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Regulation of Cerebral Autoregulation by Carbon Dioxide

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ABSTRACT

Cerebral autoregulation describes a mechanism that maintains cerebral blood flow stable despite fluctuating perfusion pressure. Multiple nonperfusion pressure processes also regulate cerebral perfusion. These mechanisms are integrated. The effect of the interplay between carbon dioxide and perfusion pressure on cerebral circulation has not been specifically reviewed. On the basis of the published data and speculation on the aspects that are without supportive data, the authors offer a conceptualization delineating the regulation of cerebral autoregulation by carbon dioxide. The authors conclude that hypercapnia causes the plateau to progressively ascend, a rightward shift of the lower limit, and a leftward shift of the upper limit. Conversely, hypocapnia results in the plateau shifting to lower cerebral blood flows, unremarkable change of the lower limit, and unclear change of the upper limit. It is emphasized that a sound understanding of both the limitations and the dynamic and integrated nature of cerebral autoregulation fosters a safer clinical practice. **(ANESTHESIOLOGY 2015; 122:196-205)**

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.[1] 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).[2] The original conceptualization was proposed by Lassen[3] 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.[4,5] 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.[2] 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.[2,3] For an individual patient, these means may either underestimate or overestimate the true values. Indeed, it was cautioned by Drummond[4] 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[6] but also in cardiac patients undergoing cardiopulmonary bypass with α-stat acid–base management.[7] The position of the lower limit also depends on the mechanism of hypotension. For example, Fitch *et al.*[8] 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

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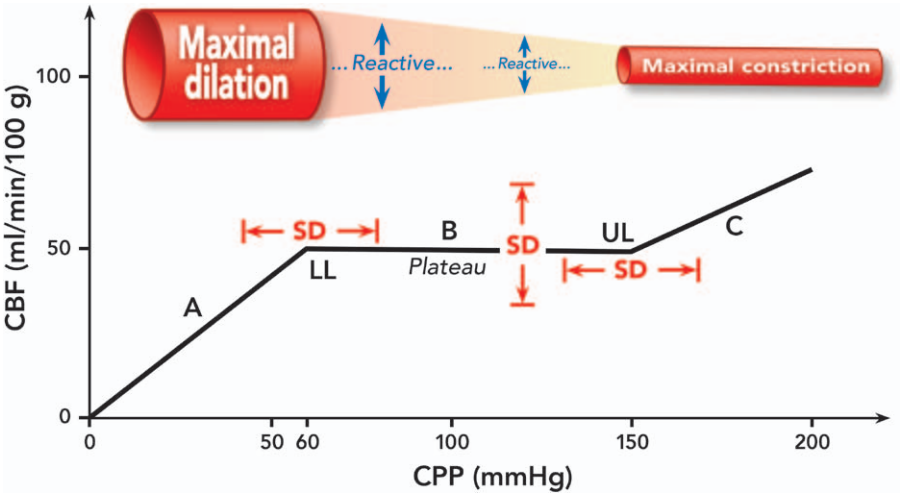

Fig. 1. Cerebral autoregulation is visualized as a correlation plot between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP). CBF remains stable between the lower limit (LL) and the upper limit (UL) (portion B, plateau). CBF is pressure passive at the CPP range below the lower limit (portion A) and above the upper limit (portion C). This illustration uses a CPP of 60 mmHg as the lower limit, a CPP of 150 mmHg as the upper limit, and a CBF of 50 ml/min per 100 g as the plateau. However, these regularly quoted numbers are not fixed; rather, they vary interindividually and intraindividually depending on a variety of factors. Therefore, we take a note of SD to emphasize that these parameters have a wide range of distribution. The cerebrovascular reactivity is also illustrated.

process. 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,[9–11] and change in arterial blood carbon dioxide partial pressure ($Paco_2$) is frequently encountered in clinical care.[12,13] 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[14] 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 ($Paco_2$ = 70 to 90 mmHg) compared with normocapnia ($Paco_2$ = 30 to 40 mmHg). Also in dogs, Häggendal and Johansson[15] showed that the lower limit occurred at an MAP of 50 to 60 mmHg under normocapnia ($Paco_2$ = 30 to 50 mmHg); however, during hypercapnia ($Paco_2$ = 70 to 95 mmHg), the lower limit shifted to a much higher MAP of 80 to 100 mmHg. Later, Raichle and Stone[16] demonstrated in monkeys that the lower limit was shifted upward and rightward and ultimately abolished by acutely increasing $Paco_2$ in a stepwise manner ($Paco_2$ = 33, 48, 57, and 70 mmHg, respectively).

