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Review Article

Mechanisms of cerebrovascular autoregulation and spreading depolarization-induced autoregulatory failure: a literature review

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Abstract: Cerebrovascular autoregulation maintains brain hemostasis via regulating cerebral flow when blood pressure fluctuation occurs. Monitoring autoregulation can be achieved by transcranial Doppler ultrasonography, the pressure reactivity index (PRx) can serve as a secondary index of vascular deterioration, and outcome and prognosis are assessed by the low-frequency PRx. Although great changes in arterial blood pressure (ABP) occur, complex neurogenic, myogenic, endothelial, and metabolic mechanisms are involved to maintain the flow within its narrow limits. The steady association between ABP and cerebral blood flow (CBF) reflects static cerebral autoregulation (CA). Spreading depolarization (SD) is a sustained depolarization of neurons with concomitant pronounced breakdown of ion gradients, which originates in patients with brain ischemia, hemorrhage, trauma, and migraine. It is characterized by the propagation of an extracellular negative potential, followed by an increase in O_2 and glucose consumption. Immediately after SD, CA is transiently impaired but is restored after 35 min. This process initiates a cascade of pathophysiological mechanisms, leading to neuronal damage and loss if consecutive events are evoked. The clinical application of CA in regulating CBF is to dilate the cerebral arteries as a compensatory mechanism during low blood pressure, thus protecting the brain from ischemia. However, transient impairment of CBF autoregulation due to the mechanism regulated by SD autoregulation has not been reported previously. In this review, we found that SD serves as a vital factor that disrupts CBF autoregulation, and these findings provide insight into the mechanical complexities of SD-induced autoregulatory failure.

Keywords: Mechanism, cerebrovascular autoregulation, autoregulatory failure, spreading depolarization (SD)

Introduction

Recent studies have shown the association between cerebral blood flow (CBF) and metabolic biochemistry and vascular smooth muscle modifications to achieve physiological cerebrovascular homeostatic pressure [1]. The brain itself has the ability to maintain homeostasis by internal mechanisms to obtain sustained cerebral flow while blood pressure fluctuation occurs. This ability is known as autoregulation [2].

To date, there are multiple known mechanisms that all contribute to autoregulation. Four important theories have been proposed to explain autoregulation: the myogenic mechanism involving changes in cerebrovascular resistance, muscle contraction, and ionic smooth muscle interaction [3]; the metabolic mechanism involving the balance between supply and demand, CO_2 concentration, and nitric oxide (NO)-mediated activation [4-6]; the neurogenic mechanism involving sympathetic neural control [7]; and the endothelial cell-related factor mechanism involving humoral stimuli [8].

Spreading depolarization (SD) involves the vascular system by driving progressive autoregulation into failure, thus leaving an altered blood flow in cerebral regions with an already increased demand of supply. This causes pronounced disruption of inherent metabolic mechanisms, altered ionic exchange and release, and disturbances in synaptic signaling with resulting neuronal loss [9].

This review aimed to highlight the importance of the intrinsic autoregulatory process in the cerebral arteries and how SD functions in autoregulatory disruption.

Cerebrovascular autoregulation

The regulation of CBF is a complex and integrated process that is related to the structures of all layers of the vessel wall, including the endothelial cell layer, smooth muscle layer, outer layer of the vessel wall, neurons and glial cells in the brain parenchyma, intracranial blood and cerebral spinal fluid (CSF), and extracellular interstitial fluid [10]. This regulation refers to the ability to preserve CBF at a relatively constant level, even in the presence of cerebrovascular perfusion pressure (CPP) fluctuations. Generally, the CPP ranges between 50-60 mmHg for the lower limit and 150-160 mmHg for the upper limit, meaning that this regulation is effective. The CBF is kept constant at 40-50 mL/100 g/min over the range of arterial blood pressures (ABPs) from 50 to 160 mmHg [11]. When the upper limit of autoregulation is broken, an increase in blood flow to the brain leads to excessive CBF to the maximum limit. When the autoregulation reaches the lower limit, the pressure cannot guarantee effective cerebral flow. However, the upper and lower limits of autoregulation are not absolute. They are affected by many factors, such as increased renin secretion, chronic hypertension (associated with increased sympathetic tone), and boundary value of perfusion pressure. Conversely, sleeping, physiological low blood pressure in athletes and hemorrhage-induced pathological hypotension, the presence of angiotensin-converting enzyme inhibitors, extended hypoxemia, or hypercarbia causes the threshold value of the blood perfusion pressure to decrease [7, 12]. Additionally, when adjusting for severe acute hypertension or low blood pressure, the CBF becomes weakened or even completely loses its regulating effect in cases of severe cerebral infarction, brain injury, and aneurysmal subarachnoid hemorrhage (SAH). The exact mechanism underlying self-regulation is unclear. Possible mechanisms include myogenic, endothelial cell-related factor, neurogenic, and "metabolism" or "fluid" mechanisms, which are more indicative of vasomotor function than metabolic regulation. These mechanisms will be discussed in more detail in this review.

