British Journal of Anaesthesia **111** (3): 361–7 (2013)
Advance Access publication 24 April 2013 · doi:10.1093/bja/aet122

BJA

Sympathetic regulation of cerebral blood flow in humans: a review

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Editor's key points

- There are very few methodologically sound studies exploring sympathetic regulation of CBF.
- This review suggests that sympathetic system plays little role in regulating CBF under normal physiological conditions.
- Importantly, during cerebral vasospasm, decreasing sympathetic tone may offer therapeutic benefit.

Summary. Cerebral blood flow (CBF) is regulated by vasomotor, chemical, metabolic, and neurogenic mechanisms. Even though the innervation of cerebral arteries is quite extensively described and reviewed in the literature, its role in regulation of CBF in humans remains controversial. We believe that insufficient attention has so far been focused on the potential role of the innervation of the cerebral vasculature in cerebral autoregulation in humans. We have performed an extensive search and selection of available literature on electrical, chemical, and surgical manipulations of the sympathetic innervation of cerebral arteries, and the effects of circulation sympathetically active agents on CBF. Studies on (surgical) ganglion block show a role of sympathetic tone in preventing increases in CBF in humans, which are consistent with the view based on animal studies. Both direct innervation of the cerebral arteries from cervical ganglia and stimulation of adrenergic receptors by circulating sympathomimetics prevent sudden increases of CBF associated with hypertension and hypercapnia. We postulate that under normal physiological conditions neurogenic control has little influence on cerebral autoregulation as other methods of control (vasomotor, chemical, and metabolic) are dominant. In severely challenging circumstances, such as delayed cerebral ischaemia after subarachnoid haemorrhage, these methods might be overwhelmed, increasing the relative importance of neurogenic, sympathetic control of CBF. This insight might lead to future therapeutic possibilities.

Keywords: cerebrovascular disorders; haemodynamics; neurophysiology; sympathetic nervous system

The human brain is exquisitely sensitive to changes in cerebral blood flow (CBF). For optimal function and survival of neurones in the face of changing physiological conditions, elaborate mechanisms have evolved to maintain optimal CBF, and to ensure that regionally and globally a favourable balance between oxygen supply and demand is maintained.

Lassen was one of the first to demonstrate the complexities of cerebral autoregulation (CA), the process by which CBF is kept at a constant level when mean systemic arterial pressure is between ~50 and 150 mm Hg.[1] It has been demonstrated that the autoregulation-induced alterations in CBF are mediated and modulated by several mechanisms such as cerebral myogenic vasomotor responses, arterial carbon dioxide tension, arterial oxygen tension, cerebral metabolism, and neurogenic control. In healthy subjects, the lower limit of CA was shown to be variable.[2] As a result, there is no clear evidence to inform decisions on minimum acceptable intra-operative systemic arterial pressures, in healthy patients, let alone those with cerebrovascular disease requiring anaesthesia. There are several pathological situations causing alterations in CBF as a result of dysregulation, where our knowledge is incomplete. For example, the dysautoregulation seen after acute and chronic ischaemic stroke results in impaired CBF and is associated with subsequent and structural changes.[3 4] Another example is delayed cerebral ischaemia after subarachnoid heamorrhage (SAH), causing significant delayed morbidity and mortality after SAH. Even though a vast amount of research has been conducted on potential methods to prevent and treat delayed cerebral ischaemia, nimodipine remains the only treatment proved to improve outcome.[5]

The myocardial blood flow is also subject to autoregulation; and here manipulations (decreases) of sympathetic tone of the myocardial vasculature (by electrical stimulation) has been shown to improve myocardial blood flow and clinical outcome in patients with myocardial ischaemia responding poorly to traditional pharmacological coronary vasodilatory therapy.[6–8] Two types of innervation of cerebral

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vessels are distinguished: extrinsic innervation of extra-parenchymal arteries (from cervical ganglia, otic and sphenopalatine ganglia, and trigeminal ganglion) and intrinsic innervation of intra-parenchymal arterioles (from brain stem nuclei such as the nucleus coeruleus).[9 10] The question arises whether manipulation of the innervations of the cerebral arteries can influence CBF in a way comparable with improvement of myocardial blood flow. If these manipulations can indeed influence CBF, then this suggests that these manipulations might form the basis of a therapeutic intervention in patients who suffer regional cerebral ischaemia as a result of a thrombotic stroke or from delayed ischaemia after subarachnoid haemorrhage.

