

# Modern and Evolving Understanding of Cerebral Perfusion and Autoregulation

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## Keywords

- Cerebral perfusion • Cerebral blood flow • Autoregulation
- Lower limit of autoregulation • Cerebrovascular reactivity • Cerebral ischemia
- Beach chair position • Cerebral perfusion pressure

## Key Points

- Significant changes in anesthetic management for optimizing cerebral perfusion have occurred over the past 5 to 10 years. Perhaps the most important of these changes has been a reinterpretation of older autoregulation studies that have resulted in raising the lower limit of autoregulation to approximately 70 mm Hg to 80 mm Hg, and not the previously used 60 mm Hg.
- Tremendous variability in the lower limits of autoregulation exists among individuals. Using a percentage reduction below baseline blood pressure as a lower limit may result in better optimization of cerebral perfusion than using absolute blood pressure values.
- Other changes in practice for the general anesthesiologist include correcting blood pressure for height differences between the site of blood pressure measurement and the brain, particularly in the sitting position, to account for the hydrostatic gradient. Rare cases of severe brain damage have been reported that may be related to hypoperfusion in the beach chair position.
- Multiple physiologic and drug interactions that affect cerebral perfusion occur during every general anesthetic, and understanding the best way to optimize cerebral blood flow may potentially improve outcomes. Newer research on flow-metabolism coupling points to regional control of cerebral blood flow by the neurovascular unit, with glial cells playing a central role.

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## INTRODUCTION

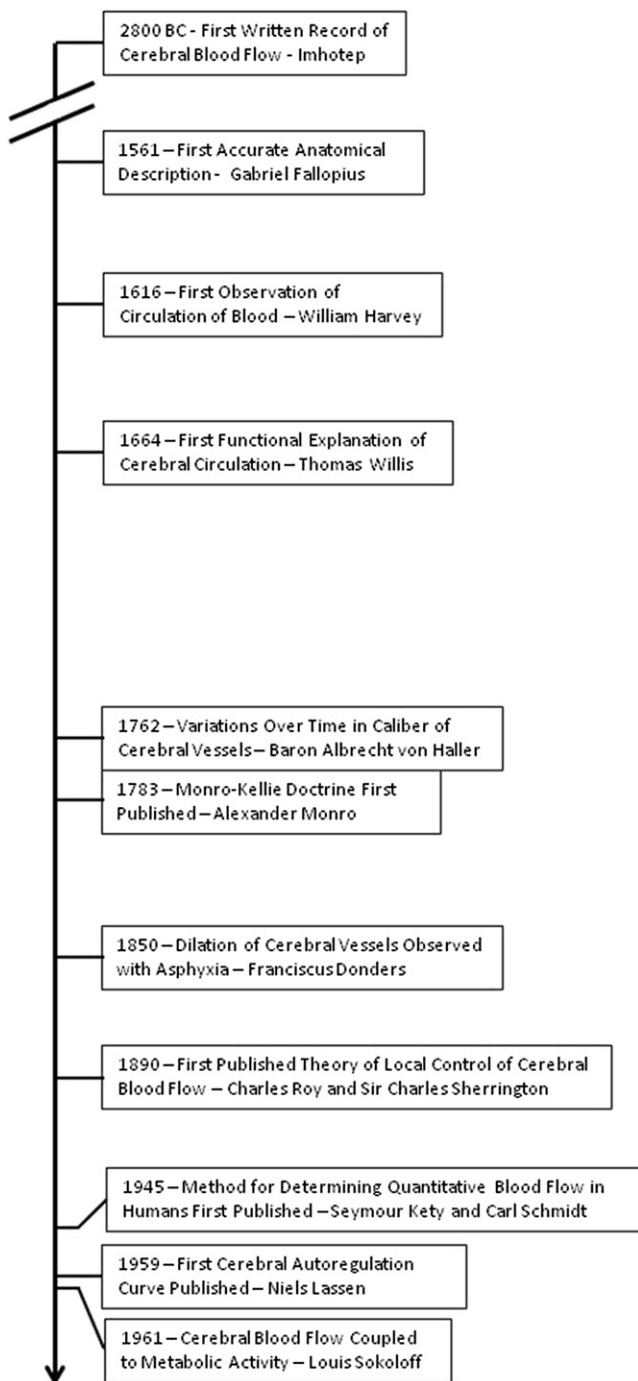
Defining the parameters that affect cerebral perfusion and understanding the pathophysiologic conditions that result in a supply and demand mismatch is of paramount concern for anesthesiologists. Stroke is one of the most devastating perioperative complications, and can occur with an incidence of 0.1% to 1.0% in patients undergoing noncardiac, non-neurological procedures, using national database statistics [1]. It is difficult to estimate what percentage of these perioperative strokes are related to embolic phenomena versus hypoperfusion, but hypoperfusion was strongly implicated as a causative factor in the multicenter randomized controlled trial Perioperative Ischemic Evaluation Study (POISE), in which patients receiving perioperative beta blockade had a twofold increased risk of stroke compared with patients who received placebo [2]. Retrospective single-institution studies have also found a significant relationship between perioperative stroke and intraoperative hypotension [3]. In contrast, a recent review of the literature noted that hypoperfusion was causative in only 6.6% of the 301 strokes identified [4]; yet, several studies have suggested that hypoperfusion may exacerbate the effect of microemboli. The indirect evidence suggests that “low” mean arterial pressure (MAP) may increase the risk of a perioperative stroke in certain high-risk individuals, but defining “low” for all patients and all procedures is problematic.

The goal of this article was to enhance the reader’s understanding about factors that affect cerebral blood flow (CBF), and to reexamine some misperceptions from earlier clinical studies on cerebral autoregulation and their impact on clinical practice. Rarer neurologic complications, such as ischemic optic neuropathy related to the prone and steep Trendelenburg positions, and severe brain damage in the sitting position, that highlight the potentially deleterious impact of patient position on cerebral perfusion are also discussed.

## FUNDAMENTALS OF CBF

Humans have long been interested in cerebral perfusion and the brain as far back as 2800 BC, but it was not until the mid-1900s that the first techniques to measure CBF were developed by Kety and Schmidt (Fig. 1) [5–7]. We now have at least 18 different methods for measuring CBF, with newer tools of analysis, such as functional magnetic resonance imaging and positron emission computed tomography, that can demonstrate 3-dimensional images of CBF to a resolution of less than 1 cm [6]. Widespread use of these newer techniques should improve our understanding of cerebral perfusion to better guide our clinical practice.

Inherent to understanding perfusion of the brain is first understanding the immense metabolic requirement of the brain. The brain makes up only 2% of the body weight, but receives as much as 15% to 20% of the cardiac output, approximately 50 to 60 mL/100 g brain tissue/min, or 750 to 1000 mL/min in an adult. It consumes as much as 20% of the total oxygen requirement at resting conditions at 3.3 mL/100 g brain tissue/min [5,6]. Of the oxygen used, 40% is devoted to what is known as basal metabolism: homeostasis of



**Fig. 1.** Timeline of important milestones in the history of cerebral perfusion research. *Data from Refs. [5-7].*

the neuronal networks, providing adenosine triphosphate (ATP) to maintain ion gradients, and providing substrate for the central nervous system to communicate (ie, neurotransmitters, polypeptides, complex proteins). The other 60% is necessary for what is known as activation or functional metabolism: the energy required to support electrophysiologic function and to allow the neurons of the brain to communicate [5,6]. Because of its high metabolic activity and relatively low energy storage capacity, the brain is especially vulnerable to interruption of oxygen and substrate delivery.

### Circle of Willis

In its most simple description, the circle of Willis is a continuous arterial circle that forms at the base of the brain by interconnections between branches of the left and right internal carotid arteries and the vertebrobasilar system. This circle is made because of formation of an anterior communicating artery that connects the left and right internal carotid systems between both anterior cerebral arteries, and the formation of posterior communicating arteries bilaterally that connect the carotid systems to the vertebrobasilar system between the middle cerebral arteries and the posterior cerebral arteries. Willis seemed to put it best after he made his anatomic discovery when he wrote “if by chance one or two should be stopt, there might easily be found another passage instead of them” [7]. The circle receives blood from 4 distinct sources that directly come from branches of the aorta with both internal carotid arteries being fed via the common carotid artery and both vertebral arteries being fed via the subclavian arteries. It should be noted that there is significant variance in the human population, with some studies suggesting that fewer than half of the population possess a complete circle of Willis.

### Control of CBF

There are several different mechanisms controlling CBF. The brain has adapted the ability to match CBF with metabolic rate through a variety of physiologic mechanisms, better known as flow-metabolism coupling. This coupling can occur regionally and is governed by several mechanisms that serve as the basis of how the brain is able to meet its unique demands. It is useful to separate these mechanisms into separate components with the understanding that they are still interrelated and can work either in concert or in opposition.

