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REVIEW

Multimodal brain monitoring in fulminant hepatic failure

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Abstract

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. Cerebral edema and intracranial hypertension are common causes of mortality in patients with FHF. The management of patients who present acute liver failure starts with determining the cause and an initial evaluation of prognosis. Regardless of whether or not patients are listed for liver transplantation, they should still be monitored for recovery, death, or transplantation. In the past, neuromonitoring was restricted to serial clinical neurologic examination and, in some cases, intracranial pressure monitoring. Over the years, this monitoring has proven insufficient, as brain abnormalities were detected at late and irreversible stages. The need for real-time monitoring of brain functions to favor prompt treatment and avert irreversible brain injuries led to the concepts of multimodal monitoring and neurophysiological decision support. New monitoring techniques, such as brain tissue oxygen tension, continuous electroencephalogram, transcranial Doppler, and cerebral microdialysis, have been developed. These techniques enable early diagnosis of brain hemodynamic, electrical, and biochemical changes, allow brain anatomical and physiological monitoring-guided therapy, and have improved patient survival rates. The purpose of this review is to discuss the multimodality methods available for monitoring patients with FHF in the neurocritical care setting.

Key words: Fulminant hepatic failure; Cerebral edema; Multimodality methods; Intracranial hypertension; Liver transplantation

Core tip: Cerebral edema and intracranial hypertension are common causes of mortality in patients with fulminant hepatic failure (FHF). The management of

patients who present acute liver failure starts with determining the cause and an initial evaluation of prognosis. Regardless of whether or not patients are listed for liver transplantation, they should still be monitored for recovery, death, or transplantation. The purpose of this review is to discuss the multimodality methods available for monitoring patients with FHF in the neurocritical care setting.

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INTRODUCTION

Fulminant hepatic failure (FHF) is a complex clinical condition that is only partially understood and remains a major clinical challenge[1,2]. Hepatic encephalopathy (HE) associated with intracranial hypertension is a severe neurologic complication and the leading cause of death among patients with FHF[3].

The management of patients who present acute liver failure starts with determining the cause and an initial evaluation of prognosis[3]. In the past, neuromonitoring was restricted to serial clinical neurologic examination and, in some cases, intracranial pressure (ICP) monitoring. Over the years, this monitoring has proven insufficient because brain abnormalities were detected at late and irreversible stages[4]. The need for real-time monitoring of brain functions to favor prompt treatment and avert irreversible brain injuries led to the concepts of multimodal monitoring and neurophysiological decision support. New monitoring techniques, such as brain tissue oxygen tension, continuous electroencephalogram (cEEG), transcranial Doppler (TCD), and cerebral microdialysis (MD), have been developed. These techniques enable early diagnosis of brain hemodynamic, electrical, and biochemical changes, allow brain anatomical and physiological monitoring-guided therapy, and have improved patient survival rates[4,5].

The purpose of this review is to discuss the multimodality methods available for the monitoring of patients in the neurocritical care setting.

MONITORING INTRACRANIAL PHYSIOLOGICAL VARIABLES

Invasive ICP monitoring

ICP monitoring is indicated for brain swelling due to FHF and involves the use of catheters, which can be implanted into epidural, subdural-subarachnoid, or intraventricular spaces through a burr hole. The latest catheters allow real-time and continuous ICP data acquisition. The objective of ICP monitoring is to maintain ICP below 20 mmHg and have adequate cerebral perfusion pressure (CPP) = arterial blood pressure (ABP) - ICP. The ideal management of CPP should take cerebral metabolic and hemodynamic data into account in order to avoid excessive cerebral hyperemia, as well as uncoupling of cerebral blood flow and metabolism[6,7]. Despite a lack of evidence that treatment of elevated ICP can improve survival rates of patients with FHF, it is generally accepted that Grade 3-4 HE patients, especially those awaiting liver transplantation, should undergo ICP monitoring[6,7]. ICP higher than 40 mmHg and prolonged low CPP < 50 mmHg are strongly associated with poor neurological recovery in FHF patients who are traditionally bad candidates for liver transplantation[8].