Regarding the upper limit, Ekström-Jodal *et al.*[17] showed in dogs that autoregulation was conserved until 225 mmHg (MAP) during normocapnia; however, during moderate hypercapnia ($Paco_2$ = 40 to 60 mmHg), the autoregulatory pressure range was shorter, with an upper limit of 150 mmHg, and during more marked hypercapnia ($Paco_2$ >60 mmHg), the upper limit was as low as 125 mmHg.

In human subjects, McCulloch *et al.*[18] found that the threshold at which hypercapnia significantly impaired autoregulation averaged 56 mmHg ($Paco_2$) during sevoflurane anesthesia and 61 mmHg during propofol anesthesia. In patients undergoing cardiopulmonary bypass, Murkin *et al.*[19] showed that α-stat acid–base management preserved, whereas pH-stat (carbon dioxide supplementation) impaired

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

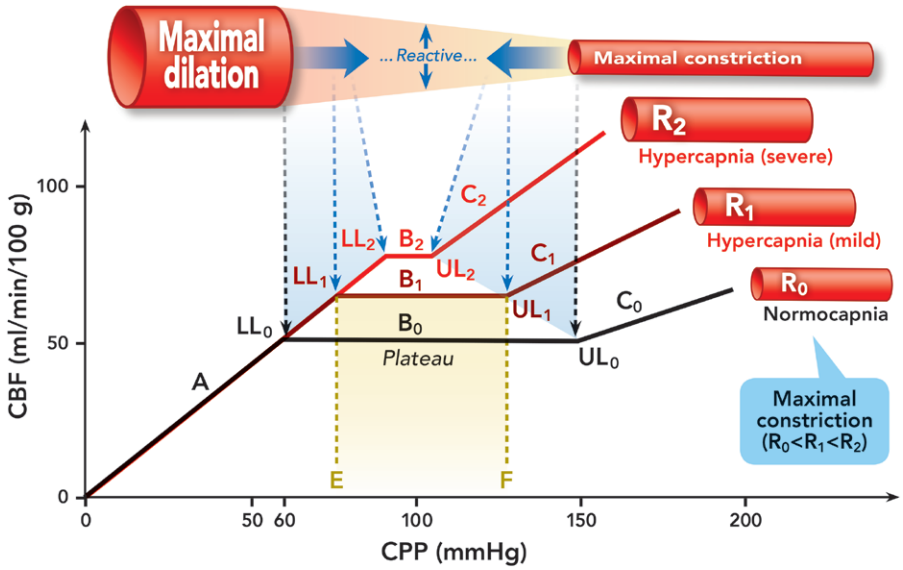

Fig. 2. Effect of hypercapnia on cerebral autoregulation. Autoregulation curves are in *black* at normocapnia and *red* at hypercapnia. Cerebral resistance vessels are illustrated in *red/pink*. The *bold solid blue arrows* indicate the dynamic shift of the maximally dilated and constricted cerebral resistance vessels at hypercapnia. The *dashed black and blue lines/arrows* indicate the lower and upper limits at normocapnia and hypercapnia, respectively. A = the curve below the lower limit; B = the plateau at normocapnia (B_0), mild hypercapnia (B_1), and severe hypercapnia (B_2); C = the curve above the upper limit at normocapnia (C_0), mild hypercapnia (C_1), and severe hypercapnia (C_2); CBF = cerebral blood flow; CPP = cerebral perfusion pressure; LL = the lower limit at normocapnia (LL_0), mild hypercapnia (LL_1), and severe hypercapnia (LL_2); R = calibers of cerebral resistance vessels at normocapnia (R_0), mild hypercapnia (R_1), and severe hypercapnia (R_2); UL = the upper limit at normocapnia (UL_0), mild hypercapnia (UL_1), and severe hypercapnia (UL_2).

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[21] 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.*[22] in newborn piglets subjected to bleeding showed that hypocapnia failed to further decrease CBF when MAP was reduced to 38 mmHg or less even though it could produce a substantial decrease in CBF at an MAP of 45 mmHg or above.

