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Brain Perfusion In Sepsis

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Abstract: Brain dysfunction is a frequent complication of sepsis, usually defined as "sepsis-associated encephalopathy" (SAE). Its pathophysiology is complex and related to numerous processes and pathways, while the exact mechanisms producing neurological impairment in septic patients remain incompletely elucidated. Alterations of the cerebral blood flow (CBF) may represent a key component for the development of SAE. Reduction of CBF may be caused by cerebral vasoconstriction, either induced by inflammation or hypocapnia. Endothelial dysfunction associated with sepsis leads to impairment of microcirculation and cerebral metabolic uncoupling that may further reduce brain perfusion so that CBF becomes inadequate to satisfy brain cellular needs. The natural autoregulatory mechanisms that protect the brain from reduced/inadequate CBF can be impaired in septic patients, especially in those with shock or delirium, and this further contributes to cerebral ischemia if blood pressure drops below critical thresholds. Sedative agents alter cerebro-vascular reactivity and may significantly reduce CBF. Although disorders of brain perfusion and alteration of CBF and cerebral autoregulation are frequently observed in humans with sepsis, their exact role in the pathogenesis of SAE remains unknown. Brain perfusion can further become inadequate due to cerebral microcirculatory dysfunction, as evidenced in the experimental setting. Microvascular alterations can be implicated in the development of electrophysiological abnormalities observed during sepsis and contribute to neurological alterations in septic animals. The aim of this review is to provide an update on the pathophysiology of brain perfusion in sepsis, with a particular focus on human clinical investigation and novel tools for CBF monitoring in septic patients.

Keywords: Sepsis, encephalopathy, brain dysfunction, cerebral hemodynamics, autoregulation, cerebral blood flow, carbon dioxide, microcirculation.

1. BRAIN DYSFUNCTION DURING SEPSIS

1.1. Definition of Sepsis-Associated Encephalopathy (SAE)

Septic shock and related multi-organ failure (MOF) remain a major cause of morbidity and mortality in intensive care units (ICUs) worldwide [1]. The infectious stimuli, associated with a widespread reaction characterized by the release of numerous circulating pro-inflammatory molecules, can potentially impair the function of several organs [2]. Brain dysfunction occurs early during sepsis and is commonly characterized by the development of an altered mental state; however, cerebral abnormalities are also described in late course of sepsis, often accompanied by MOF, hypotension and other systemic events [3, 4]. Hippocrates first reported the association between infections and cerebral dysfunction more than 2500 years ago [5], and sir William Osler also described, later on, the occurrence of "delirium" in patients with ongoing sepsis [6]. Nevertheless, concomitant hepatic or renal failure, electrolyte and metabolic disturbances, altered glucose homeostasis, hypotension, hypoxemia, hypothermia or neurological side-effects of different pharmacological agents may concomitantly occur in septic patients, rendering the discrimination between sepsis-related brain dysfunction and encephalopathy from other causes a potentially difficult task [7].

Sepsis-associated encephalopathy (SAE) can be defined as a diffuse or multifocal brain dysfunction associated with an infectious illness (a) without clinical and laboratory evidence of intracranial infection and/or (b) without conditions unrelated to the infectious process that would significantly alter brain function [8]. The diagnosis should therefore exclude structural brain lesions or primary pathologies of the central nervous system (i.e. meningitis or stroke), other neurological diseases (i.e. epilepsy), a toxic-metabolic cause, fat embolism syndrome and anoxic brain injury [9]. Moreover, acute inflammatory encephalopathies, such as acute disseminated encephalomyelitis or acute hemorrhagic leucoencephalopathy, should be also considered apart from SAE, because of their specific immuno-mediated inflammation of central nervous system (CNS) structures and response to corticosteroids [10].

1.2. Epidemiology, Clinical Features and Diagnosis

The occurrence of SAE is variable but is one of the most common forms of encephalopathy encountered in critically

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ill patients [11, 12]. In a large cohort of mechanically ventilated patients, mostly septic or with acute pneumonia, altered mental state was observed in 66% of them at some point during the ICU stay [11]. In a prospective study of 1758 patients admitted to a medical ICU, 217 of them experienced a neurological complication; encephalopathy was present in one third of patients, and SAE was the most frequent etiology [12]. In a series on 69 non-sedated patients with bacteraemia, 70% of them had clinical signs of brain dysfunction and half of them showed severe encephalopathy [9]. In two large cohort studies of septic patients, acute mental state abnormalities were described in more than 20% of them [13]. The heterogeneity of SAE rate among these studies may probably be due to the different definitions of sepsis and SAE used. As such, more than 60% of patients with neurological changes during critical illness patients also had evidence of brain lesions abnormalities on brain magnetic resonance imaging [14], while abnormalities of electroencephalography (EEG), including clinically silent epileptiform patterns, were present in all septic patients, regardless of the presence of clinical brain dysfunction [15, 16].

The most common manifestation of SAE is an alteration of mental state, ranging, from mild disorientation or lethargy to stupor and coma [17]. Most patients have fluctuant changes in mental status, especially in the early course of the infectious process where SAE may often be the first manifestation of severe sepsis [18]. Usually the neurological exam does not show focal motor deficits. Myoclonus, asterixis and rigidity are rare and should raise the possibility of a toxic-metabolic encephalopathy. Focal asymmetric neurological signs mandate to rule out structural brain lesions, either primary or secondary to septic ischemic emboli. Cranial nerves are usually spared whereas clinical signs of peripheral nerve alterations, like loss of tendon reflexes, should raise the possibility of sepsis-associated critically ill polyneuromyopathy [19]. Finally, alteration of the neuro-endocrine axis (e.g. adrenal and vasopressin insufficiency) and autonomic dysfunction (e.g. blood pressure variations, arrhythmias, irregular breathing) may be other manifestations of SAE [20]. Given the variable clinical manifestations of SAE, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or the Assessment to Intensive Care Environment (ATICE) have been used to score altered mental state in this setting, however the Glasgow Coma Scale (GCS) remains the most popular tool and has been used to evaluate brain dysfunction in septic patients with MOF [3, 21, 22].

There are no diagnostic tests with high specificity for SAE, so that the clinical, electrophysiological (Electroencephalogram, EEG; Somato Sensory Evoked Potentials, SSEPs), biochemical (neuron-specific enolase, NSE; S-100β protein) or imaging (Magnetic Resonance Imaging, MRI) criteria may be useful. Young *et al.* demonstrated that EEG is the most sensitive in the diagnosis of SAE, with mild diffuse slow waves even in patients without clinical abnormalities [15]. Also, EEG could be useful in the differential diagnosis of coma in critically ill septic patients, especially to detect unexpected clinically silent non-convulsive status epilepticus [23]; in a large cohort of patients continuously monitored with EEG, septic patients had a higher rate of seizures than those without sepsis (32% vs. 9%) and sepsis on admission was the only significant predictor of seizures and of poor outcome [24]. In one study using SSEPs, an increase of peak latencies in cortical and sub-cortical component of dorsal column-medial lemniscus pathway (84% and 34% of all cases) was remarked. The impairment of these pathways was associated with severity of illness and had good correlation with the degree of brain dysfunction [25]. Finally, serum levels of NSE and S-100β protein have been shown to correlate with poor outcome in septic shock patients [26]. Magnetic resonance imaging (MRI) showed variable degrees of vasogenic edema, related to blood-brain barrier (BBB) breakdown, or ischemic lesions surrounding the Virchow-Robin spaces in septic brain [27]. Damage to the gray matter may include bilateral lesions of basal ganglia and thalamus. Although not specific for brain dysfunction during sepsis, MRI can identify patients developing structural cerebral lesions during severe sepsis and septic shock and potentially help in patient prognostication.

