

Stroke

American Stroke
AssociationSM

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American
Heart Association



Sympathetic Control of the Cerebral Vasculature in Humans

J.W. Hamner, Can Ozan Tan, Kichang Lee, Michael A. Cohen and J. Andrew Taylor
Stroke 2010;41;102-109; originally published online Dec 10, 2009;

DOI: 10.1161/STROKEAHA.109.557132

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2010 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/41/1/102>

Subscriptions: Information about subscribing to *Stroke* is online at

<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:
410-528-8550. E-mail:

journalpermissions@lww.com

Reprints: Information about reprints can be found online at

<http://www.lww.com/reprints>

Sympathetic Control of the Cerebral Vasculature in Humans

J.W. Hamner, BS; Can Ozan Tan, PhD; Kichang Lee, PhD;
Michael A. Cohen, PhD; J. Andrew Taylor, PhD

Background and Purpose—The role of the sympathetic nervous system in cerebral autoregulation remains poorly characterized. We examined cerebral blood flow responses to augmented arterial pressure oscillations with and without sympathetic blockade and compared them with responses in the forearm circulation.

Methods—An oscillatory lower body negative pressure of 40 mm Hg was used at 6 frequencies from 0.03 to 0.08 Hz in 11 healthy subjects with and without α -adrenergic blockade by phentolamine.

Results—Sympathetic blockade resulted in unchanged mean pressure and cerebral flow. The transfer function relationship to arterial pressure at frequencies >0.05 Hz was significantly increased in both the cerebral and brachial circulations, but the coherence of the relation remained weak at the lowest frequencies in the cerebral circulation.

Conclusion—Our data demonstrate a strong, frequency-dependent role for sympathetic regulation of blood flow in both cerebral and brachial circulations. However, marked differences in the response to blockade suggest the control of the cerebral circulation at longer time scales is characterized by important nonlinearities and relies on regulatory mechanisms other than the sympathetic system. (*Stroke*. 2010;41:102-109.)

Key Words: cerebral blood flow ■ hemodynamics ■ sympathetic nervous system ■ transcranial Doppler

Cerebral perfusion is maintained constant over a wide range of systemic pressures through counterregulatory changes in cerebrovascular resistance. Original studies of cerebral flow responses¹ supported a counterregulation against changes in arterial pressure encompassing the time scale from minutes to hours. However, the recent ability to assess cerebral blood flow velocity on a beat-by-beat basis has allowed the observation that cerebral flow is regulated not just over minutes and hours, but also on shorter time scales of only a few beats.² Data suggest that blood flow responses are dampened in response to pressure changes over periods as short as 15 seconds and that this dampening becomes progressively greater over longer time periods.³ Thus, the relationship between pressure and flow in the cerebrovasculature is a high pass filter⁴ wherein slower changes in pressure are effectively counterregulated, whereas faster oscillations pass through relatively unaffected.

Despite the fact that this autoregulatory capacity of the cerebral vasculature is of critical importance, the underlying physiology remains incompletely understood. A number of different, and possibly overlapping, physiological mechanisms such as the sympathetic nervous system, endothelial derived nitric oxide, and vascular myogenic responses could

play some part in cerebral autoregulation, but the specifics of their respective involvement remain largely unknown. For example, the cerebrovascular bed is well innervated by sympathetic nerve fibers,⁵ but their role in autoregulation is poorly understood and highly controversial.^{6,7} However, when nerves along the arteries of the brain that have connections to the cervical sympathetic chain have been sectioned or stimulated, responses have been either absent or inconsistent.⁸ There are some inferential data suggesting that the sympathetic nervous system may play a role in cerebrovascular regulation, but only two studies have directly examined this possibility in humans. Zhang et al⁹ used complete ganglionic blockade by trimethaphan and found that the gain relation between cerebral flow and systemic pressure almost doubled, indicating that the degree of cerebral counterregulation to pressure fluctuations was reduced by removal of all autonomic neural effects. The other, more recent study used prazosin, an α -adrenoreceptor antagonist, and found a modest attenuation of cerebral flow response to a single, brief (approximately 3 beats) hypotensive stimulus in 6 volunteers.¹⁰ These two studies suggest an autonomic, and perhaps primarily sympathetic, role in cerebral blood flow control.

If the sympathetic system is indeed involved in control of cerebral blood flow, it is critical to know its relative impor-

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

Received May 6, 2009; final revision received September 15, 2009; accepted October 7, 2009.

From the Cardiovascular Research Laboratory (J.W.H., C.O.T., J.A.T.), Spaulding Rehabilitation Hospital, Boston, Mass; Physical Medicine and Rehabilitation (C.O.T., J.A.T.), Harvard Medical School, Boston, Mass; Harvard-MIT Division of Health Sciences & Technology (K.L.), Massachusetts Institute of Technology, Cambridge, Mass; and the Department of Cognitive and Neural Systems (M.A.C.), Boston University, Boston, Mass.

