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Cardiac Output and Cerebral Blood Flow

The Integrated Regulation of Brain Perfusion in Adult Humans

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ABSTRACT

Cerebral blood flow (CBF) is rigorously regulated by various powerful mechanisms to safeguard the match between cerebral metabolic demand and supply. The question of how a change in cardiac output (CO) affects CBF is fundamental, because CBF is dependent on constantly receiving a significant proportion of CO. The authors reviewed the studies that investigated the association between CO and CBF in healthy volunteers and patients with chronic heart failure. The overall evidence shows that an alteration in CO, either acutely or chronically, leads to a change in CBF that is independent of other CBF-regulating parameters including blood pressure and carbon dioxide. However, studies on the association between CO and CBF in patients with varying neurologic, medical, and surgical conditions were confounded by methodologic limitations. Given that CBF regulation is multifactorial but the various processes must exert their effects on the cerebral circulation simultaneously, the authors propose a conceptual framework that integrates the various CBF-regulating processes at the level of cerebral arteries/arterioles while still maintaining autoregulation. The clinical implications pertinent to the effect of CO on CBF are discussed. Outcome research relating to the management of CO and CBF in high-risk patients or during high-risk surgeries is needed. **(Anesthesiology 2015; 123:1198-208)**

THE brain, as a vital organ, disproportionately receives about 12% of cardiac output (CO) even though it weighs only 2% of the body weight.[1] Cerebral blood flow (CBF) is regulated by a set of powerful mechanisms that include cerebral autoregulation,[2] neurovascular coupling,[3] and cerebrovascular carbon dioxide and oxygen reactivity.[4] It is common to presume that a stable blood pressure or a fluctuating blood pressure as long as it is within the autoregulatory range will not lead to a noticeable change in CBF according to cerebral autoregulation. However, evidence shows that, even though the blood pressure remains stable or within the autoregulatory range, an alteration in CO, either acutely[5–9] or chronically,[10–19] leads to a change in CBF. Thus, it is pertinent to understand the effect of CO on CBF within the framework of cerebral autoregulation, a mechanism describing the effect of cerebral perfusion pressure on CBF.

Optimal organ perfusion is fundamental to avoiding tissue ischemia and overperfusion. There are two common theories to explain the relationship between organ perfusion and systemic hemodynamics. The first is based on an analogy to Ohm's law: organ perfusion depends on arterial blood pressure and vascular resistance of the organ. The other is based on the distribution of CO: the blood flow of each organ is a portion of CO that is determined by the value of CO and the percentage of share based on the organ's metabolic need.[1]

The effect of CO on CBF is a topic that has not been reviewed specifically. However, it is a clinically relevant issue because both acute and chronic changes in CO are frequently encountered in clinical care. In addition, it seems that a revision of the traditional framework of cerebral autoregulation is needed to integrate the effects of cerebral perfusion pressure and CO on brain perfusion in one concordant context. This is an important consideration because blood pressure and CO are related but different systemic hemodynamic parameters, and they usually change simultaneously and may exert distinctive effects on brain perfusion.[20]

The aims of this review are (1) to examine the evidence of the association between CO and CBF under varying

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conditions in adult humans, (2) to present a revised conceptual framework that integrates different regulatory mechanisms of brain perfusion, and (3) to discuss the relevant clinical implications.

Effect of Acute Change in CO on CBF

Evidence

A distinct association between CO and CBF was demonstrated in young healthy volunteers whose central blood volume was decreased *via* lower body negative pressure[5,7–9] or standing up[6] and increased *via* leg tensing,[6] albumin infusion,[8] or normal saline infusion[9] (table 1). Each percentage change in CO corresponded to a 0.35% change in CBF, that is, there is about a 10% CBF decrease for a 30% CO reduction based on eight data pairs from five previous studies (R^2 = 0.9, fig. 1). This association was unlikely to have been confounded by a change in either blood pressure or carbon dioxide because both parameters remained relatively stable except two studies in which carbon dioxide had a clinically significant drop after standing up[6] and lower body negative pressure,[7] respectively. It was also unlikely to be ascribed to a change in cerebral metabolic activity, because these studies were done in resting and unanesthetized subjects. Therefore, the association between CO and CBF is a causal relationship. The finding that β_1-adrenergic blockade concurrently attenuated the increase in both CO and CBF induced by cycling corroborates this proposition.[21]

