REVIEW

Cerebral hemodynamic and metabolic changes in fulminant hepatic failure

Modificações da hemodinâmica e metabolismo cerebral na insuficiência hepatica fulminante

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ABSTRACT

Intracranial hypertension and brain swelling are a major cause of morbidity and mortality of patients suffering from fulminant hepatic failure (FHF). The pathogenesis of these complications has been investigated in man, in experimental models and in isolated cell systems. Currently, the mechanism underlying cerebral edema and intracranial hypertension in the presence of FHF is multi-factorial in etiology and only partially understood. The aim of this paper is to review the pathophysiology of cerebral hemodynamic and metabolism changes in FHF in order to improve understanding of intracranial dynamics complication in FHF.

Keywords: hepatic insufficiency; intracranial hypertension; brain edema.

RESUMO

O edema cerebral e a hipertensão intracraniana (HIC) são as principais causas de morbidade e mortalidade de pacientes com insuficiência hepática fulminante (IHF). A patogênese dessas complicações tem sido investigada no homem, em modelos experimentais e em sistemas celulares isolados. Atualmente, o mecanismo subjacente ao edema cerebral e HIC na presença de IHF é multifatorial em etiologia e pouco compreendido na literatura. O objetivo deste trabalho é revisar a fisiopatologia das alterações hemodinâmicas e metabólicas cerebrais na IHF, visando melhorar a compreensão da complicação da hemodinâmica encefálica na IHF.

Palavras-chave: insuficiência hepatica; hipertenção intracraniana; edema encefálico.

Acute liver failure, also known as fulminant hepatic failure (FHF), embraces a spectrum of clinical entities characterized by acute liver injury, severe hepatocellular dysfunction, and hepatic encephalopathy. This is an uncommon, but not rare, condition with approximately 2,000 cases annually in the United States and a mortality rate ranging from 50% to 90%, despite intensive care therapy[1,2]. Cerebral edema leading to intracranial hypertension complicates approximately 50% to 80% of patients with severe FHF (grade III or IV coma), in whom it is the leading cause of death[2,3,4].

Brain edema in FHF patients is a relatively recent concept. In a 1944 report of 125 autopsies of military patients who had died from a condition he called fatal hepatitis (previously referred to as idiopathic acute yellow atrophy of the liver), Lucké[5] noted little alteration in the brain except for edema, but did not describe cerebral herniation. The first reports of brain edema and cerebral herniation as complications of FHF only emerged in the 1980s[6,7]. It is also noteworthy that brain edema and intracranial hypertension are not recognized common features of chronic liver failure, despite some case reports and small series[8,9]. The recent recognition of brain edema in FHF patients could be due to the advances in FHF patient care. Previously, FHF patients were dying from early hepatocellular insufficiency complications, mainly hemorrhage or sepsis[5].

Changes in cerebral hemodynamics and metabolism have been widely reported in patients with FHF[10]. Findings suggest that hemodynamic and metabolic changes occur in progressive phases which, if not reversed, can result in brain death. In the earliest phase, cerebral blood flow is low and coupled with low metabolic demands of the brain[11]. As the disease progresses, cerebral blood flow becomes excessive (uncoupled) in relation to metabolic demand[12], systemic cerebrovascular autoregulation is impaired[13], intracranial blood pressure (ICP) decreases[12], and cerebral swelling develops[14].

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There is a clear need to characterize these physiologic changes and their progression in order to facilitate clinical management of FHF patients. A delay or reduction in cerebral swelling could potentially provide time for medical treatment to restore liver function or allow for the diseased liver to be replaced.

The aim of this paper was to review the pathophysiology of cerebral hemodynamic and metabolic changes in FHF in order to improve understanding and monitoring of intracranial dynamic complications in FHF.

PATHOPHYSIOLOGY OF INTRACRANIAL HYPERTENSION IN FHF PATIENTS

Cerebral edema and intracranial hypertension complicates approximately 75% to 80 % of patients with FHF and grade III or IV encephalopathy, in whom it remains a leading cause of death. Currently, the mechanism underlying cerebral edema and intracranial hypertension in the presence of FHF is multi-factorial in etiology and only partially understood[15]. Putative contributing mechanisms include cytotoxicity as a result of osmotic effects of ammonia, glutamine, other amino acids, and proinflammatory cytokines. Cerebral hyperemia and vasogenic edema occur due to disruption of the blood-brain barrier with rapid accumulation of low molecular substances. Dysfunction of sodium-potassium adenosine triphosphatase (ATPase) pump with loss of autoregulation of cerebral blood flow has been implicated as a cause of hyperemia[10,11].