In the context of drug-induced hypotension, serial works by Artru *et al.*[23–25] showed that the cerebrovascular response to hypocapnia was abolished in dogs during hypotension to an MAP of 50 mmHg induced with sodium nitroprusside,[23,24] trimethaphan,[23] and nitroglycerin.[25] In contrast, Matta *et al.*[26] showed that the cerebrovascular response to hypocapnia was attenuated, but not abolished, during nitroprusside-induced hypotension (MAP = 60 mmHg) in patients anesthetized with isoflurane. Similarly, Endoh *et al.*[27] showed that nicardipine, nitroglycerin, and prostaglandin E_1-induced hypotension (MAP = 55 to 60 mmHg) attenuated, but did not abolish, the cerebrovascular hypocapnia response in patients anesthetized with propofol and fentanyl.

With regard to the hypotension induced by anesthetic agents, Okuda *et al.*[28] showed that the cerebrovascular hypocapnia response was abolished at an MAP of 45 mmHg induced by halothane in baboons. Artru *et al.*[24] showed in dogs that the cerebrovascular response to hypocapnia was partially preserved during isoflurane-induced hypotension to an MAP of 50 mmHg. In patients, Matta *et al.*[26] found that the cerebrovascular carbon dioxide reactivity was attenuated during isoflurane-induced hypotension as low as 60 mmHg (MAP).

Collectively, there is ample evidence demonstrating that the cerebrovascular reactivity to hypocapnia is significantly attenuated or abolished during hemorrhage-, drug-, or anesthesia-induced hypotension.[21–28] However, these studies do not directly tackle the question of how hypocapnia affects cerebral autoregulation. The effect of hypotension on cerebrovascular hypocapnia reactivity and effect of hypocapnia on cerebrovascular pressure reactivity, that is, autoregulation, are related but distinctive issues. The former is typically studied *via* investigating the change in CBF following a change in $Paco_2$ under hypotensive condition, whereas the latter *via* investigating the change in CBF following a change in CPP at 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.[29]

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.*[29] 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.[21–28] 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.*[30] 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.[22,29] 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

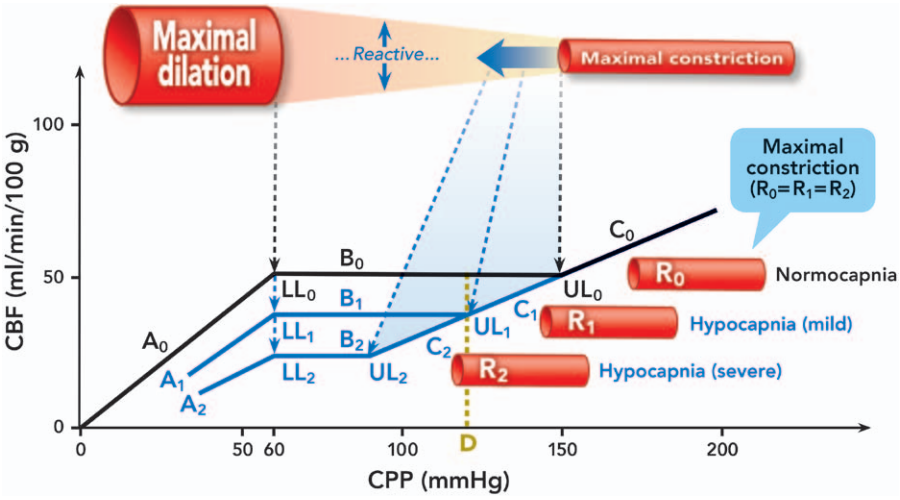

Fig. 3. Effect of hypocapnia on cerebral autoregulation. We speculate that the calibers of the maximally constricted cerebral resistance vessels at normocapnia and hypocapnia are the same. Autoregulation curves are in *black* at normocapnia and *blue* at hypocapnia. Cerebral resistance vessels are illustrated 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 (A_0), mild hypocapnia (A_1), and severe hypocapnia (A_2); B = the plateau at normocapnia (B_0), mild hypocapnia (B_1), and severe hypocapnia (B_2); C = the curve above the upper limit at normocapnia (C_0), mild hypocapnia (C_1), and severe hypocapnia (C_2); CBF = cerebral blood flow; CPP = cerebral perfusion pressure; LL = the lower limit at normocapnia (LL_0), mild hypocapnia (LL_1), and severe hypocapnia (LL_2); R = calibers of cerebral resistance vessels at normocapnia (R_0), mild hypocapnia (R_1), and severe hypocapnia (R_2); UL = the upper limit at normocapnia (UL_0), mild hypocapnia (UL_1), and severe hypocapnia (UL_2).