However, differences among the methodologies used to alter CO and measure CO and CBF should be considered during data interpretation. In these studies, the CO was altered *via* an acute change in central blood volume using different maneuvers, and the CO was measured using different methods even though the CBF was always assessed using transcranial Doppler (TCD; table 1). There is a chance that methodologic heterogeneity could cause inconsistent results. In addition, the practice of using TCD-measured middle cerebral artery blood flow velocity as a CBF surrogate has been cautioned against, especially in patients with cerebrovascular diseases.[22,23]

In contrast, a recent study failed to define an association between cardiac index and CBF with both parameters measured using magnetic resonance imaging techniques in 31 healthy subjects of 50 to 75 yr.[24] There are a multitude of differences between this study and the previous studies summarized in table 1. The most prominent is that the CO (and CBF as a consequence) was not acutely altered compared with that of the previous studies. It is worth noting that the fractional CBF, defined as the ratio of CBF to CO, was inversely correlated with cardiac index (R^2 = 0.22, P = 0.008), implying that when the CO is decreased, the brain shares an increasing percentage of CO.[24]

Mechanism

When the CBF was changed during acute central blood volume alteration, there must be a change in cerebrovascular resistance to account for the flow change because the blood pressure remained relatively stable. Indeed, three of four studies showed an increase in cerebrovascular resistance assessed using TCD pulsatility ratio during lower body negative pressure,[5,7,8] and two studies showed a decrease during albumin or normal saline infusion.[8,9] The common causes of a change in cerebrovascular resistance are (1) a change in cerebral perfusion pressure *via* autoregulation,[2] (2) a change in cerebral metabolic activity *via* neurovascular coupling,[3] (3) a change in arterial blood carbon dioxide partial pressure *via* ventilation change,[25] and (4) a change in sympathetic nervous activity *via* the sympathetic innervation of the cerebral resistance vessels.[26] The first three options are essentially excluded based on the study conditions.[5,7–9] Therefore, by exclusion, this attributes the increase in cerebrovascular resistance to the sympathoexcitation incurred by central blood volume alteration.[8]

During acute central blood volume alteration, the extent of the CBF change is much smaller (about one third) than the change in peripheral regional blood flow.[5,8] This may be because of either the relatively minor role the sympathetic nervous system plays in the brain perfusion compared with the periphery[26–29] or the countering effects by other robust CBF-regulating mechanisms that the periphery lacks. Physiologically, the differential extent of vasoconstriction in different vascular beds shunts the flow from the periphery to the brain because brain perfusion is a priority during acute CO reduction.

However, direct evidence of how the simultaneous acute changes in CO and CBF are mediated by the sympathetic nervous system is lacking, and therefore, the mechanism(s) responsible for the acute change in CBF because of an acute change in CO remains largely speculative.

Effect of Chronically Reduced CO on CBF

Evidence

Extensive evidence shows that CBF is reduced in patients diagnosed with chronic heart failure compared with that of control who do not have cardiac insufficiency (table 2).[10–19] The extent of the CBF reduction correlates with the severity of the chronic heart failure assessed using New York Heart Association functional classification[14] and left ventricular ejection fraction.[18] The CBF reduction is reversed by interventions including cardiac transplantation,[13–15] cardiac resynchronization therapy,[17,19] cardioversion,[30] and captopril treatment[10–12] (fig. 2). Overall, a causal relationship between CO and CBF in patients with chronic heart failure is implied. This proposition is corroborated by a recent study that showed an exaggerated cerebral hypoperfusion in the upright posture in patients with heart failure compared with age- and sex-matched healthy controls.[31]

However, the methodologic heterogeneity and limitations of these studies should be recognized. The sample size in the intervention studies, especially those with cardiac

Table 1. Studies Investigating Simultaneous Changes in Cardiac Output and Cerebral Blood Flow *via* Central Blood Volume Alteration in Unanesthetized Healthy Volunteers

