In with the new and out with the old: enter multivariate wavelet decomposition, exit transfer function

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The human brain makes up only 2% of body weight, although it consumes more than 20% of oxygen and glucose at rest, with almost all adenosine triphosphate within the brain being produced by oxidative metabolism of glucose (3). In addition to a great need for substrate provision and by-product clearance, the metabolic circumstances in the brain are compromised by a limited intracellular capacity for energy storage. These two characteristics, combined with the paramount importance of brain function compared with other end organs, necessitate precise regulation of cerebral blood flow (CBF). Regulation of CBF is achieved through several factors including metabolic, myogenic, and neurogenic control, as well as systemic blood flow (10). Specifically, the primary controllers of CBF are partial pressure of arterial CO₂, cerebral metabolism, cardiac output, and the autonomic nervous system (11, 19). The role of the autonomic nervous system has been particularly difficult to assess due to a number of factors stemming from the redundant mechanisms at play involving a combination of neurovascular coupling, arterial blood gases, and systemic blood flow (19).

The role of the sympathetic arm of the autonomic nervous system has been particularly suspected to play a role in CBF regulation (7), as this system is crucial for regulating blood flow/vascular resistance systemically. However, the role the sympathetic nervous system (SNS) plays in regulating the cerebrovasculature has been thought to be limited to providing baseline tonic influence (lowering resting CBF) and then also by buffering CBF, albeit only at very high levels of perfusion pressure (1, 6). Understanding how and when the SNS influences CBF regulation not only has basic exploratory science importance but also will affect our understanding of how a number of clinical conditions impact cerebrovascular health, particularly autonomic disorders. A small number of studies have attempted to assess the role of the SNS in actively regulating CBF in humans; however, these studies have focused on SNS control during large perturbations in blood pressure (i.e., 40-mmHg repetitive swings or 30-mmHg rapid decreases), which obviates direct translation to the real world setting, as well as utility in clinical populations (5, 9). Furthermore, these studies have relied on transfer function analyses, which assumes that perfusion pressure is the only factor influencing CBF and that perfusion pressure and CBF interactions are linear and stationary, a circumstance that is almost certainly not possible considering the multifactorial regulation of CBF (5, 20). Lastly, the majority of previous studies evaluating the SNS influence on CBF regulation have used phentolamine as their drug of choice, which creates problems for interpretation, as this is a nonspecific α₁- and α₂-blocker with agonistic effects of muscarinic and histamine receptors, factors that can directly influence CBF regulation themselves (4, 15).

In the current issue of the American Journal of Physiology-Heart and Circulatory Physiology, Saleem et al. (16) present results of a blinded randomized placebo-controlled trial designed to determine the effects of sympathetic blockade on cerebral autoregulatory dynamics at rest in healthy young individuals. The rationale was to understand 1) the role the SNS plays in CBF regulation at rest and 2) the relative impact of changes in partial pressure of arterial CO₂ in the relationship between perfusion pressure and CBF when examining the role of the SNS. After being randomized into two groups, nine individuals were chosen to receive a 0.5 mg/kg oral dose of α₁ inverse agonist prazosin or placebo. All assessments were completed in the morning, both before and 120 min after either prazosin or placebo. After the collection of continuous recordings of resting beat-by-beat blood pressure (Finometer) and middle cerebral artery blood velocity (MCAv; transcranial Doppler), as well as breath-by-breath partial pressure of end tidal CO₂ (PETCO₂) for 6 min duration, data was analyzed using both the typical transfer function analysis that assumed a linear and stationary relationship (with and without multiple coherence function to account for PETCO₂) and the wavelet phase synchronization analysis (with and without a second term in the equation to account for PETCO₂). As well-described by Saleem et al. (16), wavelet phase synchronization essentially used portions of continuous data (i.e., wavelets; in this case a version of the Morlet wavelet) of varied duration to fit to both blood pressure and MCAv, which then allows for analysis of phase between input and output. Together, this analysis can generate information both from spectral and temporal domains of nonstationary signals. The primary findings of this study are critical and provide important new insight into the mechanism of CBF regulation. First, Saleem et al. (16) showed that the SNS is responsible for nonlinear and nonstationary regulation of perfusion pressure-CBF relationships assessed using wavelet phase synchronization, particularly those occurring at 30-60-s duration cycles. Second, the SNS did not alter the linear relationship between perfusion pressure and CBF. Third, PETCO₂ influenced both the nonstationary, nonlinear relationship and linear relationships between perfusion pressure and CBF. It was concluded that 1) the SNS plays a critical role in CBF regulation, 2) wavelet decomposition analysis provides more sensitive detection of changes in CBF under some cir-
cumstances compared with that possible through transfer function, and 3) changes in PETCO2 do not significantly impair the sensitivity of wavelet decomposition analysis to detect the role of the SNS on CBF regulation.

