Cerebral blood flow (CBF) is tightly controlled to meet the disproportionately high metabolic rate of the brain and to wash out the large amount of metabolic wastes thus produced. Multiple physiological processes are engaged in the regulation of CBF. Cerebral autoregulation is a mechanism that maintains a stable CBF for a given magnitude of cerebral metabolic rate in spite of fluctuation of cerebral perfusion pressure (CPP). The original conceptualization was proposed by Lassen who, in 1959, insightfully took the data from 11 groups of subjects reported in 7 different studies and drew the first plot. Lassen’s approach was carefully reviewed and critiqued. Nonetheless, cerebral autoregulation is regularly referenced in clinical practice to guide arterial blood pressure management in both neurological and non-neurological patients, with or without increased intracranial pressure.

Cerebral autoregulation is visualized as a correlation plot of CBF (axis of ordinate) against CPP (axis of abscissas) (fig. 1). The three key elements of the autoregulation curve are (1) the lower limit, (2) the upper limit, and (3) the plateau. The lower and upper limits are the two sharp inflection points indicating the boundary of pressure-independent flow (the plateau) and the start of pressure-passive flow. The most quoted numbers are the lower limit (CPP) = 60 mmHg, the upper limit (CPP) = 150 mmHg, and the plateau (CBF) = 50 ml/min per 100 g. It needs to be pointed out that these numbers are the means of various groups of subjects in the studies, without any note of the range of distribution or SD. For an individual patient, these means may either underestimate or overestimate the true values. Indeed, it was cautioned by Drummond that there are enormous interindividual and study-to-study variations in the lower limit. The very wide range of the distribution of the lower limit, 40 to 110 mmHg, can be recognized not only in young and healthy volunteers but also in cardiac patients undergoing cardiopulmonary bypass with α-stat acid-base management. The position of the lower limit also depends on the mechanism of hypotension. For example, Fitch et al. showed in baboons that during hemorrhagic hypotension, the lower limit resided at a mean arterial pressure (MAP) that was 65% of the baseline value, whereas during drug-induced hypotension (halothane alone, halothane plus trimetaphan, and halothane plus nitroprusside), the lower limit shifted to a lower MAP that was 35 to 40% of the baseline value.

The execution of cerebral autoregulation relies on the robust cerebrovascular reactivity that engenders dilation to a decrease in CPP and constriction to an increase in CPP (fig. 1). However, cerebrovascular reactivity is not exclusively linked to CPP. Changes in other physiological processes, notably, carbon dioxide, can also alter cerebral vasomotor tone and thus regulate CBF. Intuitively, perfusion pressure and nonperfusion pressure CBF-regulating processes interact and integrate at the point of cerebrovascular resistance regulation; thus, the effect of the interplay of distinct processes on CBF may differ to a stand-alone...
EDUCATION

Therefore, cerebral autoregulation should be regarded as a mobile instead of a fixed plot when nonperfusion pressure processes are also involved. Ignorance of this dynamic and integrative nature of CBF regulation can be risky in clinical practice because the position and shape of the autoregulation curve may have shifted away from what we normally assume. Although the above cited numbers may apply in some young, healthy, normotensive, nonanesthetized, and resting subjects and when perfusion pressure is the only process engaged in CBF regulation, they may not be suitable in other circumstances. We emphasize that the autoregulation curve conceived by Lassen is not a one-size-fits-all phenomenon; rather, its position and shape may change following changes in pertinent physical, medical, neurological, or physiological conditions. Therefore, proper arterial blood pressure management in the effort of CBF optimization can only be fulfilled when the influences of nonperfusion pressure processes on cerebral autoregulation are appreciated.

Carbon dioxide is a known powerful modulator of cerebral vasomotor tone, and change in arterial blood carbon dioxide partial pressure (\(\text{PaCO}_2\)) is frequently encountered in clinical care. The influence of carbon dioxide on cerebral autoregulation has not been specifically reviewed. A sound understanding of this topic facilitates clinical decision making and promotes a culture of “safe” practice. On the basis of the published large animal and human data and some speculation on the components that are without direct data support, we present a detailed discussion of the integrated effect of carbon dioxide and perfusion pressure on the cerebral circulation.