Continuous perioperative measurement of ICP has been associated with a FHF survival rate of 54%-74%. Invasive ICP monitoring is especially risky in FHF patients with coagulopathy, for whom the incidence of intracranial bleeding due to catheter placement ranges from 5% to 22%[9,10]. Recombinant factor Ⅶ (rFⅦa) can be an alternative method for preventing intracranial hemorrhage associated with ICP placement. Acidosis can lead to low effectiveness of rFⅦa, therefore requiring its correction before use[5,11].

Cerebral edema and intracranial hipertensina (IH) are complications in approximately 75% to 80% of patients with FHF and grade Ⅲ or Ⅳ encephalopathy, which remains a leading cause of death. The physiopathology of these two complications still remains poorly understood, but may be related to vasogenic edema, cytotoxic edema, or cerebral hyperemia[8,12]. Vasogenic edema is the consequence of a breakdown of the blood brain barrier, while cytotoxic edema is related to the glutamine osmotic effects in the astrocytes that results in cerebral edema. On the other hand, hyperemia can be caused by failure of the sodium-potassium adenosine triphosphatase pump[8] and/or the accumulation of certain substances such as cytokines, products of the necrotic liver, or glutamine, which lead to vasodilatation of the microcirculation. Brain edema and hyperemia can lead to IH, with decreased cerebral perfusion pressure, cerebral ischemia, and herniation[8,12].

NON-INVASIVE ICP MONITORING

Optic nerve ultrasound

The optic nerve has a sheath which is continuous with the dura mater of the brain. The subarachnoid space of the optic nerve sheath communicates with the brain and the subarachnoid space, meaning that optic nerve sheath diameter (ONSD) can be influenced by changes in the pressure of cerebrospinal fluid in the cranial cavity. ONSD has been increasingly used to monitor ICP in many different clinical settings, and is measured by an ultrasound probe placed on the eyes[13,14]. A linear correlation between ICP and ONSD measurements has been reported, and a significant reduction in ONSD occurs after draining the cerebrospinal fluid. The cut-off value of ONSD suggested to indicate ICP greater than 20 mmHg was 5.2 mm[15]. However, scant information

is available regarding the use of ONSD in patients undergoing liver transplantation. Kim *et al*[13] concluded that patients undergoing liver transplantation are susceptible to severe bleeding disorders and elevated ICP during the procedure, reporting two cases of patients who underwent liver transplantation at different stages. In one case with severe hepatic encephalopathy, ONSD was measured before transplantation, yielding a value of 6.4 mm. Meanwhile, measurements made in the other case after reperfusion of the graft yielded a value of 5.7 mm. These data demonstrate that measurement of ONSD is a useful method for evaluating patients with FHF undergoing liver transplantation.

Transcranial color-coded duplex ultrasonography

Midline shift (MLS) is a known prognostic factor for unfavorable outcome after the development of intracranial hemorrhage in patients with severe brain injury[16]. In clinical practice, the repetition of computed tomography is mostly used to monitor MLS. However, the examination leads to increased radiation exposure and requires the transport of critically-ill patients, which are associated with increased morbidity and mortality in these patients[17]. Transcranial color-coded duplex sonography (TCCD) represents a non-invasive bedside alternative to radiological methods. TCCD measurements are valid for the diagnosis and monitoring of various neurological diseases, including IH[18,19]. Furthermore, monitoring MLS *via* TCCD safely predicts early mortality and prognosis of conservative clinical treatment of hemispheric ischemic stroke[18]. Unlike ischemic stroke, intracranial hemorrhage MLS is caused by both the volume of hematoma and the formation of edema, which can make outcomes difficult to predict[20]. Patients with FHF who develop brain swelling and IH can benefit from this method, although it has not yet been described in the literature.

Brain computer tomography and magnetic resonance images

Brain images have traditionally been used to diagnose strokes, but are also useful in ruling out other causes of changes in mental status[21]. Furthermore, a non-contrast computer tomography (CT) scan of the brain can disclose brain swelling, compressed basal cisterns, hydrocephalus, mass effect, and midline shift, which can be indicative of increased ICP. However, the absence of these findings does not exclude the presence of brain swelling[22], which may be better visualized through magnetic resonance imaging (MRI) of the brain[21]. The imbalance in the homeostasis of cell volume consequent to elevation of cerebral ammonia concentration can be disclosed in MRI by the proton spectroscopy findings of decreased myo-inositol and choline signals[23]. Moreover, magnetization transfer ratio measurements of fast fluid-attenuated inversion recovery sequences and diffusion-weighted images can be used to detect abnormalities in white matter, thereby reflecting elevated ammonia concentrations in the central nervous system that facilitate the diagnosis of brain swelling in patients with FHF[23,24].