1.3. Outcome and Therapy

Septic encephalopathy is not only an unpleasant confusion state but represents a severe organ dysfunction and may contribute to poor outcome in septic patients [3, 13, 28]. The greatest the severity of SAE, as assessed by the GCS, the highest the risk of death, with a mortality rate of 16% when GCS was 15, 20% when GCS was 13-14, 50% when GCS was 9-12, up to 63% in comatose patients (GCS < 9) [3]. In another study, septic patients with altered mental status had a higher mortality than those without [13]. In a large cohort of mechanically ventilated patients, the majority of them admitted for severe sepsis, it was demonstrated that ICU-related delirium was independently associated with longer hospital stay, worse cognitive recovery and higher mortality [11]. It appears that SAE may also actively participate to the development of long-term cognitive dysfunction after critical illness [29]. Unfortunately, there is no specific treatment of SAE and outcome depends on the appropriate treatment of the underlying disease. Recently, the use of activated protein C appeared to be beneficial on the evolution of SAE in septic patients [30]. Several drugs, including dopexamine, inhibitors of inducible nitric oxide synthase (iNOS), corticosteroids, magnesium and antioxidants, have shown promising results in experimental sepsis, however no clinical data on the efficacy of these interventions are currently available [31-34]. Given the absence of specific therapeutic interventions, treatment of SAE is mainly supportive, aimed to limit SAE-related secondary cerebral damage. Targeting brain perfusion and providing adequate oxygen and nutrients supply seem reasonable in this context.

2. PATHOGENESIS OF SAE: A SHORT OVERVIEW

Sepsis-associated encephalopathy is a poorly understood condition and little is known about this clinical process. The pathophysiology is likely to be multifactorial (Fig. **1**) [35]. The concept of altered brain function related to the presence in the blood, and possibly in the brain, of micro-organisms or their toxins is considered obsolete as altered CNS function is observed also in patients without bacterial blood stream invasion [36]. Disseminated cerebral microabscesses have been suggested as a cause of SAE [37], although this has not been reported in more recent post-mortem studies [38]. The specific role of specific bacterial products like endotoxin is unlikely, as the incidence of SAE is similar in Gram-positive

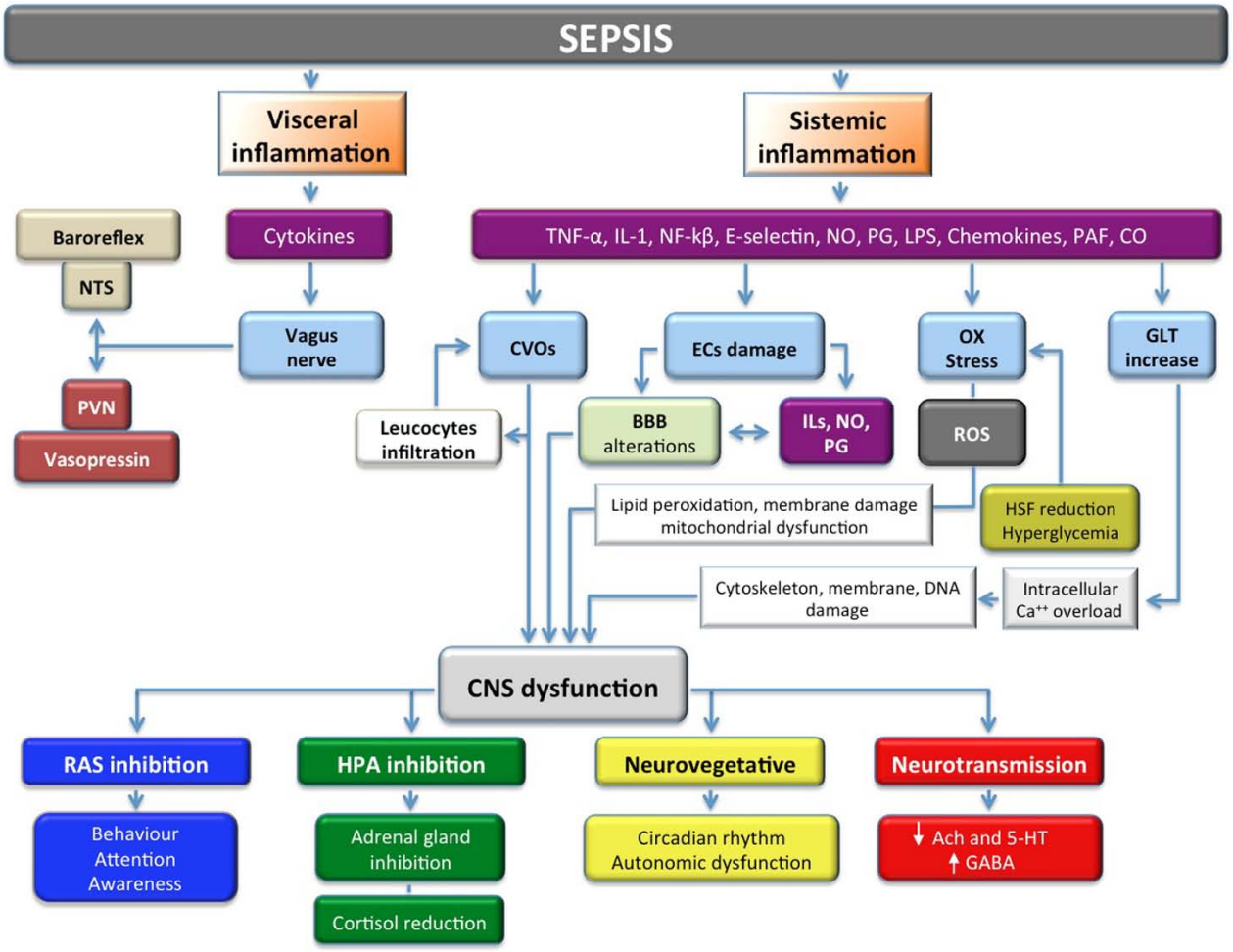

Fig. (1). Schematic representation of mechanisms involved in the pathogenesis of sepsis-associated encephalopathy. Proinflammatory cytokines are released during sepsis. They can either activate vagal fibres or enter the brain causing neurologic dysfunction (see text for details). 5-HT, serotonin (5-hydroxytryptamine); Ach, acetylcholine; BBB, blood-brain barrier; CNS, central nervous system; CO, carbon monoxide; CVOs = circumventricular organs; ECs, endothelial cells; GABA, gamma-aminobutyric acid; GLT, glutamate; HPA, hypothalamic-pituitary-adrenocortical; HSF, heat-shock factors; IL, interleukin; LPS, lipopolysaccharide; NF-kβ, nuclear factor kappa B; NO, nitric oxide; NTS, nucleus tractus solitarius; PAF, platelet activating factor; PG, prostaglandin; PVN, paraventricular nuclei; RAS, reticular activation system; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.

and Gram-negative bacteremia, as well as fungemia and even sepsis with unidentified pathogens [13]. Encephalopathy occurs also in non-infectious conditions, such as pancreatitis or trauma, suggesting that it would be mostly related to the systemic inflammatory response [39, 40].

The role of inflammation on brain dysfunction has been widely investigated in several *in vitro* or experimental models of sepsis; although some of the reported findings have also been confirmed in the human setting, the pathogenesis of brain dysfunction mostly relies on laboratory data. Circulating pro-inflammatory mediators can promote vascular permeability of the cerebral endothelium, which separates the blood from the brain parenchyma, thus permitting to several substances to exert toxic effects on neuronal cells. Tumor necrosis factor-alpha (TNF-α) selectively altered BBB permeability in brain microvessel endothelial cells without disrupting tight junctions [41]. Endothelial cells treated with interferon-gamma (IFN-γ) also exhibited significant morphological changes with increased permeability [42]. Inflammatory mediators have also direct effects on brain functions; the subarachnoid injection of TNF-α altered cerebral metabolism and increased cerebrospinal fluid lactate, by activating the production of nitric oxide (NO) [43]. Also, TNF-α can upregulate the expression of aquaporin-4 channels and associated edema as well as astrocytosis through activation of its receptor [44]. The intra-cerebral administration of interleukin-1 and IFN-γ in animals induced the same slow-waves EEG patterns than those observed in patients with SAE [45, 46].