Effect of Hypercapnia on Cerebral Autoregulation

Hypercapnia increases CBF by cerebral vasodilation. Thus, there are two pertinent queries when considering its effect on cerebral autoregulation. The first is how it affects the lower limit. The combined vasodilatory effects imposed by hypotension and hypercapnia could shift the lower limit rightward. The other query is how it affects the upper limit. The dilation induced by hypercapnia could adversely affect the hypertension-induced constriction, rendering a leftward shift of the upper limit.

Harper in 1966 was among the earliest to show in dogs that the lower limit was lost and the pressure–flow relationship became linear during severe hypercapnia (\(\text{PaCO}_2 = 70\) to 90 mmHg) compared with normocapnia (\(\text{PaCO}_2 = 30\) to 40 mmHg). Also in dogs, Häggendal and Johansson showed that the lower limit occurred at a mean arterial pressure (MAP) of 50 to 60 mmHg under normocapnia (\(\text{PaCO}_2 = 30\) to 50 mmHg); however, during hypercapnia (\(\text{PaCO}_2 = 70\) to 95 mmHg), the lower limit shifted to a much higher MAP of 80 to 100 mmHg. Later, Raichle and Stone demonstrated in monkeys that the lower limit was shifted upward and rightward and ultimately abolished by acutely increasing \(\text{PaCO}_2\) in a stepwise manner (\(\text{PaCO}_2 = 33, 48, 57,\) and 70 mmHg, respectively).

Regarding the upper limit, Ekström-Jodal et al. showed in dogs that autoregulation was conserved until 225 mmHg (MAP) during normocapnia; however, during moderate hypercapnia (\(\text{PaCO}_2 = 40\) to 60 mmHg), the autoregulatory pressure range was shorter, with an upper limit of 150 mmHg, and during more marked hypercapnia (\(\text{PaCO}_2 > 60\) mmHg), the upper limit was as low as 125 mmHg.

In human subjects, McCulloch et al. found that the threshold at which hypercapnia significantly impaired autoregulation averaged 56 mmHg (\(\text{PaCO}_2\)) during sevoflurane anesthesia and 61 mmHg during propofol anesthesia. In patients undergoing cardiopulmonary bypass, Murkin et al. showed that \(\alpha\)-stat acid–base management preserved, whereas \(\beta\)-stat (carbon dioxide supplementation) impaired autoregulation.
autoregulation. In ventilated very low-birth-weight infants, Kaiser et al.\(^{20}\) found that autoregulation was progressively impaired and cerebral perfusion became progressively pressure passive with escalating hypercapnia. However, none of these human studies examined in detail how the plateau, the lower limit, and the upper limit are affected by hypercapnia.\(^{18–20}\)

In light of these studies, we propose the following construct as illustrated in figure 2 to explain the effect of hypercapnia on cerebral autoregulation. The ensuing discussion in this section is based on this figure unless specified otherwise. The plateau shifts upward during hypercapnia due to the cerebral vasodilation being induced.

When CPP is decreasing, cerebral resistance vessels dilate until the lower limit is reached. However, with hypercapnia-induced dilation, maximal dilation and therefore the lower limit is reached at a higher CPP during hypercapnia than normocapnia, that is, the lower limit is shifted rightward. For example, at point E on the CPP axis at normocapnia, cerebral resistance vessels are not maximally dilated yet because the CPP is higher than the lower limit; however, for the same CPP at hypercapnia, cerebral resistance vessels are already maximally dilated due to the additional dilation imposed by hypercapnia. We overlap the portions of the autoregulation curve below the lower limit based on the premise that the calibers of the maximally dilated cerebral resistance vessels at hypercapnia and normocapnia are the same. This premise is plausible if there is truly a fixed size limit to which cerebral resistance vessels can dilate. Otherwise, a different construct would ensue.

When CPP is increasing, cerebral resistance vessels constrict until the upper limit is reached. However, at hypercapnia, the upper limit is reached at a lower CPP than normocapnia, that is, the upper limit is shifted leftward due to the antagonism of the hypertension-induced vasoconstriction by the hypercapnia-induced vasodilation. For example, at point F on the CPP axis at normocapnia, cerebral resistance vessels are not maximally constricted yet because the CPP is lower than the upper limit; however, for the same CPP at hypercapnia, they are already maximally constricted due to the case that further constriction is negated by hypercapnia. Because different degrees of hypercapnia exert differing strengths of dilation, the calibers of the maximally constricted cerebral resistance vessels are different at differing severity of hypercapnia. As a consequence, the portion of the autoregulation curve above the upper limit at hypercapnia does not overlap with normocapnia and has a steeper slope.