Autoregulation monitoring

The applications of xenon-enhanced computed tomography (Xe-CT) made it possible to study regional CBF [13]. In recent years, single photon emission computed tomography (SPECT) and positron emission tomography (PET) methods have been widely used to measure CBF [14, 15]. Current commonly used methods are the N_2O measurement method, radioactive nuclide, SPECT, PET, and transcranial Doppler ultrasonography (TCD). Among them, TCD has been widely used for cerebral autoregulation (CA) assessment in the clinic for its mobility, low cost, real-time monitoring, and non-invasive approach. TCD has the advantages of being performed in bed or during an operation. TCD can measure CBF velocities in large intracranial vessels, immediately visualizes vascular flow, and detects dynamic changes of the flow, without anatomical imaging [16].

Pressure reactivity index

The pressure reactivity index (PRx) is a moving correlation coefficient of mean arterial pressure and intracranial cerebral pressure, reflecting the tone response of the vascular smooth muscle due to changes in transmural pressure, and it is useful as a secondary index of vascular deterioration [17]. When this association is high, it reflects disturbed autoregulation by a nonreactive behavior of the cerebral vessels. It records changes within 20 s to 2 min in frequencies between 0.05-0.008 Hz and has been used to define the autoregulation-oriented optimal cerebral perfusion pressure (CPP), at which the patient should be treated. Patients with a mean CPP close to the optimal CPP are likely to have a favorable outcome than those patients whose CPP is distant from the optimal CPP [18].

Low frequency pressure reactivity index

The autoregulation index of low frequency pressure reactivity (L-PRx) measures values by-the-minute, instead of by-the-second, of changes in vasoreactivity and the level of disturbance in vascular responses. It records frequencies of 0.016-0.0008 Hz, with a moving time window of 20 min, mainly for outcome prognosis [19].

Cerebrovascular myogenic mechanism of autoregulation

Pressure induces an increase in the smooth muscle cell membrane potential, which most likely occurs by modification of the activity of the ATP-sensitive and calcium (Ca^{2+})-activated potassium channels in the plasma membrane.

The rate of potassium leakage from cells to the extracellular space is regulated by plasma membrane potassium conductance and is the primary determinant of resting membrane potential [20]. The precise mechanism of the mechanochemical coupling is unknown. However, it has been shown that the membrane potential regulates the intracellular Ca^{2+} concentration through voltage-gated Ca^{2+} channels. The intracellular Ca^{2+} concentration is the principal regulator of smooth muscle cell tone by Ca^{2+}/calmodulin myosin light chain kinase-mediated phosphorylation of the regulatory light chains of myosin, with subsequent interaction of actin and myosin. The sequence is endothelium-independent, and the arterial constriction in response to luminal pressure is an intrinsic myogenic reflex [20].

The changes of pressure are accompanied by changes of flow; therefore, the *in vivo* responses of the cerebral vessels to hemodynamic changes are most likely a combination of pressure- and flow-induced mechanisms [21-24]. Thus, one can hypothesize that changes in flow contribute to the CA of CBF. In other words, when systemic pressure changes *in vivo*, then the diameter of the cerebral vessels correspondingly changes as well; thus, changes of CBF are determined by the combined effects of both pressure and flow.

A comprehensive model for myogenicity that consists of three interrelated but distinct phases has been proposed by Osol *et al*.: 1) The initial development of myogenic tone (MT); 2) Myogenic reactivity (MR) to subsequent changes in pressure; and 3) Forced dilatation (FD) at high transmural pressures. The three phases span the physiological range of transmural pressures (e.g., MT, 40-60 mmHg; MR, 60-140 mmHg; FD, > 140 mmHg in the cerebral arteries) and are characterized by distinct changes in cytosolic calcium, which do not parallel arterial diameter or wall tension, and therefore suggest the existence of additional regulatory mechanisms [25].

