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This study tested the hypothesis that sympathetic activation via the carotid baroreflex directly influences cerebral vasomotion during seated upright rest. This study also examined the effects of pulsatile neck pressure (NP) and neck suction (NS) during seated upright rest in healthy human subjects. Changes in mean arterial arterial pressure (MAP) and mean middle cerebral arterial velocity (MCA *V* mean), were measured. The power spectral density (PSD) of MAP at 0.1Hz increased during pulsatile NP and NS. The PSD of MCA *V* mean at 0.1Hz was much greater during NP than that of NS. There were no significant differences between end-tidal CO_2 between each condition. These findings suggest that cerebral vasoconstriction during NP was a result of the autoregulatory response to the NP mediated pulsatile changes in arterial pressure and the NP induced sympathetically mediated vasoconstriction.

INFLUENCE OF THE CAROTID BAROREFLEX ON
CEREBRAL BLOOD FLOW DURING
SEATED UPRIGHT REST

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LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
ABP	Arterial Blood Pressure
ECG	Electrocardiogram
$ETCO_2$	End Tidal Carbon Dioxide
HR	Heart Rate
MAP	Mean Arterial Pressure
MCA *Vmean*	Mean Middle Cerebral Artery Blood Velocity
NIRS	Near Infrared Spectroscopy
NP	Neck Pressure
NS	Neck Suction
PSD	Power Spectral Density
$PaCO_2$	Pressure of Arterial Carbon Dioxide
ScO_2	Cerebral Tissue Oxygenation
Sec	Seconds
TCD	Transcranial Doppler

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CHAPTER I

Introduction

The peripheral vasculature is under tight control of the autonomic nervous system and the carotid baroreflex plays a key role in the regulation of beat to beat blood flow and arterial blood pressure control (Wray *et al.*, 2004). A number of investigations have used the application of brief periods of neck pressure (NP) and neck suction (NS) to evaluate carotid baroreceptor function at rest. (Potts *et al.*, 1993; Potts & Raven, 1995; Fadel *et al.*, 2001). Specifically, Wray *et al.* (2004) demonstrated that the use of sinusoidal NP as a dynamic sympathoexcitatory stimulus entrained all the end organ measurements of the carotid baroreflex (CBR), ranging from cardiac chronotropic effects to alterations at the level of skeletal muscle microcirculation and the muscle tissue oxygenation. In contrast, cerebral blood flow regulation is thought to be different from that in the peripheral circulation, because changes in sympathetic activity appear to have little or no effect on cerebral blood flow.

Cerebral autoregulation has both a static and dynamic component. Static cerebral autoregulation has an important protective feature in that it has the ability to maintain cerebral blood flow constant over a wide range of perfusion pressures from 60-150 mmHg in order to prevent changes in cerebrovascular volume in the closed space of the cranial vault (Strandgaard & Paulson, 1984; Paulson et al., 1990). Whereas, dynamic cerebral autoregulation has the important regulatory mechanism that diminishes the

oscillations in cerebral blood flow despite increased oscillations in cerebral perfusion pressures. Both metabolic and myogenic mechanisms are thought to be major factors in the cerebral autoregulatory response to changes in arterial pressure. However, animal studies have shown that cerebral arteries are richly innervated with sympathetic nerve fibers (Nielsen & Owman, 1967; Nelson & Rennels, 1970; Edvinsson, 1975). The superior cervical ganglion innervate the cerebral vessels (Iwayama *et al.*, 1970). The density of vascular innervation in different areas of the brain is heterogeneous (Edvinsson, 1975). However, the role of the autonomic nervous system in the control of the cerebral circulation remains controversial.

Until recently, changes in sympathetic tone were thought to have a limited effect on cerebral blood flow at normal arterial PCO_2 ($PaCO_2$) values. During normotension, intense electrical stimulation of sympathetic nerves has little or no effect on cerebral blood flow (Alm & Bill, 1973; Heistad *et al.*, 1978; Sercombe *et al.*, 1979) while sympathetic denervation generally does not increase cerebral blood flow (Mueller *et al.*, 1977; Heistad *et al.*, 1978; Marcus & Heistad, 1979; Sadoshima *et al.*, 1981). In an apparent overlooked investigation in primates direct stimulation of either the superior sympathetic ganglion nerve or the stellate ganglion reduced internal and external carotid and vertebral blood flow into the brain (Meyer *et al.*, 1967). In humans, Zhang et al. demonstrated that dynamic cerebral autoregulation was attenuated by ganglion blockade using trimethaphan, a competitive antagonist for acetylcholine receptors which blocks the sympathetic nervous system, and from these data Zhang et al. also suggested that

autonomic neural control of the cerebral circulation was tonically active and likely played a significant role in the regulation of beat-to-beat cerebral blood flow.

Although sympathetic innervation appears to have little effect on cerebral blood flow under normocapnic resting conditions in both animals and humans, the direct effect of sympathetic nerves on cerebral blood flow has been observed under a specified set of conditions. Pearce and D'alecy (Pearce & D'Alecy, 1980) demonstrated that in dogs the increase in cerebral vascular resistance induced by hemorrhage was eliminated by α-adrenergic blockade. They further demonstrated that sympathetic vasoconstriction contributed approximately 5% to the control of pre-hemorrhage cerebral vascular resistance. These findings suggest that the cerebrovascular response to hemorrhage was a balance between autoregulatory vasodilation and sympathetic vasoconstriction. Likewise, patients with idiopathic orthostatic intolerance exhibit an excessive decrease in cerebral blood flow upon standing despite sustained systemic blood pressure (Jordan *et al.*, 1998). In these patients, however, α-adrenoreceptor blockade blunted the decrease in cerebral blood flow during head up tilt (HUT) and as there was no change in mean arterial pressure, the decrease in cerebral perfusion must have been result of cerebral vasoconstriction (Jordan *et al.*, 1998). More recently during a patient's liver resection surgery, anesthesia induced hypotension was corrected with a 0.1mg I.V. infusion of Metaoxidrin (Phenylephrine), an α_1 receptor agonist, resulting in an increase in systemic arterial pressure accompanied with a 20% reduction in cerebral tissue oxygenation (ScO_2).

