic measurement system (MedGraphics CPX/D, Medical Graphics, St. Paul, MN). Metabolic and gas exchange measurements were accomplished through analysis of the concentration and volume of oxygen consumed per minute (VO₂), volume of carbon dioxide produced per minute (VCO₂), minute ventilation (V_E), and partial pressure of end-tidal oxygen (P_{ET}O₂) and carbon dioxide (P_{ET}CO₂). Prior to beginning exercise, participants were fitted with a nose clip and standard mouth piece attached to a pneumotach (Medical Graphics, St. Paul, MN) and worn throughout the testing procedure. Manual flow calibrations were performed with a three-liter syringe while gas calibrations were performed with manufacturer recommended gases of known concentration. All calibration procedures were accomplished immediately prior to each testing session. Breath-by-breath data for VO₂, VCO₂ and V_E was averaged over the last 30 seconds of each 3 minute stage. The ventilatory threshold (VT) was determined using the following

methods: 1) V-slope method (Vslope) was determined from the slope of ventilation curves constructed from the VCO₂ and VO₂ and divided into two regions. Each region was fitted with linear regression lines and the intersection between the two lines was chosen as the VT [13]; 2) Maximal P_{ET}CO₂ immediately prior to the decline in P_{ET}CO₂. This point has also been identified as a reproducible measure of VT (peak P_{ET}CO₂) [14]; and 3) the lowest value of V_E/VCO₂ (nadir-V_E/VCO₂) during the incremental exercise test. Previous studies have suggested that the point at which the nadir V_E/VCO₂ occurs is an accurate method for the non-invasively determine VT [15]. All plots used to determine VT were examined by two blinded investigators. In the case of a disagreement a third investigator examined the VT plots.

Cerebral Blood Flow Measurements

Cerebral blood flow velocity (CBFV) was measured continuously at rest and throughout the exercise session with TCD ultrasound through the left MCA (Companion Series Transcranial Doppler Ultrasound, Nicolet Vascular, Madison, WI). Ultrasound conducting gel was applied to a 2-MHz transducer probe which was secured to the head (Mark IV, Nicolet Vascular, Madison, WI). The fixation of the ultrasound probe to the measurement area was ensured using a Marc 500 Spencer Probe Fixation System (Spencer Technologies, Seattle, Washington), which consists of a specialized headgear that has a build-in 2-MHz transducer probe that can be held in a fixed position so that no changes in insonation angle can occur during exercise. The proximal segment of the MCA was insonated through the temporal window approximately 1 cm above the zygomatic arch at a depth of 45-60 mm depending on the cranial thickness [16]. Cerebral blood flow velocity was defined as the mean of maximum and minimum flow velocities averaged over time throughout the cardiac cycle. Beat-by-beat TCD signals, accompanied by the ECG recordings, were electronically exported to a computer for off-line analysis. The signals recorded during resting conditions were averaged over the 3 min rest period. Data were also analyzed at each of the three VT points described previously at peak CBFV and maximal oxygen uptake (VO₂max). At each of these intensities the TCD signal was averaged for 30 sec to include no less than 30 waveforms for the determination of mean blood flow velocity. This technique has been demonstrated to provide valid and reproducible information regarding changes in CBFV in the MCA [17, 18].

Statistical Analysis

Data are presented as mean ± standard deviation (SD). All statistical analyses and graphic presentations were accomplished using Graphpad Prism® (v 4.0, San Diego, CA). Analysis by one-way repeated measures ANOVA was used to determine the main effect of exercise on each of the variables. Bonferroni's multiple comparisons analysis was used to determine statistical differences between rest and each of the VT points elicited by the exercise protocol when appropriate. Pearson's correlation coefficient was used to calculate the correlation coefficient between CBFV and V-slope, nadir-V_E/VCO₂, and peak-P_{ET}CO₂. Stepwise linear regression was conducted to determine the best predictor of the reduction in CBFV during exercise. An alpha level of 0.05 was chosen as the criterion for significance.

RESULTS

The study was completed by all the recruited subjects. Participant's had a mean weight of 70.1 kgs (± 6.4) and a height of 1.74 m (± 8.1). The VO₂ increased significantly (*p*<0.0001) between rest, all VT measurements and VO₂max (Table 1). The VCO₂ demonstrated a significant increase (*p*<0.0001) from rest to all VT measures and VO₂max (Table 1). Ventilation also demonstrated a significant increase (*p*<0.0001) from rest to VT and VO₂max (Table 1).

