Autonomic control of the cerebral circulation is most important for dynamic cerebral autoregulation

To the editor: The debate whether sympathetic nerves influence cerebral blood flow (CBF) has been raging for over a century as summarized 30 years ago (1, 3). By then it was clear that there are prominent species differences in the response of the cerebral circulation to vasomotor nerves; sympathetic activity plays a greater role in regulating CBF in primates than rodents or cats. For humans, our early work showed that orthostatic stress (which reduces cardiac output and increases sympathetic activity) causes cerebral vasoconstriction, but only when the orthostatic stress is strong, and much less than the systemic circulation (2). Importantly, the autonomic contribution to CBF regulation depends critically on the rate of change of blood pressure. That is, autonomic effects are most prominent for dynamic autoregulation when blood pressure and CBF change over ~10–30 s and less so for steady-state autoregulation, which may be dominated by vasomotor escape (8). Thus, after ganglionic blockade, dynamic autoregulation was lost (6, 8). Finally, as noted by both camps of this Point/Counterpoint (4, 5), we were surprised that ganglionic blockade did not prevent the reduction in CBF during orthostasis (7). However we would suggest that this result be interpreted cautiously. Although autonomic neural responses are not obligatory for the regulation of CBF during orthostasis (which may be quite different than mechanisms of metabolic CBF regulation), there likely is sufficient redundancy in circulatory control that more than one pathway or mechanism is operative. Certainly recent failed attempts to define a single mediator of exercise hyperemia have taught this lesson clearly.

References


Sympathetic activity does influence cerebral blood flow

To the editor: The role of sympathetic nerves originating primarily from the superior cervical ganglia (SCG) in modulating resistance vessels tone is clearly demonstrated (1, 3). One of the most intriguing tools for studying the sympathetic role in modulating the cerebral blood flow (CBF) is to investigate it indirectly. Cervical spinal cord stimulation (cSCS) is well known to increase CBF (4, 5). By affecting the sympathetic tone during CBF it is possible to confirm indirectly its role in mediating the CBF effects of SCs. We studied CBF in rabbits (1) in basal conditions, 2) during sympathetic trunk stimulation (STS) at the neck, 3) during SCs (210 μs, 80 Hz, 2/3 motor threshold, for 20 min), and 4) during simultaneous SCs and STS (10 V, 10 Hz, 0.5 ms, for 1 min). A reduction of CBF was evident in every case soon after starting STS. At the end of the stimulation, the effect disappeared immediately. In 50% of the animals showing an increase of CBF during SCs, STS produced only 25–30% of its effect, whereas in the remaining 50%, vasoparalysis was comparable to the one observed in basal conditions. These data suggest that a decrease (65–70%) of cervical sympathetic excitability (functional reversible sympatheticolysis) occurs as a consequence of SCs and indirectly confirms the role of sympathetic activity in influencing CBF (6). According to Strandgaard and Sigurdsson (2), sympathetic activity plays a small role in autoregulation but few demonstrations are provided in favor of the lack of any role in modulating CBF.

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TO THE EDITOR: The current Point:Counterpoint article in the Journal of Applied Physiology (7, 8) highlights that, during wakefulness, because of the other more powerful regulatory influences on CBF—autoregulation, cerebrovascular CO2 reactivity, and, potentially, cardiac output—the potentially role of SNA is “masked.” One very common situation, however, in which this “unmasking” of SNA control of CBF might occur is during sleep—particularly during rapid eye movement (REM) sleep, where dramatic fluctuations in blood pressure (6) and elevations in CBF exceed that of non-REM sleep and wakefulness (3). Elegant animal studies incorporating continuous recording of SNA in the superior cervical ganglion (1) conclude that SNA directed to cerebral vessels increases with acute hypertension, but not with hypotension, suggesting that it serves a protective function for the cerebral microcirculation, and not a regulatory role for maintenance of systemic arterial pressure. If such a powerful influence can be extrapolated to sleep, then it seems possible that this mechanism could act to protect the brain against potentially damaging intravascular pressure changes or hyperperfusion especially during REM sleep. The absence of this response might, in part, underline the high incidence of stroke or hemorrhage during sleep, particularly after the longest period of REM sleep (5). Thus, because of sleep-related reductions in cerebral metabolism (3), cerebrovascular CO2 reactivity (4), and cerebral autoregulation (2), it seems that the situation in which SNA is most needed, and most likely, to control CBF is during sleep.