Cerebrovascular metabolic mechanism of autoregulation

One of the pathways for metabolic regulation may lie in venular-arteriolar communication [26] of carbon dioxide (CO_2). Venous CO_2 produced by metabolism can diffuse to the arterioles, governed by a time constant of the order of 20 s [27]. The arteries have the capacity to react either by dilatation or constriction when a stimulus such as CO_2 takes in place. When an elevated arterial blood CO_2 pressure flows into the capillaries and diffuses into the interstitial fluid, the blood flow set point increases. As an increase in capillary pressure increases capillary blood flow until a new constant state is reached, this is the outcome of CBF under hypercapnic conditions. A small increase in capillary O_2 is also expected due to the interaction between CO_2 and oxyhemoglobin dissociation; therefore, by this expected increase, the CBF decreases and the O_2 extraction fraction remains constant [28].

Other studies have shown that in human and rat cerebral arteries, (1) an increase in flow elicits constrictions; (2) a signaling mechanism of flow-induced constriction of the cerebral arteries involves enhanced production of reactive oxygen species (ROS) and cyclooxygenase activity (COX) and is mediated by 20-hydroxyeicosatetraenoic acid (20-HETE) via thromboxane A_2/prostaglin H_2 (TP) receptors (thromboxane A2/prostaglandin H2 receptors and attenuated by scavenging ROS); and (3) simultaneous pressure- and flow-induced constriction is necessary to provide effective autoregulation of CBF [29].

Several mechanisms appear to match local blood flow for metabolic requirements; pH, adenosine, ATP, NO, and local neural mechanisms all appear to be involved. The study of muscle activation (contraction) is, in some respects, simpler compared with the study of brain activation. In the brain, astrocytes may be central regulators in the neurovascular unit through their perivascular endfeet by using potassium ions, prostaglandins, ATP, and adenosine, which are critical in brain activities [30].

Cerebrovascular mechanical autoregulation

It is known that tissue flow in the brain is approximately 50-55 mL/100 g/min. Under physiological conditions, the human brain accounts for approximately 2% of the total body weight. However, it receives approximately 20% of the cardiac output, demands 20% of the oxygen in the body [10], uses 20% of the body's resting metabolism, and sodium-potassium pumps consume approximately half of that

20% to maintain ionic homeostasis, which is mainly disrupted by spreading depolarization (SD) [9].

In a study from Diamond *et al*., a biophysical model includes dynamic cerebral autoregulation, which modulates the cerebral arteriole compliance to control cerebral blood flow. Pial arteries and veins are assumed to have constant compliance. When the arterial blood pressure reaches the cerebral circulation, it causes an increase in cerebral arteriole pressure (AP) and arteriole blood flow (ABF). If this increase reaches above the physiological threshold, the autoregulation becomes activated (the threshold of autoregulation activation makes arteriole compliance go to a lower limit), then autoregulation acts by decreasing arteriole compliance (AC) and cerebral arteriole volume (AV) but increases arteriole resistance (AR); the increased AR interacts with the higher AP to lower the ABF to a lower limit. A sustained CBF during this modulation is the expected autoregulation [28]. This response normally has a 2-s delay and occurs within 2-10 s. CBF disturbance occurs by an acute change in arterial blood pressure, and the response occurs much sooner than the mean arterial blood pressure restoration can be detected [31].

Cerebrovascular neurogenic mechanism and endothelial cell-related factors by neurovascular coupling

An increase in cerebral activity is followed by a quick increase in CBF to the activated brain areas, O_2 demand, and glucose consumption. This coupling is mediated by biochemical and electrical interactions with chemical agents among neurons, astrocytes, the endothelium, and smooth muscle cells [10]. Neural and stromal cells are grouped into a functional entity called a neurovascular unit [32, 33]. Astrocytes respond to neuronal activity by increasing the Ca^{2+} concentrations. The activation of Ca^{2+} in astrocyte endfeet is not only an essential step but also reveals a new level of complexity in the astrocyte control of neurovascular coupling; moreover, vasodilative or constrictive agents are released in response to external factors, suggesting that these cells contribute to the control of CBF changes [34-36].