More importantly, sepsis-induced systemic inflammation can directly affect brain homeostasis by triggering the two important pathways that are implicated in the response to stress and in the immune system modulation: the circumventricular organs (CVOs), which lack a BBB and have a direct communication with circulating mediators of sepsis and the vagus nerve, which is triggered by visceral inflammation [7]. Once systemic and/or visceral inflammation are detected by these pathways, an abnormal activation of brain signaling

spread to behavioural, neuroendocrine and neurovegetative structures, affecting directly microglial and neuronal cells functions and modulating neurosecretion and neurotrasmission [47, 48]. Inflammation rapidly alters the function of hypothalamus, which regulates the endogenous production of corticosteroids and can modulate the inflammatory response [49] and may significantly impair the reticular activating system functions, which control consciousness and attention [50]. The cholinergic and serotoninergic releases are altered, while an increase in the γ-aminobutyric acid receptor density is observed in the forebrain of septic rats [51, 52]. Brain tissular norepinephrine and epinephrine concentrations are decreased in the forebrain and brain stem of septic animals together with the down-regulation of the cerebral β-adrenergic system [53]. Also, a significant and early increase of plasma aromatic aminoacids during abdominal murine sepsis was found to be associated with encephalopathy development [54]. The activation of CVO also promotes the entry of leucocytes into the CNS, with further increase of local inflammation [55].

Several other mechanisms may be involved in the development of SAE. Sepsis produces an imbalance between the production of reactive oxygen species (ROS) and the corresponding repair system, the so-called oxidative stress. Reactive oxygen species trigger lipid peroxidation in the cerebral vessels and the surrounding parenchyma, which eventually cause structural membrane damage and promote inflammation [56]. Cerebral oxidative stress can also be triggered by the decrease of heat-shock factors or by hyperglycemia [57, 58]. Bacterial endotoxin and inflammatory cytokines increase cerebral tissue levels of glutamate *via* the up-regulation of iNOS; glutamate can trigger brain cells damage by allowing high intracellular levels of calcium and the activation of several enzymes that alter cell structures, such as components of the cytoskeleton, membrane, and DNA [59]. Within the brain parenchyma, the activation of astrocytes *via* the toll-like receptors by the mediators of inflammation [60] can further increase the vulnerability of neurons to glutamate and free radical-mediated injuries [56, 61, 62]. Moreover, sepsis also alters the synthesis of ascorbate, which may provide antioxidant and protective effects on neurons in response to glutamate and ROS release [63]. The complement system, which normally contributes to eliminate bacteria, may be excessively activated during sepsis and have deleterious effect through the activation of glial cells, secretion of proinflammatory cytokines and generation of other toxic products on brain function [64]. Edema formation could be further promoted by the activation of aquaporin channels, which regulate the presence of water in the brain tissue and may altered during sepsis [65]. Alterations in the glucose uptake and metabolism or regional deregulation of intracellular calcium homeostasis have also been suggested to contribute to the pathogenesis of SAE [50, 66]. All these pathways cause mitochondrial dysfunction by inhibiting the mitochondrial electron transport chain and uncoupling oxidative phosphorylation, which ultimately leads to bioenergetic failure and apoptosis of brain cells [38, 58].

The complex signaling network that is implicated in these phenomena include the production of nitric oxide (NO), through the activation of the inducible form of NO synthase (iNOS) [67, 68], the release of pro-inflammatory cytokines and their receptors from neurons, astrocytes and microglial cells [69, 70], as well as the production of prostaglandins, which are key mediators in the brain response to inflammatory stimuli [71, 72]. Finally, a number of other mediators are involved in the cerebral brain response to systemic inflammation, such as chemokines, macrophage migrating inhibitory factor, angiotensin, endothelin, platelet activating factor, superoxide radicals and carbon monoxide [73].

3. ALTERATIONS IN BRAIN PERFUSION DURING SEPSIS

A decrease in brain perfusion has been evoked as a major determinant of SAE [74]. Alterations of systemic blood flow, associated with tissue hypo-perfusion and poor oxygen distribution, are a key feature of sepsis [2]; indeed, several studies have tried to evaluate the link between cerebral perfusion abnormalities and brain dysfunction in sepsis. As brain perfusion is dependent, amongst all, from mean arterial pressure (MAP), which is generally reduced in severe sepsis and septic shock, it would be important to monitor the adequacy of cerebral blood flow (CBF) and oxygenation during sepsis as well as to evaluate the integrity of flow regulation, in order to adapt blood pressure levels and avoid the development of secondary brain ischemic events in such patients [38].

3.1. Cerebral Blood Flow: Normal Ranges, Physiology and Regulation

Cerebral blood flow is the blood supply to the brain in a given time. In an adult, CBF is typically 750 mL (or 50-55 mL/100 g of brain tissue/min) and represents roughly 15% of the cardiac output. It ranges from 20 mL/100g/min in the white matter to more than 70 mL/100g/min in the grey matter and is tightly regulated to meet cerebral metabolic demands [75]. Cerebral blood flow regulation is extremely complex and is determined by a number of factors, such as viscosity of blood, the diameter of cerebral blood vessels and the net pressure of the blood flow into the brain, known as cerebral perfusion pressure (CPP), which is calculated as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP) or the central venous pressure (CVP), whichever is the higher [76]. Cerebral vessels are able to maintain CBF constant through a wide range of MAP (from 50 to 150 mmHg) by altering their diameters in a process called "cerebral autoregulation" (CA); in normal conditions, a raise of MAP induce vasoconstriction whereas a reduction of MAP produces vasodilatation (Fig. **2**) [77]. This process is extremely important because when CBF exceed cellular requirements (a condition known as hyperemia), then the intracranial pressure (ICP) may rise and potentially damage brain tissue. On the other hand, low CBF (<18-20 mL/100g/min) is responsible for brain ischemia and tissue death when CBF falls below 8-10 mL/100g/min. Systemic administration of vasopressors would not produce dramatic effects on CBF, provided the BBB is not altered [78]. Pressure autoregulation is thought to be controlled by the baroceptive reflexes and both the upper and the lower limits of CA can be affected by many factors, including sympathetic nerve activity, arterial carbon dioxide tension (PaCO2) and pharmacologic agents [79-82].

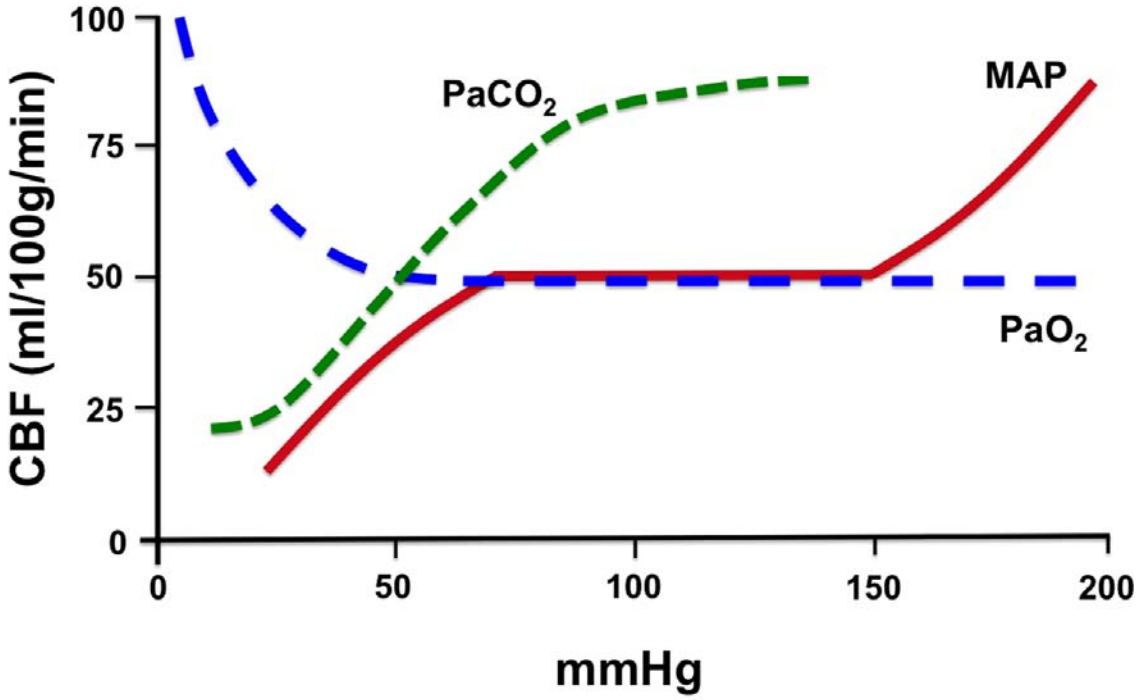

Fig. (2). Schematic representation of cerebral blood flow (CBF) variations associated with changes in mean arterial pressure (MAP, continuous line), arterial carbon dioxide tension (PaCO2, short-dotted line) and arterial oxygen tension (PaO2, large-dotted line).

