



Brain edema and intracranial hypertension in fulminant hepatic failure: Pathophysiology and management

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Abstract

Intracranial hypertension is a major cause of morbidity and mortality of patients suffering from fulminant hepatic failure. The etiology of this intracranial hypertension is not fully determined, and is probably multifactorial, combining a cytotoxic brain edema due to the astrocytic accumulation of glutamine, and an increase in cerebral blood volume and cerebral blood flow, in part due to inflammation, to glutamine and to toxic products of the diseased liver. Validated methods to control intracranial hypertension in fulminant hepatic failure patients mainly include mannitol, hypertonic saline, indomethacin, thiopental, and hyperventilation. However all these measures are often not sufficient in absence of liver transplantation, the only curative treatment of intracranial hypertension in fulminant hepatic failure to date. Induced moderate hypothermia seems very promising in this setting, but has to be validated by a controlled, randomized study. Artificial liver support systems have been under investigation for many decades. The bioartificial liver, based on both detoxification and swine liver cells, has shown some efficacy on reduction of intracranial pressure but did not show survival benefit in a controlled, randomized study. The Molecular Adsorbents Recirculating System has shown some efficacy in decreasing intracranial pressure in an animal model of liver failure, but has still to be evaluated in a phase III trial.

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Key words: Intracranial hypertension; Fulminant hepatic failure; Brain edema

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INTRODUCTION

Fulminant hepatic failure (FHF) is an infrequent but dreadful disease, defined by the appearance of hepatic encephalopathy within 8 wk after the onset of jaundice in patients with no known chronic liver disease^[1]. Most FHF patients rapidly develop electrolyte, metabolic, and coagulation abnormalities^[2]. They frequently suffer from acute renal insufficiency and/or adult respiratory distress syndrome (ARDS), leading to multiple organ failure (MOF)^[3]. They are very sensitive to infection, and frequently develop a sepsis-like syndrome, with systemic hypotension, low peripheral resistance and increased cardiac output. Modern intensive care units (ICU) have learned to treat all these conditions, and have prolonged FHF patient survival. However, in absence of liver transplantation (LT), the mortality rate of FHF patients remains high (60%-80%). Causes of death of these patients are mainly MOF, sepsis, and/or brain edema leading to intracranial hypertension and secondary brain death.

Brain edema in FHF patients is a relatively recent concept. In a 1944 report of 125 autopsies of military patients dying from what was called fatal hepatitis (previously named idiopathic acute yellow atrophy of the liver), Lucké noted little alteration in the brain, except edema, but he did not describe cerebral herniation^[4]. He hypothesized that the cerebral changes of fatal hepatitis might be attributed to loss of detoxifying function of the liver. The first reports of brain edema and cerebral herniation as complications of FHF were published in the 1970s^[5,6] and were criticized at that time. Widespread recognition that brain edema and intracranial hypertension are complications of FHF only occurred in the 1980s^[7,8]. It is also very interesting to note that brain edema and intracranial hypertension are not recognized common features of terminal chronic liver failure, despite some case reports or small series^[9,10]. 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^[4]. Improvements in ICU techniques have lengthened the survival of FHF patients. The longer course of the disease may have allowed the development of brain edema, possibly a later complication of FHF (Figure 1). Significant advances in the understanding of FHF brain edema have been made this last decade, but the exact pathophysiological mechanisms underlying development of brain edema and intracranial hypertension in FHF are still not entirely clear and are

likely to be multifactorial^[11]. The aim of this paper is to review the pathophysiology of intracranial hypertension in FHF in order to improve understanding and management of this complication.