Studies	Sample Size (n)	Intervention	ΔCO (%) (Method)	ΔCBF (%) (TCD)	MAP (mmHg)	Carbon Dioxide	Conclusions and Comments on Cerebrovascular Resistance Change
Levine *et al*.[5]	13	LBNP (55 mmHg)	−30% (inert gas rebreathing)	−16%	82 → 88	N/A	CO and CBF velocity are decreased by LBNP. The magnitude of cerebral vasoconstriction is much smaller than the peripheral vasoconstriction; 17% increase in TCD pulsatility ratio (cerebrovascular resistance index).
van Lieshout *et al*.[6]	10	Standing up	−38% (−1.9 l/min; model flow)	−16% (67 → 56 cm/s)	−9	5.3 → 4.7 kPa (Pa_{CO_2})	Leg tensing attenuates standing-related reduction in cerebral perfusion as it stabilizes CO. Cerebrovascular resistance change was not reported.
		Leg tensing	+38% (+1.8 l/min; model flow)	+11% (56 → 63 cm/s)	No change	4.6 → 4.9 kPa (Pa_{CO_2})	
Brown *et al*.[7]	13	LBNP (50 mmHg)	−44% (6.9 → 3.8 l/min) (impedance cardiography)	−19% (71 → 57 cm/s)	86 → 91	37 → 31 mmHg (ET_{CO_2})	LBNP causes parallel decreases in CO and CBF velocity; 16% increase in pulsatility ratio (cerebrovascular resistance index).
Ogoh *et al*.[8]	7	LBNP (16 mmHg)	−18% (6.5 → 5.3 l/min) (acetylene rebreathing)	−6% (66 → 62 cm/s)	96 → 99	42 → 40 mmHg (Pa_{CO_2})	Linear relationship between CO and CBF velocity during rest and exercise; 8% increase in cerebrovascular resistance index (MAP/MCA Vmean) during LBNP; 14% decrease in cerebrovascular resistance index during albumin infusion.
		25% albumin infusion (2.8 ml/kg)	+30% (6.5 → 8.5 l/min) (acetylene rebreathing)	+11% (66 → 73 cm/s)	96 → 91	42 → 41 mmHg (Pa_{CO_2})	
Ogawa *et al*.[9]	12	LBNP (30 mmHg)	−35% (4.2 → 2.8 l/min) (impedance cardiography)	−4% (67 → 64 cm/s)	80 → 77	41 → 40 mmHg (ET_{CO_2})	Changes in central blood volume cause parallel changes in CO and CBF velocity. No change in cerebrovascular resistance index (MAP/MCA Vmean) during LBNP; 25% decrease in cerebrovascular resistance index during albumin infusion.
		Normal saline infusion (30 ml/kg)	+21% (4.2 → 5.1 l/min) (impedance cardiography)	+8% (67 → 73 cm/s)	80 → 82	41 → 40 mmHg (ET_{CO_2})	

CBF = cerebral blood flow; CO = cardiac output; LBNP = lower body negative pressure; MAP = mean arterial pressure; MCA Vmean = mean middle cerebral artery blood flow velocity; TCD = transcranial Doppler; Δ = change; − = decrease; + = increase.

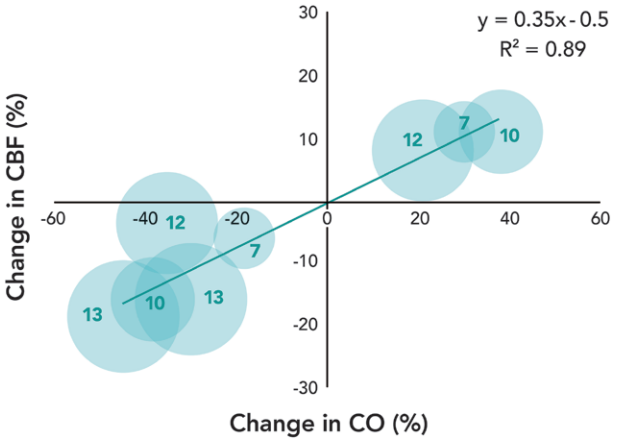

Fig. 1. Correlation between changes in cardiac output (CO) and cerebral blood flow (CBF) in unanesthetized healthy volunteers during central blood volume alterations.[5–9] All data are reported in table 1. The diameter of the *dot* represents the sample size that is also indicated by the number inside of each *dot*.

transplantation, was small.[13–15] The increased blood pressure after cardiac transplantation can confound the interpretation of the effect of improved CO on CBF.[13,15] In rodents, captopril treatment can further reduce the lower limit of cerebral autoregulation after nephrectomy,[32] decrease infarction size *via* CBF improvement after ischemic stroke,[33] and restore cerebral autoregulation after hemorrhagic stroke.[34] Therefore, studies with captopril treatment can be confounded by the direct effect of captopril on CBF regulation.[10–12]

Mechanism

The mechanism underlying the CBF reduction in patients with chronic heart failure is unclear but likely related to the neurohormonal activation incurred by a failing heart. The hyperactivity of both the sympathetic nervous system and the renin–angiotensin–aldosterone axis provokes vasoconstriction of not only the peripheral vascular beds but also the cerebral vascular bed.[35–38] The circulating and locally formed angiotensin II may contribute to the decrease of CBF *via* the AT1 receptors expressed in cerebrovascular endothelial cells and in the brain regions controlling cerebral circulation.[39] Similar to the effect of acute CO reduction on CBF, the differential extent of vasoconstriction of different vascular beds shunts the flow from the periphery to the brain in patients with chronic heart failure, resulting in a lesser extent of CBF reduction than both the CO and the peripheral blood flow.[35]