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SYMPATHETIC NERVES INFLUENCE THE CEREBRAL CIRCULATION

TO THE EDITOR: The cerebral circulation receives a dense supply of perivascular adrenergic nerves, located in the adventitia close to the smooth muscle cells. They extend along with the arterioles when they enter the brain substance but do not extend to the intracerebral microvasculature that receive fibers emanating in the brain stem and from local cortical neurons (1). The smooth muscle cells contain adrenergic α- and β-receptors, and neuropeptide Y1 receptors that can modify vessel

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AUTONOMIC NERVOUS SYSTEM INFLUENCES DYNAMIC CEREBRAL BLOOD FLOW

TO THE EDITOR: It seems reasonable to surmise that the potential effect of increases in sympathetic nerve activity on cerebral blood flow (CBF) depends on the physiological conditions and that the influence of such activation has a different response to that which occurs in the peripheral vasculature (7, 8). Indeed, a number of studies have demonstrated that CBF was decreased by increased sympathetic activity during specific conditions, i.e. hypertension, despite there being no evidence of change in CBF during resting control conditions (1, 6). In addition, and especially in humans, it is difficult during steady-state changes in CBF to identify autonomic control of CBF because of the integration of other powerful regulatory mechanisms, i.e., cerebral autoregulation and arterial Pco2. Cardiac output clearly influences steady-state CBF (2), while this phenomenon is attenuated during exercise from rest despite the resetting of the cardiopulmonary baroreflex without change in its sensitivity (3), indicating that the influence of cardiac output may depend on blood volume distribution rather than autonomic control. However, this finding also suggests that the arterial baroreflex control of cardiac output influences dynamic CBF regulation (5). Moreover, during a more dynamic condition, such as acute hypotension induced by ischemic cuff occlusion/release, cerebral vasoconstriction by sympathoexcitation is readily apparent because cerebral vascular conductance decreases when arterial blood pressure increases. This arterial baroreflex control of the cerebral vasculature is attenuated by α-adrenoreceptor blockade (4).

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tone; circulating agonists are prevented from reaching the receptors by the blood-brain barrier (BBB) (1). Early studies showed little influence of the sympathetic system on cerebral blood flow but a strong influence on intracranial pressure regulation, cerebral blood volume (capacitance function), and cerebrospinal fluid formation (3).

The systemic application of agonists was largely negative because of the BBB. In 1976 two independent studies suggested that stimulation of the sympathetic nerves can extend the upper limit of the autoregulation (4). Also the lower limit of autoregulation can be modified by the sympathetic nerves (2). It should be pointed out that it applies to physiological conditions and at normal blood pressure levels (5).

The clinical situation in critically ill subjects is more complex where the limits of the autoregulation sometimes are jeopardized (6). The autoregulation is at its limits and intracranial pressure, cerebral blood volume, and blood pressure can influence cerebral blood vessel tone and flow (1). The need to pharmacologically elevate low blood pressure by the use of \( \alpha \)-adrenergic agonists (phenylephrine) can result in vasoconstriction, in particular if the BBB is leaky.

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ROLE OF A RUDIMENTARY SYMPATHETIC NERVOUS SYSTEM ON CEREBRAL BLOOD FLOW

TO THE EDITOR: Many basal biological systems exist widespread in most species and most organs, but are expressed to a varying extent. This notion also holds true for the sympathetic nervous system (SNS), which is strongly expressed in, e.g., the heart and muscles, but also in brain, albeit in a more rudimentary and localized function. The SNS’s effect on cerebral blood flow (CBF) regulation is well established, as the limits of CBF autoregulation are shifted toward higher blood pressure levels during sympathetic activation (2, 4) (autoregulation of CBF denotes that within certain physiological limits of blood pressure CBF is independent of blood pressure). So far, Point and Counterpoint hardly disagree, but Counterpoint would argue that the role of SNS in the brain is essentially limited to this sole function (5). By contrast, Point argues that SNS brain effect has more widespread functions in the regulation of systemic circulation (6).

The SNS predominantly exerts its effect on the larger cerebral resistance vessels, whereas the autoregulatory response is mainly exerted through the smaller resistance vessels (1, 3). This could explain why changes in sympathetic activity under normal physiological conditions are not reflected in profound
changes in CBF, the sympathetic and autoregulatory response counterbalancing each other.

We would like to offer a suggestion to reconcile both views: The effects of SNS on CBF, mediated though a regulation of the larger cerebral resistance vessels, are clinically revealed only in extreme conditions where blood pressure goes beyond the normal range of autoregulation blood pressure interval. In this case, SNS may shift the limits of autoregulation to maintain CBF unchanged (2). Controversies in the literature may be explained by the presence of extreme physiological conditions where the normal balance between SNS activity and blood pressure is lost. In addition, methodological issues, such as discrepancies between perfusion and linear flow velocities may impart.