Correspondence to J. Andrew Taylor, PhD, Cardiovascular Research Laboratory, Spaulding Rehabilitation Hospital, 125 Nashua Street, Boston, MA 02114. E-mail jandrew_taylor@hms.harvard.edu

© 2009 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.109.557132

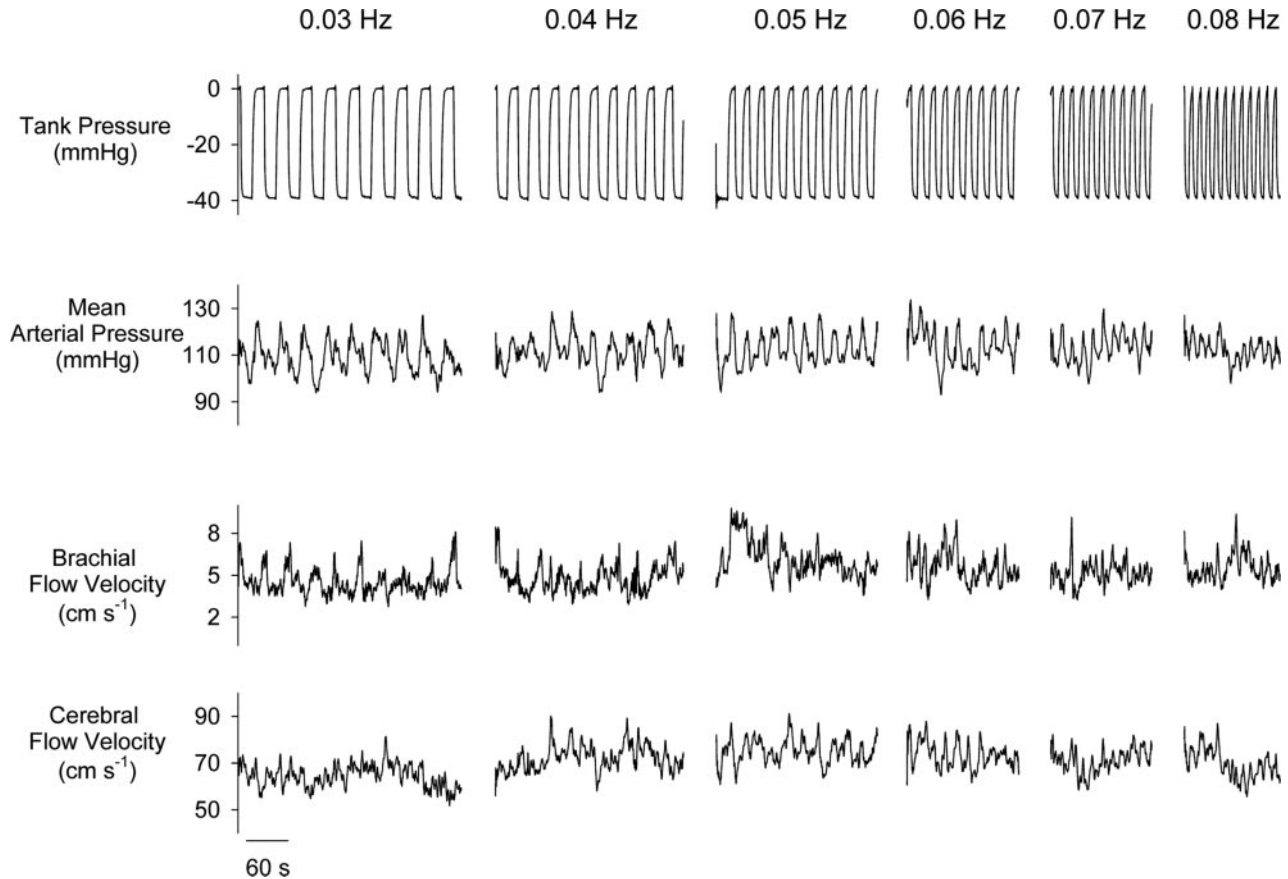


Figure 1. Hemodynamic response to OLBPN in a representative subject at baseline.

tance and the dynamics and magnitude of its effects. However, given the presence of redundant controllers, it is difficult to isolate the role of any one system by examining the cerebral circulation in isolation. By comparing the cerebral circulation with a vascular bed primarily under sympathetic control, we can use α -adrenergic blockade to discern the relative role of the sympathetic nervous system in cerebrovascular control. If sympathetic control is prepotent at some time scales, but not others, it would profoundly affect our understanding of cerebral blood flow control and treatment of pathophysiologies related to sympathetic dysregulation.

Materials and Methods

Subjects

Eleven volunteers aged 21 to 40 years (4 females) gave informed consent for this study. Volunteers were nonsmokers free from cardiovascular and neurological disorders and cardioactive medications. Participants were normotensive and refrained from alcohol, caffeine, and rigorous exercise at least 24 hours before study. This protocol was approved by the Institutional Review Boards of the Hebrew Rehabilitation Center for Aged and Spaulding Rehabilitation Hospital and conformed to the Declaration of Helsinki.

Instrumentation

For each subject, a 20-gauge catheter was inserted into an antecubital vein for drug infusion. Subsequently, subjects were instrumented for electrocardiographic lead II (Dash 2000; General Electric), beat-by-beat photoplethysmographic arterial pressures (Finapres; Ohmeda), and oscillometric brachial pressures (DASH 2000; General Electric). Brachial pressures were a check for photoplethysmographic finger

pressures throughout the study session. Subjects were instrumented for measurement of blood flow velocities in the middle cerebral and brachial arteries (2- and 4-MHz probes; Multidop T2, DWL). The transcranial Doppler ultrasonograph probe was positioned to measure cerebral flow velocity at the M1 segment of the middle cerebral artery at a depth of 50 to 65 mm. A custom probe fixation device held the probe in place. The brachial Doppler ultrasonograph probe was placed to measure brachial artery flow velocity at the antecubital fossa ipsilateral to the infusion site. Expired CO_2 was monitored by an infrared carbon dioxide analyzer (Vacumed) connected to a nasal cannula. All signals were digitized and stored at 500 Hz (Windaq; DATAQ Instruments and PowerLab, ADInstruments).

