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Cerebral Blood Flow Autoregulation in Sepsis for the Intensivist: Why Its Monitoring May Be the Future of Individualized Care

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Abstract

Cerebral blood flow (CBF) autoregulation maintains consistent blood flow across a range of blood pressures (BPs). Sepsis is a common cause of systemic hypotension and cerebral dysfunction. Guidelines for BP management in sepsis are based on historical concepts of CBF autoregulation that have now evolved with the availability of more precise technology for its measurement. In this article, we provide a narrative review of methods of monitoring CBF autoregulation, the cerebral effects of sepsis, and the current knowledge of CBF autoregulation in sepsis. Current guidelines for BP management in sepsis are based on a goal of maintaining mean arterial pressure (MAP) above the lower limit of CBF autoregulation. Bedside tools are now available to monitor CBF autoregulation continuously. These data reveal that individual BP goals determined from CBF autoregulation monitoring are more variable than previously expected. In patients undergoing cardiac surgery with cardiopulmonary bypass, for example, the lower limit of autoregulation varied between a MAP of 40 to 90 mm Hg. Studies of CBF autoregulation in sepsis suggest patients frequently manifest impaired CBF autoregulation, possibly a result of BP below the lower

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limit of autoregulation, particularly in early sepsis or with sepsis-associated encephalopathy. This suggests that the present consensus guidelines for BP management in sepsis may expose some patients to both cerebral hypoperfusion and cerebral hyperperfusion, potentially resulting in damage to brain parenchyma. The future use of novel techniques to study and clinically monitor CBF autoregulation could provide insight into the cerebral pathophysiology of sepsis and offer more precise treatments that may improve functional and cognitive outcomes for survivors of sepsis.

Keywords

hemodynamics; cerebrovascular circulation; sepsis; oximetry; critical care; physiologic monitoring

Background

Sepsis is estimated to affect 31 million patients yearly worldwide[1] and is associated with significant morbidity and mortality, adding an estimated US$20 000 to the cost of an affected patient's care.[2–4] Management of hypotension is fundamental to sepsis treatment although appropriate blood pressure (BP) targets have been debated for decades.[5–11] The recent High versus Low Blood-Pressure Target in Patients with Septic Shock trial found no difference in mortality or in the use of renal replacement therapy for patients randomized to a mean arterial pressure (MAP) goal of 65 to 70 mm Hg versus 80 to 85 mm Hg.[12] Less renal replacement therapy was needed, though, in the subset of patients with chronic hypertension randomized to the high versus low MAP target. Although these findings suggest that the aggressive use of vasopressors is unnecessary in some patients, others may benefit from a higher MAP.[13–15] Cerebral perfusion represents a physiological-based minimum end point in critical illness which may allow intensivists to develop individual MAP goals to protect neurologic, and possibly other organ, function.[16,17]

Treatment of hypotension in sepsis follows the principle that maintaining MAP above the lower limit of cerebral blood flow (CBF) autoregulation (LLA), thought to be between 50 and 60 mm Hg, should ensure cerebral perfusion.[11] This is based on Lassen's review in which he plotted CBF and MAP data from 11 human studies.[18] The resulting autoregulation curve showed increasing CBF as MAP rose to 50 to 60 mm Hg and a plateau of constant CBF when MAP was greater than 60 mm Hg.[18] New technologies make it possible to create this curve for each patient at the bedside.[19] Studies using transcranial Doppler (TCD) and near-infrared spectroscopy (NIRS) in patients undergoing cardiopulmonary bypass show that upper and lower limits of autoregulation vary greatly and unpredictably.[19,20] In fact, the LLA ranged from 40 to 90 mm Hg between individuals.[20] Although time spent below the LLA intraoperatively is associated with acute kidney injury,[17] cognitive dysfunction,[21] major morbidity, and operative mortality,[22] time spent above the upper limit of autoregulation (ULA) is associated with postoperative delirium.[23] In patients with traumatic brain injury (TBI) and subarachnoid hemorrhage, CBF autoregulation metrics have a prognostic value[24,25] and are recommended for consideration to guide BP management in TBI.[26–30] Individualizing MAP targets based on CBF autoregulation in sepsis might prove similarly advantageous. The goal of this study was to provide a narrative review of CBF

autoregulation in sepsis. A search on PubMed, Embase, Cochrane, and Scopus through August 8, 2015 identified 1925 unique references. Additional references were collected by hand-searching. We use these data to provide an overview of CBF autoregulation-monitoring methods and to make recommendations for future research in hopes of improving outcomes for patients surviving sepsis.