In summary, during hypercapnia, the plateau of the autoregulation curve is shifted upward and shortened, the lower limit is shifted rightward, and the upper limit is shifted leftward. The extent of these changes depends on the severity of hypercapnia. At severe hypercapnia when cerebral resistance vessels are maximally dilated, the plateau is lost and the pressure–flow relationship is linear.

**Effect of Hypocapnia on Cerebral Autoregulation**

Hypocapnia decreases CBF by cerebral vasoconstriction. As such, there are two pertinent queries relating to its effect on
cerebral autoregulation. The first is how the lower limit moves because the effects of hypotension and hypocapnia on cerebral resistance vessels are opposite; one dilates and the other constricts. The other query is how the upper limit shifts because both hypertension and hypocapnia induce cerebral vasoconstriction.

In 1965, Harper and Glass showed by bleeding dogs that when MAP was reduced to 100 mmHg from a baseline of 150 mmHg, the CBF response to hypocapnia persisted but was much reduced, and when MAP was further reduced to 50 mmHg, the CBF response to hypocapnia was lost. They proposed an “over-ride” mechanism to explain their finding by theorizing that responding to tissue ischemia and hypoxia takes precedence over the maintenance of tissue carbon dioxide homeostasis. Work conducted by Whitelaw et al. showed that nicardipine, nitroglycerin, and prostaglandin E1 ensured homeostasis. Work conducted by Whitelaw et al. showed that nicardipine, nitroglycerin, and prostaglandin E1 preserved cerebral autoregulation. The effect of hypotension on cerebrovascular carbon dioxide reactivity was attenuated during hypocapnia. Surprisingly, there is scant evidence directly addressing the latter issue. A study conducted by Artru et al. examined the effect of hypocapnia on the lower limit while the CPP was gradually decreased via hemorrhage in dogs. They found that hypocapnia did not cause a substantial shift of the lower limit which was at 61% of baseline CPP at hypocapnia and 59% of baseline CPP at normocapnia, and that the slopes of the autoregulation curve below the lower limit did not significantly differ between hypocapnia and normocapnia.

In light of these considerations, we propose the constructs illustrated in figures 3 and 4 to describe the effect of hypocapnia on cerebral autoregulation. The constructs in figures 3 and 4 are based on the distinct speculation on the effect of hypocapnia on the upper limit. The ensuing discussion in this section is based on these two figures unless specified otherwise. The plateau descends to a lower CBF with hypocapnia due to cerebral vasoconstriction.

To the best of our knowledge, the study by Artru et al. is the only one so far that directly examined the effect of hypocapnia on the lower limit. In accordance with the results in the study by Artru et al., we have kept the position of the lower limit at hypocapnia the same as normocapnia and the slope of the autoregulation curve below the lower limit at hypocapnia not significantly different from normocapnia. Nonetheless, the abundant evidence that the cerebrovascular reactivity to hypocapnia is significantly weakened or lost during hypotension makes the drawing of the autoregulation curve in the proximity of the lower limit during hypocapnia complex. One could argue that the plateau should swing upward when the CPP is critically decreased due to the attenuation of the cerebrovascular hypocapnia response by hypotension. This seems rational when considering that the “over-ride” of the hypocapnia vasoconstrictive effect could have restored the decreased CBF. Indeed, this consideration seems supported by the rabbit data presented by Czosnyka et al. where a smooth upswing of the plateau in the proximity of the lower limit was demonstrated even though it was not clear whether the curve was generated during hypocapnia. However, such speculations suggest that during hypocapnia the CBF at hypotension could be higher than normotension.

To date, the available data show that the CBF during combined hypocapnia and hypotension is not higher than that when hypocapnia and normotension are combined. In addition, “over-ride” is a mechanism dealing specifically with the effect of hypotension on cerebrovascular carbon dioxide reactivity that is different to the effect of hypocapnia on cerebrovascular pressure reactivity or autoregulation.