In humans, middle cerebral artery blood velocity (MCA V_{mean}) decreased during unilateral trigeminal ganglion stimulation (Visocchi *et al.*, 1994). In addition, in healthy subjects and in patients with cardiac insufficiency cerebral perfusion was affected by sympathetically mediated cerebral vasoconstriction as a consequence of a reduction in cardiac output. In healthy subjects, the ability to increase cardiac output and MCA V_{mean} during cycling was limited by use of cardio-selective β_1 adrenergic blockade (Ide & Secher, 2000). These observations suggest that a reduced ability to increase cardiac output (Q) induces peripheral vasoconstriction not only in the skeletal muscle (Pawelczyk *et al.*, 1992) but also in the brain. Sympathetic ganglion blockade at the cervical ganglion blunted β_1 blockade induced limitation in the rise in MCA V_{mean} (Ide & Secher, 2000) indicating that indirect sympathetic nerve activation affects cerebral blood flow in humans (Sandor, 1999). Furthermore, in patients with severe heart failure, cerebral blood flow is reduced substantially but increases after cardiac transplantation (Gruhn *et al.*, 2001). Thus, in response to a decline in Q an increased sympathetic drive appears to contribute to cerebral vasoconstriction. There is strong evidence that sympathetic vasoconstriction protects cerebral vessels during severe hypertension (Bill & Linder, 1976). In the cat model, at high blood pressures breakdown of the blood brain barrier was observed in the cerebrum, however, when the sympathetic nerves were stimulated electrically at 10-20 Hz, breakdown of the blood brain barrier was prevented. These results indicate stimulation of the sympathetic nerves innervating the brain vasculature prevented forced dilation of the arterioles and the breakdown of the blood brain barrier (Bill & Linder, 1976).

In summary these findings indicate that control of cerebral blood flow is not only mediated by perfusion pressure and $PaCO_2$, but may also be influenced by autonomic neural control.

Hypothesis

This investigation was designed to test the hypothesis that sympathetic activation via the carotid baroreflex directly influences cerebral vasomotion at rest.

This specific aim was accomplished in young healthy adult men and women by comparing mean arterial pressure (MAP), mean middle cerebral artery blood velocity (MCA V_{mean}), and cerebral tissue oxygenation (ScO_2) during seated upright rest. Control of the cerebral vasculature was assessed using transcranial Doppler (TCD) ultrasonography techniques for measurement of MCA V_{mean} and Near Infrared Spectroscopy (NIRS) measures of ScO_2, respectively. These techniques enabled the assessment of vasoconstriction and vasodilation in the cerebral vasculature at rest and during exercise. The manipulation of arterial baroreflex mediated sympathetic activity was accomplished by dynamically changing neck pressure (NP) and neck suction (NS) (Wray *et al.*, 2004).

Sample size

The number of subjects (sample size) was determined by the willingness to accept an α or type I error or a β or type II error at a 0.05 level, i.e. $Z_{\alpha} = 1.96$ (two-tailed test) and $Z_{\beta} = 1.65$. Significance was predicted to be found in the CBR mediated changes of the vasculature with a sample size of 8 subjects.

CHAPTER II

Methods

Subjects: Eight young (20-31 years) adult men (N=5) and women (N=3), (average age 26 ± 1.4 yrs, height 173 ± 4.3 cm and weight 79.5 ± 6.4 kg) volunteer subjects free from cardiopulmonary, cardiovascular, or neuromuscular disease were recruited for participation in the present investigation. On experimental day 1, each subject was familiarized with the IRB approved experimental procedures and measurements. Each subject provided written informed consent, which conformed to the Declaration of Helsinki and was approved by The University of North Texas Health Science Center Institutional Review Board. Subjects were asked to abstain from caffeinated beverages for 12 hours and strenuous physical activity and alcohol intake for at least a day prior to their study.

Measurements

On experimental day 2, each subject was instrumented accordingly to allow for continuous measurements of heart rate (HR) with electrocardiogram (ECG), and mean arterial blood pressure (MAP) by photoplethysmography using Modelflow technology (Finometer). Additionally, continuous measurements of middle cerebral arterial mean blood velocity (MCA V_{mean}) and cerebral tissue oxygenation (ScO_2) were performed by TCD techniques and near infrared spectroscopy (NIRS) respectively.

Procedure

Following instrumentation, data were collected during a 5 minute baseline period, which was followed by 6 minutes of 5 second pulses of unilateral neck pressure (NP) at + 40 Torr applied in an oscillating sinusoidal manner (0.1Hz, i.e. 5 sec on, 5 sec off for 6 minutes) and 6 minutes of 5 sec pulses of unilateral neck suction (NS) at -40 Torr (0.1Hz, i.e. 5s on, 5s off for 6 minutes). Our modified one sided neck collar allowed for stimulation of one carotid baroreceptor, while measurements of the reflex variability of cerebral blood velocity were performed in the contralateral middle cerebral artery (MCA) as well as the MCA on the stimulated side to ensure no mechanical effect of the collar on the measurements of MCA V_{mean}. The order of NP and NS were randomized amongst the eight subjects with a 5 minute rest period between trials. These physiological measures were collected at rest in the upright seated position. End tidal CO_2 ($ETCO_2$) measurements were collected during the last minute of the resting measurement period.

Techniques of Measurements

Middle cerebral artery mean blood velocity (MCA V_{mean}): Measurements of MCA V_{mean} were obtained by transcranial Doppler ultrasonography with a 2 MHz probe placed over the left and right temporal windows and fixed with an adjustable headband and adhesive ultrasonic gel.

Mean Arterial Pressure: MAP was obtained noninvasively on all subjects using finger-cuff photoplethysmography.