PATHOPHYSIOLOGY OF INTRACRANIAL HYPERTENSION IN FHF

Normal intracranial pressure (ICP) is 5 to 10 mmHg and intracranial hypertension becomes clinically relevant when ICP exceeds 20 mmHg. The main complication of severe intracranial hypertension in FHF patients is transtentorial herniation^[12]. This herniation may induce (1) compression of the posterior cerebral artery, leading to medial temporal, thalamic, and occipital lobe infarction; (2) cerebral aqueduct and subarachnoid space compression, causing obstructive hydrocephalus; and (3) brain stem compression, resulting in brain stem ischemia, haemorrhage, and death^[12]. Additionally, severe intracranial hypertension compromises cerebral perfusion pressure (CPP). By definition, CPP is the difference between mean arterial pressure (MAP) and cerebral venous pressure. As cerebral venous pressure can be approximated by ICP, CPP equals MAP minus ICP^[12,13]. An increase in ICP reduces CPP, and thus a decrease in cerebral blood flow (CBF). This reduction in CBF 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. Inside the skull, 3 different compartments can be defined: the brain, the cerebrospinal fluid (CSF) and the blood. If the volume of one of these elements increases, the volume of another compartment might decrease, resulting in some intracranial compensation capacity or compliance. If the increase in volume exceeds this compliance, any further addition of volume leads to a rise in ICP.

It is generally accepted that CSF volume is not expanded in FHF. During episodes of intracranial hypertension in FHF, ventricular spaces measured by computed tomography (CT) were either unchanged or compressed, suggesting an increase in the brain tissue or blood volume^[14,15]. In animal models and in FHF patients there is increased brain volume, secondary to edema^[5,16,17]. In this environment even a small increase in cerebral blood volume could significantly increase ICP. In fact, these two phenomena have been proposed to account for intracranial hypertension in FHF: (1) brain edema due to osmotic astrocyte swelling secondary to ammonia-induced accumulation of glutamine (ammonia-glutamine hypothesis); (2) alteration of CBF regulation with increase of the intracranial blood volume.

Brain edema in FHF (Figure 2)

Both vasogenic and cytotoxic mechanisms are implicated in the development of cerebral edema. Vasogenic brain edema occurs as a result of the disruption of the blood-brain barrier (BBB), allowing uncontrolled access of

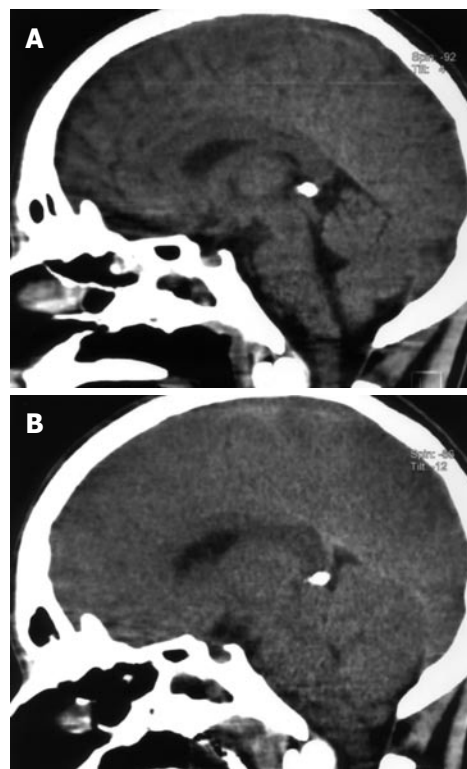


Figure 1 Computed tomography (CT) (sagittal sections) of the brain of a 17-year old man who developed fulminant hepatic failure. **A:** First CT performed in encephalopathy stage IV; **B:** Control CT performed when the patient developed unilateral fixed midriasis, showing diffuse edema, compression of the fourth ventricle and of the brain stem. The patient developed brain stem death while waiting liver transplantation, despite medical therapy and MARS treatment.

plasma components and water to the extracellular cerebral compartment. Cytotoxic edema is the consequence of impaired cellular osmoregulation in the brain, resulting in an increase of cellular water. In FHF, evidence from experimental animals and postmortem human brain supports aspects of each of these mechanisms, but it is now well established that brain edema in FHF is mainly cytotoxic^[18]. In several models of FHF, compounds to which the BBB is normally impermeable (Evans Blue or α -aminoisobutyric acid) were detected in the brain in increased concentrations^[19-21]. These observations suggest that BBB permeability is altered in FHF, which is consistent with a vasogenic mechanism. However, the ability of mannitol to reduce ICP in patients with FHF indicates that the BBB remains largely intact^[8]. Furthermore, electron microscopic studies of human brain tissue in FHF revealed no alteration in the integrity of tight junctions^[22]. Moreover, consistent with cytotoxic edema, marked intracellular swelling of perivascular astrocytes was observed. Recent magnetic resonance imaging of brain of FHF patients confirmed the predominant cytotoxic character of FHF brain edema^[23]. This suggests that FHF brain edema primarily develops within the cellular component of the brain as a cytotoxic edema, and changes in the permeability of the BBB may represent secondary events that could exacerbate edema or intracranial hypertension.

