Cerebral hemodynamics: concepts of clinical importance

Hemodinâmica encefálica: conceitos de importância clínica

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ABSTRACT

Cerebral hemodynamics and metabolism are frequently impaired in a wide range of neurological diseases, including traumatic brain injury and stroke, with several pathophysiological mechanisms of injury. The resultant uncoupling of cerebral blood flow and metabolism can trigger secondary brain lesions, particularly in early phases, consequently worsening the patient's outcome. Cerebral blood flow regulation is influenced by blood gas content, blood viscosity, body temperature, cardiac output, altitude, cerebrovascular autoregulation, and neurovascular coupling, mediated by chemical agents such as nitric oxide (NO), carbon monoxide (CO), eicosanoid products, oxygen-derived free radicals, endothelins, K^+, H^+, and adenosine. A better understanding of these factors is valuable for the management of neurocritical care patients. The assessment of both cerebral hemodynamics and metabolism in the acute phase of neurocritical care conditions may contribute to a more effective planning of therapeutic strategies for reducing secondary brain lesions. In this review, the authors have discussed concepts of cerebral hemodynamics, considering aspects of clinical importance.

Key words: cerebral hemodynamics, cerebral blood flow, cerebral autoregulation, neurovascular coupling, brain injuries, traumatic, subarachnoid hemorrhage.

RESUMO

Alterações hemodinâmicas e metabólicas do encéfalo ocorrem frequentemente em diversas doenças neurológicas, principalmente em condições de traumatismo cranioencefálico e acidente vascular encefálico, com vários mecanismos patofisiológicos lesionais. O desacoplamento resultante do fluxo sanguíneo e do metabolismo encefálico pode resultar em lesões encefálicas secundárias, principalmente nas primeiras fases, e, consequentemente, no agravamento do desfecho neurológico dos pacientes. Diversos fatores influenciam o fluxo sanguíneo encefálico, entre eles, a concentração sanguínea de gases, viscosidade sanguínea, temperatura corpórea, débito cardíaco, altitude, autorregulação cerebrovascular e acoplamento neurovascular, que é mediado por óxido nítrico (ON), monóxido de carbono (CO), eicosanoides, radicais livres derivados do oxigênio, endotelinas, potássio, íons hidrogênio e adenosinas. Melhor compreensão destes fatores é fundamental para o manejo clínico dos pacientes neurológicos críticos. A avaliação hemodinâmica e metabólica do encéfalo nas lesões encefálicas agudas pode contribuir para o planejamento de estratégias de redução das lesões encefálicas secundárias. Nesta revisão, os autores discutiram princípios da hemodinâmica encefálica, considerando os aspectos de importância clínica.

Palavras-Chave: hemodinâmica cerebral, fluxo sanguíneo cerebral, autorregulação cerebral, acoplamento neurovascular, traumatismo encefálico, hemorragia subaracnóidea.

Head trauma and stroke are conditions typically associated with impaired cerebral blood flow (CBF) and metabolism, although some pathophysiologic mechanisms may differ between them[1-4]. Impairments in the CBF and metabolism can lead to secondary brain injuries, particularly in the early weeks, consequently worsening the clinical outcome[5-6]. Assessment of both cerebral hemodynamics and metabolism in the acute phase of these conditions may contribute to a more effective planning of therapeutic strategies for reducing secondary brain lesions[7].

The objective of this review was to address concepts of cerebral hemodynamics, considering aspects of clinical importance.

NORMAL CBF

The human brain represents approximately 2% of total body weight, yet it receives approximately 20% of cardiac output and uses 20% of total body oxygen consumed under normal conditions. In this situation, most of the energy of the brain is obtained exclusively from aerobic metabolic process.

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Therefore, impairment in the supply of nutrients and oxygen to the brain can cause cellular damage.

CBF varies directly with cerebral perfusion pressure (CPP), which is defined as the difference between mean arterial and intracranial pressures, and inversely with cerebrovascular resistance (the sum of vascular resistance to flow, particularly at the level of the small pial arteries and penetrating pre-capillary arterioles). The contribution of any given cerebral vessel to overall CBF is defined by factors, such as its radius and length, and both blood viscosity and pressure.

