Sympathetic regulation of cerebral blood flow in humans: a review

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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.5–8 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).\textsuperscript{9,10} The question 
arises whether manipulation of the innervations of the cere- 
bral 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 inter- 
vention 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 cerebro- 
vascular innervation, but still this remains the subject of con- 
siderable controversy.\textsuperscript{11,12} This debate is attributable to the 
differences observed in cerebrovascular response to either 
electrical stimulation or pharmacological agents in labora- 
tory environments. This has led to contradictory findings, 
the causes of which have been summarized by Sandoor\textsuperscript{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 condi- 
tions 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 Sup- 
plementary 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\textsuperscript{14–16} 
and parasympathetic\textsuperscript{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 sympa- 
thetically 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.\textsuperscript{19} Early studies used the Kety– 
Schmidt method which applies a 10 min period of inhalation of 
15% N\textsubscript{2}O and determines brain uptake from the 
venous and arterial N\textsubscript{2}O concentration–time curves.\textsuperscript{20} This 
technique was modified in 1953 to achieve results within 
20 min.\textsuperscript{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 circu- 
lation cannot be totally separated from intra-cranial circula- 
tion (although the contamination in the N\textsubscript{2}O method is only 
\(\sim 6.5\%\)),\textsuperscript{20} so differences in CBF could be either obscured 
or overestimated. This problem has been overcome using 
\([^{15}\text{O}]\text{H}_2\text{O-PET}\) to quantitatively assess CBF with high spatial 
resolution, but this method has not been used in the 
studies discussed in this paper.\textsuperscript{22} Some groups use magnetic 
resonance angiography (MRA) or digital subtraction angio- 
graphy (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 radio- 
logical findings to physiology is difficult. The N\textsubscript{2}O method 
and methods using radioisotopes and radiological methods 
take time, so immediate effects are hard to measure. Larsen and colleagues\textsuperscript{23} showed that transcranial Doppler 
sonography (TCD) can be used as an indirect way to deter- 
mine CBF by measuring CBF velocity (CBFV). This method is 
non-invasive and can be performed in real time, but is not re- 
liable 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.\textsuperscript{24} Also, NIRS accuracy might suffer from con- 
tamination of the signal by extra-cranial signals from the 
scalp, which can suffer marked vasoconstriction induced by 
systemically acting agents.\textsuperscript{25}

All the above mentioned methods can be used to deter- 
mine 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 \(\sim 10\ s\), so cerebral vaso- 
reactivity can be measured, as is applied in analysis of 
carotid stenosis.\textsuperscript{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.\textsuperscript{27} Other methods try to elicit a sympa- 
thetic response, for example by head-up tilt, hand-grip 
test, or exercise. Because of the profound effects of CO\textsubscript{2} 
concentration on CBF,\textsuperscript{28} changes in blood CO\textsubscript{2} concentra- 
tions induced by hyperventilation or by carbogen (a 
CO\textsubscript{2}/O\textsubscript{2} mixture) inhalation have also been used to assess 
CBF vasoreactivity.\textsuperscript{29}

Possibly the most important development in understand- 
ing 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
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.48 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 α₁ 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 α₂-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 α₂-adrenergic receptors, clonidine generally reduces sympathetic tone by decreasing norepinephrine release.
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.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>%F</th>
<th>Age</th>
<th>Pathology</th>
<th>CBF(V)</th>
<th>CO₂</th>
<th>Other parameters</th>
<th>Ganglion</th>
<th>Method</th>
<th>Uni-/bilateral</th>
<th>Effect</th>
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<tbody>
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<td>Gupta and colleagues57</td>
<td>20</td>
<td>0</td>
<td>28</td>
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<td>Y</td>
<td>AP, ECG, SO₂, and HR</td>
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<td>Lidocaine</td>
<td>Uni/bilat.</td>
<td>↑</td>
</tr>
<tr>
<td>Harmel and colleagues58</td>
<td>13</td>
<td>NR</td>
<td>44</td>
<td>Several</td>
<td>N₂</td>
<td>Y</td>
<td>AP, SO₂</td>
<td>Inf</td>
<td>Procaine or intracaine</td>
<td>Bi</td>
<td>=</td>
</tr>
<tr>
<td>Ide and colleagues58</td>
<td>8</td>
<td>NR</td>
<td>22</td>
<td>None</td>
<td>TCD</td>
<td>Y</td>
<td>AP, HR</td>
<td>Inf</td>
<td>Lidocaine</td>
<td>Uni/bilat.</td>
<td>↑</td>
</tr>
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<td>Jeng and colleagues34</td>
<td>68</td>
<td>49</td>
<td>25</td>
<td>Other</td>
<td>TCD</td>
<td>N</td>
<td>Lumen and blood flow CCA, ECA, and ICA</td>
<td>T2</td>
<td>Surgical</td>
<td>Bi</td>
<td>↑</td>
</tr>
<tr>
<td>Kang and colleagues50</td>
<td>19</td>
<td>100</td>
<td>46</td>
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<td>MRI</td>
<td>N</td>
<td></td>
<td>Inf</td>
<td>Mepivacaine</td>
<td>Uni/bilat.</td>
<td>↓</td>
</tr>
<tr>
<td>Linden59</td>
<td>28</td>
<td>NR</td>
<td>NR</td>
<td>Stroke</td>
<td>N₂</td>
<td>Y</td>
<td>SO₂, N₂%</td>
<td>Inf</td>
<td>Lidocaine</td>
<td>Uni/bilat.</td>
<td>↑</td>
</tr>
<tr>
<td>Ohta and colleagues39</td>
<td>16</td>
<td>12</td>
<td>NR</td>
<td>Other</td>
<td>Xe-IV</td>
<td>Y</td>
<td>AP, Pao₂</td>
<td>Inf</td>
<td>Mepivacaine</td>
<td>Uni/bilat.</td>
<td>=</td>
</tr>
<tr>
<td>Scheinberg37</td>
<td>19</td>
<td>NR</td>
<td>47</td>
<td>Stroke</td>
<td>N₂</td>
<td>N</td>
<td>AP, Pao₂, and glu/O₂ use</td>
<td>Inf/sup</td>
<td>Surgical</td>
<td>Bi</td>
<td>↑</td>
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<tr>
<td>Shenkin and colleagues61</td>
<td>7</td>
<td>NR</td>
<td>44</td>
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<td>N₂</td>
<td>Y</td>
<td>AP, SaO₂, SvO₂, pH, CVR, and O₂ use</td>
<td>Inf</td>
<td>Surgical</td>
<td>Bi</td>
<td>↑</td>
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<tr>
<td>Suzuki and colleagues53</td>
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<td>NR</td>
<td>NR</td>
<td>Vasospasm</td>
<td>DSA</td>
<td>N</td>
<td></td>
<td>Sup</td>
<td>Surgical</td>
<td>Uni/bilat.</td>
<td>↑</td>
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<tr>
<td>Treggiari and colleagues50</td>
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<td>89</td>
<td>41</td>
<td>Vasospasm</td>
<td>DSA</td>
<td>N</td>
<td></td>
<td>Sup</td>
<td>Bupivacaine and clonidine</td>
<td>Both</td>
<td>↑</td>
</tr>
<tr>
<td>Umejama and colleagues61</td>
<td>6</td>
<td>0</td>
<td>NR</td>
<td>None</td>
<td>SPECT</td>
<td>N</td>
<td></td>
<td>Inf</td>
<td>Mepivacaine</td>
<td>Uni/bilat.</td>
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<tr>
<td>Yokoyama and colleagues62</td>
<td>8</td>
<td>NR</td>
<td>47</td>
<td>Other</td>
<td>NIRS</td>
<td>N</td>
<td></td>
<td>Inf</td>
<td>Mepivacaine</td>
<td>Uni/bilat.</td>
<td>↑</td>
</tr>
</tbody>
</table>