Table 1. Gas Exchange and Cerebral Blood Flow Velocity Measurements at Rest and VO₂max

Gas Exchange Measures	Rest	VO ₂ max
Time (s)		782 ± 43
VO ₂ (L/min)	0.33 ± 0.13	2.90 ± 0.80‡
VCO ₂ (L/min)	0.32 ± 0.17	3.47 ± 0.78‡
RER	0.99 ± 0.16	1.21 ± 0.08‡
V _E (L/min)	14.0 ± 8.1	109.3 ± 28.2‡
P _{ET} O ₂ (mm Hg)	110.3 ± 7.7	112.0 ± 6.6
P _{ET} CO ₂ (mm Hg)	32.2 ± 4.7	37.1 ± 5.9†
V _E /VO ₂	41.3 ± 10.7	38.4 ± 7.1
V _E /VCO ₂	41.6 ± 4.2	31.7 ± 5.2‡
Cerebral Blood Flow Velocity Measures		
CBFVmin (cm/s)	39.9 ± 8.9	37.7 ± 6.2
CBFVmax (cm/s)	82.6 ± 14.1	115.1 ± 16.5‡
CBFVmean (cm/s)	53.3 ± 12.7	62.9 ± 10.8†

VO₂, volume of oxygen consumed per minute; VCO₂, volume of carbon dioxide produced per minute; RER, respiratory exchange ratio; V_E, minute ventilation; P_{ET}O₂, partial pressure of oxygen; P_{ET}CO₂, partial pressure of carbon dioxide, CBFV, cerebral blood flow velocity. Data are presented as Mean ± standard deviation. Values compared to rest, *=*P*<0.05; †=*P*<0.01; ‡=*P*<0.001.

There was a significant main effect for P_{ET}O₂ and P_{ET}CO₂ (*p*<0.001) from rest to VT and VO₂max (Table 2). The P_{ET}O₂ decreased significantly from rest to V-slope (*p*<0.01), nadir-V_E/VCO₂, and peak-P_{ET}CO₂ (*p*<0.0001). Thereafter, the P_{ET}O₂ demonstrated a trend to increase from all VT measures to VO₂max.

The reported significances are the result of the one-way repeated measures ANOVA. There was a significant increase for CBFV during the exercise test to VT, after which there was a decline to end exercise (*p*<0.0001). Specifically, there was a significant increase in mean CBFV from rest to the peak cerebral blood flow velocity (*p*<0.01) and between rest and VO₂max (*p*<0.001). The peak CBFV occurred at 620.7 seconds of the exercise test and then demonstrated a significant decrease between peak velocity and VO₂max (*p*<0.01) (Fig. 1).

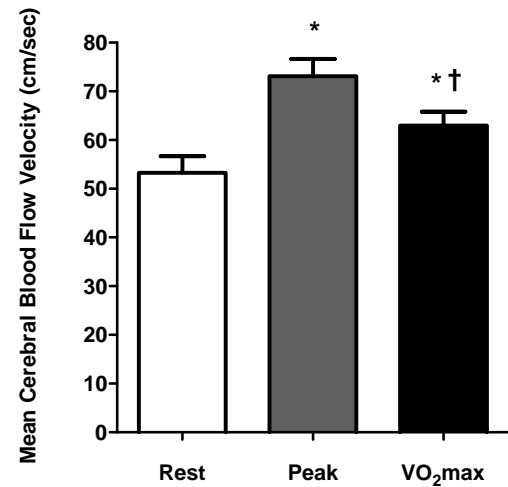


Fig. (1). Mean cerebral blood flow velocity at rest, peak cerebral blood flow, and VO₂max. VO₂max, maximal oxygen consumption. All data are expressed as mean ± SEM. *=*P*<0.05 from rest; † = *P*<0.05 from peak.

Table 2. Gas Exchange Measurements at Ventilatory Threshold Levels

	V-Slope	Nadir V _E /VCO ₂	Peak P _{ET} CO ₂	P-Value for ANOVA
Time (s)	579 ± 150	573 ± 177	613 ± 169	0.52
VO ₂ (L/min)	2.04 ± 0.75	2.05 ± 0.76	2.17 ± 0.73	0.29
VCO ₂ (L/min)	2.19 ± 0.80	2.19 ± 0.80	2.35 ± 0.78	0.42
RER	1.07 ± 0.08	1.06 ± 0.07	1.08 ± 0.09	0.79
V _E (L/min)	61.0 ± 23.9	56.6 ± 18.1	61.0 ± 17.5	0.56
P _{ET} O ₂ (mm Hg)	104.6 ± 6.9	102.7 ± 4.3	103.2 ± 4.4	0.16
P _{ET} CO ₂ (mm Hg)	40.9 ± 5.1	42.6 ± 3.7*	42.6 ± 3.8*	0.01
V _E /VO ₂	30.2 ± 7.2	28.0 ± 2.8	29.1 ± 3.	0.20
V _E /VCO ₂	27.9 ± 4.2	26.4 ± 2.4*	26.5 ± 2.5*	0.04
Cerebral Blood Flow Velocity Measures				
CBFVmin (cm/s)	39.5 ± 11.7	41.3 ± 12.5	41.3 ± 14.6	0.31
CBFVmax (cm/s)	112.2 ± 26.6	115.1 ± 22.7	113.8 ± 29.2	0.66
CBFVmean (cm/s)	66.3 ± 17.1	68.0 ± 14.5	69.8 ± 18.5	0.61