Cerebral blood flow monitoring

Cerebral blood flow (CBF) can generally be maintained in the presence of varying CPP. However, this relationship is not linear in severe brain injury due to impaired cerebral autoregulation[25,26]. In such cases, assessment based on CPP alone can be inaccurate, as measurements assume that cerebral vascular resistance remains constant, which is not the case in serious brain injuries[24]. Therefore, direct monitoring of CBF can help in the management of patients with severe brain injury.

The gold standard method for CBF study is the Kety-Schmidt technique. This technique assesses the area between the curves of arterial and venous washout of a freely diffusible indicator such as nitrous oxide and calculates global CBF from the absorption rate of the indicator in brain tissue[26,27]. Radioisotopes such as krypton-85 and xenon-133 can also be used for CBF study in combination with compact scintillation detectors and microprocessors, as well as the indocyanine green dye dilution technique, which involves non-invasive near-infrared spectroscopy (NIRS) and the thermodilution method[28,29]. The principle of spectroscopy is based on the application of light in the near-infrared wavelength to assess, quantitatively and qualitatively, the molecular components related to tissue oxygenation. Based on deoxyhemoglobin and oxyhemoglobin concentrations in the tissue, NIRS is a non-invasive method which allows for the gathering of information for calculating tissue oxygenation[30]. Other techniques that evaluate CBF include: CT with xenon, CT by single photon emission tomography (SPECT), positron emission oxygen-15 tomography (PET), perfusion CT, and perfusion imaging by MRI[31,32]. SPECT studies the spatial distribution of the radioactive isomer technetium-99 (Tc-99) and its local metabolism in the brain. Since these radionuclides are unusual in the human body, Tc-99 metabolism or its connection may not be identical to the native molecule, and therefore difficulties in the interpretation of results may occur[33]. SPECT provides only a relative measurement of radioactivity and allows for the comparison of physiological parameters such as blood flow in different areas of the brain[34,35].

Cerebrovascular resistance, according to Davies *et al*[10], tends to decrease during the course of FHF and can be influenced by the use of pharmacological agents (*i.e.*, sedatives and inotropes). Previous studies have shown increased blood flow in the basal ganglia of patients with minimal HE, which suggests an increased supply of ammonia to these areas, with resultant astrocyte dysfunction and cognitive impairment.

Nielsen *et al*[36] evaluated CBF of FHF patients *via* the NIRS method. This method detects changes in cerebral perfusion pressure and constitutes a non-invasive method that, in conjunction with transcranial Doppler, may detect brain hyperperfusion before the manifestation of increased intracranial pressure.

TCD is a non-invasive method that measures cerebral blood flow velocity (CBFV). Access of ultrasound waves to the intracranial environment is possible through the "ultrasonic windows", namely the temporal, orbital, suboccipital, and submandibular windows. Thus, placing one transducer against these ultrasonic windows allows the obtention of the spectra of blood flow velocity *vs* time for some cerebral arteries[37].

The previously mentioned arteries can be assessed every 1 mm to 2 mm along their lengths given the pulsed emission ultrasonic waves, which allow controlled modulation depth of the sampling area[38]. The examiner should acquire the most intense audible signal and best blood flow velocity spectra possible by adjusting the position and transducer angle so that the incidence angle between the emitted ultrasound beam and blood vessel is close to zero[39]; thus, more accurate measurements of blood flow velocity can be made.

TCD has proven a valuable method in studies of cerebral hemodynamics due to its high temporal resolution, non-invasiveness, portability, and ability to measure CBFV in real time. CBFV indirectly represents CBF if the cross-sectional area of the vessel is assumed to remain constant with fluctuations in arterial pressure. There is evidence that, despite variations in ABP, the caliber of the vessel does not change significantly[40,41], thereby validating the method for clinical use.