#### *Chemical/metabolic control*

*The neurovascular unit.* Current research indicates that the control of flow-metabolism coupling is primarily mediated through neurovascular units consisting of cerebral blood vessels, glial cells whose endfeet wrap around the vessels, and perivascular nerve fibers innervating the cerebral vessels and the glial cells (Box 1). The glial cells appear able to “sense” increased neuronal activity and release diffusible vasodilatory substances from the endfeet, thereby affecting CBF. More specifically, increased neuronal activity results in an increase in glial intracellular calcium, causing a release of ATP and glutamate [8]. ATP is involved in recruiting adjacent glial cells to respond as a unit via

**Box 1: Control of CBF**

*Control of CBF is centered around the neurovascular unit, which consists of the following:*

- Perivascular nerve fibers innervating glial cells and blood vessels
- Glial cells with endfeet that wrap around cerebral vessels
- Cerebral vessels

Diffusible substances are secreted by the nerve fibers and glial cells, which affect CBF and increase connectivity of the neurovascular unit. The vascular endothelium also contributes to control of CBF. Glutamate affects both metabolism and CBF.

propagation of calcium waves. One of the many effects of glutamate is to stimulate production of nitric oxide (NO), which is a cerebral vasodilator and thought to be involved in the regulation of flow-metabolism coupling. Glutamate also activates glial cells via metabotropic glutamate receptors with subsequent calcium signaling and arachadonic acid formation. Arachadonic acid, or its lipid derivatives, serve as vasodilatory or vasoconstrictor substances released by the glial endfeet surrounding the cerebral blood vessels. NO, K<sup>+</sup>, H<sup>+</sup>, brain metabolites, such as adenosine and lactate, and O<sub>2</sub> influence the direction of vascular tone [9]. K<sup>+</sup> and H<sup>+</sup> ions are produced by synaptic transmission, and increases in their concentrations stimulate cerebral vasodilation. Glutamate uptake by glial cells generates sodium waves that subsequently increase glucose uptake and metabolism. The increased lactate production from this metabolism is used by neurons as an energy substrate [8]. Glutamate increases connectivity of glial cells with neurons and capillaries (the neurovascular unit) as it affects both metabolism and CBF. The glial cells (astrocytes) play a vital role in local flow-metabolism coupling.

The perivascular nerve endings of cerebral vessels are also thought to be involved in flow-metabolism coupling via release of neurotransmitters, such as norepinephrine, acetylcholine, substance P, somatostatin, cholecystokinin, vasoactive intestinal peptide, calcitonin gene-related peptide, epoxyeicosatrienoic acids (EETs), and others [10]. EETs are arachidonic acid metabolites, which are potent cerebral vasodilators and are also produced by astrocytes and the vascular endothelium. The source of innervation for this cerebral microvasculature (or “intrinsic innervation”) is unknown in humans, but is thought to arise from the nucleus basalis, locus coeruleus, and raphe nucleus in animals [6]. The extrinsic innervation for flow-metabolism coupling is discussed later in this article.

*Carbon dioxide.* CO<sub>2</sub>, the main by-product of aerobic respiration, is a potent cerebral vasodilator and provides a very basic model of regulation by shifting blood toward more metabolically active tissues. A linear relationship exists between CBF and CO<sub>2</sub> tension throughout normal physiologic values of CO<sub>2</sub> (20–75 mm Hg), with an approximate 2% to 6% change in CBF per mm Hg CO<sub>2</sub> [6,11,12]. The effect of changes in CO<sub>2</sub> on CBF depends on the underlying

vascular tone and competing demands on CBF, as there is a point of maximal vasodilation (and vasoconstriction) beyond which the vessel cannot further alter its diameter. For example, profound hypotension can greatly diminish  $\text{CO}_2$  reactivity because the cerebral vessels are maximally vasodilated. Similarly, hypercapnia can impede autoregulation for the same reasons.

The mechanism of  $\text{CO}_2$  reactivity is related to changes in the pH of the extracellular fluid surrounding the brain. Low-pH solutions topically applied to the brain surface cause vasodilation, whereas high-pH solutions cause vasoconstriction.  $\text{CO}_2$ , unlike  $\text{H}^+$  ions, readily diffuses across the blood brain barrier and cerebral endothelium [6]. Consequently,  $\text{CO}_2$  changes have a relatively quick effect on CBF, but metabolic acidosis has little immediate effect on CBF. Because the cerebrospinal fluid actively eliminates bicarbonate with prolonged hyperventilation and normalizes its pH, effects on CBF typically revert to baseline within approximately 6 hours, even though the arterial partial pressure of  $\text{CO}_2$  ( $\text{PaCO}_2$ ) may remain low. Thus, acute correction of  $\text{PaCO}_2$  after prolonged hyperventilation can lead to pronounced increases in CBF, which may have deleterious effects on patients with raised intracranial pressure (ICP) [6].

The change in vascular tone caused by  $\text{CO}_2$  is partially mediated by NO, as inhibitors of NO synthase will diminish the vasodilatory response to hypercapnia. NO modulation of cerebrovascular tone occurs through combined activation of ATP-sensitive and calcium-activated potassium channels in animal studies [13]. Indomethacin, an inhibitor of cyclooxygenase and prostaglandin formation, will partially inhibit the vasodilatory response to increasing  $\text{CO}_2$  concentrations in humans. Experimental studies in animals show that application of prostaglandin E2 (PGE2) after indomethacin administration will restore the cerebrovascular reactivity to baseline, as PGE2 is thought to stimulate production of endothelial NO synthase [14]. Studying these mechanisms at this level of complexity has been difficult, as they have been shown to differ depending on the animal studied.

*PaO<sub>2</sub>, arterial O<sub>2</sub> content, and rheology.* Oxygen ( $\text{O}_2$ ), also exhibits regulatory capacity, as CBF increases when  $\text{O}_2$  levels start to drop below 60 mm Hg in humans [15]. Early studies in normocapnic rats showed that CBF significantly increased at  $\text{PaO}_2$  levels as high as 85 mm Hg, but that marked increases up to 500% of baseline CBF occurred within 1 to 2 minutes at a  $\text{PaO}_2$  of 25 mm Hg [16]. NO synthase inhibitors given to humans partially blocked this response, suggesting that it is partially regulated by NO [17]. Chemoreceptors in the periphery and neuraxis, and hyperpolarization of vascular smooth muscle via ATP-dependent potassium channels, may also contribute to hypoxia-induced vasodilation [6].

Hypoxemia increases CBF to a greater degree than hemodilution, at the same arterial  $\text{O}_2$  content ( $\text{CaO}_2$ ) [18]. Hemodilution has been well documented in animal and human studies to increase CBF and raise the lower limit of autoregulation (LLA) [18,19]. Both the decreased viscosity with improved rheology, and reduced  $\text{CaO}_2$  are responsible for the increase in CBF with hemodilution, based on studies in animals [20]. Although NO is involved in

cerebral vasodilation with reduced  $\text{CaO}_2$  from hypoxemia, it does not appear to contribute to increased CBF with reduced viscosity [18].

*Temperature.* Temperature-induced changes in CBF are a reflection of changes in the cerebral metabolic rate of  $\text{O}_2$  ( $\text{CMRO}_2$ ). As a patient's temperature drops, there is a corresponding drop in  $\text{CMRO}_2$  from both basal and functional metabolism, estimated to be approximately 7% for each  $1^\circ\text{C}$  between  $37^\circ\text{C}$  and  $27^\circ\text{C}$  [5]. Isoelectric electroencephalogram (EEG) occurs at temperatures of 18 to  $20^\circ\text{C}$ . Pharmacologic suppression, which only affects functional metabolism, is synergistic with hypothermic suppression until EEG silence. At that point,  $\text{CMRO}_2$  can be reduced only by further drops in temperature [6]. Numerous smaller studies have documented the improved survival and outcomes using mild to moderate hypothermia in traumatic brain injury (TBI) and other pathologic states, and the deleterious effects of hyperthermia. Larger randomized controlled trials of hypothermia in traumatic brain injury and during clipping of cerebral aneurysms have not demonstrated a beneficial effect for all patients [21,22]. Hypothermia seems to be neuroprotective during vulnerable periods of cerebral ischemia in successfully resuscitated cardiac arrest patients [23].

One of the few studies in humans with hyperthermia and controlled ventilation showed that increasing temperatures to  $41.8^\circ\text{C}$  with propofol anesthesia decreased  $\text{O}_2$  extraction by 1.6-fold and increased middle cerebral artery blood flow velocity by 1.5-fold, with partial impairment of autoregulation [24]. It was suggested that the decreased  $\text{O}_2$  extraction was a consequence of a similar increase in CBF, and that  $\text{CMRO}_2$  may actually have been stable. In animals,  $\text{CMRO}_2$  increases up to  $42^\circ\text{C}$ , and then falls to baseline values or lower at  $43^\circ\text{C}$ , presumably because of metabolic dysfunction and impending cell death. In contrast to anesthetized subjects with controlled ventilation, research in awake, spontaneously ventilating humans and animals revealed that CBF decreased with hyperthermia, largely because of an associated increase in ventilation and reduced  $\text{PaCO}_2$  (Box 2) [25].