Tissue perfusion in the brain is approximately 50 to 55 mL/100 g/min. As blood perfusion is progressively reduced, oxygen extraction from hemoglobin, which is indicated by arteriovenous difference in oxygen, increases without clinical manifestation. When blood perfusion reaches 25 to 30 mL/100 g/min., electroencephalographic (EEG) abnormalities and consciousness alterations may occur. As blood perfusion falls further to below approximately 20 mL/100 g/min., EEG becomes isoelectric and neurons increasingly switch to anaerobic metabolism, with concomitant increased production of lactate and hydrogen ions. Once perfusion reaches 10 to 12 mL/100 g/min., neurotransmission is lost, sodium-potassium pumps fail and cytotoxic edema ensues. In the absence of cerebral hypothermia, perfusion of less than 6 to 10 mL/100 g/min. triggers tissue death cascade mediated by calcium and glutamate[8]. These data emphasize the importance of CBF assessments in neurocritical patients: no clinical signs are associated with low CBF until its values have reached the threshold of functional neuronal impairment, which is close to the one of permanent neuronal injury. Therefore, early recognition of low CBF states can help identifying and treating patients before the occurrence of ischemic brain lesions.

other metabolites in the arterial endothelium (metabolic mechanism). Recently, sympathetic neural control has been implicated as one of the mechanisms of cerebral autoregulation (neurogenic mechanism)[9].

The basic concept of cerebral autoregulation usually involves either the static or dynamic relationship between ABP, or CPP, and CBF. In the assessment of static cerebral autoregulation, CBF (or CBF velocity) is first measured at a constant baseline ABP (or CPP), followed by another steady state CBF (or CBF velocity) measurement after pharmacological manipulation of ABP. If static cerebral autoregulation is preserved, mean CBF (or CBF velocity) is expected to remain constant, despite changes in ABP (or CPP) that in most cases lie in the 60 to 150 mmHg range. In the absence of a constant CBF, cerebral autoregulation is considered impaired. The concept of dynamic cerebral autoregulation is based on the temporal response of autoregulatory mechanisms promoting fast restoration of CBF to its original value. This response normally occurs within two to ten seconds upon CBF disturbance by a sudden change in ABP. Measurement of dynamic cerebral autoregulation offers the advantage of investigating beat-to-beat variations of pressure-flow in cerebral circulation and of differentiating response time of the mechanism[2,9]. Dynamic cerebral autoregulation may be assessed by comparing continuous measurements of cerebral blood velocity with simultaneous measurements of spontaneous fluctuations in ABP.

The lower and upper limits of static pressure autoregulation (usually in the 60 to 150 mmHg range) are variable and can be influenced by a number of factors, such as: hematocrit and hemoglobin concentration, blood levels of CO_2, O_2, and H^+, brain temperature, cardiac output, and altitude (Fig 1). In chronic hypertension, values for lower and upper limits

CBF REGULATION
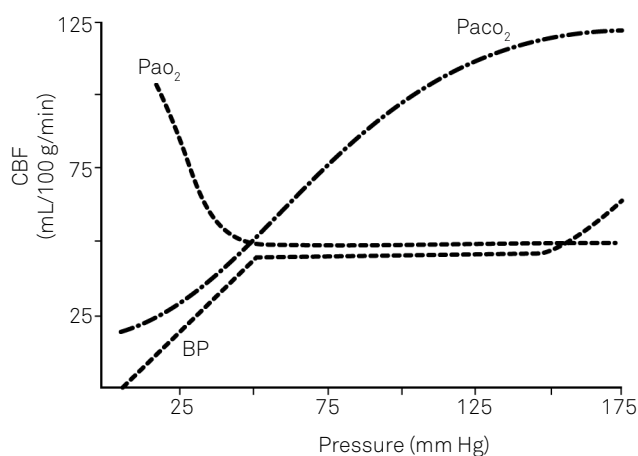
Cerebral autoregulation

Cerebral or pressure autoregulation is the inherent ability of blood vessels to keep CBF relatively constant over a wide range of arterial blood pressure (ABP) levels by the interplay of numerous physiological mechanisms.