TCD can provide indirect information on CBF and ICP in patients with FHF[22]. Changes in the shape of the spectral diastolic wave can be an early sign of IH and impaired cerebral perfusion pressure. In addition, the final stages of IH can lead to large attenuation of diastolic blood flow velocity (BFV)[42].

ICP changes can influence cerebral blood circulation, which may be assessed with TCD. Currently, TCD publications are trying to predict ICP curves in a non-invasive manner. The pulsatility index (PI) is defined by the following formula: Systolic velocity - diastolic velocity/mean velocity, and is increased when cerebrovascular resistance is elevated. Increased ICP may lead to PI elevation, especially if there is an impairment of cerebral autoregulation. In this case, when diastolic blood pressure equals ICP, there is cessation of intracranial diastolic flow[43]; a further increase in ICP (oscillating flow) may appear during flow progress in the systole. During diastole, critically high ICP, CVR, and distended intracranial arteries eject the blood in a retrograde direction. When net forward flow is seriously reduced, severe ischemic brain damage or brain death may occur. In critical IH, the intracranial waveform degrades to become a small systolic spike and then disappears altogether[44]. The relationship between TCD-hemodynamic patterns and the different states of ICP reinforces the idea that TCD can be useful for determining the optimal range of arterial blood pressure for adequate cerebral blood flow dynamics in FHF patients[45,46].

Cerebral autoregulation (CA) is impaired in patients with FHF, and CBF has been described as correlating with ICP in FHF[23]. CA is characterized by CBF remaining relatively constant despite variations in CPP. This physiological response acts to protect the brain from the harmful effects (*i.e.*, ischemia or hyperemia) of large oscillations in perfusion pressure. Lassen *et al*[47] use the term "autoregulation" to explain the relatively constant values of blood flow encountered during hypotension induction. However, autoregulation has been confused with other dynamic adjustment processes. Strictly speaking, autoregulation refers only to the brain's vascular response to changes in CPP, and is sometimes referred to specifically as pressure autoregulation. Brain vessels also dilate or contract as a physiological response to cellular metabolic activity, but should not strictly be called autoregulation. The influence of neuronal metabolism on CBF should be referred to as metabolic regulation of the flow-metabolism coupling[47,48].

The methods used to estimate changes in cerebral perfusion are TCD ultrasound and clearance of xenon-133, while CT demonstrates stable CBF. Other techniques reflect tissue perfusion and estimate changes in CBF such as jugular arteriovenous difference in oxygen ($AVDO_2$), electromagnetic flow meters, near-infrared spectroscopy, laser Doppler flowmetry, and venous occlusion plethysmography[49].

With changes in technology, particularly the advent of TCD and high temporal resolution examination, it has become possible to calculate an index for static CA[50], which relates cerebrovascular resistance to blood pressure, according to the following formula[51]: ΔCVR%/ΔCPP% (CVR - cerebrovascular resistance); where it is assumed that CPP = ABP - ICP, with the value of ICP being negligible and thus ABP replacing CPP[50].

However, the nature of the estimates, the need for invasive procedures to change ABP, the inherent risk of exposing the patient to exhaustion of self-regulatory reserves, and the emergence of new dynamic CA study methods has reduced the use of the static method for evaluating CA in clinical studies[51,52].

Abdo *et al*[46] evaluated BFV by TCD in five patients with FHF and compared the results against a control group who had associated critical neurological conditions without FHF. Despite the limitations of the study, the authors concluded that patients with FHF may have a dominant pattern of brain hypoperfusion, with an average velocity below normal values and an increased pulsatility index, possibly due to an increase in ICP. The authors suggested that proper measurement by this method improves brain perfusion and prevents hypoxia in these patients. Another study that used TCD demonstrated that CA of CBF was re-established after the onset of HE improvement in patients with FHF[53].

NEUROPHYSIOLOGICAL MONITORING

Electroencephalogram

Electroencephalogram (EEG) is a non-invasive method which analyzes spontaneous brain electrical activity and is performed by placing electrodes on the scalp with the aid of a conductive paste which, besides affixing the

electrodes, allows for the proper acquisition of the signals that constitute the brain's electrical activity[54]. Initially, a spontaneous recording of brain electrical activity is made while the patient is awake and conscious. If possible, this activity is also recorded during drowsiness and sleep. Recording during these different states increases the sensitivity of the method in detecting various defects, including patients with severe brain pathologies[21,54].