How the upper limit is affected by hypocapnia is not clear due to the lack of data. There are two lines of speculation. If we hypothesize that the calibers of the maximally constricted cerebral resistance vessels are the same between hypocapnia and normocapnia, the construct in figure 3 applies. In this case, the upper limit shifts leftward due to the “background” constriction induced by hypocapnia. For example, at point D on the CPP axis at normocapnia, cerebral resistance vessels are not maximally constricted yet. However, for the same CPP at
hypocapnia, they are maximally constricted as a result of the additional constriction imposed by hypocapnia. We overlap the portions of the autoregulation curve above the upper limit at hypocapnia and normocapnia. The overlap is plausible in considering that, for a given CPP higher than the upper limit, the CBF at hypocapnia should be maximally constricted as a result of the additional constriction imposed by hypocapnia. We speculate that the calibers of the maximally constricted cerebral resistance vessels at normocapnia and hypocapnia are the same. Autoregulation curves are in black at normocapnia and blue at hypocapnia. Cerebral resistance vessels are illustrated in red/pink. The bold solid blue arrow indicates the dynamic shift of the maximally constricted cerebral resistance vessels at hypocapnia. The dashed black and blue lines/arrows indicate the lower and upper limits at normocapnia and hypocapnia, respectively. A = the curve below the lower limit at normocapnia (A₀), mild hypocapnia (A₁), and severe hypocapnia (A₂); B = the plateau at normocapnia (B₀), mild hypocapnia (B₁), and severe hypocapnia (B₂); C = the curve above the upper limit at normocapnia (C₀), mild hypocapnia (C₁), and severe hypocapnia (C₂); CBF = cerebral blood flow; CPP = cerebral perfusion pressure; LL = the lower limit at normocapnia (LL₀), mild hypocapnia (LL₁), and severe hypocapnia (LL₂); R = calibers of cerebral resistance vessels at normocapnia (R₀), mild hypocapnia (R₁), and severe hypocapnia (R₂); UL = the upper limit at normocapnia (UL₀), mild hypocapnia (UL₁), and severe hypocapnia (UL₂).
the same as normocapnia because the flow resistances determined by the calibers of cerebral resistance vessels are the same.

The other line of speculation is to hypothesize that the caliber of the maximally constricted cerebral resistance vessels at hypocapnia is smaller than normocapnia due to the extra constriction imposed by hypocapnia. In this case, the construct in figure 4 may apply. The upper limit may or may not shift rightward even though we opt for a rightward shift in this discussion. This line of speculation is shared by Paulson et al. who believed that, at hypocapnia, the upper limit shifted rightward and as a consequence, the plateau was lengthened. However, neither Paulson et al. nor the two studies cited by Paulson et al. specifically studied the effect of hypocapnia on the upper limit. Future research is warranted to address this unknown aspect.

In summary, at hypocapnia, the plateau of the autoregulation curve shifts downward; any change in the lower limit is unremarkable; however, how the upper limit moves is not clear.

### Methodological Considerations

We have discussed the integrated effect of carbon dioxide and perfusion pressure on the cerebral circulation based on the published large animal and human experimental data and some speculation on the aspects that are without data. Effort has been made to ensure that the available data and the proposed conceptualization do not conflict. Nonetheless, challenges exist due to the differences in the methods used by previous investigators that include study subjects, CPP manipulation, \( \text{PaCO}_2 \) manipulation, CBF measurement, and anesthesia choice (table 1). Data do not automatically deliver concepts or theories, and it is especially unlikely that a single data set could do so. To establish a complete theory, careful data analysis and logical extrapolation are needed in addition to some speculation on the components that are without direct data support.

Studies on the relationship between distinct physiological processes can be confounded by unrecognized or unmeasured processes associated with the processes being studied. Sympathetic nervous activity can be a confounder when studying the effect of hypercapnia on cerebral circulation. Busija and Heistad showed that the hypercapnia-induced increase in CBF was further increased by bilateral sympathetic withdrawal via bilateral superior cervical ganglionectomy during acute hypercapnia in sleeping lambs. Zhang et al. showed that the sensitivity of cerebral vasoreactivity to hypercapnia was attenuated by augmented sympathetic activity induced via lower body negative pressure in healthy young subjects. Moreover, it is known that hypercapnia can increase sympathetic activity alone and with hypoxia. Collectively, this evidence suggests that the hypercapnia-induced increase in CBF is buffered by sympathetic nervous activity. During anesthesia, sympathetic activity is altered, ranging from inhibition to stimulation depending on the anesthetic agent being used, implying that sympathetic activity could confound a study on the effect of hypercapnia on cerebral circulation in anesthetized subjects.