#### *Neurogenic control*

In addition to the extensive network of perivascular nerve endings associated with the neurovascular unit discussed previously, neurogenic control of CBF

### **Box 2: Physiologic parameters affecting CBF**

- Carbon dioxide
- $\text{PaO}_2$ /arterial  $\text{O}_2$  content
- Temperature
- Viscosity/rheology
- Sympathetic/Parasympathetic stimulation
- Myogenic control/autoregulation

Anemia increases CBF by its effect on viscosity/rheology and arterial  $\text{O}_2$  content.

is also mediated via sympathetic (adrenergic), parasympathetic (cholinergic), and sensory neurons that innervate vessels outside of the brain tissue, sometimes referred to as the “extrinsic innervation” [26]. The extrinsic system of neurogenic control of CBF is thought to exert its most pronounced effect on the large cerebral arteries. The sympathetic nervous system associated with the superior cervical ganglion influences vascular tone to maintain blood pressure below the upper limit of autoregulation [27]. Sympathetic stimulation can alter the autoregulatory curve and push it to the right, possibly providing a protective effect during periods of acute hypertension [28,29]. Intense stimulation of the sympathetic nervous system has been shown to cause a significant decrease in CBF, whereas local blockade of the sympathetic nervous system can provide a significant increase in CBF [28,30]. In a study using baboons, in which autoregulation was intact to 35% of baseline blood pressure when hypotension was drug induced, autoregulation was intact to only 65% of baseline blood pressure when hypotension was induced by controlled hemorrhage, suggesting that activation of the sympathetic nervous system during hemorrhage contributed to a higher LLA [31]. The role of lower cardiac output in this scenario was not elucidated, but numerous studies suggest that acute hypovolemia may narrow the range of autoregulatory capacity and raise the LLA via activation of the sympathetic nervous system.

The parasympathetic nervous system is associated with the sphenopalatine and otic ganglia and is more functional during disease or injury states, such as Alzheimer disease, with decreased cholinergic innervation [26]. However, both the cholinergic and adrenergic nerves are thought to be involved in exercise-induced changes in CBF and metabolism. Sensory neurons work through the trigeminal ganglion and are important for pain sensation [26]. The discovery of trigeminal neurons in mediating migraine pain via the vasodilator, calcitonin gene-related peptide (CGRP), has led to the development of triptan drugs that inhibit release of CGRP presynaptically and cause cerebral vasoconstriction.


#### *Myogenic control/autoregulation*

In the healthy resting human, CBF is kept constant over a wide range of cerebral perfusion pressures (CPP) via cerebral vasoconstriction and vasodilation. This concept is known as *autoregulation* and seems to exist in humans, as well as in other vertebrates. It is a process whereby changes in CPP cause changes in cerebrovascular resistance to maintain a constant CBF. Cerebral autoregulation protects the brain from hypoxia at low CPP, and against hyperemia, capillary leakage, and vasogenic edema at high CPP. As the cerebral vessels have limits to how wide they can dilate and how small they can constrict, there are limits to this autoregulatory capacity, and if exceeded, blood flow becomes *pressure passive* and is subject to changes in systemic blood pressure. The LLA is the CPP when there is maximal cerebral vasodilation. The upper limit of autoregulation (ULA) is the CPP where there is maximal cerebral vasoconstriction (Fig. 2). Autoregulatory ranges vary greatly among individuals and within an individual depending on other influences on vascular tone (eg, PaCO<sub>2</sub>, hemoglobin concentration, anesthetic agents). Older



Factors Decreasing Cerebral Blood Flow

Factors Increasing Cerebral Blood Flow

	CBF	CMRO <sub>2</sub>			CBF	CMRO <sub>2</sub>
<b>Vasoactive Drugs</b>				<b>Vasoactive Drugs</b>		
<i>Hypotensive Agents</i>				<i>Hypotensive Agents</i>		
β Blockers	↓/0	↓/0		Calcium Channel Blockers	↑/0	↑/0
α <sub>2</sub> Agonist	↓	↓/0		Nitric Oxide Donors	↓/0/↑	↓/0
Nitric Oxide Donors	↓/0/↑	↓/0		<i>Vasopressors/Inotropes/Chronotropes</i>		
<i>Vasopressors/Inotropes/Chronotropes</i>				<i>Vasopressors/Inotropes/Chronotropes</i>		
α <sub>1</sub> Agonist	↓/0	0		β Agonist	↑	↑
Dopamine (high dose)	↓	0		β Agonist (BBB open)	↑↑↑	↑↑↑
Norepinephrine	↓/0	0/↑		Dopamine (low dose)	↑↑	0
Vasopressin	0	0		Norepinephrine (BBB open)	↑	↑
<b>Anesthetic Drugs</b>				Epinephrine	↑	↑
<i>Intravenous Agents</i>				Epinephrine (BBB open)	↑↑↑	↑↑↑
Barbiturates	↓↓	↓↓		<b>Anesthetic Drugs</b>		
Etomidate	↓↓	↓↓		<i>Intravenous Agents</i>		
Propofol	↓↓	↓↓		Ketamine	↑↑	0/↑
Benzodiazepines	↓	↓		Ketamine (w/ other anesthetics)	↓/0	↓/0
Synthetic Opioids	0	↓/0		<i>Volatile Agents</i>		
<i>Volatile Agents</i>				<i>Volatile Agents</i>		
Xenon	↓(Gray)/↑(White)	↓		Nitrous Oxide	↑↑	0/↑
Isoflurane (0.5 - 1 MAC)	0	↓↓		Isoflurane (2 MAC)	↑↑	↓↓↓
Sevoflurane (0.5 - 1 MAC)	↓/0	↓/↓↓	Sevoflurane (2 MAC)	↑↑	↓/↓↓↓	
Desflurane (0.5-1 MAC)	↓	↓↓	Desflurane (2 MAC)	↑↑	↓↓	
<b>Physiologic Parameters</b>			<b>Physiologic Parameters</b>			
PaCO <sub>2</sub> < 40 mm Hg	↓↓	0	Temperature > 37° C	↑	↑	
PaO <sub>2</sub> > 300 mm Hg	0/↓	0	PaO <sub>2</sub> < 60 mm Hg	↑↑	0	
Temperature < 37° C	↓	↓	PaCO <sub>2</sub> > 40 mm Hg	↑↑	0	
Viscosity (↑)	↓	0	Anemia	↑	0	

\*The above parameters assume that blood pressure is within the normal autoregulatory window

\*\*It should be noted these are isolated effects, and that the effect of simultaneous factors may be additive or they may diminish or completely abolish an effect on CBF.

Fig. 2. Pharmacology of CBF. Drugs and physiologic parameters that affect CBF and autoregulation. \*, \*\*

texts have cited limits of autoregulation in healthy patients under normal physiologic conditions at a CPP of 50 mm Hg (approximate MAP of 60 mm Hg) at the LLA and 140 mm Hg (approximate MAP 150 mm Hg) at the ULA. Reinterpreting these older studies for clinical translation has led to a revision of the LLA to a MAP of 70 mm Hg in healthy adults, (see section Lower Limit of Autoregulation that follows) [6].

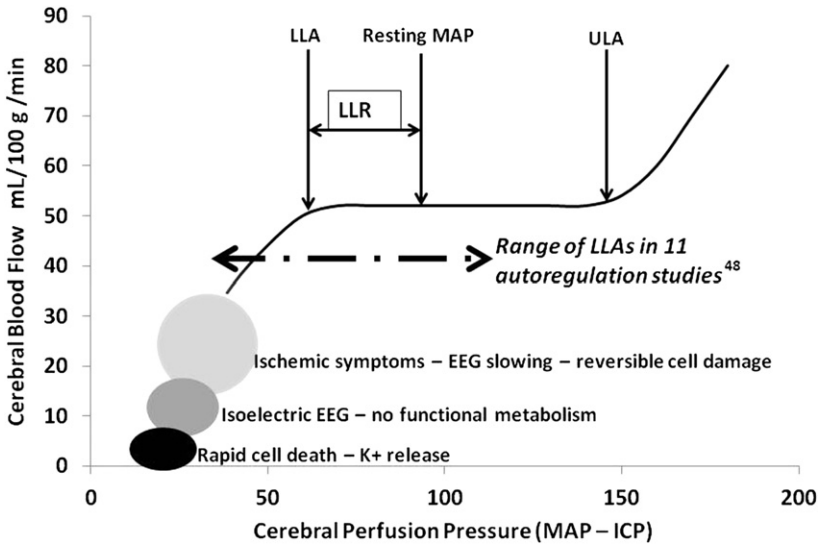
The process by which autoregulation occurs is unknown but is relatively slow, taking approximately 2 or more minutes for CBF to adjust to baseline values after an acute drop in MAP. Autonomic innervations of the central nervous system and NO may have contributory roles to the mechanism of autoregulation [32]. Increases in transmural pressure are known to induce an endothelium-derived factor that induces smooth muscle depolarization. This depolarization causes a conformational change in the actin-myosin complex of the smooth muscle cells within seconds and results in vasoconstriction. Recent research has detected mechanoreceptors within the smooth muscle cells themselves. Depolarization of these nonselective mechanosensitive ion channels results in an influx of  $Ca^{++}$  and smooth muscle constriction. Increased flow velocity exerts increased shear stress and can cause vasoconstriction independent of transmural pressure [26].

## LOWER LIMIT OF AUTOREGULATION

Historical interpretation of the LLA for cerebral ischemia

The LLA commonly refers to the MAP (or CPP) on the CBF versus MAP (or CPP) autoregulatory curve in which the cerebral blood vessels are maximally dilated, and in which CBF becomes pressure passive if MAP (or CPP) is further lowered (Fig. 3). In the past, the LLA has erroneously been thought of as an absolute number for all patients. Instead, it varies among and within individuals, and depends on the state of multiple other physiologic parameters and pharmacologic agents that may influence cerebral sympathetic tone and limit the extent of autoregulatory capacity. It has received great attention because of the implications for blood pressure management under anesthesia in normal and diseased states. Because intact neurologic function cannot be assessed, even with today's best technology, under moderate to deep sedation or general anesthesia, anesthesiologists have always been interested in defining the lower limit of "safe" blood pressure whereby adequate cerebral perfusion is ensured if blood pressure is maintained above this lower limit. Although one could always keep the MAP, no lower than baseline values to ensure adequate CPP, this practice may have the unintended consequences of increased bleeding in some procedures, and could promote harmful side effects of increased blood transfusion, or other fluid or vasoactive medication administration.