The ammonia-glutamine hypothesis: Cortical astrocyte swelling is the most common observation

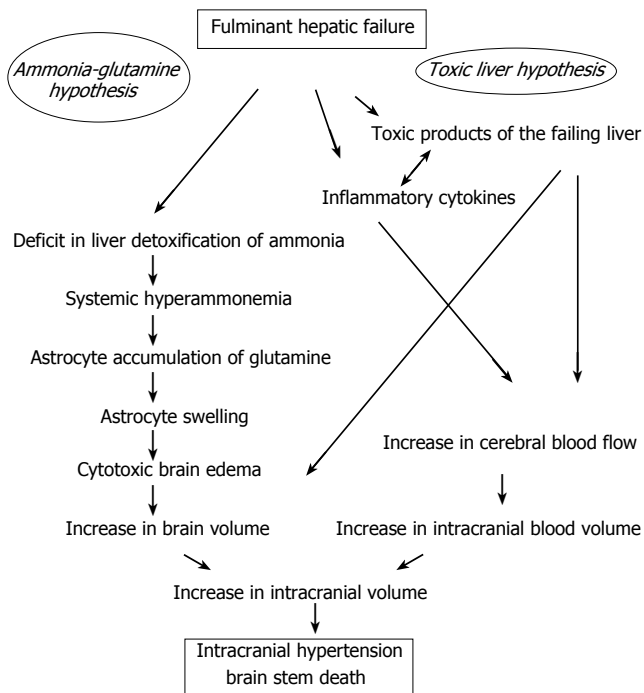


Figure 2 Schematic representation of the hypotheses explaining intracranial hypertension and brain stem death in fulminant hepatic failure.

in neuropathological studies of brain edema in FHF. Astrocytes are the most numerous cell type in the brain and occupy about one-third of the cortical volume^[24]. Astrocytes have several critical metabolic functions involved in the maintenance and regulation of the extracellular microenvironment. They participate in water regulation in the brain, detoxify ammonia and maintain normal levels of extracellular glutamate. Hyperammonemia is prevalent in acute liver failure. In the brain, ammonia is detoxified to glutamine via the amidation of glutamate by an astrocytic enzyme, glutamine synthetase. Glutamine leaves the astrocyte by passive diffusion into the extracellular space where it is taken up by neurons and converted to glutamate. There is clear evidence of increased brain glutamine concentrations in animal FHF models^[25] and in postmortem samples of FHF^[26]. Brusilow first proposed that this glutamine accumulation is the link between hyperammonemia and edema via altered osmoregulation^[27]. In astrocyte cultures, ammonia induces cell swelling^[17,28]. Brain swelling and intracranial hypertension have been documented in humans with hyperammonemic conditions^[29]. In rats, a continuous infusion of ammonia is associated with brain edema or intracranial hypertension^[30] which is reduced by inhibition of glutamine synthesis with methionine-sulfoximine^[31-33]. The relationship between hyperammonemia, glutamine and ICP was recently demonstrated in humans^[34]. Although there is much clinical and experimental evidence in support of the glutamine hypothesis, prevention of brain edema in FHF by inhibition of glutamine synthesis has not been successful in humans.