It has taken several decades for physiologists to improve our understanding of the physiological purpose of cerebrovascular innervation, but still this remains the subject of considerable controversy.[11 12] This debate is attributable to the differences observed in cerebrovascular response to either electrical stimulation or pharmacological agents in laboratory environments. This has led to contradictory findings, the causes of which have been summarized by Sandor[13] in detail. The most important causes of these contradictory results are:

- Species-related differences in adrenergic receptor distribution.
- The use of time consuming (sometimes inappropriate) methods of CBF measurements.
- Variable blood–brain barrier permeability in different experimental set-ups.
- Confounding autoregulatory mechanisms and conditions such as hyper/hypocapnia, alkalosis/acidosis, or concomitant release of dilating factors or neurotransmitters.

A systematic search of the literature for studies that avoid these confounds or correct for them, as described in the Supplementary Appendix, showed that there was insufficient data for a meta-analysis, and thus we instead will describe (but not analyse) the existing literature. The focus of this review is the role of the sympathetic nervous system (SNS) as too few studies address the influence of trigeminal[14–16] and parasympathetic[17 18] pathways. When considering the role of SNS on CBF, two main pathways can be identified and will be discussed separately: (i) innervation of vessels by sympathetic nerve fibres originating from the sympathetic ganglia or brain stem nuclei; (ii) effects of circulating sympathetically acting agents.

Paradigms used to measure or challenge CBF and CA

CBF can be estimated in several ways. A comparative review can be found elsewere.[19] Early studies used the Kety–Schmidt method which applies a 10 min period of inhalation of 15% N_2O and determines brain uptake from the venous and arterial N_2O concentration–time curves.[20] This technique was modified in 1953 to achieve results within 20 min.[21] Also radioisotopes have been used, calculating CBF from brain uptake of isotopes as detected by scintillation detectors or single photon emission computed tomography. These methods suffer from the fact that extra-cranial circulation cannot be totally separated from intra-cranial circulation (although the contamination in the N_2O method is only ~6.5%),[20] so differences in CBF could be either obscured or overestimated. This problem has been overcome using [^{15}O]H_2O-PET to quantitatively assess CBF with high spatial resolution, but this method has not been used in the studies discussed in this paper.[22] Some groups use magnetic resonance angiography (MRA) or digital subtraction angiography (DSA) to estimate flow in cerebral vessels based on contrast enhancement or size of the vessel. These methods are unable to detect small effects, and translation of radiological findings to physiology is difficult. The N_2O method and methods using radioisotopes and radiological methods take time, so immediate effects are hard to measure. Larsen and colleagues[23] showed that transcranial Doppler sonography (TCD) can be used as an indirect way to determine CBF by measuring CBF velocity (CBFV). This method is non-invasive and can be performed in real time, but is not reliable when the diameter of the insonated vessel changes. Another more recently applied method to estimate CBF is by the use of near-infrared spectroscopy (NIRS). NIRS can provide quantitative data on changes in CBF, but provides less exact qualitative data, and only allows assessment of regional CBF.[24] Also, NIRS accuracy might suffer from contamination of the signal by extra-cranial signals from the scalp, which can suffer marked vasoconstriction induced by systemically acting agents.[25]

All the above mentioned methods can be used to determine CA, as effects of changes in MAP on CBF(V) can be determined. Several paradigms have been applied to do so. The thigh cuff technique creates a sudden decrease of arterial pressure (AP) by 20% for ~10 s, so cerebral vasoreactivity can be measured, as is applied in analysis of carotid stenosis.[26] Lower body negative pressure (LBNP) can induce longer periods of decreased AP or oscillating AP, as has been used in analysis of orthostatic hypotension. Also the Valsalva manoeuvre can be used to elicit a relative standard transient decrease in AP and to analyse the response of CBFV.[27] Other methods try to elicit a sympathetic response, for example by head-up tilt, hand-grip test, or exercise. Because of the profound effects of CO_2 concentration on CBF,[28] changes in blood CO_2 concentrations induced by hyperventilation or by carbogen (a CO_2/O_2 mixture) inhalation have also been used to assess CBF vasoreactivity.[29]

Possibly the most important development in understanding CA is the study of dynamic CA. Static CA is the steady-state relation between CBF and AP, whereas dynamic CA represents the transient response of the CBF–AP relationship. This concept is based on observations of relatively fast recovery of CBF (within seconds) when it is being challenged by, for example, a sudden decrease in

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