Protocols

Oscillatory Lower Body Negative Pressure

To create controlled blood pressure oscillations of varying frequencies, oscillatory lower body negative pressure (OLBNP) was applied similar to previously described.³ The subject's lower body was sealed in a tank and a vacuum pump connected to a timing mechanism-controlled suction intervals. Suction was applied at 40 mm Hg across 6 frequencies: 0.03, 0.04, 0.05, 0.06, 0.07, and 0.08 Hz. These progressed from lowest to highest and with decreasing duration (Figure 1). The duration at each frequency provided 10 oscillations so that the range of frequencies encompassing the previously observed cerebral auto-regulation³ could be studied reliably over a relatively short period of time.

Sympathetic Blockade

To effect α -adrenergic sympathetic blockade, subjects received intravenous phentolamine as a 0.14- $\mu\text{g}/\text{kg}$ bolus followed by 0.014- $\mu\text{g}/\text{kg}/\text{min}$ infusion. This dosage effectively blocks sympathetic effects on the vasculature based on previously published data.¹¹ After commencement of the phentolamine infusion, each subject rested quietly for approx-

Table 1. Mean Values at Each OLBNP Frequency With and Without Blockade

	Two-Way Analysis of Variance	Condition	OLBNP Frequency					
			0.03 Hz	0.04 Hz	0.05 Hz	0.06 Hz	0.07 Hz	0.08 Hz
R-R interval, ms	Freq $P=0.13$	Baseline	1059±58	1035±53	1026±54	1031±51	1027±48	1007±47
	Cond $P<0.01$	Sympathetic Blockade	841±32	810±29	805±32	803±33	786±34	765±31
	Freq×Cond $P=0.51$							
Mean arterial pressure, mm Hg	Freq $P=0.59$	Baseline	90.5±2.6	90.5±3.0	92.2±3.3	93.2±3.6	92.8±3.6	94.1±3.3
	Cond $P=0.76$	Sympathetic Blockade	91.7±3.6	92.4±3.0	91.5±2.9	91.0±2.7	90.5±3.0	91.9±2.9
	Freq×Cond $P=0.50$							
Brachial flow, cm s ⁻¹	Freq $P=0.53$	Baseline	3.22±0.46	3.14±0.47	3.35±0.51	3.43±0.52	3.26±0.51	3.18±0.52
	Cond $P<0.01$	Sympathetic Blockade	5.46±0.56	5.68±0.54	5.81±0.60	5.91±0.61	6.13±0.63	6.28±0.70
	Freq×Cond $P=0.51$							
Cerebral flow, cm s ⁻¹	Freq $P=0.73$	Baseline	71.1±6.3	70.6±6.3	69.9±6.4	70.1±6.2	69.2±6.4	68.4±6.1
	Cond $P=0.81$	Sympathetic Blockade	70.1±6.2	69.0±6.2	69.0±6.4	69.2±6.5	69.3±6.7	68.3±6.4
	Freq×Cond $P=0.92$							
CO ₂ , mm Hg	Freq $P=0.13$	Baseline	37.3±2.05	36.5±2.16	35.8±1.98	35.6±2.13	33.0±2.38	35.6±2.38
	Cond $P<0.01$	Sympathetic Blockade	32.8±2.25	31.91±2.01	31.3±1.83	31.3±1.88	30.6±1.92	30.4±2.07
	Freq×Cond $P=0.84$							

Freq indicates frequency; Cond, condition; Freq×Cond, frequency and condition interaction term.

imately 5 minutes before the OLBNP protocol was repeated exactly as described previously.

Data Analysis

Data were analyzed using custom software written in Matlab (Version 7.1; Mathworks). The 500-Hz waveforms of arterial pressure and cerebral and brachial blood flows were decimated to 5 Hz and low pass filtered with a cutoff of 0.4 Hz to provide mean values. Filtering, as opposed to interpolated means, was used to provide signals that were independent of possible changes in the electromechanical delay from R-wave to generation of a pressure–flow pulse. These mean waveforms as well as breath-by-breath CO₂ and R-R intervals were subsequently averaged within each OLBNP frequency to provide overall means. Power spectral density estimates were calculated by Welch average modified periodogram method.¹² For each OLBNP frequency, the filtered time series was divided into 5 segments of equal length that overlapped by 50%. This windowing was chosen to provide equal confidence in coherence across the range of OLBNP frequencies and so that an estimated squared coherence of >0.49 indicated a significant spectral relation. The signals in each segment were linearly detrended, smoothed through a Hamming window, and fast-Fourier transformed. Spectral power estimates were averaged across all windows. The product of the pressure signal with the complex conjugate of the cerebral or brachial flow velocity signals provided the cross spectrum from which coherence and transfer functions were derived. Confidence intervals and precision of estimate for the transfer function were derived based on the level of coherence from standard random process theory.¹³ We examined coherence and gain between arterial pressure and brachial flow and arterial pressure and cerebral flow at each OLBNP frequency. Gain was weighted by its precision to obtain the most accurate means for statistical analysis. In this way, unreliable estimates received appropriately small weights when group averages and statistics were computed.¹⁴

Statistics

Log transformations were applied to spectral powers and the inverse hyperbolic tangent to coherence to provide estimates with asymptotically standard distributions.¹³ The Box-Cox transformation was applied to all other data to ensure normality.¹⁵ However, for ease of

interpretation, values and confidence intervals presented here are standard units. To account for the precision of the transfer function estimates, a weighted two-way analysis of variance was used to determine the effects of frequency and sympathetic blockade on gain, and a standard two-way analysis of variance was used to determine the effects for all other variables. If a significant interaction between frequency and condition was observed, paired *t* tests (weighted *t* tests for gain) were performed to determine at which frequency a significant effect of sympathetic blockade occurred. Differences were considered significant when $P<0.05$. Values are reported as mean±SE.