Normal intracranial pressure (ICP) is 5 to 10 mmHg and intracranial hypertension becomes clinically relevant at ICPs exceeding 20 mmHg. Severe intracranial hypertension compromises cerebral perfusion pressure. By definition, cerebral perfusion pressure is the difference between mean arterial pressure and cerebral venous pressure. As cerebral venous pressure can be approximated by ICP, cerebral perfusion pressure is equal to mean arterial pressure minus ICP[14]. An increase in ICP reduces cerebral perfusion pressure, and thus decreases cerebral blood flow. This reduction in the cerebral blood flow may cause cerebral ischemia or infarction, resulting in neurological deficits in FHF survivors. A rise in ICP is the mechanical consequence of an increase in the intracranial volume. The central nervous system (CNS) is protected by the skull, which is rigid and incompressible. Within the skull itself, three different compartments can be defined: the brain, cerebrospinal fluid and blood. If the volume of a given compartment decreases, this results in some intracranial compensation capacity or compliance. When the volume of another compartment decreases, resulting in some intracranial compensation capacity or compliance, and increase exceeds this compliance, any further addition of volume leads to a rise in ICP (Monro-Kellie Theory)[10,11].

PATHOPHYSIOLOGY OF BRAIN EDEMA IN FHF

Role of ammonia-glutamine

The main determinant molecule involved in astrocyte swelling, at least triggering this pathological condition, is ammonia. Astrocyte glutamine synthetase plays an ammonia-detoxifying role by amidation of glutamate to glutamine[16,17]. In hyperammonemic conditions, glutamine is increased in astrocytes and astrocyte swelling occurs. In rats with induced hyperammonemia, astrocyte swelling reduced when an inhibitor of glutamine synthetase, methionine sulphoximine, was administered[18]. This could explain why the edema is focused primarily on the astrocyte, because the neurons, capillaries and other general membranes of the CNS have unusually low water permeability[19]. Glutamine could have a relevant role in oxidative/nitrosative stress as a critical factor in ammonia-induced cell injury [20]. The increase in brain glutamine appears to be an early event, as evidenced by the two-fold increase seen only 24 hours after performance of portocaval anastomosis in rats[21]. Inhibition of glutamine formation results in amelioration of ammonia-induced swelling in rat brain *in vivo* and in isolated astrocytes *in vitro*[22]. Accumulation of glutamine alone, however, does not provide a complete explanation for the development of brain edema. Other elements must be involved to account for the development of brain swelling[23]. One possibility is the involvement of other organic osmoles, such as alanine. Alanine, which can be generated from transamination of glutamine, is also increased in rat brain of FHF models. Notably, whereas glutamine increases rapidly in the early stages of hepatic encephalopathy and remains elevated to the same extent during coma stages, alanine continues to progressively rise concomitant with worsening hepatic encephalopathy[23,24]. Other organic osmoles, such as myo-inositol or taurine, appear to be unchanged or only slightly decreased in experimental models with FHF[25].

Role of the blood-brain barrier

Astrocytes are important components of the blood-brain barrier. Any change in astrocytes also implies a potential change in integrity of the blood-brain barrier. In addition, three major causes of astrocyte swelling are considered: 1) cellular edema; 2) vasogenic edema; and 3) aquaporins. Of these three, the latest to be reported are aquaporins, described in 1992 as water channels. Subsequently, many isoforms have been identified[26]. Aquaporin 4 is the most important of the aquaporins in the development of cerebral edema observed in FHF. It is highly expressed in the plasma membrane of astrocytes and abundant in astrocyte cells bordering the subarachnoid space, ventricle and blood vessels[26].

High levels of aquaporin 4 were noted in areas where astrocytes come into direct contact with capillaries, ependymal layer and pia. In addition, the basolateral membrane of the ependymal cells lining the subfornical organ is positive

for aquaporin 4. The sites of aquaporin expression in the brain suggest a role in the transport of water across the blood-brain barrier and thus in cerebrospinal dynamics and the formation of brain edema[7]. Therefore, aquaporins are also associated with apoptosis in the CNS[26].

With regard to vasogenic edema, the ion channels, exchangers and transporters are important factors in cell volume regulation[26,7]. Changes in these systems may result in the loss of ion homeostasis and the subsequent accumulation of intracellular water[27]. These ion transporters and exchangers include Na-K-Cl cotransporter-1, which plays an important role in cell swelling/brain edema. The activation of Na-K-Cl cotransporter-1 is important in astrocyte swelling by ammonia where this activation is mediated by Na-K-Cl cotransporter-1 as well as its oxidation/nitration and phosphorylation[28]. Alterations in blood-brain barrier permeability, if present, appear to play a more secondary and/or facilitating role as opposed to being the central determinant of brain water accumulation in FHF[29].