Neurocognitive Impairment

A relevant question that deserves discussion is what the consequences of the reduced cerebral perfusion are in patients with chronic heart failure. It is counterintuitive to assume that long-term suboptimal brain perfusion is inconsequential. Indeed, abundant evidence shows that the prevalence of cognitive dysfunction is inappropriately high in patients diagnosed with chronic heart failure.[40–45] The odds ratio for cognitive impairment in patients with chronic heart failure is 1.62 with the 95% CI of 1.48 to 1.79 ($P < 0.0001$) based on a systematic review.[43] The extent of cognitive impairment parallels the severity of chronic heart failure.[42,44,46] Both cardiac resynchronization therapy[47,48] and transplantation[49,50] improved the impaired cognition.

Chronic heart failure is also linked to abnormal brain aging and Alzheimer disease.[51–54] The relentless cerebral hypoperfusion and neurohormonal hyperactivity likely contribute to the dysfunction of the neurovascular unit.[53,54] The neuronal energy crisis facilitates protein synthesis abnormalities that include impaired clearance of amyloid β and hyperphosphorylation of τ protein, ending up with the formation of amyloid-β plaques and neurofibrillary tangles.[54,55]

Despite the plausible notion that there is a link among chronic heart failure, cerebral hypoperfusion, and neurocognitive dysfunction, caution is needed before claiming a causal relationship because these chronic conditions share risk factors. In addition, not every patient with neurocognitive impairment has chronic heart failure and *vice versa*.

Disease States Demonstrating CO–CBF Association

Vasospasm

The goal in treating vasospasm induced by subarachnoid hemorrhage is to restore the reduced CBF. One of the strategies is to augment the CO with the hope of improving the cerebral perfusion. A clinical study found that a 46% increase in CO *via* dobutamine infusion led to a significant increase in CBF (from 25 to 35 ml min^{-1} 100 g^{-1}) in the brain regions perfused by the vasospastic arteries.[56] The increase in cerebral perfusion took place despite a decrease in mean arterial pressure from 113 to 108 mmHg. The result of this study was corroborated in a separate study that showed the clinical reversal of the ischemic symptoms by dobutamine infusion combined with hypervolemic preloading in 78% of symptomatic patients.[57] Intraaortic balloon pump counterpulsation has also been tested in this patient population. In a report of 15 cases in which this treatment was used in patients who also had neurogenic stress cardiomyopathy, it was concluded that the use of intraaortic balloon pump counterpulsation was effective in preventing the delayed ischemic neurologic deficits.[58]

Ischemic Stroke

In patients with acute ischemic stroke in the middle cerebral artery territory, an association between CO and TCD-estimated CBF was demonstrated in the affected, but not the unaffected, brain region when using hypervolemic hemodilution combined with dopamine–dobutamine infusions.[59] Intraaortic balloon pump counterpulsation was also found to increase TCD-estimated CBF by 21 and 11% in patients with acute ischemic stroke whose left ventricular ejection fractions were 28 and 44%, respectively.[60] Intraaortic

Table 2. Cerebral Blood Flow at Baseline and/or after Various Interventions in Patients with Chronic Heart Failure