Results

Figure 1 shows the effect of OLBNP in a representative subject. Note the consistency of the resultant arterial pressure oscillations and the differing response between vascular beds; cerebral blood flow tracks pressure only at higher frequencies, whereas brachial flow demonstrates the reverse. There was no effect of OLBNP frequency on mean values of any variable (Table 1), but arterial pressure fluctuations were greatest at the slowest frequencies (Table 2). Sympathetic blockade resulted in significant tachycardia but no change in arterial pressure. Cerebral flow was unchanged with blockade, whereas mean brachial flow increased (Table 1). Surprisingly, arterial CO₂ showed a consistent decrease across all frequencies of OLBNP after sympathetic blockade.

Arterial pressure and cerebral and brachial flow oscillations in response to OLBNP were increased with sympathetic blockade, although there were differing responses across frequency (Table 2; Figure 2). The greatest increases in arterial pressure fluctuations with sympathetic blockade occurred at the slowest frequencies, whereas the greatest increases in cerebral blood flow oscillations occurred at the highest. In fact, at 0.03 Hz OLBNP, there was no significant increase in the amplitude of cerebral blood flow oscillations

Table 2. Spectral Variables at Each OLBNP Frequency With and Without Blockade

Two-Way Analysis of Variance			OLBNP Frequency					
			Condition	0.03 Hz	0.04 Hz	0.05 Hz	0.06 Hz	0.07 Hz
Arterial pressure	Freq $P<0.01$	Baseline	10.2±2.70	8.60±1.52	8.52±1.67	9.89±1.94	7.12±1.50	5.65±0.90
Spectral density, mm Hg ² Hz ⁻¹	Cond $P<0.01$	Sympathetic Blockade	38.5±7.97*	38.3±7.02*	22.9±5.24*	17.5±4.30	15.1±3.33*	8.87±2.06
	Freq×Cond $P<0.01$							
Brachial flow	Freq $P=0.17$	Baseline	0.16±0.04	0.11±0.03	0.05±0.02	0.09±0.03	0.07±0.02	0.08±0.04
Spectral density, cm ² s ⁻² Hz ⁻¹	Cond $P<0.01$	Sympathetic Blockade	0.56±0.30	0.54±0.29	0.33±0.12	0.33±0.13	0.33±0.10	0.34±0.10
	Freq×Cond $P=0.16$							
Cerebral flow	Freq $P=0.83$	Baseline	5.57±1.18	4.24±0.98	3.03±0.70	4.18±0.97	2.98±0.81	3.44±0.80
Spectral density, cm ² s ⁻² Hz ⁻¹	Cond $P<0.01$	Sympathetic Blockade	10.9±3.93	14.9±4.69*	13.5±3.47*	15.4±4.24*	19.7±4.95*	16.4±3.27*
	Freq×Cond $P<0.05$							

* $P<0.05$ versus baseline at the OLBNP frequency.

Freq indicates frequency; Cond, condition; Freq×Cond, frequency and condition interaction term.

($P=0.25$). Brachial flow oscillations, in contrast, showed no frequency dependence with blockade. An example of this differential effect of sympathetic blockade at slower frequencies can be seen in Figure 3. In the absence of sympathetic buffering, brachial flow closely tracks arterial pressure oscillations, whereas cerebral flow shows a biphasic response indicative of autoregulatory responses to both the pressure fall and rise with each pressure fluctuation.

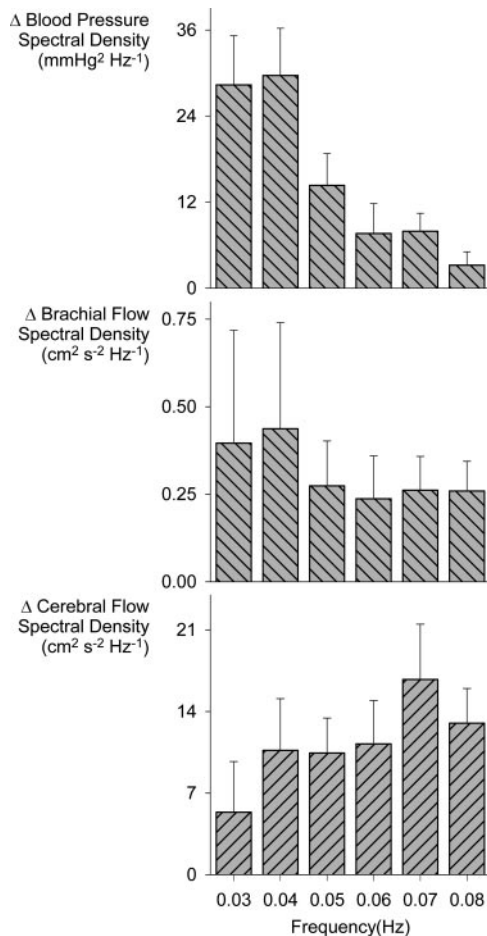


Figure 2. Change in spectral density with sympathetic blockade.