Hypocapnia is achieved via hyperventilation in all studies we referenced. However, hyperventilation itself can be a confounder. Alexander et al. showed that hyperventilation caused a consistent increase in blood pressure and decrease in cardiac output in patients anesthetized with propofol and remifentanil. The associated changes in blood pressure and cardiac output can confound studies on the effect of hypocapnia on cerebral circulation due to the influence of systemic circulation on cerebral perfusion.

A variety of anesthetic agents were used in previous studies (table 1). Type of anesthesia can also be a confounder. It is known that volatile agents cause an increase in CBF due to the intrinsic cerebral vasodilatory property, whereas propofol representing intravenous agents exerts the opposite effect. As a result, volatile agents impair cerebral autoregulation while propofol preserves it, somewhat resembling hypercapnia and hypocapnia, respectively. Therefore, the effect of carbon dioxide on cerebral autoregulation should also be considered in the context of the anesthetic agent being used.

We focused our discussion on the integrated effect of carbon dioxide and perfusion pressure on the cerebral circulation. Although it is important to understand the physiology comprehensively, we did not include every aspect that engages in CBF regulation. Oxygen is one of these aspects that deserve emphasis. In 1940s, Kety and Schmidt showed that the threshold for hypoxic cerebral vasodilation was at a peripheral oxygen saturation of 90% in healthy volunteers, much higher than previously reported. Brown et al. argued that it is the arterial blood oxygen content that is fundamentally important in the regulation of CBF. On the mechanism, adenosine, nitric oxide, cyclic nucleotides, and adenosine triphosphate–sensitive K+ channels are all implicated as being responsible for the hypoxia-induced cerebral vasodilation. On the interplay among oxygen, carbon dioxide, and perfusion pressure on the cerebral circulation, it was found that the cerebrovascular carbon dioxide reactivity was attenuated during acute hypoxia and the impairment of dynamic cerebral autoregulation during isocapnic hypoxia could be prevented with hypocapnia. Conversely, brain tissue oxygen tension is regulated by carbon dioxide and perfusion pressure, resembling the well-known CBF regulation by carbon dioxide and CPP, respectively. This observation reflects that one of the fundamental goals
### Table 1. Details of the Methods Used in the Studies Cited