HEMODYNAMIC CHANGES

Understanding the regulation of cerebral blood flow and the coupling of cerebral blood flow to metabolism are essential to following the changes that take place in critical injury of the CNS, as occurs in patients with FHF[29].

Regulation of cerebral blood flow

The brain has a unique capacity to adjust blood flow to changes in functional and metabolic activity (flow-metabolism coupling or metabolic regulation), changes in perfusion pressure (pressure autoregulation), or alterations in arterial content of oxygen or carbon dioxide (oxygen or carbon dioxide vasoreactivity)[30]. In addition, cerebral blood flow can be altered through the direct influence of connections between specific centers in the brain and blood vessels (neurogenic regulation)[31].

In patients with FHF, a wide spectrum of values of cerebral blood flow has been reported, ranging from abnormally low to abnormally high levels[31]. This broad spectrum of cerebral blood flow in FHF most likely reflects a real situation where cerebral blood flow is subjected to the influence of multiple factors[32], such as disease severity, systemic hemodynamic or extrahepatic complications. Despite these variations, it is now generally accepted that cerebral oxidative metabolism is preserved in FHF, with cerebral blood flow usually remaining higher than the metabolic needs of the brain (so-called luxury perfusion)[31,32].

Coupling of cerebral blood flow to metabolism

Under normal circumstances, cerebral blood flow is tightly matched to the level of the brain's requirement for oxygen and glucose; this match is referred to as flow-metabolism coupling or metabolic regulation. During seizure activity, both glucose utilization and blood flow can increase by 200% to 300%. Conversely, when the level of cerebral metabolism is reduced, such as during barbiturate anesthesia or coma, a commensurate reduction in blood can be seen[33]. Temperature also has an important influence, as glucose utilization in most regions of the CNS changes by approximately 5% to 10% for each degree Celsius change in body temperature[34]. Although many proposed mediators have been shown to induce vessel dilatation and increase local flow, the exact mechanism involved is currently unknown[33,34,35].

Extracellular pH change may be the mechanism by which metabolism influences blood flow as both hydrogen ions and lactate accumulate in areas of increased metabolism[33]. The resulting decrease in pH causes local vasodilation, possibly by altering membrane permeability or receptor function[34]. Changes in extracellular potassium (K^+) occur with neuroactivation, which leads some investigators to speculate that this ion is the mediator of flow-metabolism coupling. Topical application of K^+ causes cerebral pial arterioles to dilate in a concentration-dependent fashion[35,36]. In addition, during initial seizure activity, pH remains unchanged, while increases in the extracellular concentration of potassium cations are evident (K^+). These observations support the role of extracellular K^+ concentration as a regulator of the blood flow response to changes in metabolism[36].

Adenosine has received much attention as a putative mediator between neuronal activity and the supply of substrates. This purine derivative is rapidly produced by the degradation of adenosine triphosphate via 5'-nucleotidase reaction and is a potent dilator of cerebral vessels[36,37]. Numerous findings point to adenosine as an attractive candidate for the coupling of blood flow to oxidative metabolism. Initial rapid and significant elevations in extracellular adenosine occur during increased cerebral metabolic activity, hypotension, hypoxia, and seizure[36,38]. Adenosine levels double after only five seconds of ischemia and increase six-fold after the onset of hypoxia during which time cerebral blood flow begins to rise significantly[38].

Prostaglandins and other eicosanoids (products of arachidonic acid metabolism) can be rapidly synthesized and released by cerebral microvessels and have been postulated as putative mediators coupling metabolism and blood flow[38,39,40,41,42]. With the exception of the vasodilator prostacyclin, arachidonic acid derivatives are potent vasoconstrictors at low concentrations. Nitric oxide (NO) may be an important mediator in the control of cerebral circulation[43,44,45]. Nitric oxide causes vasorelaxation, and intravenous administration of NO synthetase inhibitor results in a dose-dependent reduction in cerebral blood flow[46,47].