Blood pressures lower than a predetermined LLA do not necessarily result in immediate and irreparable brain damage. The duration and extent of the decrease in CPP below the LLA are important, with less dramatic decreases being tolerated for longer duration. Awake healthy subjects developed symptoms of cerebral ischemia at CBF of 24 to 38 mL/100 g/min [33]. Although most studies



**Fig. 3.** Autoregulation curve. The cerebral vasculature maintains a stable CBF over a wide range of CPP (typically CPP 60–140 or MAP 70–150 mm Hg). The lower end of the autoregulatory range is the LLA, where there is maximal cerebral vasodilation. The ULA is when there is maximal cerebral vasoconstriction. The area between the baseline MAP and the LLA is known as the lower limit reserve (LLR). Symptoms and signs (EEG slowing) of cerebral ischemia occur at approximately 24 to 38 mL/100 g/min CBF and neuronal damage is still reversible. Functional metabolism ceases between 15 and 6 mL/100 g/min with an isoelectric EEG, and neurons will eventually die. Destruction of cell integrity occurs at approximately CBF <6 mL/100 g/min and rapid cell death ensues. The lower the CBF at ischemic levels, the shorter the duration allowable before irreversible neuronal damage. The dashed-dotted line represents the range of LLAs from 11 autoregulation studies in awake humans. (Data from Drummond JC. The lower limit of autoregulation: time to revise our thinking? *Anesthesiology* 1997;86(6):1431–3.)

in anesthetized humans and primates report that EEG or evoked potential changes do not occur until CBF declines to approximately 20 mL/100 g/min [34,35], preexisting neuronal injury may raise that threshold to as high as 39 mL/100 g/min [36]. Other factors that may reduce O<sub>2</sub> delivery, such as anemia or low PaO<sub>2</sub>, or increase in CMRO<sub>2</sub>, may raise the CBF threshold in which ischemia develops. In anesthetized primates at a CBF of 15 mL/100 g/min, functional metabolism ceases as demonstrated by an isoelectric EEG, and below 6 mL/100 g/min, cell integrity is potentially irreversibly threatened [37]. Although irreversible brain damage will not occur if a patient's MAP briefly drops below his or her LLA, keeping the MAP above the LLA should provide some margin for error, assuming other physiologic conditions are normal.

Determination of the LLA for a population is problematic. As noted previously, careful reconsideration of the early studies on autoregulation has resulted in a revised recommendation to maintain MAP at 70 mm Hg or higher in major anesthesia texts [6]. This number was derived from the mean LLA of the studies

examined by Drummond in his brief review [38]. It has always been standard practice in articles to list the mean values with the standard deviations (SDs). As an unintended consequence of this practice, the focus of the data lies with the mean values, which when used as a cutoff point will not encompass a large proportion of the subjects and their variability. Using the mean value plus 1 SD should encompass 68.2% of the values in a normally distributed bell-shaped curve; the mean value plus 2 SDs, 95.9%; and the mean value plus 3 SDs, 99.7%. Drummond attempted to rectify this misconstrued extrapolation of autoregulation studies by denoting the ranges of the LLAs within multiple autoregulation studies in awake patients, instead of using only the mean LLAs (Box 3) [38]. The range of mean LLAs was 57 to 91 mm Hg, with 5 of these 7 studies obtaining a mean LLA of 70 mm Hg or higher. Moreover, if the ranges of LLAs within studies were examined, every study had the upper range of LLA above 70 mm Hg, and 4 of the 7 studies had the upper range of LLA at 100 mm Hg or higher. Notably, these autoregulation studies were performed in awake individuals, and presumably CMRO<sub>2</sub> will be reduced in patients under general anesthesia. Further, many of our anesthetic agents are cerebral vasodilators and may provide another “buffer” to preventing inadequate cerebral perfusion; yet, unfavorable physiologic conditions, which lower CBF or raise the LLA, such as hypocapnia and anemia, may also be present, which may decrease the margin for “error” or harm on lowering the blood pressure.

#### Defining LLA as a percentage reduction of MAP below baseline

Drummond [38] advocated revisiting what we considered a “safe” LLA by using percentage reductions from baseline resting MAPs as a way to address the extreme interpatient variability in absolute LLA values. This practice is standard management in neuroanesthesia. Strandgaard [39] demonstrated in 1976 that awake normotensive subjects’ mean LLA was approximately 74% ± 12% of baseline, or a 26% ± 12% reduction from baseline MAP. In patients with uncontrolled hypertension, the LLA was 79% ± 10% of baseline MAP, or a 21% ± 10% reduction from baseline MAP (see Box 3). Ischemic symptoms developed in both groups at approximately 55% of baseline MAP, or a 45% reduction.

These percent reductions for LLAs are consistent with the recent nested case-control study of Bijker and colleagues [3], who studied more than 48,000 patients retrospectively and identified 42 patients with an ischemic stroke within 10 days of surgery. These stroke cases were matched by age and type of surgery to 252 control patients and adjusted for potential confounding factors. They found a statistically significant association with the duration that the intraoperative MAP was

#### **Box 3: The lower limit of autoregulation**

After reexamination of multiple autoregulation studies, the LLA has been shifted upward to 70 mm Hg in major texts.

This LLA will not encompass all patients, as there is tremendous interindividual variability in the LLA. Using a percent reduction from the baseline blood pressure as a method to estimate the LLA may accommodate this variability.

decreased more than 30% from baseline and the occurrence of an ischemic stroke within 10 days after surgery [3]; however, half of these 42 patients with stroke had carotid endarterectomy surgery and 6 had surgery for tumors of the head and neck. Only 13 cases of stroke occurred after general surgical procedures.

In sharp contrast to the previously mentioned work on the LLA are the multiple studies from Sharrock and colleagues [40] demonstrating that MAPs of 50 to 55 mm Hg are well tolerated by patients undergoing hip surgery in the lateral decubitus position using epidural local anesthetic infusions and intravenous epinephrine infusions. Early studies by this group without the epinephrine infusions had a “number of patients” with symptoms of cerebral ischemia, such as yawning, nausea, or drowsiness associated with cardiac indices lower than 1.8 L/min/m<sup>2</sup>. When the low-dose epinephrine infusions were added, cardiac output was increased with a similar MAP, and the symptoms of cerebral ischemia abated. These studies imply that cardiac output either directly or indirectly affects CBF, as CPP reportedly stayed constant.

### **EFFECT OF SIMULTANEOUS FACTORS ON CBF: CLINICAL SCENARIOS**

Patient condition and anesthetic management impose multiple simultaneous factors that can affect CBF, CMRO<sub>2</sub>, cerebrovascular reactivity, and autoregulation. Consideration of the underlying vascular tone and the severity of the physiologic condition and dosage of anesthetic should be made when assessing adequacy of cerebral perfusion (Box 4). This section provides several examples of the effects of multiple simultaneous factors on CBF.

#### **Effect of carbon dioxide on autoregulation in awake and anesthetized subjects**

Baseline autoregulation studies are typically performed at PaCO<sub>2</sub> of approximately 40 mm Hg, and they demonstrate the range of blood pressure over which an individual can alter their cerebrovascular tone to maintain a constant CBF. Because CO<sub>2</sub> also alters the vascular tone, at higher PaCO<sub>2</sub> levels it will impose underlying vasodilation and alter the ability of the vasculature to further dilate with low MAP. Aaslid and colleagues [41] used transcranial Doppler and insonation of the middle cerebral artery in awake humans to demonstrate that the fastest rate of regulation of CBF velocity using thigh cuff deflation occurred with hypocapnia (PaCO<sub>2</sub> of 22.2 mm Hg, highest tone) and the slowest with hypercapnia (PaCO<sub>2</sub> of 46.9 mm Hg, lowest tone) [41]. At even higher PaCO<sub>2</sub> levels (50–61 mm Hg) under remifentanyl plus sevoflurane anesthesia (1.0%–1.1% end tidal concentration), McCulloch and colleagues [42], using transcranial Doppler, demonstrated that autoregulation

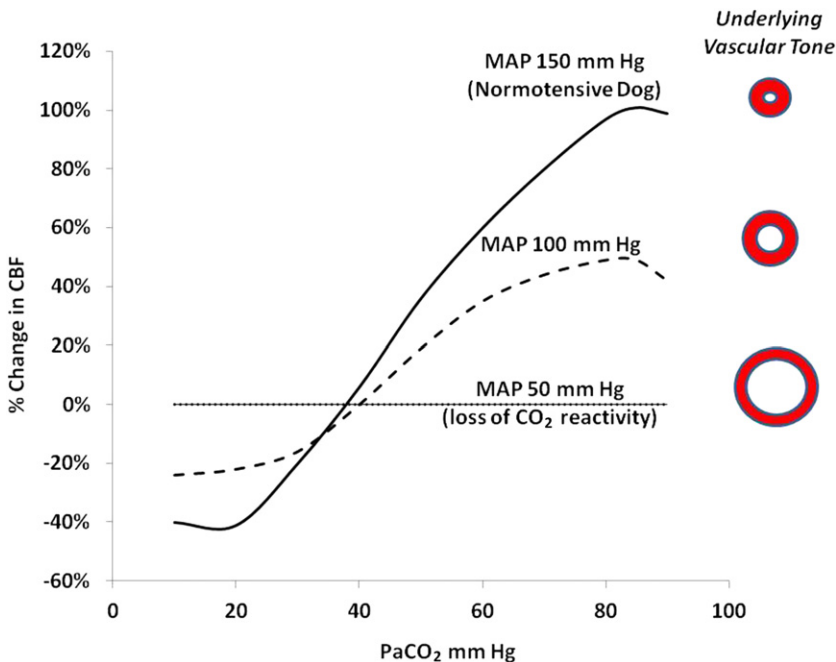
#### **Box 4: Underlying vascular tone affects response on CBF**