The control of CBF is dependent not only on MAP but also on four other major determinants, including chemical, metabolic, neural and myogenic factors (Fig. **3**) [77]. Although this division may be somewhat artificial and these control mechanisms probably operate in concert, it is useful to consider each separately. CBF is extremely sensitive to changes in arterial PaCO2 (chemical), displaying marked increases during moderate hypercapnia and reduction during hypocapnia. Changes in CBF in response to changes in PaCO2 are referred to as cerebral CO2-reactivity (COR).

The magnitude of cerebral circulatory response is approximately 5% change in CBF for each 1 mmHg change in PaCO2, within a range of 25 to 60 mmHg [83]. In contrast, acidosis and alcalosis, for blood pH values ranging from 6.7 to 7.6, have little effect upon the CBF [84]. Changes in PaCO2 are detected by carotid artery chemoreceptors and this regulatory mechanism can be altered by a lesion of the tegmental reticular formation [77]. The effect of PaCO2 seems to be related to changes in local brain perivascular pH rather than direct carbon dioxide action on smooth vascular cells, but could also be mediated by K^+-dependent channels or adenosine, while vasodilatation induced by hypercapnia can be abolished by prostaglandin synthesis inhibition [85-89]. Astrocytes contribute in maintaining the homeostasis of the extracellular compartment in CNS and may profoundly influence central CO2 chemoreactivity and respiratory control [90]. Importantly, cerebrovascular dilatation induced by hypercapnia is markedly attenuated by moderate hypotension, which contributes to exhaust the capacity of cerebral vessels to further dilate [83]. On the opposite, with marked hypercapnia, the capacity to maintain a constant CBF during hypotension is lost, and CBF will decline as CPP declines [91]. Finally, CBF is less sensitive to changes in arterial oxygen tension (PaO2) over the normal physiological ranges. If arterial PaO2 falls below 50 mmHg, pronounced increase of CBF occurs (at 30 mmHg CBF is almost double than at 100 mmHg PaO2). Conflicting results have been published on the effects of hyperoxia on cerebral perfusion; moderate hyperoxia induced a mild decrease in CBF in healthy volunteers [92], while ventilation with 100% of oxygen has only minimal effects upon CBF in patients with traumatic brain injury [93].

Local cerebral blood flow (CBF) is also tightly coupled to neuronal activity (metabolic) so that CBF may adjust to the level of energy generation in the brain ("neurometabolic coupling"). The regional cerebral metabolic activity is represented by the metabolism of oxygen (CMRO2) and glucose [94]. The precise mechanisms responsible for this coupling remain elusive and alterations in the concentrations of local metabolites or the generation of several vasoactive chemical substances (i.e., H and K ions, adenosine, vasoactive intestinal peptide-VIP or products of arachidonic acid) have been proposed as pivotal mediators [95, 96]. Astrocytic processes extensively unsheathe cerebral arterioles and, through the link between neuronal synapses and the cerebral vasculature, are in a strategic position to convey cellular signals to the blood vessels [97]. The brain metabolism can also significantly affect the magnitude of CBF modification to changes of PaCO2; indeed, factors that reduce neurons activity (e.g. sedation reduces oxygen and glucose consumption) reduce the cerebral circulation response to hypercapnia [98], while mild hypercapnia itself may cause a suppression of cerebral metabolic rate of oxygen up to 13% [99]. Importantly, some discrepancies exist in the relationship between CBF and glucose metabolism and oxygen consumption; one hypothesis is that part of cerebral metabolism would use lactate generated by the metabolism of glucose in the astrocytes, through the activation of glycolitic pathways [100]; lactate itself showed

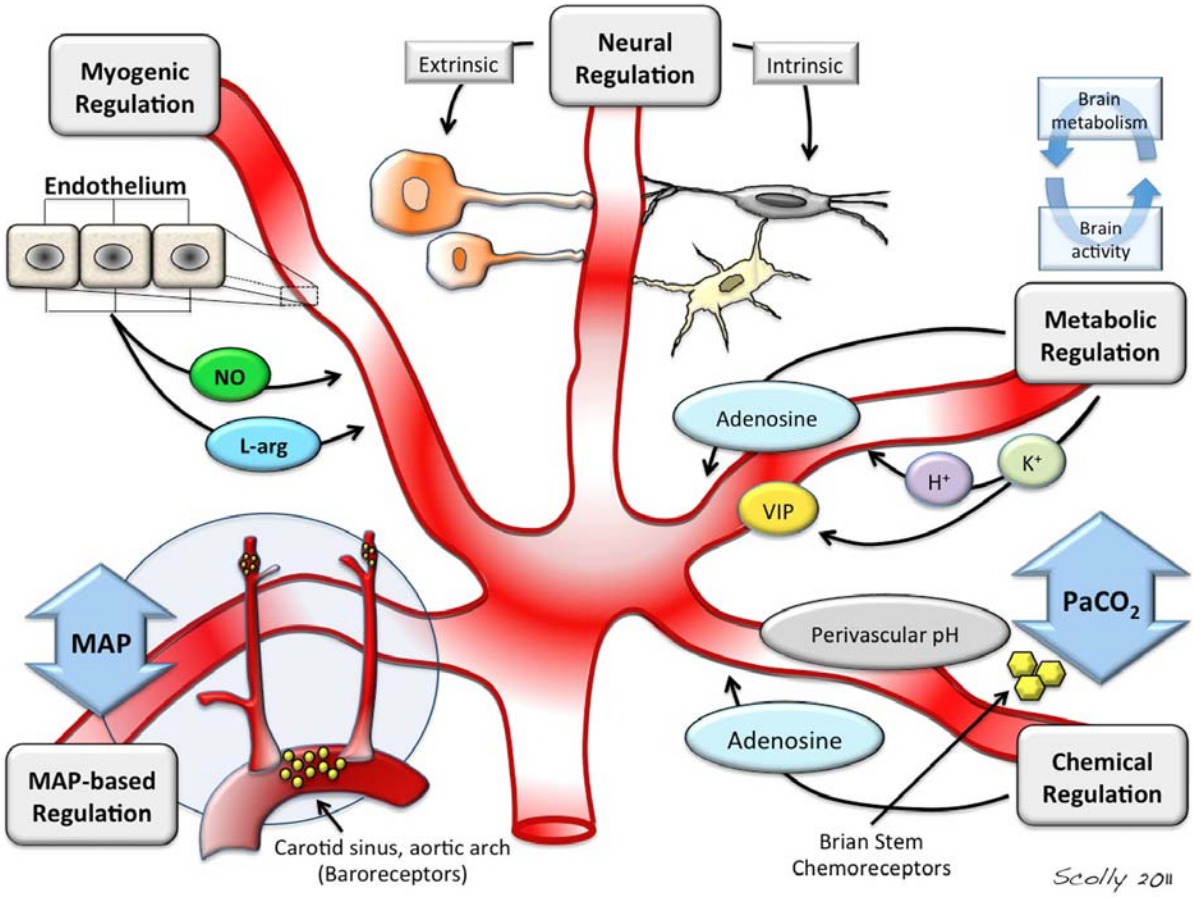

Fig. (3). Schematic representation of multiple mechanisms of cerebrovascular control. The control of cerebral blood flow is dependent on five major determinants: mean arterial pressure, and chemical, metabolic, neural and myogenic factors (see text for details).
L-arg, L-arginine; NO, nitric oxide; PaCO2, arterial carbon dioxide tension; VIP, vasoactive intestinal peptide.

some vasodilating effect on cerebral arterioles and could contribute to modulated brain perfusion in response to cerebral cells demand [101, 102].

