

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 haemorrhage (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

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 Sandor¹³ 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 elsewhere.¹⁹ Early studies used the Kety–Schmidt method which applies a 10 min period of inhalation of 15% N₂O and determines brain uptake from the venous and arterial N₂O 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 N₂O method is only ~6.5%),²⁰ so differences in CBF could be either obscured or overestimated. This problem has been overcome using [¹⁵O]H₂O-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 N₂O method and methods using radioisotopes and radiological methods take time, so immediate effects are hard to measure. Larsen and colleagues²³ 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 CO₂ concentration on CBF,²⁸ changes in blood CO₂ concentrations induced by hyperventilation or by carbogen (a CO₂/O₂ 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

AP. Especially, the use of TCD (with its high temporal resolution) has allowed for the study and subsequent mathematical modelling of dynamic CA.^{30–33} It has been shown that transfer function analysis (a mathematical representation of the relation of input and output of a supposedly linear system) can be used to calculate amplitude gain and phase shifts in the frequency domains of the signals (after a Fourier transform of the signals). An increased amplitude gain and a decreased phase lead of CBFV to MCA curves has been associated with decreased CA. Both spontaneous arterial pressure fluctuations and fluctuations induced by manoeuvres such as LBNP can be used to determine transfer function gain or phase shifts.³³

The effects of electrical, chemical, and surgical manipulation of sympathetic innervation of cerebral arteries

A few studies have investigated the effects of electrical stimulation of either the sympathetic ganglia or the cervical spinal cord.^{34–36} They are of insufficient quality to draw conclusions, either because the measured effects are inseparable from cardiovascular effects,³⁴ or insufficient quantitative data are presented,^{35, 36} or CO₂ is not measured.³⁶

In studies on sympathetic ganglion block (either chemical or surgical), CO₂ is not always measured, heterogeneous study-populations (with different pathologies) are sometimes used and several different methods of CBF measurement are applied (Table 1). Most studies using stellate ganglion block show an increased CBF (increased CVR or CBF by N₂O method, increased CBFV in MCA by TCD, or improved angiography), most prominently on the ipsilateral side of intervention. In three studies on ganglion block, no effect on CBF was found. All used a chemical block (by percutaneous infiltration of local anesthetic), so possibly the blocks were not complete.^{37–39}

Only one study suggests a decrease of CBF after stellate ganglion block, showing a significant decrease of signal intensity and unchanged size in intra-cranial arteries.⁴⁰ Interpretation of this study is difficult because quantitative translation of MRA signal changes to CBF is unclear.

All surgical ganglionectomies showed increased CBF (maximum of +20%). Excision of the inferior cervical ganglion was shown to reduce CVR—this effect is statistically significant while the effects of surgical excision of the superior cervical ganglion are not.^{41–42} Also cerebral angiography was shown to improve after superior cervical ganglionectomy combined with carotid perivascular sympathectomy in patients with vasospasm after SAH.⁴³ These three studies have in common that all cervical sympathetic supply of cerebral vessels was disrupted. The study of Jeng and colleagues⁴⁴ on T2 sympathectomy, performing measurements 2–4 weeks after intervention, showed increased blood flow in ICA and increased flow velocities in MCA.

The effects of circulating sympathetically active agents

Selective effects of sympathetic agents on CA are hard to detect as cardiovascular effects induced by these agents can in return result in changes in CBF. Therefore, only certain types of study design might result in information about the selective effects on CBF: (i) studies in which the systemic effects of a sympathetic agent are restored (by another agent), (ii) studies in which the systemic effects of an autonomic test or SNS activating activity are blocked or counteracted by an agent, and (iii) studies in which the sympathetically active agent is administered locally in the brain by either intrathecal or intracarotid delivery.

The majority of studies that measure effects on CBF after administration of some sympathetically active agents, do not apply the above mentioned methods (see Supplementary Appendix). The studies that do, especially in those performed on patients (as opposed to healthy subjects), show great heterogeneity between studies (in pathology, agents used and CBF measurement) and within populations. Arterial or end-tidal CO₂ is hardly ever measured.

Studies in healthy subjects that do use methods to counteract the cardiovascular effects of sympathetic agents or ganglion block, more consistently measure CO₂ and always use an immediate (but indirect) way of measuring CBF by TCD (Table 2).