A sudden change in mean ABP leads to a simultaneous change in CBF initially, but it also triggers a number of other responses. For instance, ABP augmentation produces dilatation of cerebral arteries, which leads to a chain of events: changes in smooth muscle ionic permeability, muscle contraction, vessel narrowing, and increase in cerebrovascular resistance (myogenic mechanism). Concomitantly, CBF elevation due to ABP augmentation causes both increase in tissue O_2 and decrease in the concentration of CO_2 and other products of cerebral metabolism. In the absence of greater demand for O_2, a complex sequence of events restores the balance between O_2 supply and demand by means of vasoconstriction mediated by activation of nitric oxide (NO) and

CBF: cerebral blood flow.

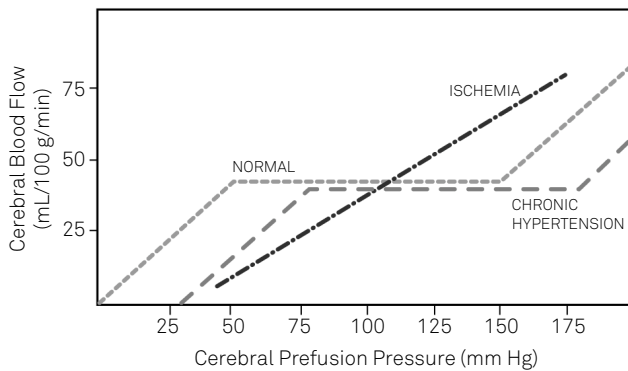**Fig 1.** Cerebrovascular autoregulation in health and effect of blood gases on the CBF. Influence of alterations in arterial blood gases and blood pressure on cerebral blood flow. Acute hypoxia triggers dilation of cerebral microcirculation and increase in CBF. Hypercapnia causes marked dilation of cerebral arterioles and CBF elevation, whereas hypocapnia causes vasoconstriction and decrease in CBF.

of pressure autoregulation are higher than those under normal conditions, resulting in a degree of resetting as high as 40 mmHg (Fig 2). Therefore, acceptable ABP levels for healthy subjects may be associated with lower CBF. During hypercapnia, cerebral vessels are dilated and have reduced capacity to further dilate in response to reductions in perfusion pressure[10]. The control of the aforementioned factors is important in order to avoid aggravation of cerebral autoregulation capacity, thereby preventing secondary cerebral lesions.

Hypoxia, ischemia, intracranial hypertension, traumatic brain injury (TBI), stroke, renal and hepatic failures, as well as sepsis can impair cerebral pressure autoregulation. Once the autoregulatory mechanisms have been abolished, CBF passively follows changes in ABP and impaired cerebral pressure (ICP). Under these conditions, the brain becomes vulnerable to ischemic or hyperemic injuries if perfusion pressure does not remain coupled with metabolic demands (Fig 2). In the TBI, patients with disturbed cerebral autoregulation, recommended CPP (greater than 70 mmHg) can be associated with severe cerebral hyperemia, predisposing the brain to hemorrhages, swelling, and intracranial hypertension. Thus, recent guidelines have suggested lower CPP levels for this patient group (60 mmHg)[11]. A recent study has demonstrated that CPP <50 mmHg and CPP <60 mmHg were associated with favorable outcomes, whereas CPP >70 mmHg and CPP >80 mmHg were associated with unfavorable outcomes in TBI patients with impaired cerebral pressure autoregulation[12].