The third factor implicated in CBF regulation is the perivascular innervation (neuro-vascular reactivity) (Fig. **3**), which depends not only on the extrinsic nerve supply from the cranial ganglia to the cerebral vasculature, but also on the intracerebral neurons linked to these vessels. Most of the extrinsic neuron fibers are sympathetic and can be summarized in three different types, each with distinct origins and neurotransmitters. The first consists of sympathetic neurons arising principally from the superior cervical ganglion (producing norepinephrine and neuropeptide-Y, thus vasoconstriction); the second consists of parasympathetic neurons in the spheno-palatine and otic ganglia (producing acetylcholine and VIP); the third consists of sensory fibers originating in the trigeminal ganglion (producing substance P and calcitonin gene-related peptide, thus vasodilation) [103]. Nevertheless, attempts to manipulate CBF by either cervical sympathectomy or symphathetic stimulation resulted in variables CBF changes in experimental models [104, 105]. Also, the parasympathetic nerves may have some effect only in pain-mediated cerebral vasodilatation while trigeminal fibers can substantially affect CBF only in particular conditions, such as hypertension and seizures [103]. Thus, CBF appears to be primarily regulated by local metabolism with only minor modulation by extrinsic nerves. Among local neuromodulators, dopaminergic axons innervate the intra-parenchymal microvessels and dopamine may directly regulate cortical blood flow [106].

Bayliss *et al*. were the first to present the myogenic basis of CA, showing that modifications of the arteriolar smooth muscle tone are elicited by changes in transmural pressure [107]. Accordingly, an increase in the transmural pressure would stretch the smooth muscle of the vascular wall, stimulating the reflex contraction of radial fibers, which eventually result in vasoconstriction [108]. A growing body of evidence suggests that endothelium-dependent pathways are the primary mediators of myogenic control of CA [109]. The endothelium appears to act as the transducer of transmural forces that would stimulate the release of vasodilating substances, such as NO and L-arginine [110, 111]. The role of NO has been confirmed by the vasodilatation of large cerebral arteries and pial arterioles in response to the application of acetylcholine *in vivo* [112]; this process was dependent on the NOS activity and could be blocked by NOS antagonist, such as N-monomethyl-L-arginine (L-NMMA) [113].

Autoregulation can be totally lost during some acute cerebrovascular disease or preserved but shifted (normally towards the right and higher values, for example in chronic hypertension) [114-117]. In such abnormal conditions, the

upper and lower ranges of MAP/CPP or PaCO2, among which CBF remain constant, can be much narrower than in normal conditions. Such ranges may be different among patients and change over time within the same subject, so that optimal MAP targets to maintain adequate brain perfusion may be difficult to predict. In sepsis, several mechanisms are implicated in altered brain perfusion and CBF regulation in septic patients.

3.2. Effects of Endothelial Dysfunction and Inflammation on Brain During Sepsis

Alterations of brain perfusion and microcirculation during sepsis are mostly mediated by the changes induced by systemic inflammation on cerebral endothelial cells [118]. In normal conditions, the cerebral endothelium has tight intercellular junctions, no fenestrations and few pynocytic vesicules, which separate blood from the brain parenchyma. The abnormal brain stimulation occurring during sepsis can activate the endothelium [119, 120], causing the expression of adhesion molecules with subsequent aggregation of circulating white blood cells and increased permeability to various neurotoxic agents [121]. The breakdown of the endothelial barrier during sepsis has been directly demonstrated by the intracerebral accumulation of radioactive tracers in several experimental studies [119]. The activation of cerebral endothelial cells is mediated by endotoxin and pro-inflammatory cytokines that, through activation of nuclear factor (NF)-kB, induce the over-expression of iNOS that further increases BBB permeability [122, 123]. This would also allow high brain concentrations of vasoactive agents, acting directly on intracerebral vessels and inducing vasoconstriction and reduction of CBF [124]. Reduction of local blood flow as well as impairment of microcirculation can contribute to leucocytes accumulation and local production of lysosomial enzymes and oxygen free radicals [125]. Reactive products of leukocytes can interact with erythrocytes membrane and reduce their deformability, which in turn facilitates red blood cells impaction in microvessels and exacerbates cerebral hypoperfusion [126]. The result of all these events is the development of perivascular edema that contributes to altered brain perfusion and is associated with neuronal injury [127, 128].

Low brain flow levels are a feature of the response to endotoxin [129]. Early reductions of CBF during experimental endotoxemia are due to cerebral vasoconstriction, both in newborn and adult animals, and these changes are not linked to hypotensive events [129, 130]. Importantly, endotoxin can suppress neuronal activity and cerebral metabolic rate [131, 132]; thus, as cerebral blood flow remains closely coupled to cerebral metabolic requirements, a concomitant reduction of brain perfusion and metabolic rates have been observed in experimental sepsis [133]. Elevated levels of TNF-α occurring during endotoxemia have powerful vasoactive effects on cerebral vessels [134]. Injection of TNF-α into the cisterna magna of rabbits produced a rapid reduction in cerebral oxygen uptake and a more prolonged reduction in CBF; this was accompanied by an increase in intracranial pressure and an increase in cerebrospinal fluid lactate [43]. Although TNF-α can both modulate vasodilatation of superficial cerebral arterioles and vasoconstriction of intraparenchymal cerebral vessels, endotoxin can impair endothelium-dependent vasodilator pathways, such as NO [135], thus promoting vessels constriction *via* prostanoids and endothelin pathways [136, 137]. Persistent exposure to endotoxin may mitigate its effects on CBF [129].

The excessive production of NO by the endothelium through the activation of iNOS is responsible for the vasodilatation found in several vascular beds during sepsis, including the brain, which may ultimately counteract the early vasoconstrictor response [138]. This complex endothelial signaling has further been highlighted in experimental studies, which showed conflicting results on the effects of iNOS inhibition on brain perfusion during sepsis did not affect CBF [43, 139-141], suggesting that CBF is also controlled by other mechanisms than NO during systemic inflammation [73].

3.3. Alteration of Brain Microcirculation During Sepsis

Microcirculatory perfusion is responsible for the fine-tuning of oxygen supply to organs [142] and microcirculatory alterations may play a key role in the pathogenesis of sepsis-related organ dysfunction [143, 144]. Moreover, cerebral endothelial cells play an important regulatory role in brain vasoregulation [145] and in maintaining a constant energy supply to brain cells [146]. Sepsis-associated microcirculatory alterations have been reported in the sublingual area, as well as in striated muscle, small bowel mucosa and liver [147-150]. Vachhrajani *et al.* showed that microvascular flow abnormalities were secondary to a marked adhesion of platelets and leukocytes to the vascular endothelium of brain venules already four hours after induced sepsis, with exaggerated response in obese mice compared to the lean animals [151]. In another study on peritonitis induced in sheep, Taccone *et al.* showed that cortical cerebral microcirculation was altered and microcirculatory abnormalities became significant at the onset of septic shock and were not prevented by aggressive fluid administration [152]. Moreover, changes in the cerebral microcirculation were not related to changes in MAP, CI or lactate, suggesting that these alterations in the brain may occur even when systemic pressure is maintained into normal ranges. Indirect data suggest these alterations may have important consequences on brain cells and function. In endotoxic animals, microcirculatory failure occurred in the early phase of sepsis, and preceded changes in evoked potential responses, indicating that altered perfusion of active neurons is responsible for electrophysiological abnormalities [153]. Microcirculatory alterations in the cortex were associated with changes in brain tissue PO2, impaired oxygen delivery and cell energy crisis (Taccone FS *et al.* Abstract - 39th SCCM Congress, 2010, Miami, USA), all of which contribute to secondary cerebral damage after sepsis. Using intravital microscopy, Comim *et al.* [154] showed a progressive increase in leucocytes and platelets adhesion within brain microcirculation, especially in the deeper brain structures, and microvascular disturbances were associated with a local production of pro-inflammatory cytokines and with the development of abnormalities in locomotor functions in septic rats. Importantly, microvascular abnormalities were attenuated by selectively blocking adhesion molecules, such as P-selectin, CD18, or intercellular adhesion molecule (ICAM)-1, or by the administration of curcumin, which blocks the interaction of leucocytes with endothelial cells

[151, 155]. Other therapeutical interventions, such as dexamethasone, magnesium or hypertonic solutions significantly improved brain microcirculation in experimental sepsis, while iNOS inhibition and norepinephrine administration did not affect capillary abnormalities in endotoxemic rats [34, 156-158]. Unfortunately, brain microcirculation is still impossible to monitor and visualize in the clinical practice without direct exposure of cerebral cortex after craniectomy and data on microvascular abnormalities are still lacking in the human setting.