One of the major insights from this study is that linear approaches to assessing the relationship between blood pressure and CBF may not be appropriate in certain scenarios, such as during spontaneous (i.e., resting) conditions. Consider that at rest, the relationship between blood pressure and CBF shows very low coherence, indicating that they are not linearly related. The analysis of nonlinear nonstationary relationships using a tool designed for assessing linear and stationary relationships is likely why there is insufficient sensitivity to detect an effect of sympathetic blockade using transfer function analysis, while the wavelet approach was capable (16). Actively increasing coherence between blood pressure and CBF using repeated squat-stand or lower body negative pressure allows for valid use of linear analysis; however, these conditions (i.e., where blood pressure is drastically and rapidly increasing and decreasing) are likely a completely different physiological condition as to that of rest and may be engaging completely different mechanisms (17). It appears from the present data that linear approaches for assessing cerebral pressure-flow relationships at rest should be interpreted parsimoniously.

Another fascinating development from the work by Saleem et al. (16) is the data indicating that sympathetic influences over cerebrovascular regulation are occurring primarily in the very low-frequency range (0.02–0.07 Hz), as opposed to the low-frequency range (0.07–0.2 Hz) where the medullary-mediated rhythmic changes in sympathetic activity occur that affect systemic vascular tone. This finding could be the result of any of the following three scenarios: 1) modulations of cerebrovascular resistance that use sympathetic circuity may not be modulated by supraspinal centers per se (and some authors have suggested there is a spinal origin of some oscillations); 2) distinct supraspinal centers other than the rostral ventral lateral medulla, such as the raphe nuclei, which may operate in a different frequency than those regulating the rhythmicity of systemic sympathetic signals, may be responsible for providing the sympathetic tonic vascular support of cerebrovasculature; and 3) prazosin specifically blocked the very low-frequency range of sympathetic modulation of the cerebrovasculature, leaving the low-frequency range intact.

In any case, these issues need to be explored further and may provide the foundation for deep new insight into the differential regulation of cerebral versus systemic vasculature.

The technical implications of this study are significant and indicate that adjusting for the asynchrony between perfusion pressure and CBF due to SNS input may be required when one is attempting to assess the regulatory influence of other factors (e.g., systemic blood flow, myogenic response, neurovascular coupling, etc.) The results of this study also have a number of crucially important physiological and clinical implications that were not directly discussed, particularly for those suffering from autonomic dysfunctions that impact the SNS. Some of these considerations stem from scenarios of chronically altered SNS control, whereas others stem from acute SNS changes. From a chronic perspective, we and others have shown altered CBF regulation after cervical or high-thoracic spinal cord injury where disruption of supraspinal SNS control over the superior cervical ganglia occurs, which is responsible for ganglionic innervation of the cerebrovasculature (12, 13). When putting this into context of the present study, it may be the case that chronic loss of SNS control over the cerebrovasculature is contributing to the three- to fourfold elevated risk of stroke when autonomic pathways are disrupted after a spinal cord injury (2, 8) (Fig. 1).

The present study also provides interesting insight into scenarios of acute changes in SNS tone. One scenario where the present data may be extremely clinically relevant is that of neurogenic shock, where there is an acute period of almost complete loss of SNS tone. The present data indicates that the
ability to maintain blood flow constant in the central nervous system (CNS) during neurogenic shock (when blood pressure drops drastically) would be impaired due to loss of the SNS regulatory mechanism described in this paper. When you combine this with the fact that most decompression surgeries occurring after a spinal cord injury occur during neurogenic shock and include large doses of vasopressor agents that can readily cross the ruptured blood-brain barrier at the site of injury (and counterproductively further constrict blood vessels at the site of injury leading to even less blood flow to the injury site), appreciation of the SNS involvement in the regulation of CNS blood flow becomes of critical clinical importance (14, 18). This may be why blood pressure maintenance during acute surgery after perforating spinal cord injury does not lead to any improvement in neurological outcome compared with not managing blood pressure (14).

In conclusion, the present study demonstrates new insight into the complex regulation of the cerebrovasculature in humans. One primary new goal of the field should be to address the capacity of wavelet decomposition analysis to examine the role of other factors involved in CBF regulation (e.g., myogenic influences/Ca\(^{2+}\) channels). The present study focused on \(\alpha_2\)-pathways involved in cerebrovascular control, and thus future studies should assess the role of \(\alpha_2\)-receptors and \(\beta\)-receptors, perhaps using medetomidine. Also, it is likely that many studies need to be reanalyzed using the new approach to better understand the role that altered sympathetic tone may be exerting on the relationship between perfusion pressure and blood flow of the CNS. From a clinical perspective, one certainly now has to be cautious in situations where SNS regulation over the CNS is impacted (either chronically or acutely), as one may be directly inhibiting the capacity of the cerebrovasculature to self-regulate, which would not only predispose to stroke but also impair the capacity for healing after many neurological injuries.

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