Astrocytes are particularly positioned as an endfoot process of blood vessels to act as signaling moderators between active neurons and local arterioles, while their other processes still interact with local synapses [37, 38]. The distribution of astrocytes makes it easy to detect neuronal activity, regulate arteriolar diameter changes, and enable blood flow to meet the additional demand of supply in the activated brain region; this process is called “neurovascular coupling”, which is a fundamental feature of brain physiology [39, 40].

Autoregulatory failure

When blood flow in the brain decreases to 25-30 mL/100 g/min (40% below normal), electroencephalographic (EEG) abnormalities and altered consciousness may occur. When flow is below 20 mL/100 g/min (60% below normal), EEG becomes isoelectric and neurons switch to anaerobic status, accompanied with a consequent increase in lactate and hydrogen ion production [41, 42]. A flow between 10-12 mL/100 g/min makes neurotransmission and sodium-potassium pumps fail, leading to cytotoxic edema. This initiates a cascade of pathophysiological mechanisms recognized as early brain injury. Many of these metabolic changes lead to endothelial dysfunction and can drive autoregulatory failure [10, 43].

Autoregulatory failure can be divided into three phases as follows. (1) Acute phase. It is known that the acute phase has a prognostic value, and it has been described in poor-grade subarachnoid hemorrhage (SAH) patients in the first few days following an event, with subsequent improvement by day 4, although a study of all-grade SAH patients showed that autoregulation was preserved in the first 2-3 days, suggesting that autoregulation is proportional to ictus severity [44]. (2) Subacute phase, which can be a continuum of the acute phase but also develop in patients with an initial intact autoregulation; it involves a delay in restoring the CBF and is commonly recognized as early brain injury [44]. (3) Delayed cerebral ischemia. This phase develops when consecutive events and prolonged periods of ischemia make neuronal restoration irreversible, leading to infarctions contributing to a high fatality and morbidity [45].

Spreading depolarization

Spreading depolarization (SD) is a sustained depolarization of neurons that have been found to originate in patients with stroke, subarach-

noid hemorrhage, intracerebral hemorrhage, brain trauma, and migraine [18], spreading at a rate of 2-6 mm/min with concomitant pronounced breakdown of ion gradients [9]. It is characterized by the propagation of an extracellular negative potential with a mean duration of 1 min or more, followed by an increase in O_2 and glucose consumption [46]. Neurotransmitters such as glutamate, acetylcholine, and γ-aminobutyric acid are highly released during SD [9]. Extreme changes between extracellular and intracellular spaces occur, such as the release of K^+ and H^+ from the cells and cells swelling caused by the entrance of Na^+, Ca^{2+}, and Cl^- ions together with water [46]. This involves cytotoxic swelling of neurons and distortion of dendritic spines [9] with consequent loss of their electrogenic properties [47], which can lead to neuronal damage if consecutive events are evoked [48, 49]. Since SD can propagate in nonischemic human brain tissue [50], restoration of sodium pump activity is crucial as well as perfusion and energy dependant [51].

Evidence suggests that SD has three main phases. The first phase involves brief hypoperfusion due to an increase in extracellular K^+ (> 20 mM) and a decrease in Ca^{2+}, leading to vasoconstriction. A decrease in Ca^{2+} blocks NO synthesis, thus inhibiting vasodilation during this early phase; the unbalanced vasoconstriction results in a transient hypoperfusion [52]. A second phase, which lasts for approximately 2 min, is the hyperemic phase. Several vasodilator molecules have been implicated in this marked hyperemia, which originates by an increase in a regional cerebral blood flow (rCBF) influx of more than 100% [53] and is driven by the increased metabolic need for oxygen and glucose [54]. However, distal tissue hypoxia may develop due to the fact that the increase in rCBF is not fully reached to match metabolic needs. Next, a neuronal response glutamate-evoked Ca^{2+} influx in post-synaptic neurons activates the production of NO and arachidonic acid metabolites [9], which contribute to arteriolar dilation [55] and propagation of SD [56]. The last phase is the oligemic period during which rCBF decreases to 69-73% of control values in the cortical regions for 1 h after spreading depression, with a decrease in vascular reactivity [30].

It has been demonstrated there is a transient impairment in CBF autoregulation immediately after SD with restoration over 35 min [57] and that SD leads to neurovascular uncoupling for an hour; however, it is likely that the coupling correlation is altered for much longer, since the shown recovery of the cerebral blood volume, signal amplitude, duration, and time to peak after SD at 60 min post-induction is minimal [58]. Although ionic gradients and subsequent water movements into cells normalize within a few minutes after SD, the metabolites recover to normal values 30 min after SD [57]. Thus, experimental models help to detect the dynamic vascular changes that can be observed after SD.