Cross-spectral analysis of the cerebral and brachial response to arterial pressure fluctuations showed profound differences between the two vessels (Figure 4). Before sympathetic blockade, cerebral flow showed increasing coherence with pressure as frequency increased and brachial flow showed uniform coherence across all frequencies. Although both vascular beds demonstrated a sharp increase in coherence with sympathetic blockade, the frequency-dependent nature of cerebral coherence was maintained. The gain relations of the two vascular beds also demonstrated distinct differences at baseline, but these were ablated by sympathetic blockade. Before blockade, only the gain relation between cerebral flow and arterial pressure demonstrated a frequency dependence with increasing gain as frequency increased, whereas the brachial flow relation to pressure was consistent across all OLBNP frequencies. Sympathetic blockade resulted in a marked increase in the gain relations for both vascular beds, but only at frequencies >0.05 Hz.

It is possible that the modest relative hypocapnia during blockade had some impact on the observed responses. Therefore, we performed an additional analysis with end-tidal CO_2 as a covariate in the two-way analysis of variance comparing frequency and blockade effects. Lower end-tidal CO_2 tended to relate to lower coherence ($P=0.08$) and lower gain ($P=0.06$). However, the observed levels of hypocapnia did not counteract the effects of sympathetic blockade, frequency, or their interaction ($P<0.01$ for all with and without CO_2 as a covariate).

Discussion

Our data clearly demonstrate the important role of the sympathetic system in regulating cerebral blood flow. This is the first work to identify the time scales on which this control operates, the magnitude of its effect, and how its relative contribution differs between vascular beds. Furthermore, these results are indicative of the uniquely powerful involvement of complimentary controllers (eg, nitric oxide release, myogenic mechanisms) in regulating cerebral perfusion.

Whether the sympathetic nervous system plays a significant role in regulation of cerebral blood flow has been a

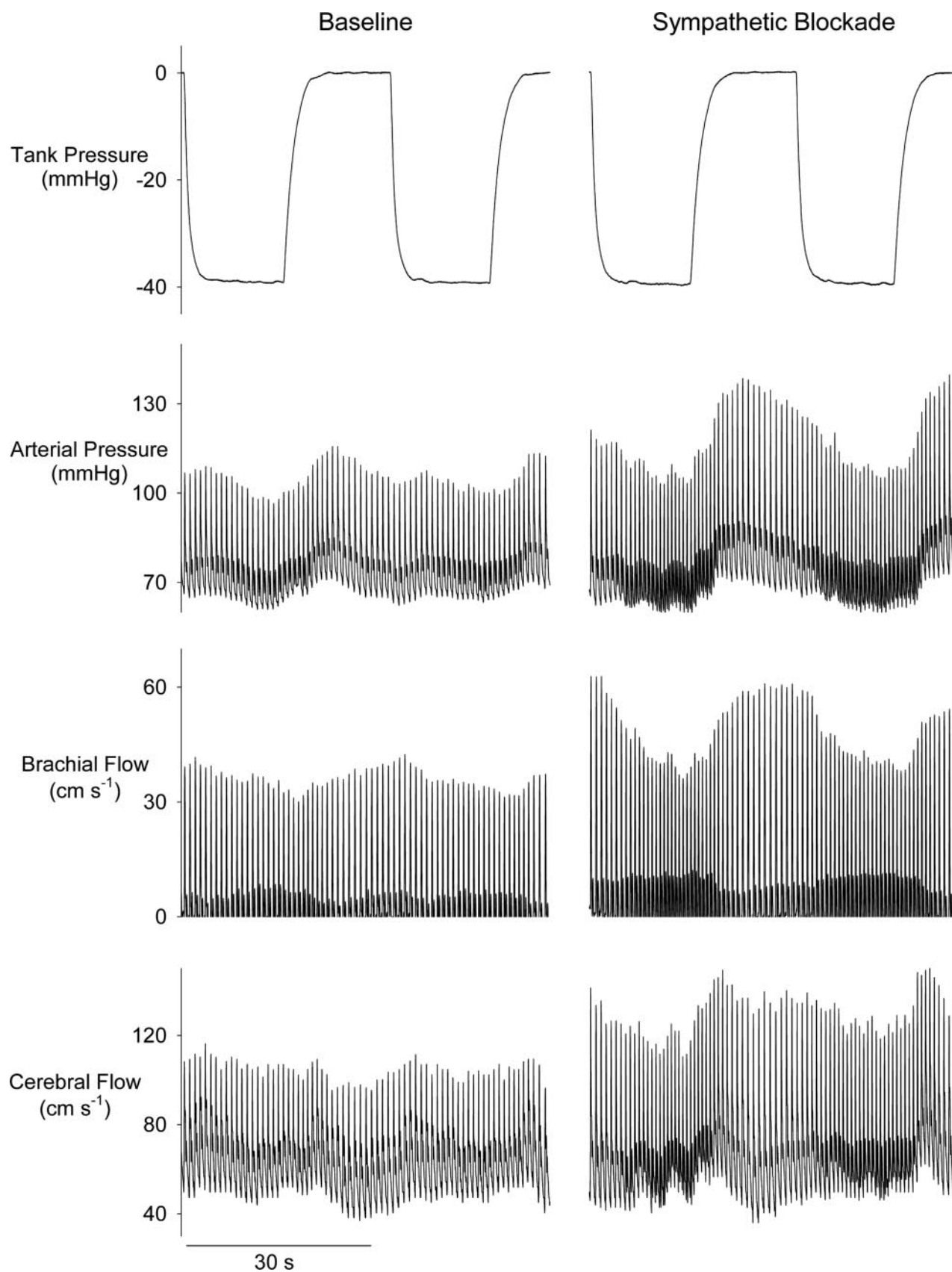


Figure 3. Effect of sympathetic blockade on pressure and flow at 0.03 Hz OLBPN in a representative subject.