Continuous video EEG (cEEG) provides long-term monitoring of brain electrical activity in critically-ill patients with altered mental status and in those at risk of secondary ischemia following acute brain injury. The main indications of cEEG are the detection of non-convulsive seizures or status epilepticus in order to investigate causes of impairment of consciousness, and to determine the prognosis of brain injury. EEG changes in hepatic encephalopathy may range from low alpha-rhythm frequency (8 Hz) mixed with bilateral theta activity, which can later develop into theta-delta with deceleration throughout both hemispheres, with or without three-phase curves. With increasing stupor, sleep activity disintegrates. In severe coma, arrhythmic delta activity diminishes, both in frequency and amplitude, and progresses to electrocerebral silence[54].

The presence of subclinical seizure is often poorly recognized in patients with grade Ⅲ and Ⅳ HE, emphasizing the importance of EEG monitoring in these patients. Cerebral ischemia has often been known to precede the onset of seizures in patients with FHF[54]. Seizures are susceptible to cerebral hypoxia and contribute to the development and perpetuation of brain swelling. During FHF, the increase in extracellular brain glutamate concentrations predisposes patients to epileptic activity[21]. Although no definitive recommendations can be made at the time of writing, the morbidity of untreated subclinical crisis should be considered concomitant with the prudent administration of anti-epileptic drugs until additional studies are established.

Bispectral index

The bispectral index (BIS) is a neurophysiological monitoring system that continuously analyzes electroencephalograms to determine the level of consciousness of patients undergoing general anesthesia. The notion of "anesthetic depth" is usually associated with training experiences or memories during surgery, in which anesthesia does not prevent consciousness or even waking-up during general anesthesia. Although EEG is the gold standard used to determine electrical activity in comatose patients, standard EEG monitoring may not be feasible for all patients who require intensive care during pretransplant[55,56].

Studies show that monitoring by BIS, which was developed in order to assist with the clinical evaluation of the degree of hypnosis with anesthesia, is useful for monitoring cases of FHF[55-57]. The BIS monitor uses the EEG signal derived from electrodes placed on the forehead that provide continuous monitoring. While monitoring for BIS has been developed to assess the level of awareness during anesthesia, this method may also be useful to assess the degree of recovery of consciousness alongside improved liver function after liver transplantation. Hwang *et al*[9] showed that the BIS may be useful for evaluating state of consciousness during the peritransplant and intensive care periods for FHF patients who develop HE.

BRAIN OXYGENATION MONITORING

Brain oxygenation monitoring after brain injury can lead to the detection or prevention of secondary ischemic episodes. The four methods used to measure cerebral oxygenation are: Jugular bulb oximetry, measurement of direct tissue oxygen tension, NIRS, and PET oxygen-15[32].

Jugular bulb oximetry

Catheterization of the jugular bulb and obtention of venous blood samples allow for an estimate of blood flow and cerebral metabolism. Monitoring blood oxygen saturation in veins that drain the brain provides an estimate of overall metabolic demand compared to oxygenation deprivation[32]. The parameter can be used as a measure of jugular venous oxygen content, as well as arteriovenous oxygen difference[57].

Monitoring the oxygen saturation of the jugular vein provides an estimate of overall metabolic demand compared to oxygenation. The parameter used can be jugular venous oxygen content or arteriovenous oxygen difference ($AVDO_2$ = $CMRO_2$/CBF; $CMRO_2$ = cerebral metabolic rate of oxygen consumption). The extent of arteriovenous oxygen difference indicates the amount of oxygen extracted by the brain. Under normal conditions, this value is a 2.8 μmol/mL (range 2.2-3.3 μmol/mL) or 6.3% volume (volume varies from 5%-7.5% oxygen) change in $CMRO_2$ or cerebral blood flow extraction[24]. A reduction in cerebral blood flow, without changes in the energetic demands, increases oxygen extraction in the cerebral tissue. Thus, the jugular vein oxygen decreases and the difference between arterial and jugular venous oxygen increases. On the other hand, a disproportionate increase in cerebral blood flow or a decrease in energy consumption decreases $AVDO_2$[57]. The limitation of the method is the non-detection of oxygen consumption changes in small brain regions[58].