Near infrared spectroscopy (NIRS) measurements of tissue oxygenation: This method is based upon the relative ease with which infrared light (700-1000nm) passes through biological tissue, and on the O_2-dependent absorption changes of hemoglobin and myoglobin. Tissue oxygenation measurements are limited to the microcirculation and, therefore, provide a beat-to-beat index of peripheral tissue oxygenation delivery relative to its use. For the present study, single fiber optical bundles were placed on the forehead over the left eye at the approximate location of the cortical externalization of the anterior cerebral artery. The near-infrared signals at four different wavelengths were sampled concurrently at a rate of 1 Hz, converted to optical densities by using algorithms and stored digitally for analysis. The near-infrared HbO_2 signal (arbitrary units) was used as an index for cerebral tissue oxygenation and has been found to provide an indirect indication of vascular responses in the microcirculation (Fadel *et al.*, 2004).

End tidal CO_2 ($ETCO_2$): was obtained using breath by breath measures of respiratory and gas exchange variables. The subject breathed through a mouthpiece attached to a low-resistance turbine volume transducer for measurement of breath volumes while respiratory gases were sampled from the mouthpiece for analysis of fractional concentrations of CO_2 via a respiratory gas mass spectrometer (Perkin-Elmer 1100).

Statistical Analysis

Descriptive statistics including means and standard of the mean of demographic information (i.e. age, height and weight) were calculated. Statistical comparisons of

physiological variables were made using a repeated-measures one-way analysis of variance (ANOVA). A Student-Newman-Keuls test of main effects was employed 'post hoc' when interactions were not significant. Power analysis of the design indicated that an N of 8-10 yields a power (0.8-0.9) for a delta value of 0.8. Statistical significance was set at $P<0.05$ and results presented as means ± SEM.

CHAPTER III

Results:

Table 1 describes the steady state hemodynamic values during rest and NP and NS periods.

Table 1. Steady-State Hemodynamics During Seated Rest, NP and NS

Table 1. Steady-State Hemodynamics Seated Rest, NP and NS			
	Control	**NP**	**NS**
HR (bpm)	69 ± 4	72 ± 4 *	68 ± 4
MAP (mmHg)	84 ± 4	92 ± 2 *	78 ± 3 *
MCA V*mean* (cm/s)	72 ± 5	69 ± 6	67 ± 6
ETCO2 (mmHg)	39 ± 0.7	37 ± 0.6	38 ± 1

Table 1. Values are means ± SE. HR is heart rate, MAP is mean arterial pressure, MCA V_{mean} is mean middle cerebral artery blood velocity. * $P < 0.05$ vs Control.

There was a significant increase in heart rate (HR) from control to NP as expected. There was no significant decrease in HR as a result of our NS stimuli. This may be due to the oscillatory 5 sec on 5 sec off technique that we used in this study. We did observe a significant change in MAP in response to both our NP and NS procedures. The average MCA V_{mean} did not change significantly during NP nor NS. All subjects remained normocapnic during control, NP and NS conditions as indicated by $ETCO_2$ measures. Arterial blood pressure (ABP), MCA V and cerebral tissue oxygenation (ScO_2) are demonstrated in a representative tracing (figure 1A) when there was no pressure stimulus. This served as the baseline measurement. When we added neck pressure over 5 second

intervals (figure 1B), there were drastic increases in the variability of MCA V and ScO_2 as measured by NIRS. We observed an attenuated ScO_2 and MCA V fluctuation during neck suction compared to neck pressure and an increase in fluctuation above the baseline average variability as seen in figure 1C.

Figure 1.

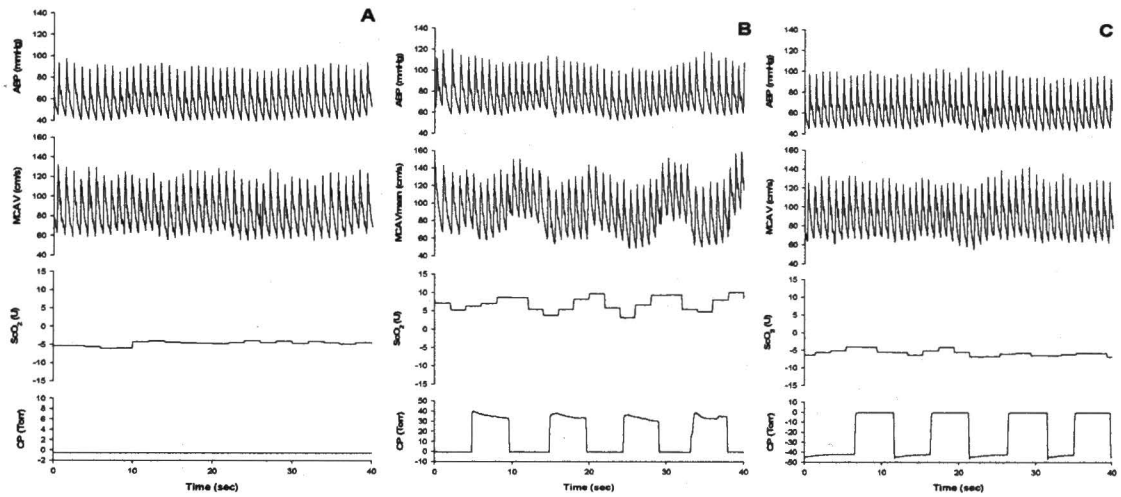

Figure 1. Representative recordings of changes in ABP (arterial blood pressure), MCA V_{mean}, and ScO_2 at 0.1Hz at control condition (**A**) ; ABP (arterial blood pressure), MCA V, and ScO_2 at 0.1Hz at during pulsatile NP (+40 Torr) (**B**) and ABP (arterial blood pressure), MCA V, and ScO_2 at 0.1Hz at during NS (-40 Torr) (**C**) at seated rest. Note that pulsatile NP (0.1Hz) increased the fluctuation of both MCA V and ScO_2, while the effect of pulsatile NS on MCA V and ScO_2 was small.

The fluctuation in MCA V_{mean} (spectral power at 0.1Hz) exceeded that of MAP (i.e. perfusion pressure) during pulsatile NP trials at rest (Figure 2A and B). The effect of the NP stimulation on the fluctuation of MCA V_{mean} was much larger than that during the NS stimulation during seated upright rest (Figure 2B). In addition, the ScO2 as indicated by NIRS had an increased variability at 0.1Hz during the NP trial (Figure 2C).