Studies	Sample Size (n)	CHF Severity	Baseline CBF (Method)	Control CBF	Intervention	ΔCO	ΔCBF (Method)	MAP (mmHg)	Conclusions and Comments
Rajagopalan *et al.*[10]	9	NYHA III/IV; LVEF = 17%	61 ml min^{-1} 100 g^{-1} (^{133}Xenon clearance)	76 ml min^{-1} 100 g^{-1}	Captopril	N/A	61 → 74 ml min^{-1} 100 g^{-1} (^{133}Xenon clearance)	95 → 85	CBF is reduced in severe CHF and restored 9 days after captopril treatment.
Paulson *et al.*[11]	5	NYHA III/IV	42 ml min^{-1} 100 g^{-1} (^{133}Xenon clearance)	68 ml min^{-1} 100 g^{-1}	Captopril	N/A	42 → 46 ml min^{-1} 100 g^{-1} (^{133}Xenon clearance)	97 → 83	CBF is reduced in severe CHF and slightly increased 180 min after captopril treatment.
Paulson *et al.*[12]	8	NYHA III/IV	45 ml min^{-1} 100 g^{-1} (^{133}Xenon clearance)	63 ml min^{-1} 100 g^{-1}	Captopril	N/A	45 → 52 ml min^{-1} 100 g^{-1} (^{133}Xenon clearance)	98 → 89	CBF is reduced in severe CHF and increased 21 days after captopril treatment.
Gruhn *et al.*[13]	12	NYHA III/IV; LVEF = 19%	36 ml min^{-1} 100 g^{-1} (single-photon emission CT)	52 ml min^{-1} 100 g^{-1}	Cardiac transplant (n = 5 only)	N/A	35 → 50 ml min^{-1} 100 g^{-1} (single-photon emission CT)	76 → 93	CBF is substantially reduced in patients with severe CHF and restored after cardiac transplant.
Choi *et al.*[14]	52	NYHA II/III; LVEF = 20%	40 ml min^{-1} 100 g^{-1} (radionuclide angiography)	49 ml min^{-1} 100 g^{-1}	Cardiac transplant (n = 4 only)	N/A	35 → 44 ml min^{-1} 100 g^{-1} (radionuclide angiography)	N/A	CBF is decreased in advanced CHF and associated with factors that represent the severity and chronicity of CHF.
Massaro *et al.*[15]	14	NYHA III/IV	N/A	N/A	Cardiac transplant	N/A	+53% (TCD)	99 → 126	CBF velocity is consistently increased after cardiac transplant.
Vogels *et al.*[16]	43	NYHA II/III; LVEF = 27%	47 cm/s (TCD)	56 cm/s	N/A	N/A	N/A	N/A	CBF velocity is significantly lower in patients with mild-to-moderate CHF than control.
van Bommel *et al.*[17]	16	NYHA III; LVEF = 28%	N/A	N/A	Cardiac resynchronization therapy	28% → 40% (ejection fraction)	47 → 58 cm/s (TCD)	N/A	Cardiac resynchronization therapy improves both left ventricle systolic function and CBF.
Loncar *et al.*[18]	71	NYHA II/III	677 ml/min (color duplex sonography)	783 ml/min	N/A	N/A	N/A	N/A	CBF is reduced in elderly males with mild-to-moderate CHF and associated with factors that represent CHF severity.
Ozdemir *et al.*[19]	22	NYHA III/IV; LVEF = 32%	N/A	N/A	Cardiac resynchronization therapy	2.9 → 3.7 l/min (CO index)	502 → 702 ml/min (color duplex Doppler ultrasound)	89 → 87	Cardiac resynchronization therapy improves both CO and CBF.

The control was from patients without history of cardiac insufficiency.

CBF = cerebral blood flow; CHF = chronic heart failure; CO = cardiac output; CT = computed tomography; LVEF = left ventricle ejection fraction; MAP = mean arterial pressure; N/A = not available; NYHA = New York Heart Association; TCD = transcranial Doppler; Δ = change; + = increase.

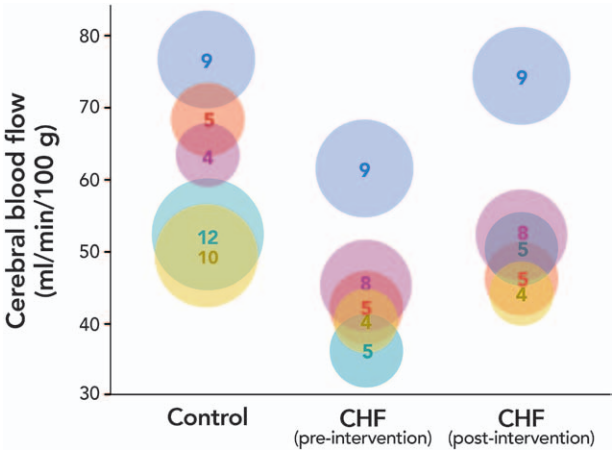

Fig. 2. Cerebral blood flow in patients diagnosed with chronic heart failure (CHF) before (preintervention) and after (postintervention) various interventions.[10–14] The control was from patients without cardiac insufficiency. All data are reported in table 2. Only the studies that reported the control, preintervention, and postintervention values of cerebral blood flow in the units of ml min^{-1} 100 g^{-1} were included. The *dots* with the same color are from the same study. The diameter of the *dot* represents the sample size that is also indicated by the number inside of each *dot*.

balloon pump counterpulsation normally decreases systolic blood pressure, increases diastolic blood pressure, and produces little or no change in mean blood pressure in normotensive patients.[61] Therefore, it is reasonable to attribute the improvement of the CBF to the augmentation of the CO during the application of intraaortic balloon pump counterpulsation.