Several of these studies show that sympathetic activity can decrease CBF or attenuates CBF increases. For example, sympathetic block doubles the CBF increase during the Valsalva manoeuvre.⁴⁵ On the other hand, a sympathetic block prevents the decrease in CBF associated with head-up tilt.⁴⁶ Also it has been shown that non-selective alpha block (by phentolamine) impairs autoregulatory responses (CBFV increased four times more with phentolamine in the face of increased MAP).⁴⁷ Similarly, i.v. infusion of trimetaphan (a so-called ganglion blocker, because it blocks the cholinergic synaptic transmission in sympathetic and parasympathetic pathways) increases CO₂ reactivity.⁴⁶ A study applying transfer function analysis on physiological fluctuations in CBFV and MAP, found no effects on transfer function gain and phase lead of CBFV to MAP during β -block or exercise.⁴⁸ Another study showed increased amplitude gain (transfer function analysis) while the phase lead of CBFV to MAP decreased during autonomic block with trimetaphan. This effect persisted during restoration of MAP by the selective α_1 receptor agonist phenylephrine.⁴⁹ Two other studies used repetitive LBNP to generate and compare arterial pressure oscillations and CBFV oscillations and confirmed the increased transfer function gain and decreased phase shifts suggestive of a deterioration of dynamic CA by phentolamine and during ganglion block by trimetaphan.^{50–51} Clonidine (a selective α_2 -adrenergic receptor agonist) attenuates the increase of CBF associated with hypercapnia.^{52–53} This finding is difficult to interpret for several reasons. Via an agonist action at α_2 -adrenergic receptors, clonidine generally reduces sympathetic tone by decreasing norepinephrine

Table 1 Overview of studies on the effects of ganglion block on CBF. F, female; CBF(V), cerebral blood flow (velocity) measurement; CO₂, carbon dioxide measurement; NR, not reported; TCD, transcranial Doppler sonography; N₂, nitrogen inhalation; MRI, magnetic resonance imaging; Xe-IV, Xenon bolus technique; DSA, digital subtraction angiography; SPECT, single photon emission computed tomography; NIRS, near-infrared spectroscopy; Y, yes; N, no; AP, arterial pressure; ECG, electrocardiogram; So₂, oxygen saturation; HR, heart rate; N₂%, blood nitrogen percentage; Po₂, partial oxygen pressure; glu, glucose; CVR, cerebrovascular resistance; CMR, cerebral metabolism rate; HT, haematocrit; Hb, haemoglobin; CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery; inf, inferior cervical ganglion (stellatum); sup, superior cervical ganglion; T2, thoracic ganglion at level T2; Other: plexus injury, sudden deafness, facial palsy, and palmar hyperhidrosis, respectively

Reference	n	%F	Age	Pathology	CBF(V)	CO ₂	Other parameters	Ganglion	Method	Uni-/bilat.	Effect
Gupta and colleagues ⁵⁷	20	0	28	Other	TCD	Y	AP, ECG, So ₂ , and HR	Inf	Lidocaine	Uni	↑
Harmel and colleagues ³⁸	13	NR	44	Several	N ₂	Y	AP, So ₂	Inf	Procaine or intracaine	Bi	=
Ide and colleagues ⁵⁸	8	NR	22	None	TCD	Y	AP, HR	Inf	Lidocaine	Uni	↑
Jeng and colleagues ⁴⁴	68	49	25	Other	TCD	N	Lumen and blood flow CCA, ECA, and ICA	T2	Surgical	Bi	↑
Kang and colleagues ⁴⁰	19	100	46	None	MRI	N		Inf	Mepivacaine	Uni	↓
Linden ⁵⁹	28	NR	NR	Stroke	N ₂	Y	So ₂ , N ₂ %	Inf	Lidocaine	Uni	↑
Ohta and colleagues ³⁹	16	12	NR	Other	Xe-IV	Y	AP, PaO ₂	Inf	Mepivacaine	Uni	=
Scheinberg ³⁷	19	NR	47	Stroke	N ₂	N	AP, Po ₂ , and glu/O ₂ use	Inf	Procaine	Uni	=
Shenkin ⁴¹	75	NR	60	Stroke	N ₂	N	CVR, CMR(O ₂), AP, HT, and Hb	Inf/sup	Surgical	Both	↑
Shenkin and colleagues ⁴²	7	NR	44	Several	N ₂	Y	AP, SaO ₂ , SvO ₂ , pH, CVR, and O ₂ use	Inf	Surgical	Bi	↑
Suzuki and colleagues ⁴³	11	NR	NR	Vasospasm	DSA	N		Sup	Surgical	Uni	↑
Treggiari and colleagues ⁶⁰	9	89	41	Vasospasm	DSA	N		Sup	Bupivacaine and clonidine	Both	↑
Umeyama and colleagues ⁶¹	6	0	NR	None	SPECT	N		Inf	Mepivacaine	Uni	↑
Yokoyama and colleagues ⁶²	8	NR	47	Other	NIRS	N		Inf	Mepivacaine	Uni	↑

Table 2 Overview of studies in healthy subjects challenging SNS, all using TCD to measure CBFV. F, female; CO₂, end-tidal or arterial CO₂ measurement; NR, not reported; HR, heart rate; AP, arterial blood pressure; CO, cardiac output; So₂, oxygen saturation; ECG, electrocardiogram; PaCO₂, arterial CO₂ pressure; HUT, head-up tilt; HV, hyper-/hypo-ventilation; Exerc., exercise; VM, Valsalva's manoeuvre; LBNP, lower body negative pressure; MP, metoprolol; TM, trimethaphan; NE, norepinephrine; PO, phentolamine; CL, clonidine; PE, phenylephrine. Effect: 1, increased transfer function gain and decreased phase shift after block; 2, more profound CBF increases after block; 3, reduced CO₂ reactivity by agonist

