Point:Counterpoint: Sympathetic activity does/does not influence cerebral blood flow

**POINT: SYMPATHETIC ACTIVITY DOES INFLUENCE CEREBRAL BLOOD FLOW**

Cerebral arteries are abundantly innervated by sympathetic fibers, but their influence on cerebral vessels was held unimportant for almost a century (2, 20). Whether there is sympathetic influence on cerebral blood flow (CBF) is important in the management of hypotensive patients. If there is no α-adrenergic influence on CBF, a low mean arterial pressure (MAP) can be increased to the cerebral autoregulation (CA) range by α-adrenergic receptor agonists and secure CBF and cerebral oxygenation (ScO2). On the other hand, if CBF is influenced by cerebral α-adrenergic stimulation, CBF and ScO2 decline while MAP increases in response to administration of the α-adrenergic agonist. In this context it is important that in humans, middle cerebral artery (MCA) mean blood velocity (Vmean) decreases in response to trigeminal ganglion stimulation (27) and CBF increases after stellate ganglion blockade (24).

Studies performed in erect and exercising healthy subjects as in patients with heart failure provide further direct and indirect support for modulation of cerebral perfusion by sympathetically mediated vasconstriction consequent to a reduced cardiac output (CO). A relationship between CBF and CO is established when standing up as both MCA Vmean and ScO2 decrease together with CO (25). This reduction in cerebral perfusion manifests although MAP increases, indicating a role for sympathetic activation in cerebrovascular resistance control. Alternatively, the orthostatic reduction in cerebral perfusion is alleged to be caused by the postural decrease in end-tidal carbon dioxide tension (PETCO2) (3). The reduction in arterial CO2 tension (PACO2) accounts, however, for only one-half of the orthostatic influence on MCA Vmean (13, 23). In support, both MCA Vmean and ScO2 increase when the standing position is supplemented by leg-muscle tensing, attenuating sympathetic activity by enhancing CO (25). This observation might be related to an effect of stroke volume on the arterial baroreceptors where dynamic input from stroke volume is important in the regulation of sympathetic activity in humans (5).

During dynamic exercise, MCA Vmean and ScO2 increase (14). However, when exercise with β-adrenergic blockade attenuates the increase in CO, e.g., from 19 to 15 l/min (19), the increase in MCA Vmean is also reduced (12). Yet the usual 25% increase in MCA Vmean is reestablished if sympathetic activity to the brain is eliminated by stellate ganglion blockade (10). Similarly, in patients with heart failure the patient’s ability to increase CO during exercise relates to the increase in MCA Vmean (11). When comparing one- with two-legged exercise, heart failure patients demonstrate a normal increase in MCA Vmean that is attenuated, or eliminated, during two-legged exercise (7, 8, 16).

An increment in CO with volume expansion increases MCA Vmean as a reduction in CO with application of negative pressure to the lower parts of the body (LBNP) decreases MCA Vmean at a maintained MAP (18). This takes place with no change in PACO2 and, therefore, cerebral vasoconstriction indicates increased sympathetic drive.

The orthostatic decrease in MAP at brain level is within the CA range, but the reduction in CO is by ~20%. Lowering MAP using trimethaphan and subsequently restoring it with phenylephrine evaluates sympathetic influence in the control of CBF during moderate LBNP (29). The similarity of reductions in mean, systolic, and pulse arterial pressures in addition to pulsatile change in MCA Vmean and PETCO2 before vs. during ganglionic blockade was taken to suggest that sympathetic vasoconstriction is not the mechanism underlying the reduction in CBF during central hypovolemia. An implicit assumption was that phenylephrine does not affect the cerebral vasculature. However, phenylephrine may lower CBF while increasing MAP (22). Against that background, the study (29) indicates that phenylephrine balances α-blockade for the brain. Among the mechanisms by which changes in stroke volume may affect CBF, altered shear stress related to changes in pulsatile flow is proposed through flow-mediated regulatory mechanisms like nitric oxide (NO) (29). NO is involved in the regulation of CBF in both animals and humans. Endothelial dysfunction is proposed to affect cerebral artery myogenic tone and CA, but its role in the regulation of CBF during central hypovolemia is not established. CA may be NO mediated (28), but in healthy subjects an exogenous NO donor does not affect the control of CBF. Similarly, inhibition of NO production does not impair dynamic CA (30) and neither affects MCA Vmean in healthy subjects (9). Thus, in humans, the role of NO in the control of CBF remains elusive.