Conclusion

Cerebral autoregulation is a physiological process in which several mechanisms are involved to maintain constant CBF by changing the mean blood pressure. This ability of the brain can be challenged in several pathologies, which can lead to cerebrovascular autoregulatory failure and concomitant neuronal damage. Adaptation and recovery of the physiological state involves the continuing interchange of ions, electrical and biomechanical interactions, as well as preservation of the synaptic interchange to achieve cerebral autoregulation.

Due to the fact that SD drives failure autoregulation, it can lead to delayed cerebral ischemia. Further studies that analyze the association between SD and autoregulation are necessary to find a viable way to maintain autoregulation in a constant physiological state and avoid consequent neuronal loss.

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References

[1] Banaji M, Tachtsidis I, Delpy D and Baigent S. A physiological model of cerebral blood flow control. Math Biosci 2005; 194: 125-173.

[2] Budohoski KP, Czosnyka M, Smielewski P, Varsos GV, Kasprowicz M, Brady KM, Pickard JD and Kirkpatrick PJ. Cerebral autoregulation after subarachnoid hemorrhage: comparison of three methods. J Cereb Blood Flow Metab 2013; 33: 449-456.
[3] Folkow B. Description Of the Myogenic Hypothesis. Circ Res 1964; 15 Suppl: 279-287.
[4] Laudignon N, Beharry K, Farri E and Aranda JV. The role of adenosine in the vascular adaptation of neonatal cerebral blood flow during hypotension. J Cereb Blood Flow Metab 1991; 11: 424-431.
[5] Goense J, Merkle H and Logothetis NK. High-resolution fMRI reveals laminar differences in neurovascular coupling between positive and negative BOLD responses. Neuron 2012; 76: 629-639.
[6] Riera JJ, Jimenez JC, Wan X, Kawashima R and Ozaki T. Nonlinear local electrovascular coupling. II: From data to neuronal masses. Hum Brain Mapp 2007; 28: 335-354.
[7] Paulson OB, Strandgaard S and Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Rev 1990; 2: 161-192.
[8] Faraci FM and Heistad DD. Regulation of the cerebral circulation: role of endothelium and potassium channels. Physiol Rev 1998; 78: 53-97.
[9] Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat Med 2011; 17: 439-447.
[10] Bor-Seng-Shu E, Kita WS, Figueiredo EG, Paiva WS, Fonoff ET, Teixeira MJ and Panerai RB. Cerebral hemodynamics: concepts of clinical importance. Arq Neuropsiquiatr 2012; 70: 352-356.
[11] Lagopoulos J. Cerebral autoregulation. Acta Neuropsychiatrica 2008; 20: 271-272.
[12] Golanov EV and Reis DJ. Oxygen and cerebral blood flow. In: Welch KMA, Caplan LR, Reis DJ, Siesjö BK, Weir B, editors. Primer on Cerebrovascular Diseases. San Diego: Academic Press; 1997. pp. 58-60.
[13] Wintermark M, Sesay M, Barbier E, Borbely K, Dillon WP, Eastwood JD, Glenn TC, Grandin CB, Pedraza S, Soustiel JF, Nariai T, Zaharchuk G, Caille JM, Dousset V and Yonas H. Comparative overview of brain perfusion imaging techniques. Stroke 2005; 36: e83-99.
[14] Mahagne MH, David O, Darcourt J, Migneco O, Dunac A, Chatel M and Baron JC. Voxel-based mapping of cortical ischemic damage using Tc 99m L,L-ethyl cysteinate dimer SPECT in acute stroke. J Neuroimaging 2004; 14: 23-32.
[15] Baron JC. Mapping the ischaemic penumbra with PET: a new approach. Brain 2001; 124: 2-4.
[16] Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E, Wechsler LR, Newell DW, Gomez CR, Babikian VL, Lefkowitz D, Goldman RS, Armon C, Hsu CY, Goodin DS; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2004; 62: 1468-1481.
[17] Santos E, Diedler J, Sykora M, Orakcioglu B, Kentar M, Czosnyka M, Unterberg A and Sakowitz OW. Low-frequency sampling for PRx calculation does not reduce prognostication and produces similar CPPopt in intracerebral haemorrhage patients. Acta Neurochir (Wien) 2011; 153: 2189-2195.
[18] Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R and Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. J Cereb Blood Flow Metab 2011; 31: 17-35.
[19] Sanchez-Porras R, Santos E, Czosnyka M, Zheng Z, Unterberg AW and Sakowitz OW. 'Long' pressure reactivity index (L-PRx) as a measure of autoregulation correlates with outcome in traumatic brain injury patients. Acta Neurochir (Wien) 2012; 154: 1575-1581.
[20] Greisen G. Autoregulation of cerebral blood flow. NeoReviews 2007; 8: e22-e31.
[21] Pohl U and de Wit C. A unique role of NO in the control of blood flow. Physiology 1999; 14: 74-80.
[22] Pohl U, Herlan K, Huang A and Bassenge E. EDRF-mediated shear-induced dilation opposes myogenic vasoconstriction in small rabbit arteries. Am J Physiol 1991; 261: H2016-2023.
[23] Sun D, Huang A, Koller A and Kaley G. Flow-dependent dilation and myogenic constriction interact to establish the resistance of skeletal muscle arterioles. Microcirculation 1995; 2: 289-295.
[24] Ungvari Z and Koller A. Selected contribution: NO released to flow reduces myogenic tone of skeletal muscle arterioles by decreasing smooth muscle Ca(2+) sensitivity. J Appl Physiol (1985) 2001; 91: 522-527; discussion 504-525.
[25] Osol G, Brekke JF, McElroy-Yaggy K and Gokina NI. Myogenic tone, reactivity, and forced dilatation: a three-phase model of in vitro arterial myogenic behavior. Am J Physiol Heart Circ Physiol 2002; 283: H2260-2267.
[26] Hester RL and Hammer LW. Venular-arteriolar communication in the regulation of blood flow.