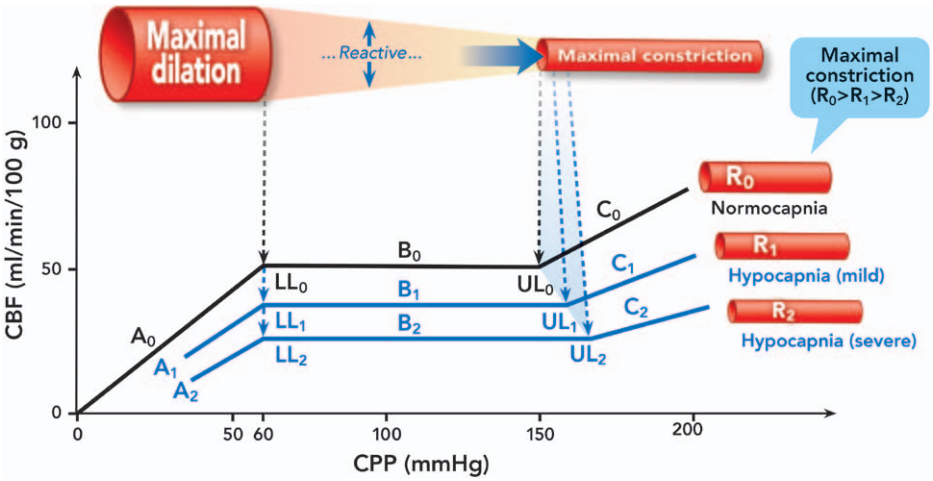

Fig. 4. Effect of hypocapnia on cerebral autoregulation. We speculate that the caliber of the maximally constricted cerebral resistance vessels at hypocapnia is smaller than normocapnia and assume that hypocapnia causes a rightward shift of the upper limit. Autoregulation curves are in *black* at normocapnia 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 (A_0), mild hypocapnia (A_1), and severe hypocapnia (A_2); B = the plateau at normocapnia (B_0), mild hypocapnia (B_1), and severe hypocapnia (B_2); C = the curve above the upper limit at normocapnia (C_0), mild hypocapnia (C_1), and severe hypocapnia (C_2); CBF = cerebral blood flow; CPP = cerebral perfusion pressure; LL = the lower limit at normocapnia (LL_0), mild hypocapnia (LL_1), and severe hypocapnia (LL_2); R = calibers of cerebral resistance vessels at normocapnia (R_0), mild hypocapnia (R_1), and severe hypocapnia (R_2); UL = the upper limit at normocapnia (UL_0), mild hypocapnia (UL_1), and severe hypocapnia (UL_2).

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

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.*[31] 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.*[14,15] 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, $Paco_2$ 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[32] showed that the hypercapnia-induced increase in CBF was further increased by bilateral sympathectomy and attenuated by bilateral electrical stimulation of the superior cervical ganglion in anesthetized cats and unanesthetized rabbits. Cassaglia *et al.*[33] also reported that the CBF was augmented by sympathetic withdrawal *via* bilateral superior cervical ganglionectomy during acute hypercapnia in sleeping lambs. Zhang *et al.*[34] 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[35] and with hypoxia.[36] 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,[37] 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.*[38] 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,[39] whereas propofol representing intravenous agents exerts the opposite effect.[40] As a result, volatile agents impair cerebral autoregulation while propofol preserves it,[41] 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[42] showed in volunteers that an inspired oxygen fraction of 0.85 to 1.0 was associated with a 13% reduction in CBF, whereas an inspired oxygen fraction of 0.1 produced a 35% increase in CBF. In 1960s, Häggendal and Johansson[15] showed that a decrease in arterial blood oxygen saturation from 90% to 20 to 30% led to an increase in CBF of 100%. Gupta *et al.*[43] found 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.*[44] 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.[45] 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[46] and the impairment of dynamic cerebral autoregulation during isocapnic hypoxia could be prevented with hypocapnia.[47] 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.[48] This observation reflects that one of the fundamental goals