CBF Autoregulation

Autoregulation of blood flow was first discovered in the kidney and subsequently in other organ systems.[18,31] The mechanisms for autoregulation integrate a variety of mechanical, chemical, and molecular signals to effect changes in vascular caliber to regulate blood flow.[32,33] In the brain, the pairing of metabolic activity and vascular tone is accomplished through a neurovascular unit comprised of a neuron, capillary, neuroglial, and all other supportive cells.[32–34] The exact composition varies based on the brain region and its associated function that can include maintenance of the blood–brain barrier, regulation of CBF, and control of angiogenesis.[33–35]

The CBF autoregulation can be understood in terms of Darcy law of flow whereby an organ's blood flow is the quotient of perfusion pressure and vascular resistance.[36] Cerebral perfusion pressure (CPP) is the difference between MAP and the higher of either central venous pressure or intracranial pressure (ICP). As this pressure difference changes along the autoregulation plateau, flow remains constant because of compensatory alterations in cerebrovascular resistance (CVR). The CVR is determined by capillary, arteriolar, and arterial diameters (ie, vasodilation and vasoconstriction) mediated by nitric oxide and arginine.[32,37,38] The metabolic demands of the neurovascular unit lead to changes in CVR that, in turn, enhance or decrease blood flow.[31,33] Mediators for this include glutamate, adenosine, vasoactive intestinal peptide, and hydrogen and potassium ions.[32,33] Carbon dioxide (CO_2) is a potent vasodilator in the brain[39] and vascular response to changes in CO_2 is measured as cerebrovascular reactivity, or CO_2 reactivity, with units of percentage change in CBF velocity per kilopascal change in end-tidal CO_2.[40] The CVR also changes in response to CPP. This can be assessed as dynamic CBF autoregulation referring to the ability of cerebral blood vessels to stabilize CBF following a rapid change in MAP.[41] Dynamic CBF autoregulation is often assessed using transfer function analysis.[42] Finally, CVR responds to nervous system innervation, though sympathetic nerves are uniquely limited to large arteries in the brain.[31] The multitude of pathways available to change CVR provides the necessary tools to autoregulate CBF effectively.

Technology for CBF Autoregulation Measurement

Bedside techniques for measuring CBF autoregulation can be divided into invasive and noninvasive methods. Invasive techniques are based mostly on monitoring CBF surrogates and include jugular venous oximetry, brain tissue oxygen monitoring, cerebral microdialysis, and laser Doppler or thermal diffusion flowmetry.[43,44] Another method uses the Kety-Schmidt technique, which uses the Fick principle, to measure CBF using arterial and venous catheters and a number of different tracers including xenon, argon, nitrous oxide, or dye.[32]

The latter technique is only suitable for intermittent measurements rather than continuous monitoring of CBF autoregulation.

The TCD is a noninvasive technique, which measures the mean velocity of blood flow in the middle cerebral artery (MCAv) where it courses through the transtemporal window.[45–48] Measurement of the MCA diameter is not standard and therefore TCD provides only a surrogate for CBF based on the assumption that MCA diameter changes minimally with changes in CPP.[48–50] In general, relative changes in TCD-derived MCAv correlate well with changes in CBF if CO_2 is near normal, but absolute measures and response to extremes of CO_2 are less valid.[51–54] Using TCD as a surrogate for CBF assumes that the MCA is a representative of the entire cerebral blood supply including the posterior circulation.[48] The TCD cannot obtain adequate readings in the transtemporal window in 8.2% of patients.[55]