Increase in cerebral blood flow and intracranial blood volume in FHF

There is a growing body of evidence that increased cerebral blood flow is of critical importance for the

development of brain edema and the high ICP that occurs in FHF patients[48,49]. Some reports describe decreased cerebral blood flow in patients suffering from acute liver failure[29], but most investigations have found high cerebral blood flow associated with intracranial hypertension in FHF[50]. Studies suggests that impaired vascular autoregulation in the brain could be responsible for this increase in cerebral blood flow and blood volume[32,50]. Patients with signs of cerebral edema and intracranial hypertension have been shown to have higher cerebral blood flow compared to patients without edema[48,50,51]. Although there is wide inter-individual variation in cerebral blood flow among FHF patients, higher cerebral blood flow has been associated with poorer prognosis[27,31]. Failure of cerebral blood flow autoregulation with consequent development of cerebral hyperemia, edema, and intracranial hypertension is typically seen late during the course of encephalopathy[29,32]. The cerebral vasodilatation in patients with FHF may result from substances produced within the bran itself, i.e., locally-induced cerebral hyperemia. The exact cause of this increased cerebral blood flow in FHF is unknown. Nitric oxide has been implicated but the increased NO in the brains of FHF patients may be secondary to an increase in cerebral blood flow, rather than a primary event. Inflammation markers (IL-1 ß, TNF alpha, IL-6) and systemic inflammatory response have been associated with increased cerebral blood flow and ICP in FHF, and with poor outcome[27]. Increased activation of N-methyl-D-aspartate receptors as a consequence of ammonia toxicity increases neuronal NO synthetase and NO production[22]. The association of systemic inflammation with impaired regulation of cerebral blood flow might be related to the role of necrotic liver in intracranial hypertension in FHF[13]. The observation that brain edema and intracranial hypertension are complications of FHF and not of chronic liver disease, lead to the hypothesis that these phenomena may, in part, result from products of acutely necrotic liver[14]. Although these findings are suggestive, the role of products from necrotic liver in cerebral edema and intracranial hypertension remains unclear[14,15].

The respective role of all these phenomena in the development of intracranial hypertension in FHF has yet to be determined. It can be hypothesized however, that brain edema (increase in brain volume) secondary to the osmotic effect of glutamine in astrocytes, and cerebral hyperemia (in blood volume) secondary to vasodilation (cytokines, products of necrotic liver, glutamine, etc.) may contribute to intracranial hypertension, resulting in brain stem herniation and brain stem death in FHF[13,14,51]. During all these FHF phenomena, the brain may respond by altering the expression of genes coding for various proteins whose role may be critical to some CNS functions, including the maintenance of cell volume neurotransmission[27,29].

Cerebral blood flow autoregulation

Cerebral autoregulation denotes the maintenance of a relatively constant cerebral blood flow despite variations in cerebral perfusion pressure. This physiological response acts to protect the brain from the harmful effects (i.e., ischemia or hyperemia) of large swings in perfusion pressure. Lassen coined the term "autoregulation" to explain the relatively constant blood flow values he found during induced hypotension[39]. However, since then, autoregulation has become confused with other dynamic regulating processes. In the strictest sense, autoregulation refers only to the cerebrovascular response to changes in cerebral perfusion pressure and is sometimes specifically referred to as pressure autoregulation. Cerebral vessels also dilate or constrict as a physiological response to cellular metabolic activity, but this is not properly termed autoregulation. The influence of neuronal metabolism on blood flow should be termed metabolic regulation or flow-metabolism coupling[40,45,46].

Three different mechanisms have been proposed to account for the cerebrovascular responses to changes in perfusion pressure. The myogenic theory states that changes in intravascular pressure alter stretch forces on vascular smooth muscle cells, and these muscle cells intrinsically contract or expand in response to varying degrees of stretch. The neurogenic theory proposes that specific brain centers have direct and indirect arterial connections and the vascular responses are mediated through these connections[41]. Finally, the metabolic theory for control of the pressure autoregulation is based on the finding that the primary determinant of regional flow is local cerebral metabolic activity (flow-metabolism coupling). Certain neuropeptides, adenosine, potassium, and hydrogen ion concentrations have all been shown to influence cerebral blood flow and have, therefore, been proposed as metabolic coupling agents. However, these unique theories may not be mutually exclusive. Since pressure autoregulation is a dynamic process, it may involve a combination of mechanisms[41,43,52].

Measuring cerebral pressure autoregulation may provide clinically useful information and is probably best understood, not as a single physical quantity with a simple metric, but rather as a distributed phenomenon, perhaps reflecting large vascular beds. There are two methods for assessing the status of cerebral autoregulation: static and dynamic[53]. Regarding static autoregulation, most investigators of cerebral autoregulation have looked at the steady-state relationship between cerebral blood flow and cerebral perfusion pressure or mean arterial pressure without considering the time course of changes in flow following changes in pressure. This approach is the static type used to derive the classic autoregulation curve cerebral autoregulation paper[45]. This curve shows a plateau region that is almost flat, corresponding to a constant cerebral blood flow for changes in mean arterial pressure over a physiological range (60-160 mmHg). In this method, cerebral