The effect of any drug or change in physiology on the CBF will depend on the underlying cerebrovascular tone.

was significantly impaired in healthy subjects. For propofol (140  $\mu\text{g}/\text{kg}/\text{min}$ ) anesthesia, the level at which significant impairment of autoregulation occurred was slightly higher,  $\text{PaCO}_2$  of 54 to 66 mm Hg. These findings are consistent with the concept of underlying vascular tone, in this case vasodilation, affecting the ability of the cerebral vessels to vasoconstrict. Moreover, McCulloch and colleagues [42] found that  $\text{CO}_2$  reactivity was greater at an MAP of 100 mm Hg than at 80 mm Hg, for both sevoflurane and propofol, presumably because the underlying vasoconstriction at higher MAP allowed the  $\text{CO}_2$  to exert a greater effect on vasodilation. At lower MAP with hypercapnia, the ability to vasodilate fully will be diminished compared with isocapnic conditions, and the LLA will be shifted to the right, or increased.

#### Effect of hypotension on carbon dioxide reactivity

Harper and Glass [43] demonstrated the effect of varying levels of hypotension on  $\text{CO}_2$  reactivity in dogs anesthetized with nitrous oxide and oxygen and intermittent small doses of thiopentone (Fig. 4). With severe hypotension

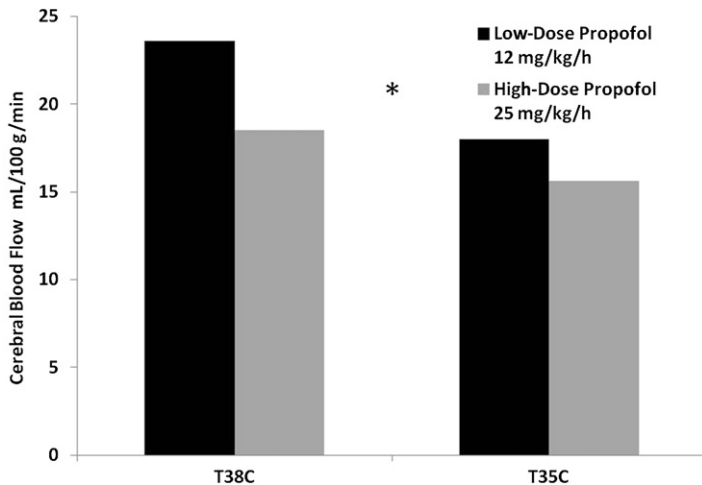


**Fig. 4.** The effect of hypotension on  $\text{CO}_2$  reactivity in dogs. In normothermic ( $T 38^\circ\text{C}$ ), normotensive (MAP 150 mm Hg) dogs, the effect of  $\text{CO}_2$  on CBF was almost linear between  $\text{PaCO}_2$  20 to 80 mm Hg. The slope of the  $\text{CO}_2$  reactivity curve decreases with moderate hypotension (MAP 100 mm Hg).  $\text{CO}_2$  reactivity is abolished with severe hypotension at a MAP of 50 mm Hg because of the maximal underlying cerebrovascular dilation caused by the hypotension. (Adapted from Harper AM, Glass HI. Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures. *J Neurol Neurosurg Psychiatry* 1965;28:449.)

(via exsanguination) at a MAP of 50 mm Hg (normotensive MAP 150 mm Hg), CO<sub>2</sub> reactivity is abolished in the dog. The cerebral vasculature is presumably maximally vasodilated and cannot respond further to increasing PaCO<sub>2</sub>. The clinical implication is that during severe hypotension, raising the PaCO<sub>2</sub> level will not necessarily increase CBF.

#### Effect of temperature and propofol dose on CBF and CMRO<sub>2</sub>

Hypothermia (35°C) and increasing propofol doses in monkeys have additive effects on CMRO<sub>2</sub> and CBF reduction (Fig. 5) [44]. No significant interaction was found between temperature and propofol dose. These findings are consistent with other data suggesting that initial reductions in temperature exert a greater effect on basal metabolism, whereas anesthetic drugs exert their effect on functional metabolism. These additive reductions in CMRO<sub>2</sub> and CBF, with good flow-metabolism coupling, may be clinically useful in situations with elevated ICP.



**Fig. 5.** The additive effects of mild hypothermia and propofol on CBF in dogs. Both propofol and mild hypothermia (35°C) decrease CBF and CMRO<sub>2</sub> with good flow-metabolism coupling in normothermic, isocapnic dogs. The effects are additive (no interaction effect), as mild hypothermia is thought to predominately affect basal metabolism and propofol affects functional metabolism. \**P* < .05 comparing normothermic with hypothermic propofol groups. (Adapted from Ouchi T, Ochiai R, Takeda J, et al. Combined effects of propofol and mild hypothermia on cerebral metabolism and blood flow in rhesus monkey: a positron emission tomography study. *J Anesth* 2006;20:208.)

#### Effect of anemia on CBF and autoregulation

Anemia increases CBF by 2 mechanisms, as discussed previously: reduced CaO<sub>2</sub> and reduced viscosity. Because the cerebral vessels are dilated with anemia, the LLA is shifted to the right. The ability of the cerebral vessels to

dilate is limited because of the preexisting dilation caused by the anemia. Maruyama and colleagues [45] demonstrated that increasing severity of anemia (hematocrit values of 40%, 20%, and 5%) in dogs progressively raises the CBF at a MAP of 100 mm Hg, such that CBF with a hematocrit of 20% is 1.7-fold that of baseline hematocrit of 40%, and CBF with a hematocrit of 5% is 3.0-fold higher than baseline. Additionally, the range of autoregulatory capacity is progressively diminished with increasing severity of anemia and the LLA is shifted to the right. The first point of significant CBF reduction in the studies by Maruyama and colleagues [45], tested at 20-mm Hg increments from MAP 100 to MAP 40 mm Hg, was 40 mm Hg with hematocrit 40%, 60 mm Hg with hematocrit 20%, and 80 mm Hg with hematocrit 5%. These findings may have significant clinical implications for patients in the intensive care unit with stenotic neurovascular lesions or acute neurologic injuries with or without elevated ICP, where current practice is to avoid transfusion and to tolerate very low hematocrits.

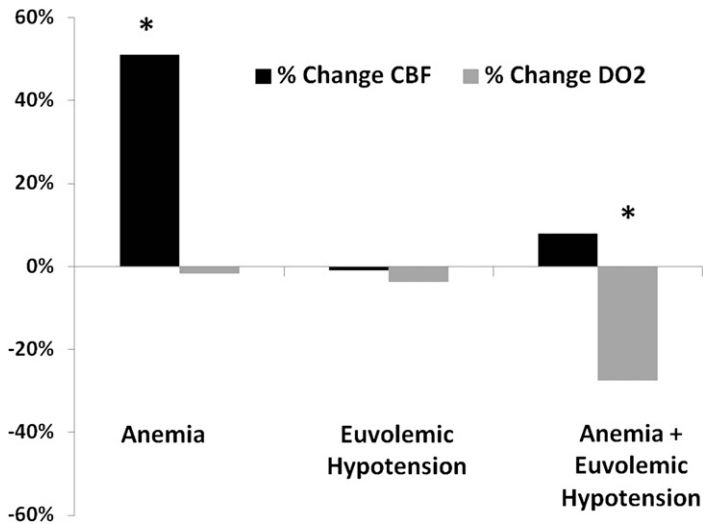
#### Effect of anemia and hypotension on CBF and O<sub>2</sub> delivery

During major surgical procedures with large and rapid blood loss, anemia and hypotension may coexist. As noted previously, anemia will superimpose underlying vasodilation on the cerebral vasculature and increase CBF to provide stable O<sub>2</sub> delivery (DO<sub>2</sub>). The ability of the vessels to further dilate with hypotension to maintain a constant CBF and DO<sub>2</sub> will be diminished. Previous experiments from our institution using microspheres to measure CBF in normocapnic, normothermic pigs anesthetized with isoflurane demonstrated this concept (Fig. 6) [46]. One group of pigs was made hypotensive (euvoletic) with labetalol (MAP from 73 mm Hg to 52 mm Hg) and maintained stable CBF and DO<sub>2</sub>. A separate group of normotensive pigs was made anemic (hematocrit from 27% to 17% with shed blood and crystalloid replacement to maintain euvolemia) and increased CBF by approximately 50% from baseline, resulting in stable DO<sub>2</sub>. When the conditions of both euvoletic hypotension and anemia were combined, however, CBF increased by only 8%, resulting in an approximate 28% decrease in DO<sub>2</sub>. Because both anemia and hypotension require cerebral vasodilation to maintain a stable DO<sub>2</sub>, the combined effects overwhelmed the capacity of the cerebral vasculature to vasodilate sufficiently, thereby decreasing DO<sub>2</sub>. Clinical implications are that patients with severe anemia may not be able to compensate for very low blood pressure to maintain stable DO<sub>2</sub> to the brain. These findings have implications for limiting the extremes of anemia and hypotension when attempting to minimize blood loss and/or avoid transfusion.