Sepsis

In studies conducted in septic patients, dobutamine infusion increased both cardiac index (from 3.4 to 4.2 l min^{-1} m^{-2} and from 3.8 to 6.3 l min^{-1} m^{-2}) and TCD-estimated CBF (from 52 to 62 cm/s and from 68 to 80 cm/s), whereas the increase in mean arterial pressure was from 85 to 91 mmHg and from 77 to 86 mmHg, respectively.[62,63] Both studies showed a better correlation between CO and CBF than between blood pressure and CBF using both the relative changes of parameters[63] and the absolute values of measurements.[62]

Disease States Demonstrating a Lack of CO–CBF Association

Head Injury

An association between changes in CO and CBF (^{133}Xe washout) was not found during treatment with phenylephrine, trimethaphan or mannitol in comatose and ventilated patients with severe head injury.[64] Phenylephrine, which is a peripheral vasoconstrictor used to increase blood pressure, actually causes a decrease in CO.[20] This may have confounded the study. An increase in perfusion pressure can lead to an increase in CBF in neurologically critically ill patients who have impaired autoregulation[65]; as a result, phenylephrine treatment likely causes opposite changes in CBF (increase) and CO (decrease).

Neurologic Surgery

CBF is normally increased after surgical resection of brain arteriovenous malformations. However, an association between changes in CO and CBF (^{133}Xe washout) based on the preresection and postresection measurements was not found in this patient population.[66] Hemodynamic variables including CO, arterial blood pressure, central venous pressure, and pulmonary artery diastolic pressure remained stable in the face of the increase in CBF. Brain arteriovenous malformations have unique hemodynamic physiology including the relatively low transnidal pressure gradient that may shunt a portion of CBF through the lesion.[67] Thus, it is speculated that after surgical resection, the portion of CBF originally going through the arteriovenous malformation reroutes through the normal brain resulting in a regionally increased CBF in the face of unchanged systemic hemodynamics.

Cardiac Surgery

Cardiac surgery with cardiopulmonary bypass is a special situation in which organ perfusion is propelled by an extracorporeal centrifugal pump. How the pump flow affects the cerebral perfusion depends on the blood gas management.[68] With α-stat management, CBF (^{133}Xe washout) is correlated with blood pressure, not pump flow.[69] With pH-stat management, CBF (argon saturation and desaturation method) is correlated with pump flow in the face of a stable blood pressure.[70] The precise mechanism(s) underlying this discrepancy is unclear. The cerebral vasodilation induced by hypercapnia may be responsible, because carbon dioxide is often added during pH-stat management but not during α-stat management.[71] Hypothermic cardiopulmonary bypass suppresses sympathetic nervous activity[72] and that may also alter the association between CO and CBF.

Hepatic Failure

An association between CO and CBF (^{133}Xe washout) was not found in patients with fulminant hepatic failure.[73] However, this study was underpowered with only eight pairs of data, and the statistical insignificance likely reflects a single outlier. This study also found that the norepinephrine-induced changes in CO and TCD-estimated CBF did not correlate with each other. However, norepinephrine primarily increases blood pressure and has unpredictable effects on CO.[74] Therefore, the study was confounded by the simultaneous change in blood pressure.

Cardiology

A study performed in patients with coronary heart disease or cardiomyopathy referred for echocardiography failed to show an association between CO and CBF.[75] However, the study was confounded by the use of common carotid artery

blood flow measured using color M-mode duplex system as a surrogate for CBF as the external carotid artery blood flow is included.

Integrated Regulation of CBF

CBF is rigorously regulated by multiple powerful mechanisms to safeguard the matching of cerebral metabolic demand and supply.[76] CO is one of the physiologic processes that contribute to CBF regulation. However, exactly how an alteration in CO, in the face of a stable blood pressure, leads to a change in CBF is not entirely clear. A proposal that integrates various CBF-regulating mechanisms, including the role of blood pressure and CO, in one concordant conceptualization seems necessary.

A conceptual framework of the integrated regulation of the brain perfusion is proposed (fig. 3). It needs to be appreciated that the various mechanisms, no matter how distinctive, all exert their regulatory effects on the same target, that is, the cerebral resistance vessels. Different mechanisms may affect different segments of the cerebral resistance vessels. For example, sympathetic stimulation constricts large cerebral arteries, whereas an increase in blood pressure constricts the arterioles.[77] The various CBF-regulating mechanisms integrate at the level of the cerebral resistance vessels and generate only one consequence that is the extent of the cerebrovascular resistance. Therefore, how CBF is changed after a change in any of the regulatory processes depends on how the different mechanisms are integrated. Different mechanisms likely have different degrees of regulatory power likely determined by the physiologic priority in the context of the clinical situation. The one with the major regulatory power plays a dominant role, whereas one with minor power plays a smaller role.