Reference	n	%F	Age	CO ₂	Other parameters	Agents	Challenge	Effect
Hamner and colleagues ⁵¹	11	36	NR	Cont.	HR, AP, ECG, and flow brachial artery	PO	LBNP	1
Jordan and colleagues ⁴⁶	6	33	29	Forced	HR, AP, ECG, and CO	TM, PE	HUT/HV	2
Kimmerley and colleagues ⁴⁷	7	28	30	Cont.	HR, AP	PO, NE		2
Lee and colleagues ⁵²	9	NR	NR	Interm.	HR, AP, O ₂ , and ECG	CL, PE	HV	3
Maekawa and colleagues ⁵³	27	52	30	Cont.	AP, ECG, temp, and So ₂	CL	HV	3
Mitsis and colleagues ⁵⁰	9	25	29	Cont.	HR, AP, and ECG	TM	LBNP	1
Ogoh and colleagues ⁴⁸	8	0	22	Interm.	HR, AP, and CO	MP	Exerc.	No
Zhang and colleagues ⁴⁹	12	25	29	Cont.	HR, AP, and PaCO ₂	TM, PE		1
Zhang and colleagues ⁴⁵	9	33	30	Interm.	HR, AP	TM	VM	2

release, causing a bradycardia and a lowering of the systemic arterial pressure. However, it also causes systemic vasoconstriction.⁵⁴ Finally, it also causes sedation, (presumed to be mediated via an agonist effect on α_2 receptors in the locus coeruleus), and if flow-metabolism coupling is intact, then sedation should result in decreased cerebral metabolism and a coupled decrease in CBF mediated by increase cerebrovascular tone, and indeed reduced CBF velocity has been shown with TCD.⁵²

Discussion

Studies on the effects of sympathetic pathways or sympathetically acting agents are abundant, but are very heterogeneous in population, type of CBF measurement, agent or challenge studied. End-tidal or arterial CO_2 is often not measured. Also most studies cannot differentiate reactive changes in CA as a result of cardiovascular effects induced by the studied challenge or agent, from direct effects on CA. Still, when considering the studies on cervical ganglion block, the majority of studies show increased CBF after block. Most convincingly, all four studies that did surgically disrupt sympathetic input from the cervical ganglia to the cerebral arteries showed increased CBF. Another six studies using a pharmacological superior ganglion block showed increased CBF. Notwithstanding their shortcomings, this shows a role of sympathetic tone in preventing increases in CBF. This is consistent with the view (based on animal studies) that sympathetic nerve activity limits cerebral vasodilatation during severe hypertension, hypoxia, and hypercapnia.^{13 55 56}

Among studies of sympathetically acting agents, those in which a ganglionic block by trimetaphan was used all show decreased capability of CA (both static and dynamic) to respond to increased AP. The same effects were found when using the α -adrenergic antagonist phentolamine. So, especially α -adrenergic receptors possibly play a significant role in CA, which is further substantiated by the finding that the α_2 -adrenergic agonist clonidine partly prevents CBF increase by hypercapnia. On the other hand, oral administration of clonidine gives unpredictable uptake, and clonidine could affect CBFV and CO_2 response indirectly because of its sedative effects (presumed to be mediated by an α_2 -adrenergic effect at the locus coeruleus). The only (methodologically suitable) study showing no effect of a sympathetically blocking agent on dynamic CA, used the β -adrenergic antagonist metoprolol.

Studies on dynamic CA showed the particular importance of analysis on a short time-scale (in min) using transfer function analysis on CBFV and AP curves. Effects of sympathetic control of cerebral vasculature could be clearly demonstrated using these methods, suggesting a role of the SNS in beat-to-beat regulation of CBF.^{49–51} In our opinion, sympathetic activity can be seen as one of the modulators of CA that determine the amount of change in CBF that can be achieved when CA is challenged by haemodynamic changes. Without challenge, the modulation is only minor.

With maximum sympathetic tone, CBF increases will be attenuated whereas decreases cannot be counteracted by this system. If sympathetic tone is minimal, CBF increases will not be counteracted by this system anymore. This means that when sympathetic tone is too high in a situation of cerebral ischaemia, it will be difficult to increase CBF without 'resetting' sympathetic tone, especially when other systems also fail (mechanical, metabolic, and chemical autoregulation). Possibly, therapeutic measures that decrease the output of sympathetic pathways towards the cerebral arteries, can help increase CBF in cases of focal ischaemia (e.g. in case of delayed cerebral ischaemia after SAH).

In conclusion, even though meta-analysis is impossible, both ganglion-block studies and studies on systemically acting sympathetically active agents do show that the SNS plays an important role in CA. 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. Conversely, surgical excision of the stellate ganglion appears to provide a modest (maximum of +20%) increase in CBF. Studies of chemical ganglion block have shown less promising results. It may be that under normal physiological conditions, myogenic control of cerebral vasomotor tone is dominant, and that neurogenic control has little influence. In severely challenging situations, such as cerebral vasospasm, myogenic control might be overwhelmed by pathophysiological factors that increase vascular tone, and manipulations that dampen sympathetic tone may well have a therapeutic benefit.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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