A few measurements derived from TCD are notable. As CBF is a pulsatile phenomenon, CBF autoregulation can be monitored in the time or frequency domain. The former relies only on spontaneous changes in CPP whereas the later uses maneuvers to change CPP.[56] A moving correlation coefficient can be calculated between MCAv and systemic MAP, termed the mean velocity index (Mx).[57] Averages of a sliding 5-minute window updated every 10 seconds for MAP and MCAv are often used.[32] Mean velocity index <0.3 is generally considered consistent with intact autoregulation; higher values are thought to indicate dependence of CBF on MAP and, therefore, impaired autoregulation.[19,49,58] This may only be reliable in the presence of slow waves (ie, every 20 seconds to 3 minutes), which are physiologic oscillations in BP, MCAv, cerebral blood volume, and CBF[59,60] as such predictable patterns decrease the signal-to-noise ratio. The pulsatility index is the difference between the systolic and diastolic velocities divided by the mean velocity and is a measure of cerebral vasoconstriction.[47,49] Finally, the Lindegaard ratio (MCA/internal carotid artery [ICA] index) is the MCAv divided by the blood flow velocity in the extracranial ICA and is believed to suggest vasospasm when greater than 1.8.[47,61]

The NIRS is a noninvasive method to monitor CBF autoregulation. Near-infrared light is transmitted from a source (either light-emitting diode or fiber-optic light) via an adhesive pad attached to the forehead and directed toward the frontal lobe. The amount of light detected by sensors positioned at set distances from the light source is a function of reflectance from the light–tissue angle, scattering from body tissues, and absorption by chromophores.[62,63] Cytochrome a, a_3 and hemoglobin are the most abundant chromophores absorbing infrared light between 700 and 1000 nm wavelength.[62,64] Bilirubin is another, contributing no significant impact on light absorption unless levels are excessive.[65,66] The absorption of near-infrared light by oxygenated hemoglobin, deoxygenated hemoglobin, and total hemoglobin is determined using 3 wavelengths of light that are relatively specific for each molecule. Light absorption is not measured directly but is inferred from changes in scattered light detected by the sensors.[63] The distance of these sensors from the light source determines the arc or depth of light absorption, which is typically fairly shallow.[67] This methodology assumes that absorption from cytochrome a, a_3 and bilirubin is minimal, proportional scattering of infrared light from the tissues remains constant, and the hemoglobin measured is contained in a fixed mixture of vessels that are approximately 70% to 75% venous and 25% to 30% arterial.[68,69] The assumption of a set venous:arterial ratio

creates a bias in measurement as the true ratio is individual and dependent on oxygen and CO_2 levels.[70] Equations used to account for variability are manufacturer specific, making regional cerebral oxygen saturation ($rSco_2$) derived from different machines nonequivalent.[63,68] Contamination of the signal from extracranial tissue is minimized when the distance between the emitter and detector is more than 4 cm.[71,72] Another method subtracts extracranial light absorption measured by a proximal detector (<4 cm from the emitter) from that absorbed from deeper tissue measured by a distal sensor. Although this should yield an oxygen saturation measurement from the superficial cerebral cortex only, studies demonstrate the correction is incomplete.[68,73] Altogether, the underlying assumptions make relative changes and trends in $rScO_2$ more reliable than the absolute value.[68,70]

Similar to TCD, a multitude of measurements derived from NIRS can be assessed and are most reliable in the presence of slow waves. The tissue oxygenation index (TOI) is the ratio of oxygenated hemoglobin to total hemoglobin. The correlation coefficient between slow wave changes in TOI and MAP is termed TOx or, more commonly, the cerebral oxygenation index (COx).[74] A COx value of <0.3 indicates intact autoregulation and the MAP with the lowest COx is considered the optimal MAP.[22] This method was validated in a piglet model where the 0.3 threshold was established using laser Doppler flowmetry to measure CBF[75] and has since been used in human studies.[19,76,77] As previously discussed regarding Darcy law of flow, the CPP can be limited by elevated ICP. The NIRS can therefore be used to describe the relationships between MAP, CBF, and ICP when an ICP monitor is available, which resulted in the development of the pressure reactivity index as the correlation coefficient between ICP and MAP.[59] Finally, NIRS can be followed during provocative testing to measure dynamic cerebrovascular reactivity.