autoregulation is evaluated daily at a mean arterial pressure of 20 to 30 mmHg by intravenous infusion of norepinephrine, and simultaneously measuring mean velocity, mean arterial pressure and cerebral perfusion pressure[53]. The most frequently-used methods for estimating changes in cerebral perfusion are transcranial Doppler ultrasonography, xenon-133 clearance, and stable CT-demonstrated cerebral blood flow[44]. Other techniques reported to reflect tissue perfusion include arterio-jugular venous oxygen difference to estimate cerebral blood flow changes, electromagnetic flow meters, near-infrared spectroscopy, laser Doppler flowmetry, and jugular venous occlusion plethysmography[44]. In dynamic autoregulation methods, an important variable influencing autoregulatory response is time, and this dynamic autoregulation is probably more clinically important than static measures[52,54,55]. This method is used to describe transient changes in cerebral blood flow after rapid changes in mean arterial pressure. According to this procedure, there is a starting delay of 2 seconds, taking up to 10-15 seconds for the baroreflex mechanism to restore pressure to its previous level. In the normal brain, cerebral blood flow volume returns to its baseline level much sooner than does mean arterial pressure, and the speed of recovery is affected by $PaCO_2$ levels. With the dynamic method, it is possible to characterize the interaction between pressure autoregulation and other variables such as PCO_2 and pharmacological agents. The most frequently-used method for estimating changes in cerebral perfusion is transcranial Doppler ultrasonography[55,56].

CEREBRAL AUTOREGULATION IN FHF

Under normal conditions, the metabolic requirements of the brain, increase or decrease in parallel with brain activity. This autoregulation occurs, independently of changes in mean arterial pressure or cardiac output, whenever blood pressure varies within the limits of 60 to 160 mmHg. Landmark studies by Larsen *et al.*[57] have clearly shown that cerebral blood flow autoregulation is lost in patients with FHF. This loss of autoregulation can be explained by the presence of vasodilatation of cerebral arterioles[31,32]. Although the pathophysiological mechanism of impaired cerebral blood flow autoregulation in FHF remains unknown, it is believed to be caused by toxic substances released from the failing liver. If loss of cerebral blood flow autoregulation in patients with FHF is of pathophysiological importance in the development of hepatic encephalopathy and cerebral edema, it must be assumed that cerebral blood flow autoregulation is reestablished shortly after hepatic recovery of liver function[57,58]. Strauss et al.[58] showed that cerebral perfusion, as determined by mean velocity in the middle cerebral artery, increased in response to an elevation of mean arterial pressure in patients with FHF. The effect of elevated mean arterial pressure on mean velocity allowed evaluation of the cerebral blood flow autoregulation curve. Defective autoregulation was observed in the patients regardless of etiology of FHF or treatment with N-acetylcysteine[58]. This finding is in accordance with the results of previous studies of FHF patients[29,57,58] and of studies on rats with thioacetamide-induced liver failure[57,58]. More importantly, cerebral blood flow autoregulation was restored shortly after improvement of hepatic function, whether spontaneous or following liver transplantation. In fact, cerebral autoregulation was re-established even before hepatic encephalopathy was completely alleviated. In the study by Strauss et al.[58], involving a small number of patients, the re-establishment of cerebral blood flow autoregulation was observed within one to two days after liver transplantation and three to four days after spontaneous hepatic recovery[57,58].

Loss of cerebrovascular autoregulation has been documented in several types of brain insult or ischemia. It has been further shown experimentally that in these injured brains, increased perfusion pressure without compensatory control of ICP results in deterioration of neurological function[57]. Pathological vasodilatation, evidenced by a marked fall in resistance in the cerebrovascular bed in response to rising pressure, is an inappropriate response for the damaged brain. This suggests that pathological cerebral vasodilation may be an important and largely-overlooked cause of increased ICP in the brain suffering an acute generalized insult such as hepatic encephalopathy in FHF[49].

FINAL REMARKS

Fulminant hepatic failure is a multisystem disorder with a high mortality rate requiring a multidisciplinary team approach for its management. Intracranial hypertension is an important cause of death in patients with FHF and, therefore, an aggressive approach to monitoring and therapy is essential if outcome is to be improved. Hepatic encephalopathy and brain edema appear to share common pathogenic roots, with a key role of ammonia and critical involvement of astrocytes in both complications. The study of one helps to understand the other: whereas FHF facilitates the study of causal relationships in a more robust manner, chronic liver failure provides the opportunity to study brain compensatory mechanisms. This integrated view also provides a better perspective to judge the pathophysiological relevance of other factors in the manifestation of the disease.