Figure 2.

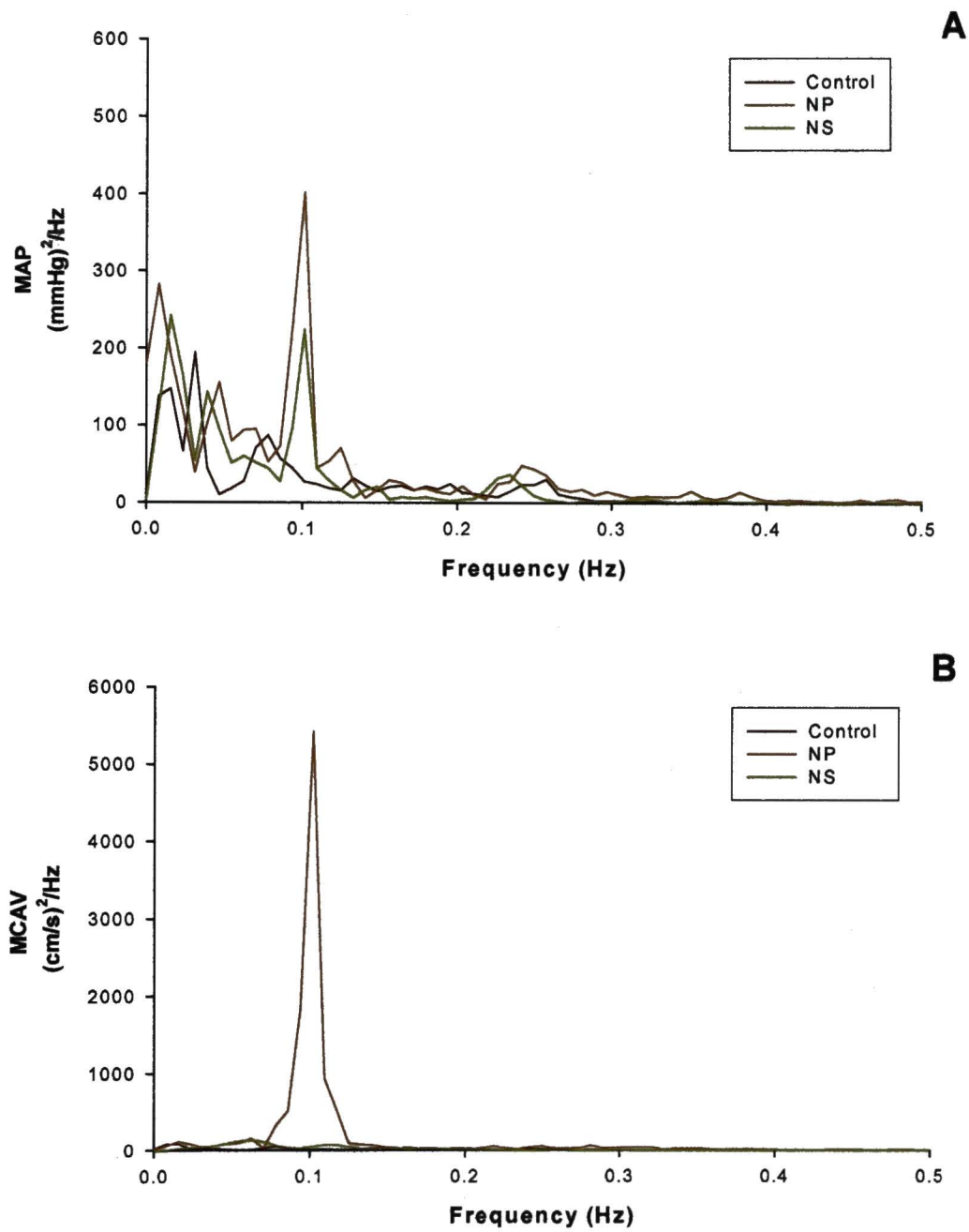

Figure 2. The power spectral density (PSD) of MAP (**A**) at all frequency range (0 – 0.5Hz) at 0.1Hz at control condition, and during pulsatile NP (+40 Torr) and (-40 Torr) at seated rest; (**B**). The power spectral density (PSD) of MCA V_{mean} at all frequency range (0 – 0.5Hz) at 0.1Hz at control condition, and during pulsatile NP (+40 Torr) and (-40 Torr) at seated rest.

Figure 2.