<table>
<thead>
<tr>
<th>First Author</th>
<th>Subject</th>
<th>Anesthesia</th>
<th>Cerebral Blood Flow Measurement</th>
<th>Cerebral Perfusion Pressure Manipulation</th>
<th>Carbon Dioxide Manipulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitch8</td>
<td>Baboon</td>
<td>Phencyclidine, thiopentone, nitrous oxide</td>
<td>$^{133}$Xe washout</td>
<td>Bleeding, halothane, trimetaphan, nitroprusside</td>
<td>Constant</td>
</tr>
<tr>
<td>Harper14</td>
<td>Dog</td>
<td>Thiopentone, nitrous oxide</td>
<td>Kety–Schmidt (krypton 85)</td>
<td>Bleeding</td>
<td>Hypoventilation</td>
</tr>
<tr>
<td>Häggendal15</td>
<td>Dog</td>
<td>Pentobarbital</td>
<td>Kety–Schmidt (krypton 85)</td>
<td>Bleeding</td>
<td>Hyperventilation, breathing carbon dioxide</td>
</tr>
<tr>
<td>Raichle16</td>
<td>Monkey</td>
<td>Phencyclidine</td>
<td>Doppler ultrasonography</td>
<td>Bleeding and metaraminol infusion</td>
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</tr>
<tr>
<td>Ekström-Jodal17</td>
<td>Dog</td>
<td>Details not disclosed</td>
<td>Kety–Schmidt (krypton 85)</td>
<td>Bleeding, thoracic aorta clamping</td>
<td>Hyperventilation, breathing carbon dioxide</td>
</tr>
<tr>
<td>McCulloch18</td>
<td>Human</td>
<td>Propofol infusion or sevoflurane, in addition to remifentanil infusion</td>
<td>Doppler ultrasonography</td>
<td>Phenytoin infusion</td>
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</tr>
<tr>
<td>Murkin19</td>
<td>Human (cardiopulmonary bypass)</td>
<td>Fentanyl, diazepam</td>
<td>$^{133}$Xe washout</td>
<td>Details not disclosed</td>
<td>Ventilation adjustment</td>
</tr>
<tr>
<td>Kaiser20</td>
<td>Very low-birth-weight infant</td>
<td>Details not disclosed</td>
<td>Doppler ultrasonography</td>
<td>Tracheal suction</td>
<td>Ventilation adjustment</td>
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<tr>
<td>Harper21</td>
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<td>Thiopentone, nitrous oxide</td>
<td>Kety–Schmidt (krypton 85)</td>
<td>Bleeding</td>
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</tr>
<tr>
<td>Whiteley22</td>
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<td>Chloralose, urethane</td>
<td>Doppler ultrasonography</td>
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</tr>
<tr>
<td>Artru23</td>
<td>Dog</td>
<td>Halothane, nitrous oxide</td>
<td>Diversion of sagittal sinus blood flow</td>
<td>Nitroprusside, trimetaphan</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Artru24</td>
<td>Dog</td>
<td>Isoflurane, nitrous oxide</td>
<td>Diversion of sagittal sinus blood flow</td>
<td>Isoflurane</td>
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<td>Nitroglycerin</td>
<td>Hyperventilation</td>
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<td>Matta26</td>
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<td>Nitroprusside, isoflurane</td>
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<tr>
<td>Endoh27</td>
<td>Human</td>
<td>Propofol and fentanyl infusion</td>
<td>Doppler ultrasonography</td>
<td>Nicardipine, nitroprusside, prostaglandin E1</td>
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<td>Okuda28</td>
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<td>$^{133}$Xe washout, electromagnetic flowmeter</td>
<td>Halothane</td>
<td>Hyperventilation, breathing carbon dioxide</td>
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<tr>
<td>Artru29</td>
<td>Dog</td>
<td>Nitrous oxide, halothane</td>
<td>Diversion of sagittal sinus blood flow</td>
<td>$^{133}$Xe washout</td>
<td>Angiotensin</td>
</tr>
<tr>
<td>Paulson31</td>
<td>Human</td>
<td>Thiopental, nitrous oxide</td>
<td>$^{133}$Xe washout</td>
<td>Angiotensin</td>
<td>Hyperventilation</td>
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</tbody>
</table>

References are tabulated in the sequence they are referenced in the text.
of cerebral perfusion is oxygen delivery. In summary, oxygen regulates CBF both alone and via an integrated mechanism that involves interplay with carbon dioxide, perfusion pressure, and maybe other physiological processes.

It needs to be noted that the flat plateau (zero tilt) of the autoregulation curve is likely an idealized drawing. In reality, cerebral autoregulation may execute on a (slightly) tilted plateau that is different to pressure-passive flow. Moreover, the sharp inflection points at both the lower and the upper limits should probably be drawn as a round “shoulder” rather than a sharp “elbow” because the former conforms to normal physiology, whereas the latter is derived as a result of statistical processing.

Clinical Implications

Cerebral autoregulation is an important mechanism in protecting the brain from ischemia and overperfusion in the face of fluctuating perfusion pressure. As such, it is regularly referenced in clinical practice when taking care of patients with or without neurologic pathophysiologies. However, ignorance of both the limitations and the dynamic/integrative nature of this concept can do more harm than good. The practice of applying a fixed number learned from textbooks or other resources in an individual patient is risky for the following reasons. First, it can either underestimate or overestimate the true value of the lower limit, the upper limit, or the plateau of an individual patient because the commonly quoted numbers are the means of the populations studied without noting the SD or range of distribution. Second, the functional status of cerebral autoregulation is not routinely monitored in clinical care. It can be impaired in a variety of situations such as traumatic brain injury and anesthesia with volatile agents. If so, CBF becomes pressure passive and a different conceptual framework is needed. Finally, nonperfusion pressure conditions or processes, such as carbon dioxide as discussed in this article, can alter the position and shape of the autoregulation curve via their modulating effect on cerebral vasomotor tone. Therefore, cerebral autoregulation is a dynamic process that is regulated by nonperfusion pressure but CBF-regulating aspects.