A variety of radiographic imaging techniques have been developed for a multidimensional assessment of CBF. Major benefits of such techniques include quantitative assessment of the entire brain rather than a single region. Drawbacks include high cost, requirement to transport patients, and provision of a one-time measurement rather than continuous monitoring. These imaging modalities include contrast-based perfusion computed tomography (CT), positron emission tomography (PET), single-photon emission CT (SPECT), xenon-based perfusion CT, and perfusion-weighted magnetic resonance imaging (MRI).[32,43,78] Newer blood oxygen level dependent– and arterial spin labeling–based functional MRI techniques have been utilized to study CBF and perfusion abnormalities in sepsis.[79] Provocative techniques such as inducing hypercarbia or administering acetazolamide can be used in conjunction with MRI, PET, and xenon or standard perfusion CT scanning. Acetazolamide inhibits carbonic anhydrase and alters CO_2 degradation in the cerebral vasculature causing increased CO_2 and vasodilatation after ingestion.[52] Acetazolamide reactivity testing is commonly used in TCD testing as a measure of cerebrovascular reactivity.

Sepsis

Sepsis is a state of diffuse immune dysregulation and altered vascular function caused by invasive pathogens.[80–82] Disruption of vascular nitric oxide plays a critical role in these

changes, resulting in vascular smooth muscle dilation, endothelial activation, and increased capillary permeability.[82] Many of the mediators of innate immunity, such as Toll-like receptors, have genetically based receptor affinity for gram-negative endotoxin, which causes early activation of the inflammatory response.[81] The effects of sepsis on the brain are multidimensional and impact autoregulation through alterations in arterial and capillary function as well as brain astrocytic and microglial function.[35,82–84] The resultant cerebral hypoperfusion/hyperperfusion and inflammatory injury may contribute to sepsis-associated cerebral impairment.[82,83,85] Understanding the effects of sepsis on CBF autoregulation is of paramount importance to developing brain-protective strategies.

Sepsis and the Brain

There is a growing body of literature on the effects of sepsis on the brain and their mechanisms.[86] Pathologically, autopsy findings include neuronal apoptosis, cerebral hemorrhage, multifocal necrotizing leukoencephalopathy, ischemia, and microabscesses.[86–89] Physiologically, there is evidence of microglial activation, neurotransmitter imbalance, particularly dopamine and acetylcholine[83,86,89], and vagus nerve stimulation with downstream effects on cerebral activity.[82] The blood–brain barrier is rendered more permeable leading to cerebral edema,[78,82] mediated in part by activated NF-κB and increased inducible nitric oxide synthase (iNOS) activity.[32]

Clinically, sepsis-associated encephalopathy (SAE) complicates sepsis in up to 71% of patients.[90] The SAE ranges in severity from mild confusion to obtundation and correlates with electroencephalogram abnormalities including seizures, absence of reactivity, triphasic waves, and prevalent δ activity.[91–95] A significant number of survivors of critical illness have decreased cognitive function, higher incidence of psychiatric disorders[4], and lower health-related quality of life.[96,97] This cognitive impairment is long-lasting, significantly different from survivors of nonsepsis hospitalizations,[98] irrespective of patient age,[99] and associated with duration of SAE.[100]

Radiographically, xenon CT and SPECT show patients with hypoactive delirium having cerebral hypoperfusion.[101,102] Survivors of sepsis demonstrate volume loss, hippocampal atrophy,[103] and white matter disruption that correlate with long-term cognitive deficits.[104] In contrast to these data suggesting hypoperfusion, cardiac surgery intraoperative hyperperfusion, as evidenced by NIRS data, is associated with postoperative delirium.[23,105] This suggests heterogeneity in CBF by etiology of delirium and demonstrates the potential importance of CBF autoregulation in understanding the pathophysiology of sepsis, SAE, and their long-term cognitive outcomes.