3.4. Brain Perfusion and Autoregulation in Experimental Sepsis

Several experimental papers have investigated cerebral perfusion during sepsis. In one study on dogs, CBF showed a 30% decrease within 15 min after endotoxin administration, while the arterial blood pressure was still not markedly changed [129]. In a second canine study, CBF decreased immediately after the administration of endotoxin and consistently remained below control values [159]. Cerebrovascular resistances (CVR) initially decreased, then progressively increased to levels significantly higher than normal and were associated with the lowest CBF levels in the later stages of shock. Nevertheless, other studies also demonstrated that CBF was unchanged during sepsis induced in rats and sheep, while others reported an increased CBF [139, 140, 160, 161]. These seemingly controversial findings may be related to different models (endotoxin vs. bacteria) and species used.

Cerebro-vascular reactivity to pressure changes was well maintained in several experimental model of sepsis [129, 138, 159], but in others reactivity to PaCO2 changes was altered [162, 163]. In one study, Hinkelbein *et al.* [164] found no significant difference in the global CBF between non-septic and septic animals, despite the presence of significant hypocapnia in the sepsis group. Although one possible explanation to these findings is that the cerebrovascular tone becomes unresponsive to carbon dioxide stimuli, authors also suggested that, during the hyperdynamic phase of sepsis, brain hyperemia might develop, which counteracts hypocapnia-mediated reduction of CBF. The role of PaCO2 is also essential in maintaining normal CA during sepsis; in one study, septic normocapnic animals showed higher increase in CMRO2 than hypocapnic animals, suggesting loss of CA and uncoupling between CBF and cerebral metabolism during sepsis at normal or high PaCO2 levels [129].

Another important factor influencing brain autoregulation in experimental models is the local inflammation. In one study, CBF was increased with preserved autoregulation in rats with pneumococcal sepsis, even if there was a right shift of the lower threshold of MAP at which CBF was kept constant [165]. Importantly, if these animals had also a direct brain injury, represented by concomitant bacterial meningitis, CA was completely impaired, suggesting that pneumococcal bacteraemia itself can trigger only cerebral vasodilatation but does not affect CA in the absence of direct brain inflammation. The importance of inflammation on brain autoregulation was also underlined in a paper by Rosengarten *et al*. in which cerebral hyperemia induced by transient carotid compression in septic rats was significantly impaired in those animals receiving high dose endotoxin and having lower MAP [166].

Although some controversy still exists, previous studies appear to demonstrate that sepsis significantly impair brain perfusion and CBF regulation. Whether modulating brain perfusion with hemodynamic augmentation and the use of vasopressors may improve brain perfusion after sepsis is still unclear. In one study on a model of sepsis induced by continuous infusion of *Pseudomonas aeruginosa* [138], CBF remained stable during the hypotension phase even if a redistribution of cardiac output in other organs than the brain was observed. Interestingly, when norepinephrine was used to restore normal MAP, cerebral perfusion was unaffected, and the same results were found after the administration of N-monomethyl L-Arginine (L-NMMA), which inhibited the NO production from iNOS. As Meyer and Lingnau [139, 140] observed a significant decrease in CBF after NOS inhibition using N-nitro-L-Arginine-Methylester (L-NAME), it is still possible that more selective iNOS inhibitors like L-NMMA, when compared to L-NAME, would leave the constitutive NOS untouched and thus prevent excessive vasoconstriction.

Finally, a significant reduction of cortical CBF despite stable cardiac output was observed in a murine model of endotoxemic sepsis; this reduction of brain perfusion occurred in parallel with decreased EEG activity and was associated with reduced glucose uptake, measured by PET-scan, and increased inflammation [167]. These data suggested that an early drop of CBF could be related to regional changes in neuronal activity and energy demand and may be independent from MAP changes in septic animals. Although different areas of the brain showed significant differences in cerebral metabolic changes during sepsis (i.e. an increase of 27 to 33 % in the septal nucleus and raphe nucleus and a decrease of 14 to 27 % in the auditory cortex, lateral geniculate, superior colliculus, hippocampus, parietal cortex, and locus coeruleus) [50], the influence of cerebral metabolic changes on brain perfusion during a septic process may add a new key of interpretation.

4. BRAIN PERFUSION IN HUMAN SEPSIS

The first study supporting the concept of reduced cerebral perfusion as a major determinant in SAE development showed, in a retrospective analysis, that hypotension was the only predictor of delirium in patients developing sepsis after surgery [168]. Moreover, in an autoptic study analyzing the brain of patients who died from sepsis, multiple ischemic lesions could be identified in different areas of the brain and were attributed to hypotensive events, which may occur in presence of preexisting cerebrovascular disease as well as in case of impairment of CBF autoregulation [38].

4.1. How to Monitor Cerebral Perfusion and Autoregulation in Septic Patients

Cerebral perfusion has been initially evaluated using the Kety-Schmidt technique, which applies the Fick principle (arterial and bulb jugular venous content at different time-points of a tracer is proportional to the global blood flow) to calculate CBF; different tracers, such as N_2O, xenon or argon have been used [169]. Using the same Fick principle, the

CMRO2 and the cerebral metabolic rate for glucose could be calculated as: [cerebral arterial oxygen (or glucose) concentration – cerebral venous oxygen (or glucose) concentration] x CBF [170]. Similarly, the indicator-dilution technique can also estimate CBF, through the injection of a dye solution (for example, indocyanine green) and arterial and bulb jugular dye concentrations, which are used to build dilution curves and calculate the mean transit time for the indicator [171]. These methods are rather invasive and time-consuming and have also a low temporal resolution.

Neuroimaging can be used to measure global and regional CBF. The CT-perfusion is nowadays routinely used in clinical practice and consists of the sequential scanning of selected brain areas during the injection of a bolus of contrast medium, when it passes through the cerebral vasculature. Various mathematical modeling can be used to process the raw data and compute quantitative analysis of CBF [172]. Additional imaging techniques include functional MRI and positron emission tomography (PET) that can both be used to measure global and regional CBF. In functional MRI, gadolinium contrast produce a reduction of T2 intensity depending on local concentration; the acquired data are processed and allow the calculation of several parameters, such as blood volume, CBF and mean transit time [173]. PET technique uses radioactive isotopes, such as oxygen or glucose, to characterize CBF and cerebral metabolic function [174]. Other techniques include single photon emission computed tomography (SPECT), which uses a gamma-emitting tracer (the 99-Technetium), and the Xenon-enhanced CT scan, which evaluates the brain distribution of Xenon, after the administration through the ventilator of a mixture of air and 28% Xenon [175].

Neuroimaging techniques are effective in measuring CBF however they cannot be used as a continuous monitoring at bedside and some side-effects or complications would be related to the exposure of patients to high doses of contrast media and/or irradiation, as well as the safety of transport from ICU to the Radiology department. In this setting, transcranial Doppler (TCD), although it does not directly measures the CBF, is a suitable non-invasive tool to assess cerebro-vascular reactivity to blood pressure and PaCO2 and to assess CA [176]. Other less studied non-invasive techniques include near infrared spectroscopy (NIRS) [177].