VO₂, volume of oxygen consumed; VCO₂ volume of carbon dioxide produced; RER, respiratory exchange ratio; V_E, minute ventilation; P_{ET}O₂, partial pressure of end-tidal oxygen; P_{ET}CO₂, partial pressure of end-tidal carbon dioxide. Data are presented as Mean ± standard deviation. *=*P*<0.05 compared to V-slope; †=*P*<0.05 compared to nadir V_E/VCO₂.

The V-slope method for determination of VT occurred at 578.6 seconds. The nadir- V_E/V_{CO_2} occurred at 572.9 seconds. The P_{ETCO_2} initially increased with a decline occurring at a mean 612.9 seconds. The time at which CBFV began to decline was not significantly different from any of the VT measurements ($p < 0.05$ for all); lowest V_E/V_{CO_2} , V-Slope, and P_{ETCO_2} . Correlation analysis demonstrated a significant relationship between the time of VT for all three VT measurements and the time point at which CBFV began to decline (V-slope, $r = 0.62$, $p = 0.02$; peak- P_{ETCO_2} , $r = 0.82$, $p < 0.001$; nadir- V_E/V_{CO_2} , $r = 0.83$, $p < 0.001$) (Fig. 2).

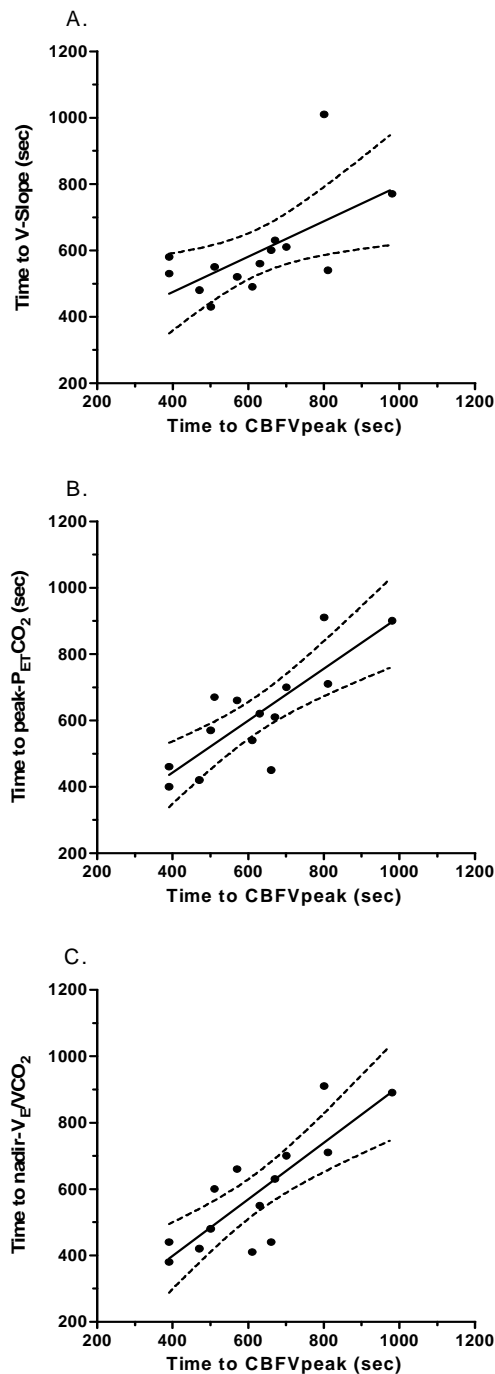


Fig. (2). Relationship between the time to peak cerebral blood flow velocity and each of the measures of ventilatory threshold. A. V-slope method; B. peak- P_{ETCO_2} method; C. nadir- V_E/V_{CO_2} method.

Despite the close temporal relationship between all of the measures of ventilatory threshold and the decline in CBFV, the results of the linear regression analysis suggested that the strongest predictor of a decline in CBFV during exercise was the nadir- V_E/V_{CO_2} (VT-V-slope, t statistic = -0.291, $p = 0.78$; VT- P_{ETCO_2} ; t statistic = -0.003, $p = 0.99$; nadir- V_E/V_{CO_2} , t statistic = 4.306, $p < 0.001$).