Am J Physiol Regul Integr Comp Physiol 2002; 282: R1280-1285.
[27] Ursino M and Lodi CA. Interaction among autoregulation, CO2 reactivity, and intracranial pressure: a mathematical model. Am J Physiol 1998; 274: H1715-1728.
[28] Diamond SG, Perdue KL and Boas DA. A cerebrovascular response model for functional neuroimaging including dynamic cerebral autoregulation. Math Biosci 2009; 220: 102-117.
[29] Toth P, Rozsa B, Springo Z, Doczi T and Koller A. Isolated human and rat cerebral arteries constrict to increases in flow: role of 20-HETE and TP receptors. J Cereb Blood Flow Metab 2011; 31: 2096-2105.
[30] Lauritzen M. Long-lasting reduction of cortical blood flow of the brain after spreading depression with preserved autoregulation and impaired CO2 response. J Cereb Blood Flow Metab 1984; 4: 546-554.
[31] Rangel-Castilla L, Gasco J, Nauta HJ, Okonkwo DO and Robertson CS. Cerebral pressure autoregulation in traumatic brain injury. Neurosurg Focus 2008; 25: E7.
[32] Moroni F and Chiarugi A. Post-ischemic brain damage: targeting PARP-1 within the ischemic neurovascular units as a realistic avenue to stroke treatment. FEBS J 2009; 276: 36-45.
[33] Stanimirovic DB and Friedman A. Pathophysiology of the neurovascular unit: disease cause or consequence? J Cereb Blood Flow Metab 2012; 32: 1207-1221.
[34] Paixao S and Klein R. Neuron-astrocyte communication and synaptic plasticity. Curr Opin Neurobiol 2010; 20: 466-473.
[35] Carmignoto G and Gomez-Gonzalo M. The contribution of astrocyte signalling to neurovascular coupling. Brain Res Rev 2010; 63: 138-148.
[36] Rusakov DA, Zheng K and Henneberger C. Astrocytes as regulators of synaptic function: a quest for the Ca2+ master key. Neuroscientist 2011; 17: 513-523.
[37] Longden TA, Dunn KM, Draheim HJ, Nelson MT, Weston AH and Edwards G. Intermediate-conductance calcium-activated potassium channels participate in neurovascular coupling. Br J Pharmacol 2011; 164: 922-933.
[38] Koehler RC, Roman RJ and Harder DR. Astrocytes and the regulation of cerebral blood flow. Trends Neurosci 2009; 32: 160-169.
[39] Arthurs OJ, Donovan T, Spiegelhalter DJ, Pickard JD and Boniface SJ. Intracortically distributed neurovascular coupling relationships within and between human somatosensory cortices. Cereb Cortex 2007; 17: 661-668.
[40] Riera JJ and Sumiyoshi A. Brain oscillations: ideal scenery to understand the neurovascular coupling. Curr Opin Neurol 2010; 23: 374-381.
[41] Hossmann KA. Viability thresholds and the penumbra of focal ischemia. Ann Neurol 1994; 36: 557-565.
[42] Astrup J, Siesjo BK and Symon L. Thresholds in cerebral ischemia-the ischemic penumbra. Stroke 1981; 12: 723-725.
[43] Durduran T, Zhou C, Edlow BL, Yu G, Choe R, Kim MN, Cucchiara BL, Putt ME, Shah Q, Kasner SE, Greenberg JH, Yodh AG and Detre JA. Transcranial optical monitoring of cerebrovascular hemodynamics in acute stroke patients. Opt Express 2009; 17: 3884-3902.