CBF Autoregulation in Sepsis

The CBF autoregulation has been studied in patients with sepsis with varying results, as shown in Table 1. Most data suggest that CBF autoregulation is impaired in early versus late sepsis.[106–112] Although Matta et al[106] found intact CBF autoregulation using TCD in patients with sepsis for <24 hours, the baseline MAP was 75 mm Hg, which is likely above the typical LLA. The most consistent finding is that CBF autoregulation appears to be impaired more often in patients with SAE versus those without SAE.[109,110,113,114] Several

studies have evaluated cerebrovascular reactivity in sepsis, generally finding it to be normal or increased.[40,106,111,115–117] Vaskó et al[115] reported increased $rSco_2$ after the administration of acetazolamide suggesting preserved cerebrovascular reactivity in patients with severe sepsis but point out that this could be artefactual. The increased $rSco_2$ was likely due to selective arteriolar vasodilation from acetazolamide which NIRS algorithms misinterpret as increased CBF given their assumption of a fixed arterial:venous ratio. Finally, 2 studies are notable regarding the pattern of CBF in sepsis. Straver et al[61] found that the Lindegaard ratio was >2 (suggesting mild vasospasm) in most patients with septic shock and that the patients with the lowest systemic vascular resistance index had a TCD pattern suggestive of vascular steal. Terborg et al[112] concluded there was vasoparalysis in sepsis based on data that autoregulation was intact but cerebrovascular reactivity decreased in patients with severe sepsis or septic shock.

Altogether this literature suggests that CBF autoregulation is a dynamic entity, changing throughout the course of sepsis. Studies that utilize CBF autoregulation monitoring over time to evaluate this relationship are lacking. We know CBF autoregulation is more often impaired in early sepsis and in patients with SAE. Impairment of CBF autoregulation could result from a MAP, below the LLA or above the ULA, or vascular dysfunction. Sepsis data typically find intact cerebrovascular reactivity, suggesting that cerebral vasculature maintains vasodilatory ability, which makes vascular dysfunction a less likely explanation for impaired CBF autoregulation in early sepsis and SAE. Given the prevalence of the vasopressor use in these studies, it is more likely that patients with impaired CBF autoregulation were below the LLA rather than above the ULA. It is important to note that most studies evaluated patients at normocapnia. Given that permissive hypercapnia is standard of care for acute respiratory distress syndrome[11], which complicates sepsis in 8.9% of intensive care unit patients[118], the effect of prolonged hypercarbia on CBF autoregulation is an important knowledge gap.

Future Directions

There is much to be learned in future investigations about CBF autoregulation in sepsis, particularly regarding its relation to the underlying pathophysiology of brain injury in the setting of sepsis. The literature reviewed above suggests a relationship between ischemia, disruption of autoregulation, and hypoperfusion. Issues that need to be clarified pertaining to CBF autoregulation and sepsis include (1) the shape of the CBF autoregulatory curve in sepsis, as it is implicit in the Surviving Sepsis Guidelines that the autoregulatory plateau seen in normal patients is retained although this hypothesis has never been tested,[11] (2) the behavior of the wide plateau described by Lassen in inflamed and dysregulated cerebral vasculature in patients with sepsis,[18] and (3) the inflection points of the upper and lower limits of autoregulation, which may not be retained or may be displaced.