Brain tissue oxygen

Quantitation of tissue oxygen pressure ($PtiO_2$) in the brain reflects the partial pressure of oxygen at the end of the capillary circuit. In ischemic situations, a fall in $PtiO_2$ is accompanied by a decrease in pH (lactic acidosis) and an increase in tissue carbon dioxide pressure, with a lack of metabolic exchange between cells and the capillary circuit. Low values indicate $PtiO_2$ tissue hypoxia and help guide therapy[59]. The patient should exhibit adequate hemoglobin content, balanced hemoglobin affinity for oxygen, and appropriate systemic arterial oxygen

content. Commonly-used sensors determine mean tissue oxygen pressure in an area of 17 mm^3. The catheter is introduced into the cerebral white matter to a depth of 25 mm below the dura mater. The cathode comprises a gold and silver anode immersed in an electrolyte solution[58,59]. The oxygen molecules diffuse into the catheter, producing a reversible reaction at the cathode in which oxygen combines with water and forms ions (OH^-). These reactions generate an electric current detected by a voltmeter, with the electrical signal subsequently digitized and transformed into a numeric value on the monitor display panel. Positioning the catheter in a circulatory border territory between the anterior and middle cerebral arteries allows for the early detection of changes in this area, which is more sensitive to flow variations[59].

Based on previous studies, the cutoff point value for cerebral ischemia monitoring with $PtiO_2$ appears to lie within the 8 to 25 mmHg range. $PtiO_2$ monitoring can provide real-time information on the regulation of brain blood flow and has been shown to have a clear impact on the management of patients with severe brain injuries, such as traumatic brain injury and hemispheric infarcts[60]. Patients with FHF who develop brain swelling and IH can benefit from this method.

Near infrared spectroscopy

As described above, this is a non-invasive technique for measuring regional cerebral oxygen saturation, as well as analyzing the difference in oxygenated hemoglobin and deoxygenated absorption spectra[61].

Studies in patients with FHF demonstrate that the monitoring of brain oxygenation provides valuable data for the clinical management of this population[62]. Oxygen and cerebral glucose consumption have been observed before signs of brain swelling, suggesting that cerebral oxygen metabolism is intact at this stage[62]. In another study, $CMRO_2$ was found to be decreased in all patients with FHF[61]. There was also evidence of cerebral ischemia, as indicated by increased $AVDO_2$. In the study, it was concluded that hyperemia alone was not related to the outcome, despite having occurred more frequently during elevated ICP. All patients with malignant intracranial hypertension previously had hyperemia[62,63]. Nielsen *et al*[36] reported that both pressure and arterial oxygen saturation were maintained during infusion with norepinephrine. Additionally, hemoglobin concentration in blood flow was not compromised. Cerebral arterial oxygenation is capable of detecting brain perfusion changes during norepinephrine infusion in patients with acute liver failure. This suggests that NIRS can be valuable in monitoring critical changes in the cerebral oxygenation and blood volume of these patients.

METABOLIC MONITORING

Brain metabolism can be evaluated by PET and MR spectroscopy, jugular oxygen saturation, monitoring of CBF, and MD. PET scans provide an estimate of the topographic view of glucose metabolism, while MRI spectroscopy qualitatively shows the lactate content of a particular brain structure[58].

MD techniques provide information on tissue metabolism, including the availability of substrates such as glucose and the production of local metabolites. This technique is based on the exchange of solutes through a semipermeable membrane that simulates the operation of a capillary and has the basic objective of monitoring the tissue availability of the different metabolites released by cells[64].

The tip of the catheter contains a semipermeable membrane that separates a solution of known composition from the extracellular fluid space. MD fluid is then analyzed to quantify metabolites. This technique allows for the study of the release of excitatory neurotransmitters such as glutamate and aspartate, as well as other neuromodulators, thereby indirectly analyzing the ischemic excitotoxicity phenomenon. It also allows for the analysis of the concentration of tissue degradation products such as glycerol. The catheter's semipermeable membrane used to study the cited substances only allows for the passage of ions of molecules with a molecular weight of less than 20000 daltons[64,65].