Cerebral blood flow autoregulation in previous studies has demonstrated restoration of cerebral autoregulation after improvement in liver function, indicating a connection between liver function and regulation of CBF.

Given the relatively small number of patients with FHF, it is imperative that future trials address the role of various therapeutic modalities during different stages of the disease in multicenter randomized clinical trials.

References

1. Hoofnagle JH, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatology. 1995;21(1):240-52. https://doi.org/10.1016/0270-9139(95)90434-4

2. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137(12):947-54. https://doi.org/10.7326/0003-4819-137-12-200212170-00007

3. O'Grady JG. Paracetamol hepatotoxicity: how to prevent. J R Soc Med. 1997;90(7):368-70.

4. Perazzo JC, Tallis S, Delfante A, Souto PA, Lemberg A, Eizayaga FX et al. Hepatic encephalopathy: an approach to its multiple pathophysiological features. World J Hepatol. 2012;4(3):50-65. https://doi.org/10.4254/wjh.v4.i3.50

5. Lucké B. The pathology of fatal epidemic hepatitis. Am J Pathol. 1944;20(3):471-593.

6. Ede RJ, Gimson AE, Bihari D, Williams R. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. J Hepatol. 1986;2(1):43-51. https://doi.org/10.1016/S0168-8278(86)80007-1

7. Canalese J, Gimson AE, Davis C, Mellon PJ, Davis M, Williams R. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. Gut. 1982;23(7):625-9. https://doi.org/10.1136/gut.23.7.625

8. Donovan JP, Schafer DF, Shaw BW Jr, Sorrell MF. Cerebral oedema and increased intracranial pressure in chronic liver disease. Lancet . 1998;351(9104):719-21. https://doi.org/10.1016/S0140-6736(97)07373-X

9. Crippin JS, Gross JB Jr, Lindor KD. Increased intracranial pressure and hepatic encephalopathy in chronic liver disease. Am J Gastroenterol. 1992;87(7):879-82.

10. Bingaman WE, Frank JI. Malignant cerebral edema and intracranial hypertension. Neurol Clin. 1995;13(3):479-509.

11. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. J Neurol Neurosurg Psychiatry. 2004;75(6):813-.21. https://doi.org/10.1136/jnnp.2003.033126

12. Muñoz SJ, Robinson M, Northrup B, Bell R, Moritz M, Jarrell B et al. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. Hepatology. 1991;13(2):209-12. https://doi.org/10.1002/hep.1840130202

13. Ganz R, Swain M, Traber P, DalCanto M, Butterworth RF, Blei AT. Ammonia-induced swelling of rat cerebral cortical slices: implications for the pathogenesis of brain edema in acute hepatic failure. Metab Brain Dis. 1989;4(3):213-23. https://doi.org/10.1007/BF01000297

14. Detry O, De Roover A, Honoré P, Meurisse M. Brain edema and intracranial hypertension in fulminant hepatic failure: pathophysiology and management. World J Gastroenterol. 2006;12(46):7405-12. https://doi.org/10.3748/wjg.v12.i46.7405

15. Traber PG, Dal Canto M, Ganger DR, Blei AT. Electron microscopic evaluation of brain edema in rabbits with galactosamine-induced fulminant hepatic failure: ultrastructure and integrity of the blood-brain barrier. Hepatology. 1987;7(6):1272-7. https://doi.org/10.1002/hep.1840070616

16. Traber P, DalCanto M, Ganger D, Blei AT. Effect of body temperature on brain edema and encephalopathy in the rat after hepatic devascularization. Gastroenterology. 1989;96(3):885-91. https://doi.org/10.1016/0016-5085(89)90917-7

17. Matkowskyj KA, Marrero JA, Carroll RE, Danilkovich AV, Green RM, Benya RV. Azoxymethane-induced fulminant hepatic failure in C57BL/6J mice: characterization of a new animal model. Am J Physiol. 1999;277(2):G455-62.

18. Gove CD, Hughes RD, Ede RJ, Williams R. Regional cerebral edema and chloride space in galactosamine-induced liver failure in rats. Hepatology. 1997;25(2):295-301. https://doi.org/10.1002/hep.510250207

19. Kallaras C, Anogianakis G, Apostolakis M, Manthos A, Sioga A, Economou L et al. Ultrastructural alterations of the rabbit sciatic nerve, spinal cord and cerebellum, following methionine sulphoximine administration. Histol Histopathol. 1994;9(1):105-12.