The effect of CO on CBF can be appreciated within the framework of cerebral autoregulation (fig. 3). When CO is decreased, the plateau descends slightly reflecting the smaller decrease in CBF, and *vice versa*; however, the overall autoregulatory mechanism is maintained. This proposition is corroborated by the finding that dynamic cerebral autoregulation is not affected by the acute change in CO.[78] Thus, this speculative proposal integrates the effects of blood pressure and CO on brain perfusion. However, how the lower and upper limits of the autoregulation curve are changed and whether the plateau tilts when the CO is altered are unknown.

The lesser extent to which CBF changes compared with that of CO or peripheral blood flow during acute or chronic

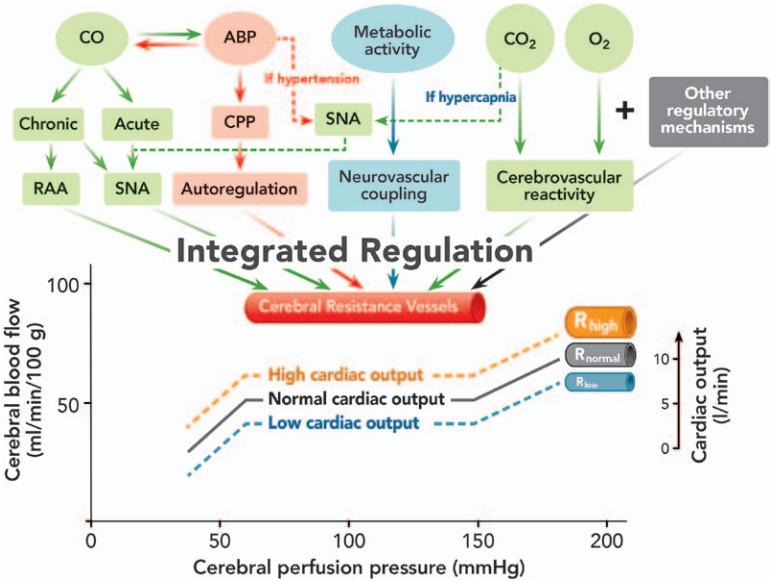

Fig. 3. The conceptual framework of the integrated regulation of brain perfusion. The cerebrovascular resistance determined by the caliber of the cerebral resistance vessels is regulated by various physiologic processes: (1) cardiac output (CO) likely *via* sympathetic nervous activity (SNA) and renin–angiotensin–aldosterone (RAA) system, depending on the chronicity of the change in CO,[5–19] (2) arterial blood pressure (ABP) and cerebral perfusion pressure (CPP) *via* cerebral autoregulation,[2,71] (3) cerebral metabolic activity *via* neurovascular coupling,[3,76] and (4) arterial blood carbon dioxide (CO_2)[4,25,71] and oxygen (O_2)[4] *via* cerebrovascular reactivity. The SNA regulates cerebral blood flow[26–29] and may play a prominent role during acute hypertension and hypercapnia[29] as a protective mechanism preventing cerebral overperfusion (*dashed line*). These various regulatory mechanisms, together with other CBF-regulatory mechanisms that are not specified here such as anesthetic effects, integrate at the level of the cerebral resistance vessels and generate only one consequence, which is the extent of the cerebrovascular resistance and, therefore, jointly regulate brain perfusion. The plateau of the autoregulation curve shifts downward when the CO is reduced and upward when augmented. The position of the plateau is determined by the caliber (R) of the cerebral resistance vessels at high (R_{high}), normal (R_{norm}), and low (R_{low}) CO. The scale of CO on the right side is smaller than that of CBF on the left side to reflect the lesser extent of change in CBF induced by an alteration of CO.

CO alterations can be explained by the fact that the extent to which CBF is changed is determined by the integrated effect of all CBF-regulating mechanisms. Other powerful CBF-regulating mechanisms unrelated to CO may buffer the effect of CO on CBF, causing a lesser flow change in the brain compared with the organs that are not influenced by these mechanisms.