The aim of this review is to reanalyze the conceptualization of cerebral autoregulation and not to deal specifically with the relationship between decreased (or increased) blood pressure and neurological outcome. This was recently reviewed. Nonetheless, a pertinent clinical question is what the practical strategy of arterial blood pressure management is when real-time cerebral perfusion and autoregulation are not monitored. Unfortunately, there is no single or simple answer. It depends on the patient’s neurologic pathophysiology including cerebral metabolic need, adequacy of perfusion, intracranial pressure, and integrity of cerebral autoregulation, in addition to the presence of cardiac disease, pulmonary disease, anemia, and so on, as well the largely unknown effects of vasoactive drugs. Clinical care should balance the needs of different organ systems. The complexity of this philosophy is illustrated, for example, with the triple “H” (hypertension, hypervolemia, and hemodilution) therapy that benefits the brain but may harm the heart and the perioperative β-blockade therapy that helps the heart but may hurt the brain. Although the cause–effect role of blood pressure in these dilemmas is hard to define, it is clear that blood pressure management is a decision characterized by priority and balance. The ultimate vindication of any intervention should be based on randomized and controlled trials demonstrating an overall beneficial outcome and this applies equally to the care of the systemic and cerebral circulations. Thus far, large meaningful trials are lacking.

The clinical implications of the effect of carbon dioxide on cerebral autoregulation are summarized in figure 5. An increase in CBF due to hypercapnia renders the match between CBF and cerebral metabolic rate tilted toward more CBF than needed if cerebral metabolic rate remains unchanged (fig. 2). This may be seen as a safer situation in terms of the maintenance of the supply of cerebral metabolic substrates. However, it needs to be noted that an acute increase in PaCO₂ not only shifts the plateau up but also shortens it. A shrunken plateau increases the chance of CBF fluctuation as CPP fluctuates. Under anesthesia, a PaCO₂ of greater than 55 mmHg should be regarded as having eliminated autoregulation. Therefore, a tighter CPP control is needed to avoid CBF fluctuation although some “protection” may come from the higher-than-needed CBF (assuming a stable metabolic demand) that would allow a greater decrease in perfusion pressure before ischemia.
If cerebral metabolic rate remains unchanged, a decrease in CBF due to hypocapnia renders the brain at risk of cerebral ischemia (figs. 3 and 4). It is true that the cerebrovascular response to hypocapnia is attenuated during hypotension secondary to hemorrhage, drug, or anesthesia. However, this “over-ride” mechanism deals specifically with the effect of hypotension on the cerebrovascular carbon dioxide reactivity, not with the effect of hypocapnia on cerebrovascular pressure reactivity (autoregulation). Studies showed that the CBF was significantly reduced during combined hypocapnia and hypotension. There is no evidence showing that the CBF during combined hypocapnia and hypotension is increased above baseline. Therefore, our cautious recommendation is to avoid hypotension during hypocapnia to decrease the ischemic risk. The decision to implement hypocapnia in clinical care should be weighed against the inherent ischemic risk it incurs. The deleterious effect of hypocapnia in patients with head trauma was reviewed. Hypocapnia was also associated with unfavorable functional outcomes at 90 days after acute stroke.

**Summary**

Cerebral autoregulation is a mechanism that maintains CBF stable despite the fluctuation of CPP. As such, it is regularly referenced in clinical care; however, ignorance of its dynamic nature and limitations can do more harm than good. Non-perfusion pressure but CBF-regulating processes such as carbon dioxide affect the efficiency of pressure autoregulation because they intercept at the same target—the cerebrovascular reactivity. The integrated effect of carbon dioxide and perfusion pressure on cerebral circulation is discussed based on the published large animal and human data and some speculation on the aspects that are without data support. We showed that during hypocapnia, the plateau ascends and shortens, the lower limit shifts rightward, and the upper limit leftward. Conversely, during hypocapnia, the plateau descends and the lower limit remains unchanged. How the upper limit is affected by hypocapnia is not clear; nonetheless, we provided two lines of speculation: one line assuming the same calibers of the maximally constricted cerebral resistance vessels at hypocapnia and normocapnia and the other assuming a smaller caliber at hypocapnia than normocapnia.

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**Competing Interests**

The authors declare no competing interests.

**Correspondence**

Address correspondence to Dr. Meng: Department of Anesthesiology and Perioperative Care, University of California San Francisco, 521 Parnassus Avenue, Suite C450, San Francisco, California 94143. mengl@anesthesia.ucsf.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology’s articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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