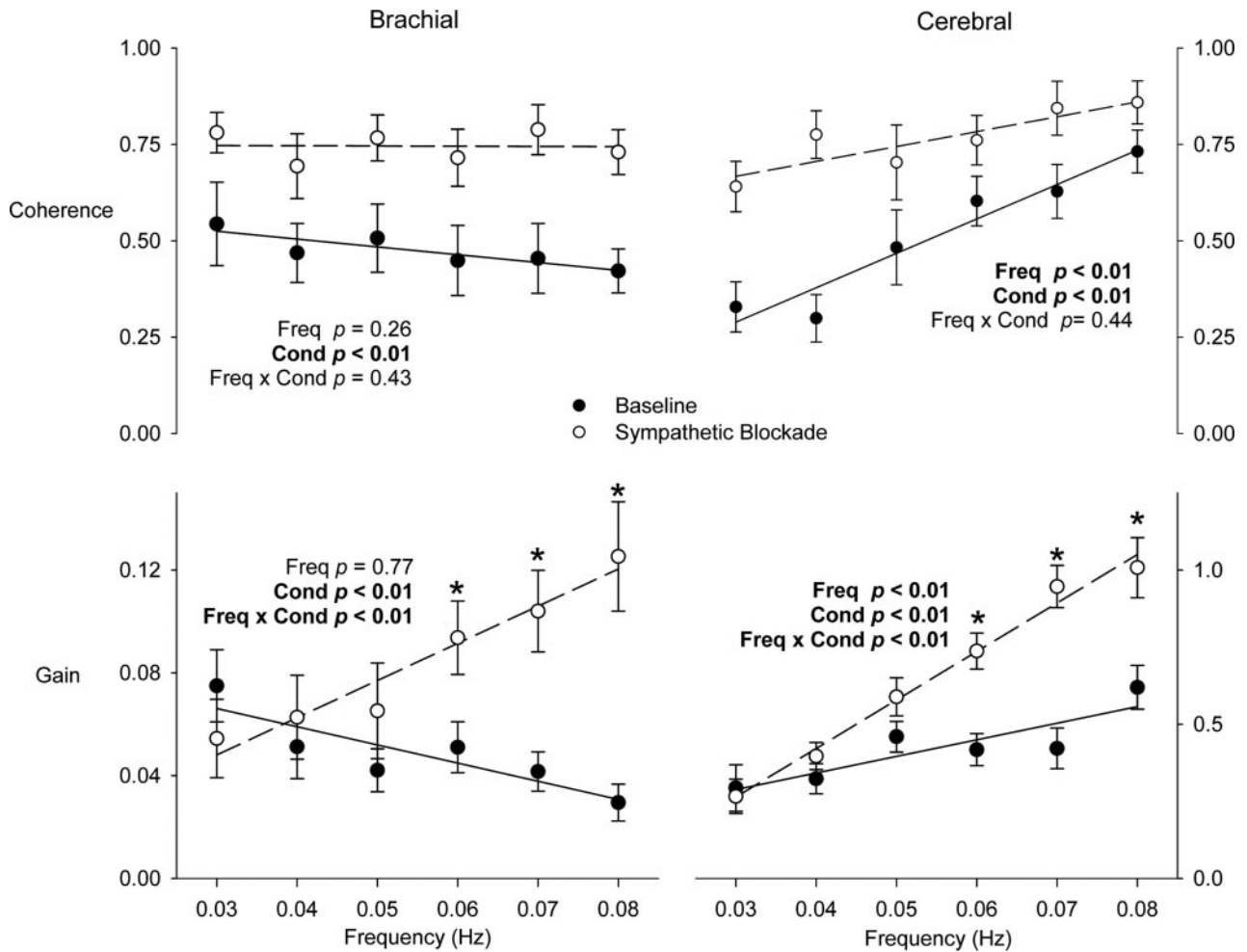


Figure 4. Coherence and gain between pressure and flow in the middle cerebral and brachial arteries with and without sympathetic blockade. Freq, Frequency; Cond, Condition; Freq \times Cond, frequency and condition interaction term. * $P < 0.05$ versus baseline at the OLBNP frequency.

controversial topic for decades. Although it has long been known that the cerebral arteries are innervated by sympathetic fibers,^{16,17} convincing evidence for their neural control of cerebral flow has been sparse. Part of the curious puzzle of nerves with no clear function may derive from interspecies differences; different animal models can produce sharply divergent findings.¹⁸ Indeed, it seems perfectly plausible that bipeds engage different autoregulatory mechanisms than quadrupeds. However, in a classic human study, Skinhoj showed no effect of sympathetic blockade on cerebral blood flow unless cerebral autoregulation was otherwise impaired.¹⁹ This would seem to stand at odds with more recent studies suggestive of a consistent sympathetic role,^{9,10} but methodologic limitations may be responsible for these seemingly contradictory findings. Studies from the 1970s and earlier used techniques such as ¹³³Xenon clearance that take ≥ 10 minutes for a single measurement, orders of magnitude slower than instantaneous transcranial Doppler measurements. Little attempt has been made to formally reconcile these older findings with recent data, and instead these two techniques are commonly considered to be measuring different “types” of autoregulation (ie, static and dynamic). Although this might be thought of as a Manichaeian construct,

our findings suggest it is broadly accurate that autoregulatory responses can be categorized as effective over either longer or shorter time scales. We found that sympathetic blockade increased in the gain relation between arterial pressure and cerebral blood flow at faster frequencies (>0.05 Hz or 20 seconds) but left autoregulatory control largely intact at slower frequencies. At even longer time scales represented by mean values over approximately 2 to 6 minutes (Table 1), there was no effect of blockade on cerebral flow. Thus, it appears that “static” autoregulation studies that have shown no effect of the sympathetic system on cerebral autoregulation¹⁹ are in fact compatible with our current data that clearly show sympathetic involvement at characteristically shorter time scales.