Clinical Implications

Acute changes in CO because of a variety of etiologies such as dehydration, blood loss, body tilt, mechanical ventilation, intraabdominal insufflation, pneumothorax, hemothorax, diuresis, vasodilation, sympatholysis, anesthetic agent, pulmonary embolization, myocardial infarction, and arrhythmia are frequently encountered in the operating room. CBF may decrease when the CO is reduced. Therefore, for the purpose of maintaining CBF, any adverse change in CO should be remedied. Goal-directed fluid therapy for the purpose of CO optimization has been shown to be associated with an improved overall outcome after intraabdominal surgeries.[79,80] However, to what degree this favorable outcome is attributable to the optimization of CBF is unknown.

It seems reasonable to advocate intraoperative monitoring of both CO and CBF in patients with reduced cardiac function or cerebrovascular obstructive diseases or during high-risk surgeries that have a greater chance of causing hemodynamic fluctuation. The currently unanswered question is how best to monitor both parameters continuously and noninvasively and which patient populations benefit the most from this strategy of care.

In the perioperative setting, it needs to be emphasized that the cerebral circulation is affected by multiple processes, and CO is one of them. Anesthesia itself affects cerebral perfusion *via* a variety of pathways that include the suppression of cerebral metabolic activity,[81] intrinsic cerebral vasodilation by volatile agents,[82] impairment of cerebral autoregulation by volatile agents,[83] suppression of the sympathetic nervous activity,[84] and disturbance of the systemic hemodynamics.[85] Therefore, the association between CO and CBF learned from studies performed in unanesthetized healthy volunteers may not always apply in the anesthetized surgical patients.

Chronic heart failure is prevalent affecting approximately 2% of the adult population and is associated with a high mortality.[86] Its prevalence increases sharply with age, affecting 10% of the population aged 65 yr or older.[87] An increasing number of patients diagnosed with chronic heart failure are expected to present to the operating room for surgery, and this poses a great challenge for perioperative care. It is judicious to avoid acute reductions of both CO and CBF on top of the chronic cardiac insufficiency and cerebral hypoperfusion. This mandates thoughtful preoperative preparation, adept appreciation of cardiovascular and cerebrovascular physiology and their interaction, and preemptively preventing circumstances that threaten cardiac performance and brain perfusion.

Studies on the association between CO and CBF in patients with major neurologic, medical, or surgical conditions are confounded by methodologic limitations. However, it seems that interventions that enhance cardiac performance may improve perfusion of the ischemic brain, especially in patients with impaired cardiac function (fig. 2).[56–60] It is important although to remember that drugs that increase blood pressure such as phenylephrine and norepinephrine may actually decrease CO.[20,74] In contrast, dobutamine and volume augmentation can increase the CO but not necessarily blood pressure. The effect of a vasopressor on CBF likely depends on the drug being used, the disease state, and the functional status of the regulatory mechanisms of brain perfusion.[88,89] Currently, long-term outcome data relevant to the choice of vasopressor in various clinical situations is lacking.

The proposed conceptualization integrating various CBF-regulating mechanisms within the framework of cerebral autoregulation has important clinical implications. The habitual thinking that how the brain is perfused is merely dependent on the blood pressure should be abandoned. The autoregulatory curve should be regarded as a dynamic process, meaning that its shape, plateau, and the lower and upper limits may change depending on the integrated effect of nonpressure but CBF-regulating mechanisms including the CO.[71] For a given value of blood pressure, even though it is deemed clinically acceptable, the CBF may be either higher or lower than that estimated by the traditional autoregulatory curve. Therefore, the management of CBF should be guided by a multifactorial but integrated framework of CBF regulation, especially in patients who are at risk of cerebral ischemia.

Overall, these recommendations are largely based on physiologic studies in healthy volunteers and patients with chronic heart failure or other diagnoses. Meaningful outcome research pertinent to the management of CO and CBF is needed to better guide clinical practice. Moreover, noninvasive or minimally invasive, reliable, and continuous CO monitoring, as well as CBF monitoring or its surrogates, need to be considered for use in high-risk patients or during high-risk surgeries.

Summary

As one of the most important systemic hemodynamic parameters, CO contributes to the regulation of CBF likely *via* the sympathetic nervous activity, with or without the renin–angiotensin system depending on the acuteness or chronicity of change. The various mechanisms that regulate the cerebral circulation integrate at the level of the cerebral resistance vessels and jointly determine the brain perfusion. The effect of CO on brain perfusion should be integrated

into the framework of cerebral autoregulation. The clinical considerations are confounded by methodologic limitations. Interventions aimed at enhancing cardiac performance and improving brain perfusion need to be tested by relevant clinical outcomes research.

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Competing Interests

The authors declare no competing interests.

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