Neurovascular coupling

Increased cerebral functional activity is accompanied by rapid increases in oxygen utilization, glucose uptake and metabolism, as well as blood flow in the activated brain areas[13,14].
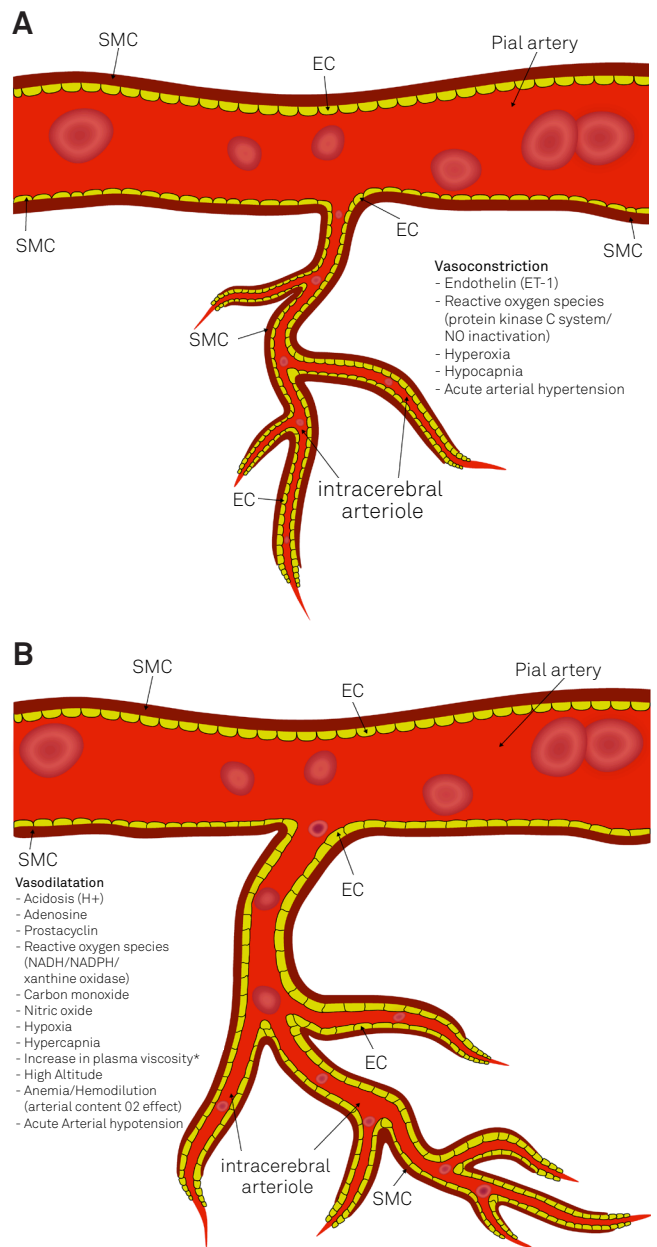
Flow-metabolism coupling in the brain is mediated by chemical agents involved in electrical and biochemical interactions among neurons, astrocytes, endothelium cells, and smooth muscle cells. The main chemical agents such as NO, carbon monoxide (CO), eicosanoids products, oxygen-derived free radicals, endothelins, K^+, H^+, and adenosines are presented as the following topics (Fig 3).

Hydrogen ions

The diameter of cerebral blood vessels, which influences CBF, is highly dependent on tissue proton (H^+) concentration[15,16]. Hypercapnic and normocapnic acidosis have been shown to cause dilation in cerebral blood vessels, and consequently increased CBF[17]. In rats, a stepwise increase

A

Vasoconstriction
- Endothelin (ET-1)
- Reactive oxygen species (protein kinase C system/ NO inactivation)
- Hyperoxia
- Hypocapnia
- Acute arterial hypertension

B

Vasodilatation
- Acidosis (H+)
- Adenosine
- Prostacyclin
- Reactive oxygen species (NADH/NADPH/ xanthine oxidase)
- Carbon monoxide
- Nitric oxide
- Hypoxia
- Hypercapnia
- Increase in plasma viscosity*
- High Altitude
- Anemia/Hemodilution (arterial content 02 effect)
- Acute Arterial hypotension

SMC: smooth muscle cell; EC: edothelium cells.
Fig 3. (A) factors that can induce vasoconstriction; (B) factors that can induce vasodilation.

CBF: cerebral blood flow.
Fig 2. Cerebrovascular autoregulation in health, chronic hypertension and during autoregulation loss. In chronic hypertension, values for lower and upper limits of pressure autoregulation are higher than those under normal conditions, resulting in a degree of resetting as high as 40 mmHg. Therefore, acceptable ABP levels for healthy subjects may be associated with lower CBF. Ischemia can impair cerebral autoregulation allowing CBF to vary directly with blood pressure leading to brain lesion.

of extraluminal proton concentration from pH 7.4 to 7.0 led to a linear increase in the cerebral vessel diameter[18]. Maximum dilation was reached at a pH of 7.0 with no further diameter increase upon lowering of pH to 6.0. The mechanism of acidosis-induced dilation consists of activation of K_{ATP} and K_{Ca} channels in response to increased extraluminal proton concentration. Moreover, cerebral artery dilatation during moderate elevations in proton concentration is highly dependent on the basal perivascular NO level, whereas at lower extraluminal pH (7.0) vasodilation becomes independent of NO and it is probably mediated by other mechanisms[15,16,19]. In contrast, the infusion of 8.4% sodium bicarbonate in TBI patients can decrease ICP, without generating metabolic acidosis[20].