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SYMPATHETIC NERVES INFLUENCE CEREBRAL BLOOD FLOW

TO THE EDITOR: A critical point of issue on whether sympathetic perivascular nerves normally regulate cerebral blood flow (CBF) is what constitutes “normal conditions” (4, 5). Arguments for the view that cerebral vascular resistance is not “normally” regulated by sympathetic activity often ignore two critical aspects, one physiological, the other behavioral. Physiological recordings of cerebral sympathetic nerve activity (SNA) from superior cervical ganglia show that cerebral SNA increases promptly in response to imposed elevations of blood pressure (pharmacological or mechanical) exceeding a threshold of 40%, but remains unchanged when blood pressure is lowered (1). Thus cerebral SNA normally plays no role in baroreflex restoration of blood pressure, but protects against cerebral hyperperfusion during large arterial pressure rises. Behavioral considerations suggest several real-life circumstances for such a protection. Large, rapid elevations in blood pressure occur naturally in fright, sexual activity, weightlifting, and sleep (3), and these may represent settings for protective rises in SNA. Notably in REM sleep, cerebral SNA attenuates CBF increases during the large blood pressure surges that characterize this state (2). Thus cerebral SNA plays a major regulatory role by limiting brain perfusion when large elevations of blood pressure occur naturally in sleep, and probably in many other normal behaviors.

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THE SYMPATHETIC “KNOCK-OUT” MODEL

TO THE EDITOR: Cerebral autoregulation (CA) is a complex of regulatory mechanisms with a wide range of response time that maintain a more or less constant cerebral blood flow (CBF) during changes in cerebral perfusion pressure. The sympathetic nerves, originating in the superior cervical ganglion and known to be present throughout the whole cerebral circulation (2) could well be part of one of those regulatory mechanisms (3, 4). Earlier studies showed that sympathetic activity had a negligible effect on CBF. However, as one needed about 15 min to determine CBF, the effect that was observed was a representation of all the regulatory mechanisms inducing changes within this timeframe, including possible changes in sympathetic activity. The introduction of transcranial Doppler (TCD) in 1982 made it possible to monitor changes in CBF beat-to-beat and differentiate between fast and slow responding regulatory mechanisms. With this method, Zhang et al. (5) found that systemic sympathetic blockade with intravenous trimethaphan did influence the short-term regulation of CA. A superior stellate ganglion blockade, effectively creating a unilateral cerebral sympathetic activity “knock-out” model, creates an unique situation, in which all other “confounding” parameters discussed in this Point:Counterpoint discussion, such as changes in cardiac output, α-adrenergic activity, nitric oxide, and carbon dioxide remain unaffected in both hemispheres. By doing so, and using TCD to determine induced changes in CBF, again the influence of the sympathetic activity was demonstrated (1). In our opinion these recent reports suggest that sympathetic activity does influence CA. However, whether this influence is clinically significant is still a matter of debate.

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WHEN NORADRENERGIC RESTRAINT OF CEREBRAL BLOOD FLOW MAKES HOMEOSTATIC SENSE

TO THE EDITOR: Lieshout and Secher (2) suggest that the relationship between mean arterial pressure (MAP) and autoregulation of cerebral blood flow is affected by the prevailing cardiac output such that when cardiac output is lowered below certain limits, cerebral blood flow, and consequently cerebral oxygenation decline as a result of effects likely mediated via α-adrenergic receptors in cerebral resistance vessels. Their hypothesis that cerebral oxygenation is directly related to cardiac output independent of MAP is intuitively appealing as whole body oxygen delivery is dependent on cardiac output and not MAP. As for the observation by Zhang and Levine (3) that stellate ganglion blockade did not attenuate the cerebral vasoconstrictor effects consequent to nonhypotensive lower body negative pressure, it is possible that circulating norepinephrine partly mediated the vasoconstrictor responses in the cerebral circulation in addition to the other mechanisms postulated.

In contrast to Strandgaard and Sigurdsson’s (1) point of view, I think that during acute hypotension, sympathetic restraint of cerebral blood flow might contribute to supporting flows and oxygenation of other vital organs and metabolically active tissues because cerebral oxygenation could still be maintained by increasing cerebral extraction of oxygen. However, cerebral blood flow and oxygenation is probably much better autoregulated than flows and oxygenation in other tissues.

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