Table 1. Details of the Methods Used in the Studies Cited

First Author	Subject	Anesthesia	Cerebral Blood Flow Measurement	Cerebral Perfusion Pressure Manipulation	Carbon Dioxide Manipulation
Fitch[8]	Baboon	Phencyclidine, thiopentone, nitrous oxide	^{133}Xe washout	Bleeding, halothane, trimetaphan, nitroprusside	Constant
Harper[14]	Dog	Thiopentone, nitrous oxide	Kety–Schmidt (krypton 85)	Bleeding	Hypoventilation
Häggendal[15]	Dog	Pentobarbital	Kety–Schmidt (krypton 85)	Bleeding	Hyperventilation, breathing carbon dioxide
Raichle[16]	Monkey	Phencyclidine	Doppler ultrasonography	Bleeding and metaraminol infusion	Breathing carbon dioxide
Ekström-Jodal[17]	Dog	Details not disclosed	Kety–Schmidt (krypton 85)	Bleeding, thoracic aorta clamping	Hyperventilation, breathing carbon dioxide
McCulloch[18]	Human	Propofol infusion or sevoflurane, in addition to remifentanil infusion	Doppler ultrasonography	Phenylephrine infusion	Hypoventilation
Murkin[19]	Human (cardiopulmonary bypass)	Fentanyl, diazepam	^{133}Xe washout	Details not disclosed	Ventilation adjustment
Kaiser[20]	Very low-birth-weight infant	Details not disclosed	Doppler ultrasonography	Tracheal suction	Ventilation adjustment
Harper[21]	Dog	Thiopentone, nitrous oxide	Kety–Schmidt (krypton 85)	Bleeding	Breathing carbon dioxide
Whitelaw[22]	Newborn piglet	Chloralose, urethane	Doppler ultrasonography	Bleeding	Hyperventilation
Artru[23]	Dog	Halothane, nitrous oxide	Diversion of sagittal sinus blood flow	Nitroprusside, trimethaphan	Hyperventilation
Artru[24]	Dog	Isoflurane, nitrous oxide	Diversion of sagittal sinus blood flow	Isoflurane	Hyperventilation
Artru[25]	Dog	Halothane, nitrous oxide	Diversion of sagittal sinus blood flow	Nitroglycerin	Hyperventilation
Matta[26]	Human	Isoflurane, fentanyl infusion	Doppler ultrasonography	Nitroprusside, isoflurane	Ventilation adjustment
Endoh[27]	Human	Propofol and fentanyl infusion	Doppler ultrasonography	Nicardipine, nitroglycerin, prostaglandin E1	Ventilation adjustment
Okuda[28]	Baboon	Halothane, nitrous oxide	^{133}Xe washout, electromagnetic flowmeter	Halothane	Hyperventilation, breathing carbon dioxide
Artru[29]	Dog	Nitrous oxide, halothane	Diversion of sagittal sinus blood flow	Bleeding	Ventilation adjustment
Paulson[31]	Human	Thiopental, nitrous oxide	^{133}Xe washout	Angiotensin	Hyperventilation

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.[49] 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.[4]

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[50] and anesthesia with volatile agents.[41] 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.[51] 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[52] and the perioperative β-blockade therapy that helps the heart but may hurt the brain.[53] 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 $Paco_2$ 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 $Paco_2$ of greater than 55 mmHg should be regarded as having eliminated autoregulation.[18] 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.

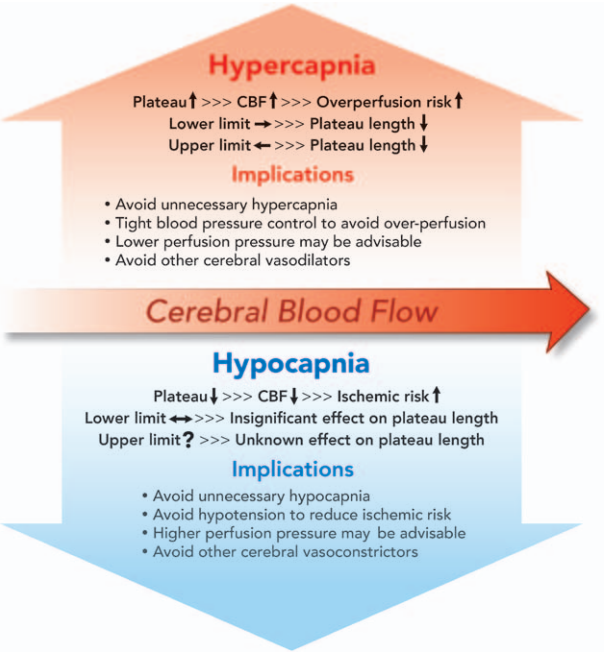

Fig. 5. Clinical implications of the effects of hypercapnia and hypocapnia on cerebral autoregulation. CBF = cerebral blood flow; ↑ = increase or upward shift; ↓ = decrease or downward shift; → = rightward shift; ← = leftward shift; ↔ = insignificant shift.

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.[21–28] 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.[24,29] 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.[54] Hypocapnia was also associated with unfavorable functional outcomes at 90 days after acute stroke.[55]

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. Nonperfusion 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 hypercapnia, 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.

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