Adenosine

Adenosine is a purine nucleoside that regulates CBF and modulates neuronal and synaptic activity[21,22]. During neuronal activity, seizures, hypoxia, and ischemia, the adenosine level increases in cerebrospinal fluid. Adenosine results from the breakdown of AMP, a product derived from ATP and ADP hydrolysis during increased neuronal activity. This neurotransmitter acts through two classes of purinergic receptors, A1 and A2[21]. A1 receptors are found in neurons and they are coupled to $G_{i/o}$ proteins, which inhibit and decrease neuronal excitability. A2 receptors seem to be present in both smooth muscle and endothelial cells of cerebral blood vessels and induce vasodilatation by releasing endogenous factors, such as prostacyclin, nitric oxide, endothelium derived hyperpolarizing factor, epoxyeicosatrienoic acids, and reactive oxygen species[21]. Furthermore, in a variety of circulatory beds, studies have documented that vasodilatation by adenosine occurs by means of a direct interaction with adenosine receptors located on the vascular smooth muscle. The effects of caffeine on cerebral circulation can be attributed to its inhibitory effects on adenosine receptors[23].

Endothelins

Endothelin-1 (ET-1) is a 21 amino acid bioactive peptide, which is predominantly synthesized and released by endothelial cells and is a potent vasoconstrictor implicated in the pathogenesis of vasospasm and delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage (SAH) patients. ET-1 is not only generated by vascular-endothelial and smooth-muscle cells, but also by neurons, astrocytes, and monocytes. Hemoglobin stimulates monocytes ET-mRNA expression, a mechanism that increases ET-1 concentration in the cerebrospinal fluid in SAH. Selective antagonists of the two ET-1 receptors (ETA and ETB) have been used for SAH-induced vasospasm in animal models, where vasospasm can be limited by blocking the detrimental effects of endogenous ET-1[24,25]. ET-1 has been reported to be released from astrocytes after hypoxia. Moreover, it has been speculated that ET-1 released from neuronal and glial cells after early ischemic damage may later contribute to delayed cerebral ischemia[24].

In animal models of TBI, brain ET-1 concentrations increase two- to three-fold, and they are associated with prolonged vasoconstriction and brain injury due to their high potency and long duration of action. Antagonists of ET-1 can reverse this vasoconstrictor response[26].

Prostacyclin

Prostacyclin is a metabolite of arachidonic acid that is produced with other prostaglandins and thromboxanes by two cyclooxygenase (COX) enzymes, COX-1 and COX-2[27]. COX-2 is expressed primarily in macrophages, fibroblasts, endothelium, vascular muscle, and constitutively in the brain. Lipopolysaccharide, adenosine 3', 5'-cyclic monophosphate (cAMP), hypoxia, inflammatory cytokines, growth factors, and hormones stimulate the expression of COX-2. Prostacyclin and analogs produce relaxation of cerebral arteries *in vitro* and *in vivo* mediated by an endothelium-independent mechanism, NO formation, potassium channels, and activation of adelynate cyclase[28]. Prostacyclin may reduce vasoconstriction elicited by SAH[29]. Beneficial effects of low-dose prostacyclin infusion have been reported in severe traumatic brain injury[30].

Reactive oxygen species

Reactive oxygen species have multiple effects on vascular cells. Oxygen-derived free radicals, such as the superoxide (superoxide anion) and hydroxyl radicals, are a subgroup of reactive oxygen species that contain one or more unpaired electrons. Superoxide dilates cerebral arterioles when generating NADH or NADPH by xanthine oxidase, mediated by potassium channels[31-33]. Reactive oxygen species play a role in the pathophysiology of cerebral vasospasm through activation of the protein kinase C system and/or inactivation of NO. In experimental models, NADPH oxidase inhibitor attenuated SAH cerebral vasospasm[34].

CO

CO is produced endogenously in the endothelium during enzymatic degradation of heme by means of heme oxygenase (HO). CO is a potent vasodilator of cerebral arterioles *in vivo* and contributes to cerebrovascular dilation induced by hypoxia and excitatory amino acids. The dilator actions of CO involve both prostacyclin and NO as permissive enablers, because prostacyclin and NO provide the background cGMP/PKG activity needed to allow CO to dilate pial arterioles via activation of Ca^{2+} channels mediated by K^+ and hyperpolarization of vascular smooth muscle cell. Considering the interaction between the mechanism of CO and NO production and given that NO provokes greater vasodilatory response than CO, one gas can interfere with the vasodilation response of the other[35-37].