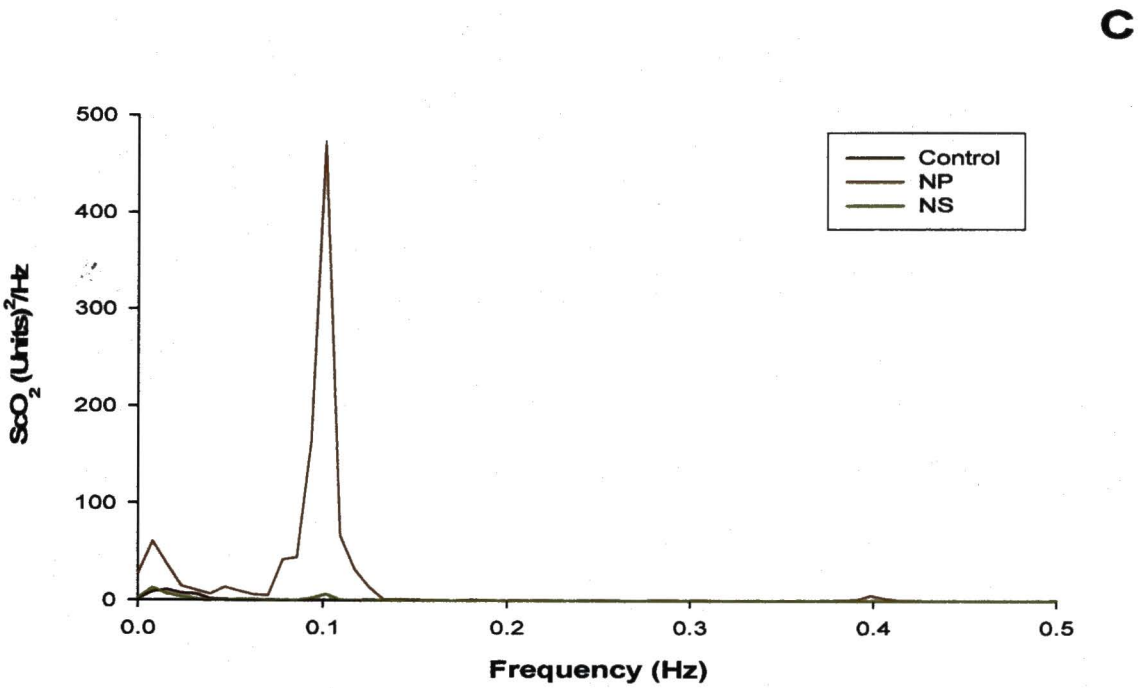

Figure 2 C. The power spectral density (PSD of ScO_2 at all frequency range (0 – 0.5Hz) at 0.1Hz at control condition, and during pulsatile NP (+40 Torr) and (-40 Torr) at seated rest.

The group mean data is presented in figure 3. During NP there was an increase in power spectral density (PSD) of MCA V_{mean} compared to the control condition P <0.05 and was much larger than that of the PSD of the MAP P <0.05. These findings suggest that cerebral vasomotion is not only caused by the changes in cerebral perfusion pressure, but also changes in sympathetic nerve activity. The average difference between variabilities between the conditions of NP and NS are significantly increased above the control condition for all three variables, MCA V_{mean} MAP and ScO_2.

Figure3.

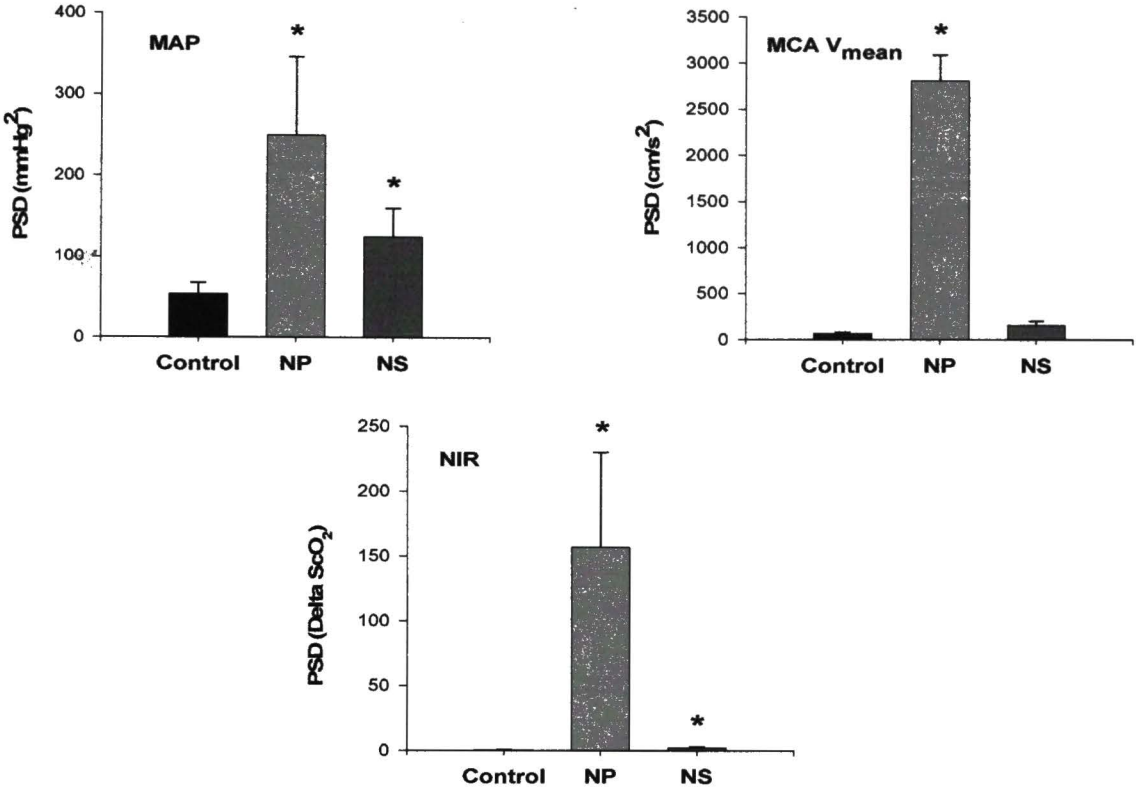

Figure 3. Group averaged PSD data (n=8) of MAP (top left), MCA Vmean (top right) and ScO_2 (bottom middle) at 0.1 Hz at control condition and during NP (+40 Torr) and NS (-40 Torr) during seated rest. * vs Control $P < 0.05$

However, the change in MCA V_{mean} from baseline is much greater than MAP in response to our neck pressure stimulus. Figure 4 describes the percent change from baseline of PSD of MAP compared to MCA V_{mean} and ScO_2 during activation and withdrawal of sympathetic nerve activity. There was a significant increase in variability during NP in MCA V_{mean} and was significantly greater than the increase in variability of MAP. The group average percent change from baseline for cerebral tissue oxygenation (ScO_2)

variability as measured by NIRS was also elevated above the variability of MAP, $P < 0.05$.

Figure 4.