DISCUSSION

Initial investigations in the area of cerebral blood flow suggest a primary regulatory mechanism was cerebral autoregulation which acted to maintain a constant level of cerebral blood flow despite changes in perfusion pressure and other demands incurred during cerebral activity. Cerebral autoregulation may be influenced by a number of factors including neurohumoral, pressure, and metabolic alterations at rest and during exercise. The distinct mechanisms which contribute to cerebral autoregulation however remain unclear and thus research in this area continues to be of great interest. A number of recent investigations have been conducted in effort to deduce the various contributions of these potential mechanisms and as such as demonstrated a close relationship between arterial content of carbon dioxide and cerebral blood flow regulation. The results of the present study demonstrate that cycle ergometry exercise in the upright position provoked a significant increase in CBFV through the MCA to approximately 78 percent of VO_{2max} at which point the CBFV significantly declined until test termination. This response in CBFV during upright cycle ergometry is similar to the responses demonstrated previously during cycling in the supine position. In addition, changes in P_{ETCO_2} were similar to the changes in CBFV demonstrating an increase to approximately 75 percent of VO_{2max} with a trend to decline beyond this point. The similarity in changes of P_{ETCO_2} and CBFV suggest a close relationship between these variables at rest and during exercise. In addition, the lowest V_E/V_{CO_2} demonstrated a strong correlation with changes in CBFV further suggesting a dependency of CBFV on carbon dioxide tension.

Exercise induced increases in both global and regional cerebral blood flow assessed by various methodologies have been reported previously [1-3, 5-7, 19]. To date these findings are contradictory to the traditional concept of cerebral autoregulation, which postulates that the volume of cerebral blood flow should remain constant over a wide range of perfusion pressures designated by mean arterial blood pressure (MAP). The changes in CBFV may therefore be augmented by mechanisms related to other physiologic alterations observed during exercise such as metabolic byproducts including H^+ ion concentration, CO_2 , adenosine, and phosphate levels. During exercise, increasing metabolic demands result in systemic vasodilation to ensure adequate blood perfusion to the working muscles [10, 20]. One of the primary metabolic byproducts capable of actively causing vasodilation in the periphery is CO_2 [21, 10]. The results of this study indicate that CBFV increases with exercise intensity to a peak velocity at or near the VT. This may be due to the inability of metabolic buffering compensation mechanisms to adapt to the production of CO_2 or to counterbalance the increase in CO_2 . This inability typically leads to hyperpnea (as indicated by the non-linear increase in V_E) and subsequent hypocapnia (as indicated by the significant decline in P_{ETCO_2}).

Exercise associated increases in global and regional cerebral blood seem to reach a peak at or near the VT and decline prior to VO_2max . Kleinerman *et al.* [3] postulated that decreased CBF is dependent on the fall in arterial PCO_2 during exercise. These authors suggest that the systemic decrease in peripheral resistance during mild exercise does not affect the cerebral circulation. Furthermore, Ide *et al.* [10] and Pandit *et al.* [22] have both hypothesized that augmentations in arterial CO_2 tension may be responsible for changes in CBFV. By utilizing a CO_2 re-breathing technique with two separate incremental protocols of increasing and decreasing concentrations of CO_2 as the inspirate; Ide and colleagues [10] have characterized a close relationship between $\text{P}_{\text{ET}}\text{CO}_2$ and CBFV within the hypocapnic - hypercapnic range. The results of Ide and colleagues strongly suggest that changes in CBFV closely follow the alterations in $\text{P}_{\text{ET}}\text{CO}_2$ throughout the hypo - hypercapnic range with greater sensitivity of CBFV in the hypercapnic compared to the hypocapnic range [10]. Interestingly, however, these theoretical postulates had not been tested in a model of dynamic exercise with physiologic changes in carbon dioxide. In the present study, the decline in CBFV is associated with the VT measurements including $\text{P}_{\text{ET}}\text{CO}_2$ thus supporting the findings of Ide and colleagues [10].

Arterial CO_2 may be a primary factor in the decline in CBFV that occurs during exercise. Determination of VT measures that incorporate CO_2 correspond to the occurrence of the decline in CBFV. This study assessed several non-invasive measures of VT to determine which best predicts the decline in CBFV during exercise. The present study supports the use of $\text{VT}-\text{V}_E/\text{VCO}_2$ measures in the assessment of a drop in CBFV during maximal exercise. The time at which the minimum V_E/VCO_2 is attained and the decline in $\text{P}_{\text{ET}}\text{CO}_2$ are ventilatory threshold measures that correlate well with the decline in CBFV that occurs during exercise. The results of this study may have significant implications in the rehabilitative field, particularly in chronic disease populations where exercise is critical to the progression of treatment but changes in cerebral blood flow may present detrimental influences to the disease severity and overall well-being of the patient.

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