In future investigations, careful consideration of the study population is necessary as sepsis is a heterogeneous disorder. The severity of illness, time since onset, and perhaps etiology of sepsis should be specified in such a study in order to minimize the sources of heterogeneity most likely to affect CBF autoregulation. Particular attention should be given to CO_2 levels including continuous end-tidal monitoring, screening for baseline CO_2 retention, and

separate analysis of patients with chronic CO_2 retention if they are included at all. The effect of vasoactive medications provides challenges to this field; however, the question of their effect is of central importance. Adherence to a single protocol of medications, MAP goal, and escalation parameters in all included patients could be used to mitigate these concerns. Continuous cerebrovascular monitoring using NIRS and an arterial catheter measuring MAP can be useful to capture the reality of CBF autoregulation during resuscitation. Provocative techniques (using acetazolamide or CO_2 alteration) could be used to further elucidate the response of the neurovascular unit to typical stimuli during sepsis. Outcomes should include organ failure, delirium, coma, and long-term cognitive function.

Conclusion

Management of the patient with sepsis has historically included maintaining organ perfusion with empiric BP goals aimed at CBF autoregulatory limits, which there is now data to suggest vary individually. The emerging availability of methods to monitor CBF autoregulation in real time provides researchers with opportunities to study the variability and importance of individualized hemodynamic goals on outcomes, and in the future, it may provide clinicians with the opportunity to individualize BP targets during sepsis.

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Table 1

Methods and Major Findings From 14 Studies of Cerebral Blood Flow Autoregulation in Sepsis by Date of Publication.[a]

Study	Patients	Methodology	Sepsis Duration, hours	Patients With Delirium, %	Major Findings
Monitoring CA over the time course of sepsis					
Matta and Stow, 1996[106]	10 patients with sepsis and altered mental status treated with sedation	TCD: MCAv • before and after phenylephrine to raise MAP 20 mm Hg • with $Paco_2$ varied between 3 and 7 kPa	<24	100	• MCAv unchanged before or after phenylephrine (CA intact) • CR normal (20.3%/kPa)
Smith, 1998[107]	15 patients with septic shock vs 9 controls with hypovolemic or cardiogenic shock	PAC: cardiac index, B-mode, and Doppler US: blood flow in common carotid	12–48	NR	• CBF proportional to cardiac index in septic shock (CA impaired) but not in hypovolemic or cardiogenic shock (CA intact)
Xie, 2014[108]	38 patients with sepsis	TCD: MCAv, Mx	NR	42	• 58% patients; Mx >0.3 (CA impaired)
Exploring the relationship between CA and delirium					
Pfister et al, 2008[114]	16 patients with sepsis, severe sepsis, or septic shock	TCD: MCAv, Mx NIRS: TOI	<48	75	• MCAv and TOI similar in patients with vs without delirium • Mx higher in patients with vs without delirium (CA impaired in delirium)
Schramm et al, 2012[109]	30 patients with severe sepsis or septic shock treated with sedation and MV	TCD: MCAv, Mx • daily for 4 days	<24	76	• 83% had Mx >0.3 (CA impaired) at some point (60% on day 1) • Mx highest on day 1 then decreased • Mx >0.3 (CA impaired) on day 1 positively associated with day 4 delirium
Pierrakos et al, 2014[113]	38 patients with sepsis	TCD: MCAv, PI • on day 1 and day 3 of sepsis	<24	55	• PI on first day highly correlated with the presence of delirium (AUC = 0.908)