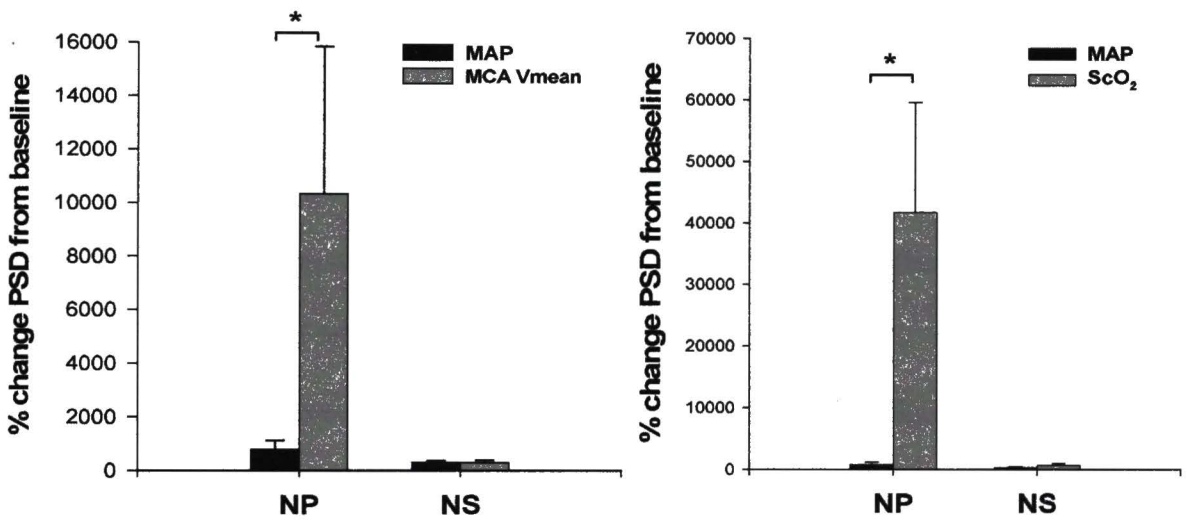

Figure 4. Group averaged % change from baseline PSD data (n=8) of MAP, MCA V*mean* at 0.1 Hz at control condition and during NP (+40 Torr) and NS (-40 Torr) during seated rest. * $P < 0.05$

CHAPTER IV

Discussion

The findings of the present study provide support for the hypothesis that the carotid baroreflex actively regulates cerebral blood flow in humans at rest and appears to assist cerebral autoregulation during sympathetic activation. These data indicate that there is a vasoconstriction above that which would be seen if cerebral autoregulation were the only factor in the maintenance of brain blood flow. This vasoconstriction is likely caused by activation of the sympathetic nervous system as evidenced in the similarity in the increased variability of MCA *Vmean* and ScO_2 above that of MAP. These data support the findings of an active role of sympathetic control of cerebral blood flow in patients with idiopathic orthostatic intolerance (Jordan *et al.*, 1998), in animals during severe hemorrhage (Pearce & D'Alecy, 1980) and in healthy humans during orthostatic challenge with and without sympathetic ganglion blockade (Zhang *et al.*, 2002).

Roatta et al., (1998), used the cold pressor test to investigate the changes in cerebral hemodynamics occurring in healthy humans during a general sympathetic adrenergic activation. As a powerful central sympathetic stimulus this test increased both heart rate and arterial blood pressure simultaneously, without changing cerebral blood flow. These findings suggested that the generalized increase in sympathetic activity resulting in peripheral vasoconstriction and a concomitant increase in arterial blood pressure also prevented concomitant increases in cerebral blood flow via cerebral autoregulation and

cerebral vasoconstriction (Roatta *et al.*, 1998). In addition, in humans, MCA V_{mean} decreased during unilateral trigeminal ganglion stimulation (Visocchi *et al.*, 1994). Furthermore, in healthy subjects and in patients with cardiac insufficiency cerebral perfusion was reduced by sympathetically mediated cerebral vasoconstriction as a consequence of a reduction in cardiac output (Ide & Secher, 2000)). Another example of the existence of sympathetic control of cerebral blood flow was observed in patients with severe heart failure in which their cerebral blood flow was substantially reduced but increased after cardiac transplantation (Gruhn *et al.*, 2001). Thus, in summary, the response of humans to a decline in cardiac output required an increase in sympathetic drive which appears to contribute to cerebral vasoconstriction. More recently during liver resection surgery, correction of anesthesia induced hypotension with the use of an alpha agonist caused an increase in blood pressure and at the same time resulted in a marked reduction in cerebral tissue oxygenation.

In an earlier investigation using primates direct stimulation of the stellate and cervical sympathetic ganglia produced significant vasoconstriction in the carotid and vertebral arteries (Meyer *et al.*, 1967). Furthermore, there is strong evidence that sympathetic vasoconstriction protects cerebral vessels during severe hypertension (Bill & Linder, 1976).

The reason for a lack of evidence of sympathetic control of cerebral blood flow in the human is not entirely clear. The present study in human subjects, used a unique dynamic protocol of activating and deactivating the carotid baroreceptors. The protocol resulted in a dynamic deactivation and activation of sympathetic activity in a reproducible and

quantifiable manner (Wray *et al.*, 2004). The operating point of the small cerebral vascular bed compared to the sum of the vascular beds involved in maintaining MAP likely play a role in these responses. Since this difference is much greater in the cerebral vasculature, sympathetic activation must play a role in the maintenance of cerebral blood flow above cerebral autoregulation. If these responses were the same for MAP and MCA V_{mean} we would suspect little contribution of SNA to the maintenance of cerebral blood flow (Figure 3). By using power spectral analysis to examine the frequency domain changes, or variability, of arterial blood pressure, middle cerebral artery blood velocity and cerebral tissue oxygenation we have been able to identify the presence of sympathetic control of cerebral blood flow of the human independent of changes in cerebral autoregulation and arterial CO_2.

Limitations

The fundamental limitation of this study is that velocity rather than flow was measured in the middle cerebral artery. Changes in velocity can reflect changes in flow only if the diameter of the insonated artery remains the same. In humans, the MCA diameter remains constant under a variety of conditions (Schreiber *et al.*, 2000; Serrador *et al.*, 2000) indicating that velocity changes measured in the middle cerebral artery do reflect changes in cerebral blood flow.

Another potential limitation of the present study is the use of near-infrared spectroscopy as an index of microcirculatory blood flow. Near-infrared spectroscopy does not directly measure blood flow, but instead provides a qualitative index of tissue oxygenation.