SAH and focal ischemia can stimulate CO overproduction by inducing HO-1 and heme augmentation. However, the precise actions of this gas under these pathologic circumstances warrant further investigation[36].

NO

NO is an inorganic labile gaseous molecule, which is released from endothelial cells and perivascular nitrergic neurons[38]. It results in cerebral vasodilatation, decrease in cerebrovascular resistance and increase in CBF. Endothelial NO also acts as an antiplatelet, antithrombotic, antiproliferative, and antiatherosclerotic agent[38]. Therefore, endothelial dysfunction and nitrergic neuronal impairment lead to cerebral circulatory disorders. The vasodilatory effect of NO in the vascular muscle is mediated by potassium channels and soluble guanylate cyclase, raising intracellular concentration of cGMP[39,40]. Relaxation of cerebral vessels in response to acetylcholine, bradykinin, vasopressin, oxytocin, substance P, histamine, sodium fluoride, endothelin, ADP, and ATP are dependent on NO production.

According to the two-stage hypothesis for delayed cerebral vasospasm[39], NO-releasing neurons are injured by oxyhemoglobin (oxyHb), leading to reduced availability of NO in vessel wall and vasoconstriction (Phase I). Increased shear stress evoked by narrowing of the arterial lumen can stimulate endothelial NO synthase (eNOS). Hemoglobin breakdown to bilirubin oxidized fragments (BOXes) increases asymmetric dimethylarginine (ADMA), an endogenous inhibitor of eNOS, in the vicinity of cerebral arteries thus further decreasing NO availability and sustaining vasospasm (Phase II). In Phase III (resolution of vasospasm), elimination of BOXes increases NO production by eNOS, resulting in the recovery of dilatory activity of endothelium. This hypothesis suggests that the treatment of delayed cerebral vasospasm should focus on preventing oxyHb neurotoxicity, inhibiting BOX production and exogenous NO delivery.

Potassium ions and channels

The membrane potential of arterial smooth muscle cell (SMC) is a determinant of vascular tone and is regulated by K^+ channels. Opening of K^+ channels in vascular SMC membranes allows K^+ to flow out of the cell, resulting in membrane hyperpolarization, whereas inhibition of K^+ channels results in membrane depolarization. K^+ channel-mediated membrane hyperpolarization closes voltage-dependent Ca^{2+} channels, which decreases Ca^{2+} entry and leads to vasodilation, while membrane potential depolarization causes vasoconstriction[41].

Four different subtypes of K^+ channels can be identified in the arterial SMC: inward rectifier K^+ (K_{ir}) channels, Ca^{2+}-sensitive K^+ (BK) channels, voltage-dependent K^+ (K_V) channels, and ATP-sensitive K^+ (K_{ATP}) channels[41]. The expression profile and functional contribution of each subtype vary according to the tissue type and caliber of the arterial segment.

Neuronal activation and astrocyte modulation have the potential to generate vasoconstriction and vasodilatation mediated by K^+ channels and membrane potential variations, according to extracellular potassium concentration. Potassium channel activator cromakalim has been shown to limit the severity of cerebral vasospasm if administered 24 hours after SAH in experimental models[42].

Effect of arterial blood gases

Oxygen

The brain has a high metabolic demand for oxygen. Acute hypoxia triggers dilation of cerebral microcirculation and increase in CBF (Fig 1)[43]. In general, CBF does not change substantially until tissue PO_2 falls below 50 mmHg[43]. As hypoxia decreases P_{O2} further, CBF can rise to 400% of resting levels[44]. Increases in CBF do not change metabolism but cause hemoglobin saturation to fall from 100% at P_{O2} >70 mmHg to 50% at P_{O2} <50 mmHg[44]. Acute hypoxia can cause an increase in the CBF by means of direct effects on cerebral arterioles. A hypoxia-induced decrease in ATP levels opens K_{ATP} channels in arteriole smooth muscle inducing hyperpolarization and vasodilation. Moreover, hypoxia rapidly increases NO and adenosine production resulting in vasodilation[45].