There is no general consensus on which is the best method to monitor CA. Testing CA requires to apply a hemodynamic stimulation, such as an increase of MAP through the administration of vasoactive agents, manipulating the ventilator to induce PaCO2 changes, the modification of venous return (i.e., thigh cuff release, application of negative body pressure, tilting test) or the compression of the carotid artery [178]. Thereafter, dynamic changes of CBF are recorded to quantify the reactivity of autoregulatory forces. This approach is limited because it only allows assessment of CA to precise time-points, i.e. during the different manipulations. Another option to assess CA, without the potentially harmful effects of hemodynamic manipulations, is to analyze the continuous dynamic trends of MAP and CBF over time In this setting, the most used tool to estimate CA is TCD, however some data suggest that cerebral near infrared spectroscopy (NIRS) could also be a valuable method [177]. Brain autoregulation could be continuously assessed by calculating the moving correlation coefficient between MAP and middle cerebral artery velocities (MCAV) (so called, Mx index) [179], or between MAP and cerebral oxygenation estimated by NIRS (Tox index) [177]. Briefly, values of MAP and MCAV are calculated every 10 seconds by bedside softwares and Mx/Tox indexes are obtained as the moving linear correlation coefficient over the last 30 consecutive values. A positive correlation coefficient indicates a close linear relationship between pressure (MAP) and flow (MCAV), thereby suggesting pressure dependency of CBF and impaired CA, while a coefficient close to zero or negative (<0.3) indicates intact CA.

Different stimuli have also been used to test the cerebro-vascular reactivity to CO2, such as altering PaCO2 by changing respiratory rate or using a breathing hold test. Recently, the intravenous injection of acetazolamide, the reversible inhibitor of the enzyme carbonic anhydrase, which induces hypercapnia lasting for approximatively 20 minutes, can result in vasodilatation of cerebral arterioles and allows testing cerebro-vascular reactivity to CO2 also in septic patients [180]. Other techniques, such as the blood oxygenation level dependent contrast (BOLD) MRI or the intraparenchymal probes to directly measure brain tissue oxygen tension (PbO2 catheters), are useful devices to estimate CBF and cerebral oxygenation in critically ill patients, however no data are available in sepsis.

4.2. Cerebral Blood Flow

Several studies on healthy volunteers or septic patients have been conducted to understand the changes of CBF during a severe infectious process, as well as brain autoregulatory capacity and metabolism (Table **1**). In experimental sepsis using endotoxin injection in healthy volunteers, Moller *et al.* [181] reported a reduction of CBF immediately after sepsis induction, which was attributed to hypocapnia occurring because of general symptoms of malaise. Cerebral oxidative metabolism was unchanged and no detectable cerebral flux of cytokines was observed, despite high systemic concentrations of these molecules. In another experiment on healthy volunteers, when sepsis was induced using an intravenous bolus of *Escherichia coli* endotoxin, CBF and CMRO2 measured few hours later were found to be preserved, despite a drop in systemic vascular resistances [182]. In septic patients, Bowton *et al.* [183] showed reduced CBF values by means of the Xenon clearance technique; low brain perfusion occurred independently from MAP values. In another small cohort (n=6) of septic patients with MOF, CBF was within normal ranges but significantly lower than awake controls; CMRO2 was also significantly reduced than control values and these alterations were associated with a significant slowering of EEG recordings [132]. A recent study in mechanically ventilated septic patients with delirium [171], CBF was assessed by dilution technique and reported to be within normal ranges (64 ± 29 mL/100g/min). Also, cerebral oxygenation was within the normal limits in all patients. In 20 patients with septic shock, Straver *et al*. [184] showed a close relationship between cerebral and systemic hemodynamics. This study showed that mean MCAV measured by TCD significantly increased if the systemic vascular resistances (SVR) decreased, suggesting a concomitant cerebral

Table 1. Clinical Studies on Cerebral Hemodynamics in Sepsis

Pts	Timing	Age	APACHE II	Severity	CBF	CBF measure	CA	COR	CMRO2	Reference
10	< 24 hrs	60	23	S,SS,Sh	-	TCD	Normal	Normal	-	[185]
10	> 48 hrs	50	31	SS	Normal	Dilution	-	Normal	Normal	[171]
16	> 48 hrs	75	23	S,SS,Sh	-	TCD	Altered *	-	Normal	[176]
8	NA	60	33	SS	Increased	NIRS	-	Reduced	-	[188]
9	< 72 hrs	52	NA	S	Reduced	Xenon-CT	-	Normal	Reduced	[183]
6	Day 2-10	48	NA	SS	Reduced	KST	-	-	Reduced	[132]
12	> 24 hrs	68	18	SS,Sh	-	TCD	-	Variable	-	[189]
15	12-48 hrs	54	22	Sh	Reduced	C-Doppler	Altered			[186]
20	NA	58	21	Sh	Increased	TCD	-	-	-	[184]
21	< 72 hrs	65	20	Sh	-	TCD	Altered	-	-	[187]
20	< 72 hrs	65	37	Sh	-	TCD	-	Reduced	-	[190]
23	NA	68	22	SS, Sh	-	TCD/NIRS	Impaired **	-	-	[177]
14	NA	NA	NA	S	-	TCD	-	Reduced	-	[180]
10	-	30	-	HV	Normal	KST	-	-	Unchanged	[182]
8	-	25	-	HV	Reduced	KST	-	Normal	Unchanged	[181]

* Only in patients with septic shock
** In case of lower MAP and higher values of PaCO2
Pts = patients; APACHE = Acute Physiology And Chronic Health Evaluation; CBF = cerebral blood flow; CA = cerebral autoregulation; COR = carbon dioxide reactivity; CMRO2 = cerebral oxygen consumption; hrs = hours; S = sepsis; SS = severe sepsis; Sh = septic shock; TCD = transcranial Doppler; NIRS = near infrared spectroscopy; NA = not available; CT = computed tomography; KST= Keyt-Schmidt technique; NA = not available; C-Doppler = Carotid Doppler; HV = healthy volunteers.

and systemic vasodilatation occur inducing an increased CBF. Also TCD abnormalities were strongly related to disease severity and outcome.

4.3. Cerebral Autoregulation

In a first study on 10 patients with sepsis and altered mental status, Matta *et al*. [185] showed that CA was intact within the first 24 hours after ICU admission, when phenylephrine infusion was used to increase MAP within the normal pleateau of autoregulation. In opposite, Smith and colleagues [186] reported loss of CA in 15 patients with septic shock, in which the changes in CBF, estimated by carotid Doppler, significantly correlated with changes in cardiac index. In a more recent study on 16 patients with different degree of sepsis severity, Pfister and colleagues [176] found disturbed CA in patients having sepsis-associated delirium but not in patients without neurological symptoms, despite similar systemic hemodynamics and baseline MAP. These alterations were associated with higher levels of inflammatory biomarkers (CRP and IL-6), of brain injury biomarkers (s100β) and poorer outcome, but not to the severity of disease, assessed by the APACHE II score, and to catecholamine requirements. Also, Taccone *et al*. [187] showed that CA was impaired in 14 out of 21 patients with septic shock, including 7 of the 14 patients with PaCO2 < 40 mmHg and 7/7 of those with PaCO2 > 40 mmHg (p = 0.046), suggesting a possible role for normal levels of carbon dioxide in the alterations of CA during sepsis. These findings were supported by Steiner *et al*. [177], who showed that CA during sepsis was significantly related to PaCO2, with higher PaCO2 levels being associated with the worse autoregulation.