20. Aitken PG, Borgdorff AJ, Juta AJ, Kiehart DP, Somjen GG, Wadman WJ. Volume changes induced by osmotic stress in freshly isolated rat hippocampal neurons. Pflugers Arch. 1998;436(6):991-8. https://doi.org/10.1007/s004240050734

21. Norenberg MD, Jayakumar AR, Rama Rao KV. Oxidative stress in the pathogenesis of hepatic encephalopathy. Metab Brain Dis. 2004;19(3-4):313-29. https://doi.org/10.1023/B:MEBR.0000043978.91675.79

22. Häussinger D, Schliess F. Astrocyte swelling and protein tyrosine nitration in hepatic encephalopathy. Neurochem Int. 2005;47(1-2):64-70. https://doi.org/10.1016/j.neuint.2005.04.008

23. Blei AT, Olafsson S, Therrien G, Butterworth RF. Ammonia-induced brain edema and intracranial hypertension in rats after portacaval anastomosis. Hepatology. 1994;19(6):1437-44. https://doi.org/10.1002/hep.1840190619

24. Swain M, Butterworth RF, Blei AT. Ammonia and related amino acids in the pathogenesis of brain edema in acute ischemic liver failure in rats. Hepatology. 1992;15(3):449-53. https://doi.org/10.1002/hep.1840150316

25. Cordoba J, Gottstein J, Blei AT. Glutamine, *myo*-inositol and organic brain osmolytes after portocaval anastomosis in the rat: implications for ammonia-induced brain edema. Hepatology. 1996;24(4):919-23. https://doi.org/10.1002/hep.510240427

26. Noble LJ, Hall JJ, Chen S, Chan PH. Morphologic changes in cultured astrocytes after exposure to glutamate. J Neurotrauma. 1992;9(3):255-67. https://doi.org/10.1089/neu.1992.9.255

27. Vaquero J, Chung C, Blei AT. Brain edema in acute liver failure. A window to the pathogenesis of hepatic encephalopathy. Ann Hepatol. 2003;2(1):12-22.

28. Bor-Seng-Shu E, Hirsch R, Teixeira MJ, Andrade AF, Marino Junior R. Cerebral hemodynamic changes gauged by transcranial Doppler ultrasonography in patients with posttraumatic brain swelling treated by surgical decompression. J Neurosurg. 2006;104(1):93-100. https://doi.org/10.3171/jns.2006.104.1.93

29. Wendon JA, Harrison PM, Keays R, Williams R. Cerebral blood flow and metabolism in fulminant liver failure. Hepatology. 1994;19(6):1407-13. https://doi.org/10.1002/hep.1840190614

30. Larsen FS. Pott F, Hansen BA, Ejlersen E, Knudsen GM, Clemmesen JD et al. Transcranial Doppler sonography may predict brain death in patients with fulminant hepatic failure. Transplant Proc. 1995;27(6):3510-31.

31. Aggarwal S, Kramer D, Yonas H, Obrist W, Kang Y, Martin M, Policare R. Cerebral hemodynamic and metabolic changes in fulminant hepatic failure: a retrospective study. Hepatology 1994;19(1):80-7. https://doi.org/10.1002/hep.1840190114

32. Larsen FS, Ejlersen E, Clemmesen JO, Kirkegaard P, Hansen BA. Preservation of cerebral oxidative metabolism in fulminant hepatic failure: an autoregulation study. Liver Transpl Surg. 1996;2(5):348-53. https://doi.org/10.1002/lt.500020504

33. Nilsson B, Siesjö BK. Evidence against H^+ as a regulator of cerebral blood flow. In: Owman C, Edvinsson L, editors. Neurogenic control of the brain circulation. Oxford: Pergamon Press; 1977. p. 295-300.

34. Kontos HA, Raper AJ, Patterson JL Jr. Analysis of vasoactivity of local pH, PCO_2 and bicarbonate on pial vessels. Stroke. 1977;8(3):358-60. https://doi.org/10.1161/01.STR.8.3.358

35. Kuschinsky W, Wahl M. Interactions between perivascular norepinephrine and potassium or osmolarity on pial arteries of cats. Microvasc Res. 1977;14(2):173-80. https://doi.org/10.1016/0026-2862(77)90016-4

36. Wahl M, Kuschinsky W. The dilatatory action of adenosine on pial arteries of cats and its inhibition by theophylline. Pflugers Arch. 1976;362(1):55-9. https://doi.org/10.1007/BF00588681

37. Park TS, Van Wylen DG, Rubio R, Berne RM. Brain interstitial adenosine and sagittal sinus blood flow during systemic hypotension in piglets. J Cereb Blood Flow Metab. 1988;8(6):822-8. https://doi.org/10.1038/jcbfm.1988.138

38. Winn HR, Rubio R, Berne RM. Brain adenosine concentration during hypoxia in rats. Am J Physiol. 1981;241(2):H235-42.

39. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev. 1959;39(2):183-238.