Recent medical literature reports that impaired cerebral mitochondrial function can occur after TBI. In patients with clinically-defined ischemia, increased cerebral oxygenation or a decrease in arteriovenous O_2 difference, the presence of decreased O_2 metabolism due to mitochondrial dysfunction should be suspected[46].

Carbon dioxide

Hypercapnia causes marked dilation of cerebral arterioles and CBF elevation, whereas hypocapnia causes vasoconstriction and decrease in CBF (Fig 1)[45]. In humans, 5% CO_2 inhalation leads to a 50% rise in CBF and 7% CO_2 inhalation causes a 100% increase in CBF[45]. The mechanism of hypercapnic vasodilation appears to involve a direct effect of extracellular H^+ on vascular smooth muscle[45]. This is supported by findings that neither bicarbonate ion nor changes in P_{CO2} alone affect the cerebral arteriole diameter[45]. Hypercapnia can increase CBF, cerebral blood volume and intracranial pressure in addition to impairing cerebral autoregulation[47]. On the other hand, hyperventilation-induced hypocapnia can decrease CBF, cerebral blood volume and ICP due to cerebral vasoconstriction and it has been used in clinical practice to control intracranial hypertension. Although contested by a number of authors, there is increasing evidence that hyperventilation produces cerebral hypoperfusion, decreased cerebral oxygenation, activation of anaerobic cell respiration, and poorer patient outcomes[45]. Furthermore, impaired CO_2 cerebrovascular reactivity reflects loss of microvascular function and can be associated with increased risk of cerebral infarction in patients with carotid occlusive disease[48,49].

Blood viscosity and hemodilution effect

Blood viscosity is an important factor determining blood flow, which depends on hematocrit, erythrocyte aggregability, and plasma viscosity[50]. Changes in arteriolar diameter associated with variation in blood viscosity have been referred to as viscosity autoregulation. This mechanism is analogous to pressure-induced autoregulation and renders the flow behavior

different to that expected in rigid tubes, in which pressure remains constant and CBF increases as blood viscosity is reduced. Factors influencing viscosity autoregulation include endothelial wall shear stress and oxygenation. In hemodilution, blood viscosity reduction accounts for approximately half of the increase in CBF, with the remainder caused by the change in arterial content of O_2. In an experimental model, a reduction of hematocrit from 32 to 18% resulted in dilation of pial arterioles and increase in CBF to maintain cerebral O_2 transport[51].

In microcirculatory paralysis, in which microcirculation is significantly dilated, an increase in viscosity leads to lower CBF. Failure to maintain constant CBF with increased viscosity during high-flow conditions may be caused by failure of further dilation of cerebral arterioles[52].

In SAH patients, anemia can worsen the patient's outcome because it may lead to cerebral ischemia by reducing oxygen availability in brain tissue[53,54]. Clinical studies suggest that hemoglobin concentrations greater than 11 g/dL may be associated with improved SAH outcomes[55,56]. On the other hand, although high hemoglobin concentrations increase blood viscosity resulting in a tendency for autoregulatory vasodilatation, there is an increase in O_2 tissue concentration leading predominantly to vasoconstriction and decreased CBF. In patients with anemia, red blood cell transfusion has also been associated with organ dysfunction and increased mortality[57,58], mediated by inflammatory substances or altered NO metabolism among other factors, predisposing to vasospasm.

Experimental evidence links anemia to reduced brain tissue oxygen pressure and increased neuron injury after acute brain injury[59]. In normal brain, compensatory vasodilation occurs at hemoglobin concentrations lower than 10 g/dL[60]. The manifestation of brain hypoxia usually occurs at even lower hemoglobin levels (e.g., <6 g/dL)[61]. However, when cerebrovascular reserve is impaired, tissue hypoxia and cell injury may develop at higher hemoglobin concentrations. There are good theoretical reasons to maintain higher hemoglobin concentration after brain injury, since the brain has stringent O_2 requirements. Most neurosurgeons prefer a hemoglobin concentration greater than 10 g/dL for patients with acute brain injury, in order to maintain optimal oxygen carrying capacity[62].