4.4. Carbon Dioxide Reactivity

In mechanically ventilated septic patients [185], authors showed that there was only a moderate reduction of cerebrovascular reactivity to PaCO2 when compared to values in awake controls, but consistent with values obtained during sedation and anaesthesia. Bowton *et al*. [183] also reported a normal response to CO2 changes in septic patients. More recently, in ongoing sepsis for more than 48 hours, CO2 reactivity was shown to be intact in 10 patients with sepsis and undergoing mechanical ventilation [171]. Hypocapnia was associated with a reduction of CBF without affecting CMRO2, which was already within low ranges at baseline. None of the characteristics of patient population, including APACHE II, temperature, MAP, CI had any significant association with CO2 reactivity. In contrast with these findings, Terborg *et al*. [188] observed, in a small cohort of brain injured patients developing severe sepsis and septic shock, that cerebrovascular reactivity to PaCO2 was severely impaired, independently of changes in MAP. Nevertheless, they assessed vasomotor reactivity in septic patients having all a pre-existing neurological illness, which may have affected

the results. In another study on 12 patients, 3 of them had normal cerebrovascular reactivity, 7 had impaired vasomotor tone while in two others the response to CO2 changes appeared to be higher than control [189], without any association of this finding with cardiovascular status, outcome and severity of illness; also, these alterations did not affect outcome. Recently, cerebro-vascular reactivity was found to be impaired in septic patients with SAE by means of acetazolamide injection test. Also, the reaction to the vasodilating stimulus was slower in septic patients than control [180]. Finally, the cerebrovascular reactivity to PaCO2 in patients with septic shock was lower than in control patients, with a significantly lower reactivity in patients receiving dexmedetomidine than propofol [190].

4.5. Summary of Human Findings and Clinical Implications

Sepsis-induced brain dysfunction can directly cause brain damage by altering brain global perfusion and microcirculation. In clinical practice, several therapeutical protocols exist to guide the management of patients suffering from severe sepsis or septic shock, including the early-goal directed therapy, the prompt antimicrobial administration or the protective lung ventilation; however, we still lack a specific neuroprotective approach to prevent or minimize secondary ischemic brain injuries occurring during sepsis. This is probably due to the limited data available in the literature on the mechanisms inducing brain hypoperfusion in septic patients; moreover, most of studies evaluating CBF in this setting showed a reduced CBF but did not provide relevant data for the role of these observations in the development of SAE.

Some studies suggested that vasoconstriction occurs at the level of cerebral arterioles and contribute to reduce CBF [180]; however, it remains still unknown if this phenomenon is secondary to the effects of circulating substances that act on brain vessels or because of impairment of microcirculation, as suggested in animal studies. Importantly, if the increase in cerebrovascular resistances is dependent from a vasoconstrictor agent, it is possible that it would be released directly within the brain parenchyma. Indeed, omental arteries placed in plasma from septic patients had diminished response to vasopressin [191], while the administration of vasopressors poorly affected CBF in septic patients [192]. We can then hypothesize that the use of vasoactive substances is unlikely to negatively influence cerebral perfusion during sepsis. Importantly, data on the cerebrovascular effects of catecholamines in experimental head injury have shown that dopamine, norepinephrine and phenylephrine all increase CBF, with the most predictable effects when norepinephrine was used, while dopamine was associated with increased brain edema and phenylephrine with a raise in intracranial pressure [193]. Thus, further studies on the effects of such vasopressors on brain perfusion during both animal and human sepsis are needed.

Other studies suggested that changes in CBF were induced by acute hypocapnia, rather than sepsis itself [181]. Conflicting data on cerebrovascular reactivity to CO2 during sepsis exist; when COR was preserved, it was shown to be lower than in awake subjects, leaving the possibility that this difference could be due to the use of sedation rather than to the septic process [185]. Studies showing reduced CO2 reactivity in septic patients did not strictly control PaCO2 using mechanical ventilation, used different timing of measurements and different vasoactive agents, making difficult to reconcile these data with previous studies [188, 189]. Considering that acute reduction of PaCO2 did not change cerebral oxygenation in healthy volunteers and septic patients [171, 181], hypocapnia should not be actively corrected in septic patients to improve brain perfusion. Furthermore, normocapnic/hypercapnic patients have an impaired autoregulation of CBF and should be considered at higher risk of brain hypoperfusion than those with hypocapnia [177, 187].

The concomitant use of sedative agents, which reduced neural metabolic rates, may be responsible for lowering brain perfusion in septic patients, accordingly to the metabolic hypothesis of CBF regulation. Importantly, sedatives are likely to modify the reactivity of brain vasculature to physiological stimuli, thus limiting the capacity of CBF to autoregulate in case of abrupt changes in PaCO2 or cerebral perfusion pressure. These data further support the concept of early interruption of sedation in critically ill patients to limit improper use of anesthetic agents and prevent the occurrence of brain hypoperfusion [194].

More than the absolute measure of CBF, the evaluation of cerebral autoregulation appears to be fundamental for the hemodynamic management of septic patients; as such, impaired CA may leave brain tissue unprotected against possibly harmful effects of blood pressure changes during sepsis, leading to cerebral ischemia. Cerebral autoregulation was often impaired in septic patients and this was more frequently altered in patients with more severe disease, such as shock or delirium [176, 187]. Thus, an early hemodynamic stabilization associated with CBF monitoring and assessment of CBF reactivity may be recommended in septic patients, especially those with the highest degree of illness severity.

Finally, we still are unable to identify the optimal threshold of MAP to target in a patient with septic shock to avoid brain ischemic events. As MAP is generally below normal ranges during sepsis, particularly when shock is present, brain perfusion become dependent on CA and the individual capacity to maintain stable CBF over a wide range of systemic pressure. In addition, given concomitant brain edema and elevated ICP above 15 mmHg can occur in septic patients, if MAP is maintained between 60 and 70 mm Hg as generally recommended, cerebral perfusion pressure may fall below 50 mmHg and potentially contribute to brain hypoperfusion [195].

CONCLUSION

Altered brain perfusion is frequent after sepsis and may contribute to the pathogenesis of sepsis-associated encephalopathy. Although the complex pathophysiology has not been fully elucidated, main factors involve direct decrease of cerebral blood flow, alterations of cerebro-vascular autoregulation, endothelial dysfunction and disorders of microcirculation, release of vasogenic inflammatory mediators, neurochemical derangements and metabolic uncoupling, which may eventually lead to cerebral hypoperfusion. This may potentially expose the brain of septic patients to secondary ischemic/hypoxic insults, brain cell dysfunction and worse

neurological recovery. Novel monitoring tools and recent clinical investigations contributed to improve our understanding of the regulation of cerebral perfusion in patients with sepsis. These studies have underlined the impact of sedatives and vasopressors on brain perfusion. Some issues are still controversial, particularly whether hemodynamic augmentation of brain perfusion after severe sepsis or septic shock may be beneficial.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

APACHE II	=	Acute physiology and chronic health evaluation
ATICE	=	Assessment to Intensive Care environment
BBB	=	Brain-blood barrier
BOLD	=	Blood oxygenation level dependent contrast
CA	=	Cerebral autoregulation
CAM-ICU	=	Confusion assessment method for the Intensive Care Unit
CBF	=	Cerebral blood flow
CI	=	Cardiac index
CMRO2	=	Cerebral metabolism rate of oxygen
CNS	=	Central nervous system
COR	=	Cerebrovascular-CO2 reactivity
CPP	=	Cerebral perfusion pressure
CRP	=	C-reactive protein
CT	=	Computed tomography
CVOs	=	Circumventricular organs
CVR	=	Cerebrovascular resistance
EEG	=	Electroencephalography
GCS	=	Glasgow coma score
ICAM-1	=	Inter-cellular adhesion molecule 1
ICU	=	Intensive Care Unit
ICP	=	Intracranial pressure
IFN-γ	=	Interferon gamma
iNOS	=	Inducible nitric oxide synthase
L-NAME	=	N-nitro-L-arginine methylester
L-NMMA	=	N-monomethyl-L-arginine
MAP	=	Mean arterial pressure
MCAV	=	Middle cerebral artery velocity
MOF	=	Multiple organ failure
MRI	=	Magnetic resonance imaging
NIRS	=	Near-infrared spectroscopy
NO	=	Nitric oxide
NSE	=	Neuron-specific enolase
PaCO2	=	Arterial carbon dioxide tension
PaO2	=	Arterial oxygen tension
PbO2	=	Brain oxygen tension
PET	=	Positron emission tomography
ROS	=	Reactive oxygen species
SAE	=	Sepsis-associated encephalopathy
SPECT	=	Single photon emission computed tomography
SSEPs	=	Somato-sensitive evoked potentials
TCD	=	Transcranial Doppler
TNF-α	=	Tumor necrosis factor alpha
VIP	=	Vasoactive intestinal peptide

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