40. MacKenzie ET, Strandgaard S, Graham DI, Jones JV, Harper AM, Farrar JK. Effects of acutely induced hypertension in cats on pial arteriolar caliber, local cerebral blood flow and the blood-brain barrier. Circ Res. 1976;39(1):33-41. https://doi.org/10.1161/01.RES.39.1.33

41. Kogure K, Scheinberg P, Reinmuth OM, Fujishima M, Busto R. Mechanisms of cerebral vasodilation in hypoxia. J Appl Physiol. 1970;29(2):223-9.

42. Kuschinsky W, Wahl M, Bosse O, Thurau K. Perivascular potassium and pH as determinants of local pial arterial diameter in cats: a microapplication study. Circ Res. 1972;31(2):240-7. https://doi.org/10.1161/01.RES.31.2.240

43. Winn HR, Rubio GR, Berne RM. The role of adenosine in the regulation of cerebral blood flow. J Cereb Blood Flow Metab. 1981;1(3):239-44. https://doi.org/10.1038/jcbfm.1981.29

44. Rangel-Castilla L, Gasco J, Nauta HJ, Okonkwo DO, Robertson CS. Cerebral pressure autoregulation in traumatic brain injury. Neurosurg Focus. 2008;25(4):E7. https://doi.org/10.3171/FOC.2008.25.10.E7

45. Panerai RB. Assessment of cerebral pressure autoregulation in humans: a review of measurement methods. Physiol Meas. 1998;19(3):305-38. https://doi.org/10.1088/0967-3334/19/3/001

46. Dirnagl U, Niwa K, Lindauer U, Villringer A. Coupling of cerebral blood flow to neuronal activation: role of adenosine and nitric oxide. Am J Physiol. 1994;267(1):H296-301.

47. Macrae IM, Dawson DA, Norrie JD, McCulloch J. Inhibition of nitric oxide synthesis: effects of cerebral blood flow and glucose utilization in the rat. J Cereb Blood Flow Metab. 1993;13(6):985-92. https://doi.org/10.1038/jcbfm.1993.123

48. Brusilow SW, Traystman R. Hepatic encephalopathy. N Engl J Med. 1986;314(12):786-7.

49. Jalan R, Olde Damink SW, Hayes PC, Deutz NE, Lee A. Pathogenesis of intracranial hypertension in acute liver failure: inflammation, ammonia and cerebral blood flow. J Hepatol. 2004;41(4):613-20. https://doi.org/10.1016/j.jhep.2004.06.011

50. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. Hepatology. 2000;32(4):734-9. https://doi.org/10.1053/jhep.2000.17687

51. Takahashi H, Koehler RC, Brusilow SW, Traystman RJ. Inhibition of brain glutamine accumulation prevents cerebral edema in hyperammonemic rats. Am J Physiol. 1991;261(3):H825-9.

52. Enevoldsen EM, Jensen FT. Autoregulation and CO2 responses of cerebral blood flow in patients with acute severe head injury. J Neurosurg. 1978;48(5):689-703. https://doi.org/10.3171/jns.1978.48.5.0689.

53. Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. Stroke. 1995;26(6):1014-9. https://doi.org/10.1161/01.STR.26.6.1014

54. Lewelt W, Jenkins LW, Miller JD. Autoregulation of cerebral blood flow after experimental fluid percussion injury of the brain. J Neurosurg. 1980;53(4):500-11. https://doi.org/10.3171/jns.1980.53.4.0500

55. Aaslid R. Cerebral autoregulation and vasomotor reactivity. Front Neurol Neurosci. 2006;21:216-28. https://doi.org/10.1159/000092434

56. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke. 1989;20(1):45-52. https://doi.org/10.1161/01.STR.20.1.45

57. Larsen FS, Ejlersen E, Hansen BA, Knudsen GM, Tygstrup N, Secher NH. Functional loss of cerebral blood flow autoregulation in patients with fulminant hepatic failure. J Hepatol. 1995;23(2):212-7. https://doi.org/10.1016/0168-8278(95)80338-6

58. Strauss G, Hansen BA, Kirkegaard P, Rasmussen A, Hjortrup A, Larsen FS. Liver function, cerebral blood flow autoregulation, and hepatic encephalopathy in fulminant hepatic failure. Hepatology. 1997;25(4):837-9. https://doi.org/10.1002/hep.510250409