Body temperature effect

In the injured brain, hyperthermia increases metabolic expenditure, blood flow, glutamate-induced neurotoxicity, neutrophil activity, and reactive oxygen species[63]. These events may further enhance the vulnerability of the brain to secondary pathogenic events, thereby exacerbating brain swelling and neuronal damage[64]. Glucose utilization in most regions of the brain changes by approximately 5 to 10% for every degree Celsius change in body temperature, underscoring the importance of preventing hyperthermia in the acute phase of severe brain injury.

Hypothermia has been proved to induce: a decrease in the rate of brain metabolism, preserving cellular energy stores and aerobic metabolism; a lower release of excitatory neurotransmitters and NO; and a protection of the blood-brain barrier, and a decrease in free radical production[65-67].

In traumatic brain injury, hypothermia was found to effectively lower elevated ICP, probably by decreasing CBF and the inflammatory response[64,68,69]. Clinical TBI studies have reported the beneficial effects of therapeutic hypothermia on secondary brain injuries and outcomes. Interestingly, mean CBF in patients with a brain temperature of 36.0 to 37.5°C was 37.8±14.0 mL/100 g/min. Lowest CBF was measured in patients with a brain temperature of <36.0°C (17.1±14.0 mL/100 g/min.). A positive trend toward improved outcome was seen in patients with mild hypothermia (35.3±0.5°C)[70].

In SAH, hypothermia has been shown to preserve cerebral autoregulation, reduce cytotoxic edema, limit metabolic alterations and inhibit acute vasospasm, during the acute phase of massive SAH in animal models[66]. The potentially beneficial influence of hypothermia on cerebral blood flow and metabolism in this crucial phase is practicable and might hold the key to further improve the outcome in SAH.

In mild to moderate hypothermia, decreases in CBF are expected to be associated with a slowing down of the cerebral metabolism[71]. However, hypothermia effects on cerebral vascular tone and flow remain a topic of debate, where both increase cerebral vascular tone with reduced CBF as well as hypothermia-induced vasodilation with increased CBF[67]. Interestingly, neurovascular and neurometabolic coupling was found to be preserved during hypothermia in experimental studies[72,73].

Cardiac output effect

There is a linear relationship between CBF velocity and cardiac output at rest and during exercise, as demonstrated under conditions of decreased and increased cardiac output by lower-body negative pressure and infusion of albumin, respectively[74]. Changing postural positions from supine to standing can also reduce cardiac output and, consequently, CBF velocity[75]. Interestingly, decreased CBF velocity was confirmed even though mean arterial pressure was increased. This is possible due to the fact that the lowering of cardiac output can be accompanied by increases in arterial pressure. Therefore, in clinical practice, blood pressure augmentation may not necessarily imply an associated increase in CBF[76]. The dependence of CBF on cardiac output is also seen in cardiac patients, in which decreased cerebral oxygenation during exercise can be noted in cardiac patients with decreased perfusion as a result of compromised cardiac output[77]. In SAH patients, left ventricular dysfunction and low cardiac output increase the risk of cerebral infarction associated with vasospasm[18,49].

High altitude effect

The mechanisms underlying the regulation of CBF during acute exposure to high altitude are complex and depend partly on the degree of hypoxic stimulus and on the cerebrovascular sensitivity to hypoxia and CO_2[78]. Upon initial arrival (days two to four) at high altitude (5050 m), CBF velocity can rise by up to 31% of values measured at sea level, returning to sea-level base values by days seven to nine[79].

Neurological disorders associated with altitude have an intimate relationship with disturbances of cerebrovascular regulation due to high altitude and with the process of acclimatization. Subjects exposed to hypoxia at high altitudes develop an increase in steady-state CBF velocity associated with impairment of cerebral autoregulation[80]. This phenomenon has been correlated with the risk of developing acute mountain sickness and high-altitude cerebral edema[80,81].

Therefore, in theory, patients with intracranial hematomas or some degree of brain swelling, irrespective of etiology, can develop or experience worsening intracranial hypertension when transferred to high-altitude locations.

FINAL REMARKS

Cerebral circulatory abnormalities are frequently found in clinical practice and can lead to secondary cerebral lesions[82,83]. A number of factors can influence CBF and its regulation (Fig 3A and 3B). Both the monitoring and control of these factors can help adjust CBF to match cerebral metabolic demands. A deeper understanding of CBF regulation in brain pathophysiology allows physicians to attain more favorable patients' outcome.

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