Sympathetic blockade increased the gain relation of arterial pressure changes to blood flow at frequencies >0.05 Hz in not only the cerebral circulation, but the brachial as well. This common response between the two vascular beds seems to indicate that sympathetic activity is most effective in a fairly narrow frequency range. This may not be surprising given frequency-dependent effects of vascular sympathetic outflow on vascular resistance were first described in the 1960s by Rosenbaum and Race.²⁰ More recently, frequency domain

approaches have generally confirmed these characteristics in a variety of animal models and tissue beds.^{21–23} In a novel approach, Stauss²⁴ measured hand skin blood flow in responses to sinusoidal median nerve stimulation and demonstrated that blood flow responded at frequencies between 0.075 and 0.10 Hz, but not at lower or higher frequencies. Although we did not examine frequencies >0.08 Hz, our findings support the hypothesis that the sympathetic nervous system selectively buffers flow against arterial pressure changes in this range.

In addition to a similar increase in gain between pressure and flow, both vessels demonstrated an increased coherence in the relation after sympathetic blockade. That is, both vessels reacted more passively or linearly to changes in pressure than in the intact state. This broad increase in linearity in both vascular beds with blockade indicates that the sympathetic nervous system is active in regulation at rest and that the observed phenomena do not reflect the characteristics of a compliance vessel in the transmission of arterial blood pressure to flow velocity. However, the increase in coherence was much more striking in the brachial bed, wherein a substantial increase in linearity of the pressure–flow relationship was observed across all frequencies. The remaining low gain despite the linearization suggests that another mechanism continued to buffer against the slowest pressure changes in the functionally denervated state. The two most likely mechanisms for this buffering would be a myogenic response in resistance vessels and/or endothelial-derived nitric oxide release. Although either or both mechanism(s) could be involved, recent work by Pyke et al²⁵ suggests that nitric oxide-dependent flow-mediated dilation responds with a roughly 0.03-Hz “dynamic” time constant (ie, 28 seconds) and has a proportional (ie, linear) response to increased shear stress. Given the strongly linear relationship, it seems likely that the nitric oxide system may be playing a role in regulating flow to the forearm vascular bed in the face of large, relatively slow arterial pressure changes during sympathetic blockade.

The cerebral vasculature, in contrast to the brachial, continued to demonstrate markedly reduced coherence in the pressure–flow relationship at the slowest frequencies after sympathetic blockade. This suggests a mechanism distinct from that regulating flow in the brachial vascular bed. Indeed, most evidence suggests that nitric oxide plays a negligible role in cerebral autoregulation; global nitric oxide synthase blockade has no effect on the spontaneous relationship between arterial pressure and cerebral blood flow²⁶ or on the “dynamic autoregulatory index” derived from the bilateral ischemic thigh cuff response.²⁷ Vascular myogenic mechanisms, although poorly understood in both animals and humans, have long been thought to be important in maintenance of cerebral perfusion.²⁸ In fact, the ability to buffer against extrinsically induced fluctuations in cerebral perfusion pressure is blocked by nifedipine in rats and preferentially so at frequencies <0.1 Hz (10 seconds).²⁹ Although no comparable human data exist, work suggests that the autoregulatory index is attenuated by the calcium channel blocker nifedipine.³⁰ Our data provide no direct evidence for vascular myogenic mechanisms, but the contrasts between the brachial

and cerebral vascular response to sympathetic blockade and our current understanding of regional vascular control strongly suggest an important myogenic role in maintenance of cerebral blood flow across longer time periods.

Limitations

One possible limitation for interpretation of these data are that arterial CO₂ was significantly decreased with sympathetic blockade during OLBPN. This unexpected effect may be due to the combination of orthostatic stress and vasodilation. Because decreased end-tidal CO₂ could lead to a decrease in cerebral blood flow,²⁸ it is possible that an increase in cerebral blood flow with sympathetic blockade was masked. However, our results suggest that the hypocapnia decreased coherence and gain, and thus, at worst, our results underestimate the sympathetic nervous system’s role in the cerebral circulation. In addition, although our data demonstrate a clear role of the sympathetic system in regulating cerebral flow, they also underscore the limitations of linear methods for characterizing autoregulation. The dramatic increases in coherence between pressure and both cerebral and brachial flows demonstrate that sympathetic control may operate, at least in part, in a nonlinear fashion. Indeed, low coherence at longer time scales in the cerebral vasculature before sympathetic blockade highlights the need for robust nonlinear approaches to understand the relationships present in the unblocked state.

Summary

The current work clearly demonstrates the role of the sympathetic nervous system in cerebral autoregulation and provides further evidence of different regulatory systems active at different time scales in the cerebral and brachial circulations. Future work should isolate the role of the vascular myogenic and nitric oxide systems in these regions while characterizing important nonlinearities to provide more complete understanding of the physiological mechanism(s) unique to cerebral autoregulation.