### **ANESTHETIC DRUGS AND VASOACTIVE AGENTS**

This section discusses pharmacologic agents available to clinicians to help optimize cerebral perfusion, CMRO<sub>2</sub>, and brain relaxation in everyday practice. Because many of the vasoactive drugs are used to lower blood pressure, results may be affected when MAP falls outside of the LLA.





**Fig. 6.** The effects of anemia and hypotension on CBF and  $O_2$  delivery. In normocapnic, normothermic pigs anesthetized with isoflurane, anemia resulted in a dramatic increase in CBF, which kept the  $O_2$  delivery ( $DO_2$ ) to the brain stable. Similarly, severe hypotension to a MAP of approximately 50 mm Hg, resulted in stable CBF and stable  $DO_2$ . When both conditions were combined, the CBF increased only 8%, resulting in a 28% drop in  $DO_2$  (\* $P < .05$ ). The degree of vasodilation by the cerebral vasculature is limited and may not provide stable  $DO_2$  under extreme physiologic conditions. (Adapted from Lee LA, Deem S, Glenn RW, et al. Effects of anemia and hypotension on porcine optic nerve blood flow and oxygen delivery. *Anesthesiology* 2008;108(5):864.)

### Calcium channel blockers

In general, calcium channel blockers (CCBs) exert their effect by inhibiting the influx of intracellular calcium via voltage-gated calcium channels on the membrane of the sarcoplasmic reticulum. This inhibition results in less intracellular calcium available, leading to a weaker contraction. CCBs can be divided into 2 categories based on the presence or absence of a dihydropyridine group. Dihydropyridine drugs include amlodipine, clevidipine, felodipine, nicardipine, nifedipine, and nimodipine, whereas nondihydropyridine drugs include diltiazem and verapamil. Calcium channels are morphologically distinct in different types of tissue, including the brain, myocardium, vascular smooth muscle, and the atrioventricular (AV) conduction system. Thus, there is intraclass variability with regard to binding selectivity of each calcium channel blocker [47].

Although most of the dihydropyridines exhibit activity in all vascular smooth muscle, decreasing cardiac afterload and providing a generalized hypotensive effect, nimodipine shows relative selectivity to the cerebral arteries at clinical doses [48]. It has been shown to provide clinical effectiveness in treating vasospasm following subarachnoid hemorrhage in humans [49]. Accordingly, a hypotensive effect is less common with nimodipine, and there is evidence

that nimodipine slightly increases CBF and cerebral metabolic rate [50]. The other dihydropyridines tend to act mainly in the periphery and have no specific effect on CBF and cerebral metabolic rate provided mean arterial pressure is kept constant [51]. Nicardipine is one of the most commonly used intravenous CCBs in the neurosurgical patient because of its ease of titration. Clevidipine, approved by the Food and Drug Administration in 2008, is degraded by plasma esterases with a half-life of approximately 1 minute, compared with nicardipine with a half-life of 4 to 5 hours [52]. Nondihydropyridine CCBs generally act on the myocardium and the AV conduction system, but also have a small cerebral vasodilatory effect with increases in CBF, and thus potential to increase ICP.

CCBs may also block the accumulation of intracellular calcium, which is involved in intracellular signaling processes in neuronal injury. Unfortunately, clinical trials have not shown benefit with CCBs, and some experts believe that more downstream pathways should be targeted [53].

#### NO donors

NO donors represent another class of drugs that can be therapeutically useful to treat acute episodes of hypertension, but these drugs have their own side effects that must be considered. All NO donors release NO in the vasculature, which then activates intracellular guanylate cyclase and increases intracellular production of cyclic guanosine monophosphate (GMP). Cyclic GMP, in turn, activates protein kinase G that inactivates myosin light chains causing smooth muscle relaxation and resultant vasodilation. The cerebral vasodilation caused by the NO donor drugs can result in significant increases in ICP.

Nitroprusside comes as a salt (sodium nitroprusside [SNP]) and for each molecule of NO that is released, there remains a potential 5 cyanide ions that can also be released and cause toxicity within 2 to 3 hours [54]. Studies on cerebral hemodynamics with SNP show variable results depending on study conditions but, for the most part, it has little effect on CBF in anesthetized neurosurgical patients [55]. Larger doses have been associated with loss of autoregulation, decreased CBF, and increased ICP. Recognizing the aforementioned concerns, the exceptionally short half-life of 3 to 4 minutes makes SNP useful when used on a short-term basis for acute control of blood pressure.

Nitroglycerin preferentially works as a venodilator and only affects arterial tone at higher clinical doses in a somewhat unpredictable way. Nitroglycerin has been shown to vasodilate the major cerebral vessels and to cause a decrease in CBF velocity but no change in CBF [56]. Other studies have shown a profound increase in ICP and decrease in CPP with nitroglycerin [57]. Hydralazine, also an NO donor, has its effects mainly at the level of the arterioles with vasodilation. It has similar effects in the brain and the periphery, causing cerebral vasodilation, increased CBF, and increased ICP.

Adenosine has direct vasodilating effects in the brain, and intravenous infusion will cause vasodilation of the major cerebral vessels, but no change in CBF [58].

It causes transient heart block (and subsequent cardiac arrest in higher doses) and is used intraoperatively to transiently stop CBF to facilitate clipping of cerebral aneurysms.

### Sympatholytics and sympathomimetics

Whether or not drugs that stimulate or antagonize the body's intrinsic sympathetic nerve system affect CBF and autoregulation depends on the starting blood pressure, the clinical dose of the drug given, whether autoregulation is already impaired, and if the blood brain barrier is open or closed [6]. As a rule, sympatholytics and sympathomimetics do not have any major direct effects on CBF outside of their effects on systemic blood pressure, with a few exceptions that will be discussed in the following paragraphs.

Alpha-1 agonists are frequently used in patients with shock and are commonly administered to patients undergoing anesthesia. Although there is potential concern with alpha agonists causing further vasoconstriction leading to decreased CBF, there is not sufficient evidence to suggest this is the case in humans. Intracarotid infusion of norepinephrine has been shown to have no effect on CBF [6], and phenylephrine has been shown not to decrease CBF intraoperatively while patients are on cardiopulmonary bypass [59]. At clinical doses, norepinephrine does carry some beta activity, which gives it different characteristics with respect to cerebral perfusion than phenylephrine.

Alpha-2 agonists used in clinical practice are clonidine and dexmedetomidine, the latter of which shows much higher specificity to the alpha-2 adrenoreceptor. Dexmedetomidine has been shown to decrease  $CMRO_2$  and CBF [60,61].

Beta agonists in lower concentrations have few direct effects on the cerebral vasculature, but in higher doses can increase  $CMRO_2$  and CBF [62]. This effect seems to be pronounced when there is a compromise in the blood brain barrier, suggesting a direct effect of beta agonists on cerebral metabolic rate [63].

It has become clear that beta-blockers in clinical use today can be thought of in 2 categories: beta antagonists and beta inverse agonists [64]. Beta agonists cause an increase in  $CMRO_2$ , and thus CBF. Beta-blockers demonstrate either no effect or a reduction in CBF [6]. Esmolol, a fast-acting beta blocker with a short half-life, has been shown to decrease anesthetic requirements, suggesting it may also decrease  $CMRO_2$  and demonstrate some inverse agonist activity in the brain [65,66].

Dopamine has also been studied extensively and used mainly as a vasopressor in certain disease states, mainly to increase blood pressure in the intensive care setting in septic shock and certain types of cerebral ischemia. The medical literature currently suggests dopamine works well to increase CBF in other populations, such as preterm infants who are hypotensive [67] and patients with TBI [68], although it is not the agent of choice. In general, it has not demonstrated any direct effects on CBF, but does cause an increase in the  $CMRO_2$  of the choroid plexus and basal ganglia [69,70].

Vasopressin, although not classically considered a part of the sympathetic nervous system, has mainly been studied in situations of cardiac arrest and

very little has been contributed on lower-dose vasopressin therapy and its effect on CBF.

#### Intravenous anesthetic agents

Most intravenous anesthetic agents, with the exception of ketamine, cause a reduction in  $CMRO_2$  and CBF, exhibiting flow-metabolism coupling. Propofol, barbiturates, and etomidate all directly cause a reduction in  $CMRO_2$  by agonizing  $\gamma$ -aminobutyric acid (GABA) sites, with a resultant decrease in CBF and ICP. Ketamine, an N-methyl-D-aspartate receptor antagonist, increases  $CMRO_2$ , CBF, and ICP in awake subjects [71]. When ventilation is controlled to prevent a rise in  $PaCO_2$ , and a background anesthetic is also given, such as a potent volatile anesthetic or a benzodiazepine, there is no increase in  $CMRO_2$ , CBF, or ICP.