Study	Patients	Methodology	Sepsis Duration, hours	Patients With Delirium, %	Major Findings
					• PI > 1.3 within 24 hours 95% sensitive, 88% specific for delirium • PI after 72 hours not related to delirium
Subira et al, 2014[110]	28 critically ill patients treated with MV	TCD: MCAv, Mx	<48	NR	Patients treated with MV: • Patients with Mx >0.3 (impaired CA) trend to less sepsis (46%) vs intact CA(73%) • Patients with Mx >0.3 (impaired CA) significantly more delirium (75%) vs intact CA (25%)
Measuring cerebrovascular reactivity (CR) and dynamic CA in sepsis					
Bowie et al, 2003[40]	12 patients with sepsis treated with sedation and MV	TCD: MCAv • at baseline and + 1 kPA ET_{CO2}	>24	NR	• 58% patients decreased CR (<17%/kPa) • 17% patients increased CR (>33%/kPA) • No correlation between CR and severity of illness or prognosis
Berg, et al, 2012[111]	16 patients with severe sepsis or septic shock treated with MV vs 9 healthy controls given lipopolysaccharide (LPS) infusion	TCD: MCAv • before and after norepinephrine titrated stepwise (5 mm Hg) to25 mm Hg higher MAP • before and after LPS (controls only) • transfer function analysis (dynamic CA)	<72	62.5	• MCAv not different in patients vs controls before or after LPS (CA intact) • Lower MAP-MCAv phase difference in patients vs controls (dynamic CA impaired)
Vaskó et al, 2014[115]	15 patients with severe sepsis vs 10 healthy controls	NIRS: $rScO_2$ • before and after 15 mg/kg intravenous acetazolamide infusion	NR	100	• Acetazolamide increased $Paco_2$ (~6 mm Hg) and $rScO_2$ (~9%) in both patients and controls (CR intact) • Change in rSc<SC>O</SC>$_2$ may be from specific

Study	Patients	Methodology	Sepsis Duration, hours	Patients With Delirium, %	Major Findings
					vasodilation of arterioles to acetazolamide vs intact CA
Berg, et al, *Clin Physiol Funct Imaging*, 2015[117]	From 2012 study: 6 patients with severe sepsis or septic shock treated with MV vs 9 healthy controls given LPS	TCD: MCAv • cRoR and mRoR with thigh cuff deflation (dynamic CA)	<72	NR; Ramsay 2–5	• cRoR decreased, but mRoR unchanged, in patients vs controls before or after LPS (dynamic CA impaired)
Berg, *FASEB*, 2015[116]	From 2012 study: 7 patients with severe sepsis or septic shock treated with MV	TCD: MCAv • before and after 30 minutes hyperventilation • transfer function analysis (dynamic CA)	<72	NR; Ramsay 4–5	• CR normal to increased (27–66%/kPa)
Determining patterns of CBF in sepsis					
Straver et al, 1996[61]	20 patients with septic shock treated with MV, vasopressors, and inotropes	PAC: SVRI TCD: MCAv, ICAv	NR	NR	• MCA/ICA ratio mostly >2 suggesting mild vasospasm • Lowest SVRI showed vascular steal
Terborg et al, 2001[112]	8 patients with severe sepsis or septic shock treated in a neurologic ICU with sedation, MV, inotropes and/or vasopressors	TCD: MCAv NIRS: $rScO_2$ • during and before/after sepsis • before and after hypoventilation	NR	NR; GCS 3–7	• CBF derived from MCAv not different during vs before/after sepsis (CA intact) • CR reduced in sepsis vs before/after sepsis • Mechanism of decreased CR in sepsis may be vasoparalysis

Abbreviations: APACHE II, acute physiology and chronic health evaluation II, a classification system for severity of illness in critically ill patients; AUC, area under the curve; CA, cerebral blood flow autoregulation; CBF, cerebral blood flow; CR, cerebrovascular reactivity, units are percentage change in CBF velocity per kPa change in end-tidal carbon dioxide; cRoR, conventional rate of regulation; $ETCO2$, end-tidal carbon dioxide concentration; ICAv, internal carotid artery flow velocity; MAP, mean arterial blood pressure; MCAv, middle cerebral artery flow velocity; mRoR, modified rate of regulation; MV, mechanical ventilation; Mx, correlation coefficient of MCAv/MAP; NIRS, near-infrared spectroscopy; NR, not reported; PAC, pulmonary arterial catheter; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PI, pulsatility index; $rScO_2$, regional cerebral oxygen saturation; SVRI, systemic vascular resistance index; TCD, transcranial Doppler; TOI, tissue oxygenation index ([oxygenated hemoglobin]/[total hemoglobin]), analogous to ScO_2; TOx, correlation coefficient of TOI/MAP; US, ultrasound.

[a]Studies are grouped by major themes including CA over the time course of sepsis, CA and delirium, CR, and patterns of CBF in sepsis.