Acknowledgments

We thank the subjects for their generous participation.

Source of Funding

This research was supported by grant HL093113 from the National Heart, Lung and Blood Institute.

Disclosures

None.

References

1. Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. *Circulation*. 1976;53:720–727.
2. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke*. 1989;20:45–52.
3. Hamner JW, Cohen MA, Mukai S, Lipsitz LA, Taylor JA. Spectral indices of human cerebral blood flow control: responses to augmented blood pressure oscillations. *J Physiol*. 2004;559:965–973.
4. Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. *Am J Physiol*. 1998;274:233–241.

5. Edvinsson L, Aubineau P, Owman C, Sercombe R, Seylaz J. Sympathetic innervation of cerebral arteries: prejunctional supersensitivity to norepinephrine after sympathectomy or cocaine treatment. *Stroke*. 1975;6:525–530.
6. Strandgaard S, Sigurdsson ST. Point:counterpoint: sympathetic activity does/does not influence cerebral blood flow. Counterpoint: sympathetic nerve activity does not influence cerebral blood flow. *J Appl Physiol*. 2008;105:1366–1367.
7. van Lieshout JJ, Secher NH. Point:counterpoint: sympathetic activity does/does not influence cerebral blood flow. Point: sympathetic activity does influence cerebral blood flow. *J Appl Physiol*. 2008;105:1364–1366.
8. McHedlishvili GI. Vascular mechanisms pertaining to the intrinsic regulation of the cerebral circulation. *Circulation*. 1964;30:597–610.
9. Zhang R, Zuckerman JH, Iwasaki K, Wilson TE, Crandall CG, Levine BD. Autonomic neural control of dynamic cerebral autoregulation in humans. *Circulation*. 2002;106:1814–1820.
10. Ogoh S, Brothers RM, Eubank WL, Raven PB. Autonomic neural control of the cerebral vasculature: acute hypotension. *Stroke*. 2008;39:1979–1987.
11. Halliwill JR, Minson CT, Joyner MJ. Effect of systemic nitric oxide synthase inhibition on postexercise hypotension in humans. *J Appl Physiol*. 2000;89:1830–1836.
12. Welch PD. The use of fast Fourier transform for the estimation of power spectra: a method based on time averaging over short, modified periodograms. *IEEE Trans Audio Electroacoust*. 1967;15:70–73.
13. Koopmans LH. *The Spectral Analysis of Time Series*, 2nd ed. New York: Academic Press; 1995.
14. Searle SR. *Linear Models for Unbalanced Data*. New York: Wiley; 1987.
15. Box GEP, Cox DR. An analysis of transformations (with discussion). *J Roy Statist Soc Ser B*. 1964;26:211–252.
16. McNaughton FL. The innervation of the intracranial blood vessels and dural sinuses. *Assoc Res Nerv Ment Dis*. 1938;18:178–200.
17. Willis T. *Cerebri Anatome: cui accessit nervorum descriptio et usus*. London: James Flesher, Joseph Martyn and James Allestry; 1664.
18. Sandor P. Nervous control of the cerebrovascular system: doubts and facts. *Neurochem Int*. 1999;35:237–259.
19. Skinhoj E. The sympathetic nervous system and the regulation of cerebral blood flow in man. *Stroke*. 1972;3:711–716.
20. Rosenbaum M, Race D. Frequency-response characteristics of vascular resistance vessels. *Am J Physiol*. 1968;215:1397–1402.
21. Guild SJ, Austin PC, Navakatikyan M, Ringwood JV, Malpas SC. Dynamic relationship between sympathetic nerve activity and renal blood flow: a frequency domain approach. *Am J Physiol Regul Integr Comp Physiol*. 2001;281:206–212.
22. Stauss HM, Persson PB, Johnson AK, Kregel KC. Frequency-response characteristics of autonomic nervous system function in conscious rats. *Am J Physiol*. 1997;273:786–795.
23. Tsai ML, Chu LW, Chai CY, Yen CT. Frequency dependent sympathetic modulation of vasomotor tone in the anesthetized rat. *Neurosci Lett*. 1997;221:109–112.
24. Stauss HM, Anderson EA, Haynes WG, Kregel KC. Frequency response characteristics of sympathetically mediated vasomotor waves in humans. *Am J Physiol*. 1998;274:1277–1283.
25. Pyke KE, Hartnett JA, Tschakovsky ME. Are the dynamic response characteristics of brachial artery flow-mediated dilation sensitive to the magnitude of increase in shear stimulus? *J Appl Physiol*. 2008;105:282–292.
26. Zhang R, Wilson TE, Witkowski S, Cui J, Crandall GG, Levine BD. Inhibition of nitric oxide synthase does not alter dynamic cerebral autoregulation in humans. *Am J Physiol Heart Circ Physiol*. 2004;286:863–869.
27. White RP, Vallance P, Markus HS. Effect of inhibition of nitric oxide synthase on dynamic cerebral autoregulation in humans. *Clin Sci (Lond)*. 2000;99:555–560.
28. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990;2:161–192.
29. Kolb B, Rotella DL, Stauss HM. Frequency response characteristics of cerebral blood flow autoregulation in rats. *Am J Physiol Heart Circ Physiol*. 2007;292:H432–H438.
30. Endoh H, Honda T, Komura N, Shibue C, Watanabe I, Shimoji K. The effects of nicardipine on dynamic cerebral autoregulation in patients anesthetized with propofol and fentanyl. *Anesth Analg*. 2000;91:642–646.