[44] Budohoski KP, Czosnyka M, Kirkpatrick PJ, Smielewski P, Steiner LA and Pickard JD. Clinical relevance of cerebral autoregulation following subarachnoid haemorrhage. Nat Rev Neurol 2013; 9: 152-163.
[45] de Rooij NK, Greving JP, Rinkel GJ and Frijns CJ. Early prediction of delayed cerebral ischemia after subarachnoid hemorrhage: development and validation of a practical risk chart. Stroke 2013; 44: 1288-1294.
[46] Sanchez-Porras R, Robles-Cabrera A and Santos E. [Cortical spreading depolarization: A new pathophysiological mechanism in neurological diseases]. Med Clin (Barc) 2014; 142: 457-462.
[47] Major G, Larkum ME and Schiller J. Active properties of neocortical pyramidal neuron dendrites. Annu Rev Neurosci 2013; 36: 1-24.
[48] Pomper JK, Haack S, Petzold GC, Buchheim K, Gabriel S, Hoffmann U and Heinemann U. Repetitive spreading depression-like events result in cell damage in juvenile hippocampal slice cultures maintained in normoxia. J Neurophysiol 2006; 95: 355-368.
[49] Kumagai T, Walberer M, Nakamura H, Endepols H, Sue M, Vollmar S, Adib S, Mies G, Yoshimine T, Schroeter M and Graf R. Distinct spatiotemporal patterns of spreading depolarizations during early infarct evolution: evidence from real-time imaging. J Cereb Blood Flow Metab 2011; 31: 580-592.
[50] Sakowitz OW, Santos E, Nagel A, Krajewski KL, Hertle DN, Vajkoczy P, Dreier JP, Unterberg AW and Sarrafzadeh AS. Clusters of spreading depolarizations are associated with disturbed cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. Stroke 2013; 44: 220-223.
[51] Woitzik J, Hecht N, Pinczolits A, Sandow N, Major S, Winkler MK, Weber-Carstens S, Dohmen C, Graf R, Strong AJ, Dreier JP, Vajkoczy P; COSBID study group. Propagation of cortical spreading depolarization in the human cortex after malignant stroke. Neurology 2013; 80: 1095-1102.
[52] Duckrow RB. A brief hypoperfusion precedes spreading depression if nitric oxide synthesis is inhibited. Brain Res 1993; 618: 190-195.

[53] Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. Brain 1994; 117: 199-210.
[54] Piilgaard H and Lauritzen M. Persistent increase in oxygen consumption and impaired neurovascular coupling after spreading depression in rat neocortex. J Cereb Blood Flow Metab 2009; 29: 1517-1527.
[55] Read SJ, Smith MI, Hunter AJ and Parsons AA. Enhanced nitric oxide release during cortical spreading depression following infusion of glyceryl trinitrate in the anaesthetized cat. Cephalalgia 1997; 17: 159-165.
[56] Gorji A. Spreading depression: a review of the clinical relevance. Brain Res Brain Res Rev 2001; 38: 33-60.
[57] Florence G, Bonvento G, Charbonne R and Seylaz J. Spreading depression reversibly impairs autoregulation of cortical blood flow. Am J Physiol 1994; 266: R1136-1140.
[58] Guiou M, Sheth S, Nemoto M, Walker M, Pouratian N, Ba A and Toga AW. Cortical spreading depression produces long-term disruption of activity-related changes in cerebral blood volume and neurovascular coupling. J Biomed Opt 2005; 10: 11004.