Table 2 Overview of studies in healthy subjects challenging SNS, all using TCD to measure CBVF. 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.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>%F</th>
<th>Age</th>
<th>CO₂</th>
<th>Other parameters</th>
<th>Agents</th>
<th>Challenge</th>
<th>Effect</th>
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</thead>
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<tr>
<td>Hamner and colleagues51</td>
<td>11</td>
<td>36</td>
<td>NR</td>
<td>Cont.</td>
<td>HR, AP, ECG, and flow brachial artery</td>
<td>PO</td>
<td>LBNP</td>
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<td>Jordan and colleagues46</td>
<td>6</td>
<td>33</td>
<td>29</td>
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<td>HR, AP, ECG, and CO</td>
<td>TM, PE</td>
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<td>Kimmerley and colleagues57</td>
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<td>28</td>
<td>30</td>
<td>Cont.</td>
<td>HR, AP</td>
<td>PO, NE</td>
<td>2</td>
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<tr>
<td>Lee and colleagues52</td>
<td>9</td>
<td>NR</td>
<td>NR</td>
<td>Interim</td>
<td>HR, AP, O₂, and ECG</td>
<td>CL, PE</td>
<td>HV</td>
<td>3</td>
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<tr>
<td>Maekawa and colleagues53</td>
<td>27</td>
<td>52</td>
<td>30</td>
<td>Cont.</td>
<td>AP, ECG, temp, and SO₂</td>
<td>CL</td>
<td>HV</td>
<td>3</td>
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<tr>
<td>Mitsu and colleagues50</td>
<td>9</td>
<td>25</td>
<td>29</td>
<td>Cont.</td>
<td>HR, AP, and ECG</td>
<td>TM</td>
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<tr>
<td>Ogho and colleagues48</td>
<td>8</td>
<td>0</td>
<td>22</td>
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<td>HR, AP, and CO</td>
<td>MP</td>
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<td>No</td>
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<td>Zhang and colleagues49</td>
<td>12</td>
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<td>HR, AP, and Paco₂</td>
<td>TM, PE</td>
<td>1</td>
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<tr>
<td>Zhang and colleagues55</td>
<td>9</td>
<td>33</td>
<td>30</td>
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<td>HR, AP</td>
<td>TM</td>
<td>VM</td>
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</table>
release, causing a bradycardia and a lowering of the systemic arterial pressure. However, it also causes systemic vasoconstriction.\textsuperscript{54} Finally, it also causes sedation, (presumed to be mediated via an agonist effect on $\alpha_2$ 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.\textsuperscript{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.\textsuperscript{13 55 56}

Among studies of sympathetically acting agents, those in which a ganglionic block by trimetaphan was used all showed decreased capability of CA (both static and dynamic) to respond to increased AP. The same effects were found when using the $\alpha_2$-adrenergic antagonist phentolamine. So, especially $\alpha_2$-adrenergic receptors possibly play a significant role in CA, which is further substantiated by the finding that the $\alpha_2$-adrenergic agonist clonidine partly prevents CBF increase by hypercapnia. On the other hand, oral administration of clonidine gives unpredictable uptake, and clonidine could affect CBV and $CO_2$ response indirectly because of its sedative effects (presumed to be mediated by an $\alpha_2$-adrenergic effect at the locus coeruleus). The only (methodologically suitable) study showing no effect of a sympathetically blocking agent on dynamic CA, used the $\beta$-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 CBV 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.\textsuperscript{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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