The observation that steady-state CBF, MCA Vmean, and ScO2 decrease on standing seems to be at odds with CA, i.e., that CBF is relatively stable within a wide range of perfusion pressures (21, 25). Comparable to what happens to skeletal muscle blood flow during exercise, regional flow is allowed to increase for as long as it does not affect MAP. However, when CO is restricted and challenges MAP, flow to exercising muscles and to the brain becomes limited (22). Stimulation of sympathetic nerves to the brain may cause a marked reduction in CBF, whereas under conditions where MAP is not challenged by a restricted CO, the influence of sympathetic stimulation on CBF is abolished (1). Or, according to Bill and Linder (1), under certain conditions stimulation of the sympathetic nerves to the brain causes a marked reduction in CBF, whereas under normal conditions the effect of such stimulation is practically nil.

An influence of the sympathetic activity on CBF is likely to explain the discrepancy between the lack of influence of MAP on CBF and ScO2 as long as the central blood volume (CBV) is maintained during anesthesia (lowest level 37 mmHg) (17), and the decrease in CBF and Vmean when MAP declines below ~80 mmHg in response to deliberate reduction in central blood volume by LBNP, head-up tilt, or hemorrhage (Fig. 1).

When considering the stimulus to the arterial baroreceptors against a background of different effects of steady vs. pulsatile pressure on baroreceptor discharge, we accept that the influence of CO on CBF may be through the pulse pressure generated by the stroke volume and detected by the
arterial baroreceptors where data from animal studies support that baroreceptors detect flow as well as pressure (4). Nevertheless, in animals the separate effects of different components of arterial pressure have not been identified (6) and also parasympathetic influence of CBF needs to be established.

Taken together, an inability to maintain, or to increase, CO adequately induces peripheral vasoconstriction not only in working skeletal muscle (19) but also in the brain (26). We take it that α-adrenergic influence on CBF is important and that administration of α-adrenergic agonists affects CBF and ScO2. As long as CBV is adequate, such an effect is masked to become evident with central hypovolemia. The exception to that rule is the patient with significant arteriosclerosis in the vessels supplying the brain for such a patient, CBF is pressure dependent but that distacts from the notion that recording of MAP does not provide information on whether CBF and ScO2 are maintained. The implication of these observations is that for the unconscious patient, routine monitoring of CBF or ScO2 needs to be established because recording of blood pressure can not in itself predict whether CBF is maintained.

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pril causes a shift of the upper limit of autoregulation toward lower values demonstrated. Blockade of the renin-angiotensin system with captopril can constrict the inflow tract and hence contribute to autoregulation, can constrict the inflow tract and thereby counteract the autoregulatory response. During hemorrhagic hypotension, the otherwise inactive sympathetic nervous system (16). It is intuitively clear that the cerebral circulation cannot take part in general cardiovascular regulation. During states of shock, where the sympathetic nervous system is activated, leading to a decrease in the perfusion of kidneys and mesenteric vascular bed, the cerebral circulation is kept functioning as long as possible and experiences only a modulating effect on autoregulation by sympathetic perivascular nerves.

The cerebral arteries are innervated like other vascular beds by neurons arising in the peripheral nervous system and also by intrinsic neurons (4, 9). Sympathetic nerves in contact with the cerebral arteries originate from the superior cervical ganglion, but unusually under normal conditions seem to have little influence on cerebral blood flow (CBF). Already Fog (3) in his early studies of pial arteries in cats found no effect of acute sympathetic, vagal, or baroreceptor denervation on the autoregulatory responses. Chronic sympathetic denervation in animals does not influence CBF autoregulation (2, 15). Electric stimulation or acute sympathetic activation with a 35% rise in blood pressure, and this shift is abolished by concomitant electric stimulation of the cervical sympathetic trunk (14).

In a study in normal humans, lower body negative pressure was used to create a baroreflex-induced activation of the sympathetic nervous system. Such activation did not alter cerebrovascular reactivity to hypercapnia or hypocapnia, as studied by medial cerebral artery velocity (7). Likewise, the same group found no effect of ganglionic blockade on cerebrovascular CO2 reactivity (10). By contrast, in a related study, where sympathetic activation was achieved by head-up tilt and sympathetic tone was removed by ganglionic blockade, a slight effect of sympathetic activation was found on CO2 reactivity (6). These findings may have been influenced by methodological errors, as discussed in detail by LeMarbre et al. (7). Interestingly, ganglionic blockade with trimetaphan did not appear to influence cerebrovascular CO2 reactivity in normotensive and hypertensive humans (13). Lower body negative pressure induces a decrease in cerebral blood flow velocity even if blood pressure is maintained by infusion of a pressor drug. This cerebral vasoconstrictor response was preserved in healthy individuals under ganglionic blockade with trimetaphan, excluding participation of the sympathetic nervous system (16).

Thus it may be concluded that the sympathetic perivascular nerves have little or no effects on CBF and its regulation under normal conditions, but may be activated to constrict the inflow tract cerebral vessels at very high or very low blood pressure. It is gratifying that this point of view was also expressed in a recent review on perivascular nerves and the regulation of cerebrovascular tone (4).

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