Benzodiazepines appear also to produce a modest reduction in CBF, but to a lesser extent than seen with other GABA agonists. This is believed to be because of a reduction in CMR and a preservation of the coupling of CMR and CBF [5]. Opioids have shown variable responses in clinical studies and seem to depend on other anesthetics concomitantly given. In general, the effects, if present, tend to be mild and may not be clinically significant.

#### Volatile anesthetic agents

Volatile anesthetic agents differ from intravenous anesthetic agents in that they reduce  $CMRO_2$  in a dose-dependent fashion, but increase CBF, particularly at concentrations greater than 1 minimum alveolar concentration. Halothane has a far greater effect on CBF than isoflurane, desflurane, or sevoflurane, which all have similar effects on cerebral vasodilation. NO and xenon vary from the halogenated anesthetics in their effects on CBF. NO is shown to increase CBF with a variable effect on  $CMRO_2$  [72]. When used as an adjunct to intravenous anesthetics, NO causes little change in CBF; however, when it is used in conjunction with volatile anesthetics, it causes a more dramatic increase in CBF and ICP [72]. Xenon seems to show a differential effect on CBF on gray matter and white matter, causing a decrease in the former and increase in the latter [73].

In general, when considering the pharmacologic effect of a drug on cerebral perfusion, one must consider the drug's effects on the cerebral vasculature if this varies from its effect on the systemic vasculature, the drug's effect on cerebral metabolic rate, the blood pressure before giving the drug, whether or not administration of the drug will bring the blood pressure outside or inside the cerebral autoregulatory window, and the patient's condition with respect to CBF,  $CMRO_2$ , and ICP (Box 5).

### **PATIENT DISEASE STATES**

Although understanding the complex nature of CBF and autoregulation is important, it is essential for a clinician to understand how to apply these concepts to an individual patient, especially when these complex mechanisms

**Box 5: Pharmacology key points**

- Pharmacologic mechanisms of optimizing cerebral perfusion include altering systemic arterial pressure, cerebral metabolic rate, and directly acting on cerebral arteries and arterioles.
- Drugs that can alter cerebral metabolic rate include not only anesthetics, but sympatholytics and sympathomimetics, especially when the blood brain barrier has been compromised.
- When considering an individual drug's effect on an individual patient, one must consider the patient's current condition and what other factors are already affecting CBF, cerebral metabolic rate, and ICP.
- There is some inconsistency in the medical literature with regard to individual drug effects on CBF, probably because of lack of control of type of anesthetic, anemia, etc. several other factors that also influence CBF such as (systemic MAP, CO<sub>2</sub> level, awake versus anesthetized, temperature, type of anesthetic).

are affected by patient disease, whether it be congenital abnormalities, acquired chronic disease, or acute injury (Box 6).

**Anatomic variants**

The most common relevant patient condition is one that will rarely be identified preoperatively, but can affect a patient's reserve for tolerating hemodynamic challenges. The anatomy of the circle of Willis varies widely in human populations, with estimates showing an intact circle of Willis in as low as 34% of the population [74–76]. There is evidence suggesting that patients with an anatomic variant of the classic circle of Willis will have different perfusion patterns and that some may be at higher risk for ischemia than others, particularly in the presence of acquired stenotic lesions [77–79].

There is significant evidence in the literature that patients with an incomplete circle of Willis, to the extent that limits collateral flow, carry a higher lifetime risk of stroke, particularly in the presence of carotid stenosis. This was best shown with prospective data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [80], but also with retrospective data showing a nonfunctional anterior collateral pathway increased the risk of

**Box 6: Patient disease state key points**

- Subclinical anatomic abnormalities can make patients more susceptible to ischemic neurologic deficits perioperatively, particularly in the presence of stenotic vascular lesions.
- Certain disease states, such as hypertension, can shift the normal cerebral autoregulation curve to the right.
- TBI can impair normal autoregulation mechanisms making blood pressure control in these patients paramount to preventing secondary brain injury.

ischemic stroke by sevenfold [81]. Additionally, the absence of posterior communicating arteries, the channel that connects the anterior circulation with the posterior circulation, was associated with border zone infarcts [82], and the fetal-type circulation has also been associated with higher rates of stroke in the medical literature with retrospective data [83]. What remains challenging about treating patients with congenital defects is they are mostly subclinical until a neurologic insult has occurred.

### Age effects

There are several common diseases that frequently accompany aging, such as cerebrovascular disease, cardiovascular disease, and neurologic disease, that each modify cerebral perfusion and autoregulation in their own way, but increasing age itself seems to have very little to no effect on dynamic autoregulation [84]. Older patients do have decreased baroreceptor sensitivity and a change in position could change CBF values significantly, but the autoregulation curve itself seems to be unaffected [85]. There is evidence that static autoregulation appears to be affected with increasing age [86]. Elderly patients also exhibit a wider range of blood pressures diurnally, and elderly patients may be subject to regional hypoperfusion during certain times of night [87]. Additionally, overall CBF decreases from childhood to middle age, which may reflect progressive neuronal loss over time [88].

At the other spectrum of age, premature infants are also a vulnerable population, as development and maturation of the cerebral vasculature usually is not complete. In premature infants weighing less than 1500 g, passive CBF is common, suggesting the autoregulatory mechanisms are still developing and are not working 20% of the time [89].

### Chronic hypertension

Patients with chronic hypertension show structural changes in the cerebral circulation, such as vascular hypertrophy and a shift in the autoregulation curve to the right producing a higher threshold for the ULA [90]. Studies in rats provide evidence that these structural changes also provide somewhat of a protective effect on the HLA and allow chronically hypertensive patients to tolerate higher blood pressures without causing a hemorrhagic stroke. Because of these changes, acute hypotension induced with an NO donor, one of the human body's intrinsic mechanisms of vasodilation, is not tolerated as well in these patients and leads to decreased perfusion during hypotension when compared with normotensive subjects [91]. There is also evidence suggesting there are subclinical regional perfusion abnormalities in the untreated hypertensive patient [92].

Treating patients with chronic hypertension does provide benefit, as evidenced by a decreased rate of ischemic stroke [93,94] and a restoration of more normal CBF dynamics [95,96]. Acute and chronic care of the chronically hypertensive patient should be undertaken carefully using the pharmacologic principles mentioned previously that favor mechanisms causing cerebral vasodilation in addition to peripheral vasodilation.

Although most studies looking at the relationship of CBF and hypertension have been in adults, a growing prevalence of hypertension in the pediatric population urges the scientific community to examine this population more closely. It has already been shown that there is an association between hypertension and altered cerebral hemodynamics in children, potentially causing new problems in childhood not previously seen [97].

### Carotid stenosis/occlusion

Carotid artery stenosis is a disease of plaque buildup associated with aging and hyperlipidemia. One main problem with the disease is that it typically remains subclinical until it has already progressed into advanced stages. Less commonly, carotid artery stenosis can develop as a complication of radiation therapy to the neck [98].

Carotid artery stenosis can lead to regional hypoperfusion if a patient's anatomy does not permit adequate collateral flow. According to analysis of the NASCET data, presence of collateral flow decreases subsequent stroke rate by as much as 60% [99]. Despite collateral flow, there is still a decrease in cerebrovascular reserve that correlates exponentially with increasing degrees of carotid stenosis [100]. The vasculature supplied by the affected carotid artery may lose its cerebrovascular reactivity [101]. Recently, investigators have found that occlusion of the external carotid artery on the same side may also increase stroke risk [102].

Although there has been much debate about when to surgically intervene with either a carotid endarterectomy or stenting, it is clear that these procedures can provide overall benefits in selected populations. Key deciding factors mainly include degree of stenosis and presence of neurologic symptoms. Procedures to alleviate carotid stenosis restore CBF and autoregulatory capacity to previously hypoperfused vasculature, and may improve some cognitive deficits induced by carotid artery stenosis [103,104].

There has been immense interest in determining the best course of treatment for carotid artery stenosis, whether it be placement of a carotid artery stent (CAS) or carotid endarterectomy (CEA). A randomized controlled trial of CAS versus CEA ("CREST" trial) demonstrated no statistically significant difference in the primary outcome (determined as combined rates of periprocedural mortality, myocardial infarction, and stroke, and ipsilateral stroke over 4 years) between the 2 groups; however, the rate of stroke (4.1% vs 2.3%,  $P = .012$ ) was higher with CAS, whereas the rate of myocardial infarction was slightly higher with CEA (1.1% vs 2.3%,  $P = .032$ ) [105]. Additionally, outcomes for patients younger than 70 years were better with CAS, and outcomes were better with CEA for patients older than 70 years or with symptomatic stenosis. Since publication of the CREST trial and some meta-analyses following it, the American Heart Association and American Stroke Association published collaborative recommendations indicating carotid endarterectomy for symptomatic patients and for older patients, and carotid artery stenting for certain asymptomatic patients of younger age [106].

Cerebral hyperperfusion syndrome (CHS) can occur after a symptom-free interval postoperatively in 1% to 3% of patients, and is thought to be caused

by an impaired autoregulatory mechanism in the affected hypoperfused tissue that takes time to recover after normal flow is restored [107–109]. It can occur up to 4 weeks after the original procedure and is associated with a symptomatic period of nausea, vomiting, headache, or other neurologic deficits. If untreated, it may lead to ipsilateral hemorrhagic stroke and death in up to 40% of patients [107]. Methods recently proposed to help prevent this complication, in addition to strict perioperative blood pressure control, include staged angioplasty, perioperative transcranial Doppler measurements, and calculating cerebral circulation time.