However, studies demonstrated a close correlation between blood flow values measured by plethysmography, the Fick method and near-infrared spectroscopy (Edwards *et al.*, 1993; Van Beekvelt *et al.*, 2001) Also, validation studies have reported a high correlation between changes in muscle tissue oxygenation and tissue ultrasound Doppler measurements during reflex responses of sympathetic activation in the human forearm (Fadel *et al.*, 2004). Together, these studies support the use of tissue oxygenation as an indirect index of microcirculatory blood flow.

Since this question was investigated in humans rather than an animal model, another important limitation is that these results come from a closed loop system. The stimulus provided was a series of 5sec on 5sec off pulses of 40 mmHg NP for a six minute period of time. Following the completion of the NP protocol and after a brief rest period, a -40 mmHg NS. 5 sec on and off protocol was applied. It is possible that after application of the initial +40, or -40 mmHg stimulus to the carotid baroreceptor, a counteraction from the aortic baroreflex attenuates the full response. Therefore, it is possible that the dynamic responses of the cerebral vasculature to NP/NS stimuli of the carotid baroreceptors may be underestimated.

Another possible limitation is the proposed siphon effect on cerebral blood flow in the upright posture. However, in a recent experiment in which the jugular vein was catheterized and the internal and external jugular veins imaged using 2D ultrasound during supine rest and upright seating, the jugular venous pressure approached zero and both internal and external jugular veins were collapsed in the upright position. This data implies that stability of cerebral blood flow becomes dependent on cerebral

autoregulation as the perfusion pressure decreases as a result of not having a siphon to support cerebral blood flow in the upright position (Dawson *et al.*, 2004).

Also, in the present study, neither brain norepinephrine spill-over nor sympathetic nerve activity were measured because of the invasive procedures required for these measurements. However, muscle sympathetic nerve activity has been found to be positively correlated with brain norepinephrine spill-over in humans and has been determined to reflect changes in central sympathetic neural activity (Lambert *et al.*, 1998).

Conclusion and Future directions

The findings of the present study strongly indicate that cerebral vasoconstriction during NP was a result of the response to NP mediated pulsatile changes in arterial pressure and the NP induced sympathetically mediated vasoconstriction. The results obtained from these studies provide a more complete understanding of the control of cerebral vasculature. Information identifying the functional role of sympathetic neural control of the cerebral vasculature in the human begins to question accepted dogma and may prove beneficial to the clinician in understanding control of cerebral perfusion when pharmacologically manipulating sympathetic activity. Many cardiovascular disease states, such as hypertension, heart failure and diabetes that are characterized by sympathoexcitation and dysfunction of the autonomic neural control of the vasculature are related to both a decreased exercise tolerance and orthostatic tolerance.

During progressive increases in dynamic exercise intensity, sympathetic control of the peripheral vasculature in active skeletal muscle is progressively opposed by local cellular mechanisms in muscle. Those local factors partially inhibit transduction of sympathetic activity at the vasculature in an effort to adequately perfuse the working muscle beds. Exercise increases brain metabolism also as reflected in a progressively decreasing cerebral metabolic ratio. Thus, a possible future direction would be to establish whether the cellular mechanisms of metabolic inhibition provide a balance between insuring adequate total and regional brain perfusion and the exercise induced increase in sympathetic vasoconstriction of the cerebral vasculature. Therefore, confirmation that the arterial baroreflex control of sympathetic nerve activity reflexly regulates cerebral blood flow at rest and during dynamic exercise is essential to answering this question. Also, evaluation of whether the relative effectiveness of baroreflex mediated sympathoexcitation on cerebral blood flow is progressively reduced by metabolic inhibition of the α_1 receptors with progressive increases in exercise intensity is an important step in addressing the hypothesis that during progressive increases in exercise intensity the associated increases in sympathetic activity along with metabolic inhibition of the vasoconstriction in the active regions of the brain enable the redistribution of cerebral blood flow.

References

ALM, A. & BILL, A. (1973). The effect of stimulation of the cervical sympathetic chain on retinal oxygen tension and on uveal, retinal and cerebral blood flow in cats. *Acta Physiol Scand* **88,** 84-94.

BILL, A. & LINDER, J. (1976). Sympathetic control of cerebral blood flow in acute arterial hypertension. *Acta Physiol Scand* **96,** 114-121.

DAWSON, E. A., SECHER, N. H., DALSGAARD, M. K., OGOH, S., YOSHIGA, C. C., GONZALEZ-ALONSO, J., STEENSBERG, A. & RAVEN, P. B. (2004). Standing up to the challenge of standing: a siphon does not support cerebral blood flow in humans. *Am J Physiol Regul Integr Comp Physiol* **287,** R911-914.

EDVINSSON, L. (1975). Neurogenic mechanisms in the cerebrovascular bed. Autonomic nerves, amine receptors and their effects on cerebral blood flow. *Acta Physiol Scand Suppl* **427,** 1-35.

EDWARDS, A. D., RICHARDSON, C., VAN DER ZEE, P., ELWELL, C., WYATT, J. S., COPE, M., DELPY, D. T. & REYNOLDS, E. O. (1993). Measurement of hemoglobin flow and blood flow by near-infrared spectroscopy. *J Appl Physiol* **75,** 1884-1889.

FADEL, P. J., KELLER, D. M., WATANABE, H., RAVEN, P. B. & THOMAS, G. D. (2004). Noninvasive assessment of sympathetic vasoconstriction in human and rodent skeletal muscle using near-infrared spectroscopy and Doppler ultrasound. *J Appl Physiol* **96,** 1323-1330.

FADEL, P. J., OGOH, S., WATENPAUGH, D. E., WASMUND, W., OLIVENCIA-YURVATI, A., SMITH, M. L. & RAVEN, P. B. (2001). Carotid baroreflex regulation of sympathetic nerve activity during dynamic exercise in humans. *Am J Physiol Heart Circ Physiol* **280,** H1383-1390.

GRUHN, N., LARSEN, F. S., BOESGAARD, S., KNUDSEN, G. M., MORTENSEN, S. A., THOMSEN, G. & ALDERSHVILE, J. (2001). Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke* **32,** 2530-2533.