Glucose is most frequently determined as the cellular energy substrate. In conditions where there is a decrease in both cerebral tissue glucose and $PtiO_2$, a reduction of capillary blood flow may be inferred[63,64]. Lactate studies can indicate the intensity of anaerobic metabolism, while glycerol studies can evaluate tissue damage since glycerol is one of the structural components in the tissue lipid layer of cell membranes[66]. Glutamate is an important excitatory neurotransmitter in the mammalian nervous system, with aspartate following in importance. These amino acids are released in the synaptic cleft after neuronal depolarization. This depolarization can be associated with tissue ischemia in states of massive release[67]. In situations of excitotoxicity, massive release of glutamate into the synaptic cleft can be seen. Thus, large inputs of calcium into the cell are observed; as a consequence, there is production of oxygen free radicals in cell membranes and the release of more fatty acids and glycerol[66]. It is recommended that the MD catheter be placed in so-called "penumbra" areas adjacent to focal lesions in order to allow monitoring of potentially recoverable brain regions[68,69]. MD is currently considered one of the most important *in vitro* sampling methods in physiology and pharmacology. Applied in neurointensive care, it is the only tool that allows continuous measurement of chemicals in the brain extracellular space and elucidation of non-ischemic forms of cerebral hypoxia[67].

The tissue volume evaluated by the MD catheter is a cylinder equivalent to the length of the dialysis membrane (10 mm) with a diameter of a few millimeters (0.6 mm). MD pumps perfuse the catheter with an artificial cerebrospinal fluid, which equilibrates with the interstice around the catheter. Balance occurs by diffusion through the dialysis membrane. Using a dialysis membrane with a 10 mm 0.3 perfusion flow L/min, the

concentration of dialyzed glucose, lactate, pyruvate, and glutamate is approximately 70% of the concentration of interstitial fluid. Samples are continuously collected and analyzed at the bedside every hour, or as needed, with the results being analyzed on trend curves[70]. When monitoring biochemical markers it is established that: Lactate/pyruvate ratio is the best marker of cerebral cortex state and early biomarkers in secondary ischemic injury glycerol and glutamate are additional markers of tissue hypoxia[70].

Brain swelling predominantly involving glial cells is often reported as a serious complication of FHF. The swelling of astrocytes may result in elevated ICP and cerebral herniation syndrome in patients with FHF[70]. Tofteng *et al*[71] found brain chemical changes in the MD of a young man with severe acute liver failure and brain swelling in the liver transplant, and found that both extracellular glutamate and glycerol levels were elevated before liver transplant, and tending to decrease after grafting. These results indicate changes in glutamate neurotransmission, arachidonic acid metabolism, lactate, and flow through the blood-brain barrier in patients with FHF.

In another study, Tofteng *et al*[72] investigated whether an increased concentration of glutamate and brain extracellular lactate preceded episodes of elevated ICP in patients with FHF (7 women and 3 men; age range 20-55 years) by inserting MD and ICP catheters into the brain. A total of 352 MD samples were collected for a median of 3 d, allowing for the analysis of approximately 1760 dialyzed samples at the bedside. It has been shown that patients with FHF feature elevated concentrations of extracellular glutamate and cerebral lactate. However, high levels of glutamate are not correlated with increased intracranial pressure, while high levels of lactate precede episodes of elevated ICP. Hyperglycolysis to lactate accumulation is involved in brain microvascular vasodilation and ICP increase in patients with FHF. Therefore, it can be concluded that brain MD at the bedside can be a valuable tool for monitoring these patients.

CONCLUSION

Patients with FHF are usually submitted for brain monitoring after undergoing liver transplantation or when they have a neurological decline. Brain monitoring in this critical phase is essential for maintaining hemodynamic, metabolic, and electrical parameters at acceptable levels. There are a myriad of methods for real time measuring of the aforementioned parameters, with each method having a particular contribution in the detection of "a brain at risk". The key point for proper patient management in order to prevent neurological complications is to combine the different methods in a multimodal approach.

The multimodal technique of extended neuromonitoring offers an advanced option for further development and investigations in animal models of FHF. Furthermore, identification of patients at risk for neurologic complications before and after liver transplant may allow for prompt neuroprotective interventions, including the optimal control of blood pressure.

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