### Traumatic brain injury

TBI is a substantial public health problem with approximately 1.7 million TBIs every year in the United States [110]. Although the most effective treatment for this disease is prevention, most medical intervention is focused around preventing secondary injury, which can affect all systems of the body. Understanding how cerebral perfusion and autoregulation can be altered in these patients is paramount to preventing secondary brain injury.

In addition to preventing common sequelae of TBI that negatively affect the brain, such as hypotension, hypoxia, hypoglycemia, hyperthermia, hypocapnia, and intracranial hypertension, the main focus of treatment of TBI is to continuously deliver oxygen to the brain, which is done by optimizing CPP, as autoregulation is frequently impaired even with mild head injuries. There have been several new methods recently published determining methods of tailoring therapy to each individual patient's "ideal perfusion pressure" by analyzing ICP waveforms in addition to arterial pressure waveforms, respiratory oscillations, transcranial Doppler, and, in some cases, short-term moderate hypocapnia [111–113]. In addition, optimizing and measuring neuronal tissue oxygenation may improve neurologic outcome [114].

In pediatric patients in whom normal CPP values vary widely depending on age, recent research has focused on the pressure reactivity index to determine the ideal CPP in children. It is being used to correlate mortality with pressures below the ideal pressure, and disability with pressures above the ideal pressure [115]. It may prove to be an important therapeutic target, as low CBF and poor autoregulatory capacity are highly correlated with poor outcomes [116].

## EFFECTS OF POSITIONING ON CEREBRAL PERFUSION

### Surgery in the beach chair position

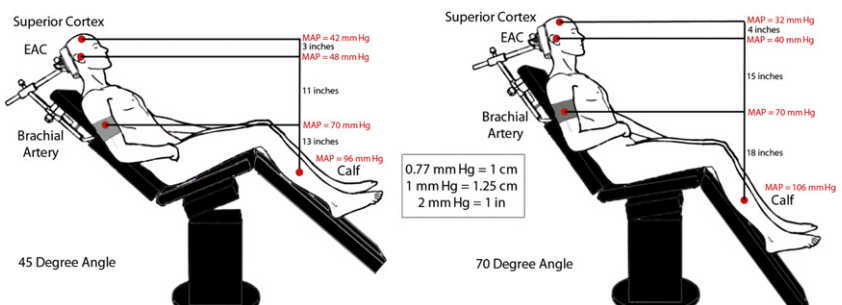
A controversial topic surrounding cerebral perfusion that has arisen in the past several years is anesthetic management of blood pressure in the beach chair position in patients receiving general anesthesia. This concern arose after a series of 4 cases was reported in 2005, detailing severe brain damage in the beach chair position for shoulder surgery [117]. These devastating injuries were thought to be the result of both surgical requests for deliberate hypotension and lack of correction of the blood pressure in the sitting position for height from the noninvasive blood pressure (NIBP) cuff to the external



auditory meatus (EAC). Although measuring blood pressure at the EAC has always been standard practice in neuroanesthesia, this concept did not effectively transmit into other surgical arenas, particularly one known for relatively minor outpatient procedures.

Correcting the blood pressure to account for height difference between the site of measurement and the brain addresses the hydrostatic gradient from the effect of gravity (Fig. 7). For every centimeter of height difference between the NIBP cuff and the EAC, 0.77 mm Hg should be subtracted from the NIBP reading on the arm or leg to approximate the true MAP at the EAC (or for every inch difference, 2 mm Hg subtracted). It is based on the theory that the cerebral circulation acts similar to a “waterfall” system subject to gravitational effects, rather than as a closed siphon system that operates independent of gravity. Since this case series and subsequent controversy, an experiment in anesthetized giraffes demonstrated that the CBF was controlled by arterial pressure without contribution from a siphon mechanism [118]. Admittedly, the waterfall concept does not fully explain cerebral circulation in instances of zero gravity; yet it appears to account for clinically relevant situations.

Many clinical studies have also been performed since this case series was published, including McCulloch and colleagues’ [119] study showing that MAP at the EAC decreased  $47\% \pm 7\%$  in the sitting position at  $45^\circ$  with an associated  $22\% \pm 7\%$  decrease in the CBF velocity in the middle cerebral artery. Systolic blood pressure was  $96 \pm 10$  mm Hg by noninvasive measurement on the arm. Another study, by Jeong and colleagues [120], demonstrated jugular desaturation to less than 50% for at least 5 minutes in 41% of patients in the beach chair position under general anesthesia, with a significantly higher proportion of desaturations in the propofol/remifentanyl group (56%) compared with the sevoflurane/50% NO group (21%,  $P = .008$ ). Jugular saturation in the sitting position in the propofol/remifentanyl group decreased by  $22\% \pm 12\%$  from supine baseline, and by  $14\% \pm 12\%$  in the sevoflurane/50% NO group.



**Fig. 7.** Beach chair position shown at  $45^\circ$  angle on left, and  $70^\circ$  angle on right. MAP calculations shown when correcting for the hydrostatic gradient from the site of the noninvasive blood pressure measurement to the brain.

Jugular desaturation was also related to MAP lower than 50 mm Hg measured at the EAC.

One practice that may further place these patients at risk for cerebral ischemia is the frequent surgical request for deliberate hypotension, particularly when it is facilitated with drugs that do not cause cerebral vasodilation. In addition to the need to correct for the hydrostatic gradient in these cases, we previously discussed how hypotension caused by low cardiac output (ie, hemorrhage, or in this situation head up position under general anesthesia) has been shown to raise the LLA compared with hypotension induced by vasoactive agents. Other issues that may predispose to inadequate cerebral perfusion are the wide variability in the LLA among individuals, the very high incidence of incomplete circle of Willis anatomy in the general population, specialized headrests and head positions that may distort the vascular anatomy in the head and neck, and previously asymptomatic stenotic vascular lesions. Despite having the “deck” stacked against adequate cerebral perfusion in these procedures, the incidence of these devastating injuries appears to be low, although no reliable mechanism for reporting exists. These procedures are typically brief, lasting only a few hours; yet, one professional liability company recently noted at least 9 lawsuits associated with neurological injuries sustained in the beach chair position with large settlement payments related to the issue of hypotension and uncorrected blood pressure in the sitting position [121].

#### Venous effect on CPP: ischemic optic neuropathy associated with prolonged prone or steep trendelenburg position

Since the late 1990s, the perioperative complication of ischemic optic neuropathy after prolonged prone spine surgery has received significant attention from anesthesiologists, spine surgeons, and neuro-ophthalmologists. In early 2012, a multicenter case-control study using 80 cases of ischemic optic neuropathy (ION) from the American Society of Anesthesiologists Postoperative Visual Loss Registry and comparing them with 315 controls from 17 centers across North America identified 6 independent risk factors for ION after prone spine surgery [122]. These 6 risk factors are male sex, obesity, use of a Wilson frame, prolonged duration of anesthesia (ie, surgery), increased blood loss, and decreased administration of colloid in the nonblood fluid administration. With the exception of male sex, these risk factors all support the theory that this complication is related to elevated venous pressure in the prone position with subsequent interstitial fluid accumulation and compromise of the vascular supply to the optic nerve. Although no animal data have yet supported this theoretical pathophysiologic mechanism, its occurrence in these 2 procedures with greatly elevated venous pressure, and in bilateral radical head and neck operations is consistent with this theory. This complication is unique because it highlights the importance of outflow pressure in CPP in non-neurosurgical procedures. Whether or not increasing the MAP in these cases is beneficial has not been tested, as it is not clear that using excessive inflow pressure will improve perfusion once the venous outflow problem has developed. Interestingly, these

patients often do not have associated cerebral injuries. Currently, there is no reliable intraoperative monitor for detecting optic nerve ischemia or dysfunction intraoperatively during general anesthesia.

### **INTRAOPERATIVE MONITORS FOR ASSESSMENT OF CBF AND CEREBRAL ISCHEMIA**

For the general anesthesiologist, use of equipment such as a transcranial Doppler, although useful, is not practical, and can require significant setup time. For high-risk cases, such as CEA, its benefit may be enormous, and obtaining a vascular technologist to measure CBF velocity intraoperatively is recommended when available. Similarly, 16-channel EEG is not likely to be used on an outpatient procedure, but may prove valuable in high-risk procedures. Alternatively, the widespread use of the bispectral index, which is a processed EEG, can provide crude assessments of frontal brain activity, and may give some indication of global adequacy of perfusion. Near infrared spectroscopy is currently widely used in research, but its reliance on trends and lack of absolute values for ischemia make its validity unclear, particularly in adults in whom skull thickness is much greater than in neonates. For anesthesiologists who work at major neurosurgical or neurotrauma centers, familiarity with ICP monitors is essential, and use of surgically placed brain tissue oxygen monitors and autoregulation testing may also be useful for guiding anesthetic management. The expansion of intraoperative evoked potential monitoring to detect cerebral ischemia, as well as injury to the spinal cord and peripheral nerves, may significantly alter anesthetic management, and can provide early warnings of injury and allow modification of surgical and anesthetic care.

The concepts discussed in this updated review should help anesthesiologists optimize management of cerebral perfusion in routine outpatient and inpatient procedures, high-risk neurosurgical and non-neurosurgical procedures, and in high-risk patients with preexisting cerebrovascular disease.

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