HEISTAD, D. D., MARCUS, M. L. & GROSS, P. M. (1978). Effects of sympathetic nerves on cerebral vessels in dog, cat, and monkey. *Am J Physiol* **235,** H544-552.

IDE, K. & SECHER, N. H. (2000). Cerebral blood flow and metabolism during exercise. *Prog Neurobiol* **61,** 397-414.

IWAYAMA, T., FURNESS, J. B. & BURNSTOCK, G. (1970). Dual adrenergic and cholinergic innervation of the cerebral arteries of the rat. An ultrastructural study. *Circ Res* **26,** 635-646.

JORDAN, J., SHANNON, J. R., BLACK, B. K., PARANJAPE, S. Y., BARWISE, J. & ROBERTSON, D. (1998). Raised cerebrovascular resistance in idiopathic orthostatic intolerance: evidence for sympathetic vasoconstriction. *Hypertension* **32,** 699-704.

LAMBERT, G. W., KAYE, D. M., THOMPSON, J. M., TURNER, A. G., FERRIER, C., COX, H. S., VAZ, M., WILKINSON, D., MEREDITH, I. T., JENNINGS, G. L. & ESLER, M. D. (1998). Catecholamine metabolites in internal jugular plasma: a window into the human brain. *Adv Pharmacol* **42,** 364-366.

MARCUS, M. L. & HEISTAD, D. D. (1979). Effects of sympathetic nerves on cerebral blood flow in awake dogs. *Am J Physiol* **236,** H549-553.

MEYER, J. S., YOSHIDA, K. & SAKAMOTO, K. (1967). Autonomic control of cerebral blood flow measured by electromagnetic flowmeters. *Neurology* **17,** 638-648.

MUELLER, S. M., HEISTAD, D. D. & MARCUS, M. L. (1977). Total and regional cerebral blood flow during hypotension, hypertension, and hypocapnia. Effect of sympathetic denervation in dogs. *Circ Res* **41,** 350-356.

NELSON, E. & RENNELS, M. (1970). Innervation of intracranial arteries. *Brain* **93,** 475-490.

NIELSEN, K. C. & OWMAN, C. (1967). Adrenergic innervation of pial arteries related to the circle of Willis in the cat. *Brain Res* **6,** 773-776.

PAULSON, O. B., STRANDGAARD, S. & EDVINSSON, L. (1990). Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* **2,** 161-192.

PAWELCZYK, J. A., HANEL, B., PAWELCZYK, R. A., WARBERG, J. & SECHER, N. H. (1992). Leg vasoconstriction during dynamic exercise with reduced cardiac output. *J Appl Physiol* **73,** 1838-1846.

PEARCE, W. J. & D'ALECY, L. G. (1980). Hemorrhage-induced cerebral vasoconstriction in dogs. *Stroke* **11,** 190-197.

POTTS, J. T. & RAVEN, P. B. (1995). Effect of dynamic exercise on human carotid-cardiac baroreflex latency. *Am J Physiol* **268,** H1208-1214.

POTTS, J. T., SHI, X. R. & RAVEN, P. B. (1993). Carotid baroreflex responsiveness during dynamic exercise in humans. *Am J Physiol* **265,** H1928-1938.

ROATTA, S., MICIELI, G., BOSONE, D., LOSANO, G., BINI, R., CAVALLINI, A. & PASSATORE, M. (1998). Effect of generalised sympathetic activation by cold pressor test on cerebral haemodynamics in healthy humans. *J Auton Nerv Syst* **71,** 159-166.

SADOSHIMA, S., THAMES, M. & HEISTAD, D. (1981). Cerebral blood flow during elevation of intracranial pressure: role of sympathetic nerves. *Am J Physiol* **241,** H78-84.

SANDOR, P. (1999). Nervous control of the cerebrovascular system: doubts and facts. *Neurochem Int* **35,** 237-259.

SCHREIBER, S. J., GOTTSCHALK, S., WEIH, M., VILLRINGER, A. & VALDUEZA, J. M. (2000). Assessment of blood flow velocity and diameter of the middle cerebral artery during the acetazolamide provocation test by use of transcranial Doppler sonography and MR imaging. *AJNR Am J Neuroradiol* **21,** 1207-1211.

SERCOMBE, R., LACOMBE, P., AUBINEAU, P., MAMO, H., PINARD, E., REYNIER-REBUFFEL, A. M. & SEYLAZ, J. (1979). Is there an active mechanism limiting the influence of the sympathetic system on the cerebral vascular bed? Evidence for vasomotor escape from sympathetic stimulation in the rabbit. *Brain Res* **164,** 81-102.

SERRADOR, J. M., PICOT, P. A., RUTT, B. K., SHOEMAKER, J. K. & BONDAR, R. L. (2000). MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* **31,** 1672-1678.

STRANDGAARD, S. & PAULSON, O. B. (1984). Cerebral autoregulation. *Stroke* **15,** 413-416.

VAN BEEKVELT, M. C., COLIER, W. N., WEVERS, R. A. & VAN ENGELEN, B. G. (2001). Performance of near-infrared spectroscopy in measuring local O(2) consumption and blood flow in skeletal muscle. *J Appl Physiol* **90,** 511-519.

VISOCCHI, M., CIONI, B., PENTIMALLI, L. & MEGLIO, M. (1994). Increase of cerebral blood flow and improvement of brain motor control following spinal cord stimulation in ischemic spastic hemiparesis. *Stereotact Funct Neurosurg* **62,** 103-107.

WRAY, D. W., FADEL, P. J., KELLER, D. M., OGOH, S., SANDER, M., RAVEN, P. B. & SMITH, M. L. (2004). Dynamic carotid baroreflex control of the peripheral circulation during exercise in humans. *J Physiol* **559,** 675-684.

ZHANG, R., ZUCKERMAN, J. H., IWASAKI, K., WILSON, T. E., CRANDALL, C. G. & LEVINE, B. D. (2002). Autonomic neural control of dynamic cerebral autoregulation in humans. *Circulation* **106,** 1814-1820.