Increase in cerebral blood flow and intracranial blood volume

Another phenomenon that has also been involved in

intracranial hypertension in FHF is the increase of intracranial blood volume and CBF. Some reports describe decreased CBF in patients suffering from acute liver failure^[35,36], but most have found high CBF associated with intracranial hypertension in FHF^[37,38]. Paulson suggests that an impairment of vascular autoregulation in the brain could be responsible for this increase in CBF and blood volume^[39]. Impaired autoregulation of CBF has been reported in animal models of FHF^[40] and in patients with FHF^[41]. The exact cause of this increase of CBF in FHF is not known. Nitric oxide (NO) has been implicated but it is possible that the increased NO in the brain of FHF patients is secondary to an increase in CBF, rather than a primary event^[18,42]. Inflammation markers (IL-1 β , TNF α , IL-6) and systemic inflammatory response have been associated with increased CBF and ICP in FHF^[37,43], with poor outcome^[44]. The association of systemic inflammation and impaired regulation of CBF might be related to the role of the necrotic liver in intracranial hypertension in FHF. 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 the acutely necrotic liver. There is experimental and clinical evidence to support this theory, the “toxic liver hypothesis”. In a rat model, cerebral edema was significantly lower in anhepatic than FHF animals^[45]. In pigs, no elevation of ICP was observed after total hepatectomy, whereas a rise in ICP was observed in pigs with FHF secondary to ischemia^[46]. Several human observations reinforced this hypothesis. During LT for FHF, it was established that ICP normalizes during the anhepatic phase and may increase during the dissection of the diseased liver and during graft reperfusion^[47,48]. The removal of the diseased liver has been linked to ICP normalization and to marked and sustained reduction of several pro-inflammatory cytokines in a case report^[49]. Moreover some patients underwent a prolonged period (up to 72 h) of an anhepatic state without neurological sequelae^[50,51]. Although these findings are suggestive, the role of products from the necrotic liver in cerebral edema and intracranial hypertension is still unknown.

The respective roles of all of these phenomena in the development of intracranial hypertension in FHF remains to be determined. It can be hypothesized that brain edema (increase in brain volume) secondary to osmotic effect of glutamine in astrocytes, and cerebral hyperemia (increase in blood volume) secondary to vasodilation (cytokines, products of the necrotic liver, glutamine, others...) may contribute to intracranial hypertension leading to brain stem herniation and brain stem death in FHF. 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 and neurotransmission. Cerebral gene expression during FHF is modified as demonstrated by differential display in rat models^[52,53]. Some genes have been more specifically studied, as GLUT-1^[54], aquaporin IV^[55], GLT-1^[52,56] and others^[57]. The exact role of this gene expression observed during FHF is still to be determined.

DIAGNOSIS OF INTRACRANIAL HYPERTENSION IN FHF PATIENTS

Intracranial hypertension should be clinically suspected in FHF patients with systemic hypertension (sustained ≥ 160 mmHg or paroxysms ≥ 200 mmHg), aggravation of hepatic encephalopathy, abnormal pupillary signs, or signs of decerebration. However, most of these clinical signs are not specific, and may be developed by patients in hepatic grade IV encephalopathy without intracranial hypertension. It was reported that brain CT is unreliable in the diagnosis of intracranial hypertension in FHF patients^[14], and there have been no reports of the value of brain magnetic resonance imaging in FHF patients for confirming the diagnosis of intracranial hypertension. The most accurate method of diagnosing intracranial hypertension is ICP monitoring. Although the advantages of this monitoring in FHF patients have not yet been demonstrated by a randomized study, ICP monitoring may be very helpful in establishing the presence of intracranial hypertension and in guiding specific therapy. Intracranial hypertension in FHF patients may suddenly rise from normal to life threatening levels within minutes. In this situation, continuous ICP monitoring may allow rapid and specific management. Several groups have included ICP monitoring in the protocol of FHF patient management^[14,47,58]. The main argument against ICP monitoring is the enhanced risk of complications in FHF patients, mainly infection and hemorrhage. In a national survey of 262 FHF patients, the complication rate of ICP monitoring was 10%. In this series, intracranial hemorrhages were the cause of death in 7 patients and the epidural transducers had the lowest complication rate (3.7%)^[59]. The complication rate of ICP monitoring in FHF patients was reported to be lower in a recent multicenter report, but is still significant^[60].

MANAGEMENT OF INTRACRANIAL HYPERTENSION IN FHF PATIENTS

General management of FHF patients is beyond the scope of this review and was presented elsewhere^[2]. The goal in the medical management of FHF patients with intracranial hypertension is to maintain ICP below 20 mmHg and CPP above 70 mmHg. Cerebral ischemia occurs if CPP is less than 40 to 50 mmHg, and LT should be contraindicated if CPP remains below 40 mmHg for two hours^[61]. This goal requires intense medical management and nursing. FHF patients should be admitted to the ICU in an institution with an active liver transplant program. FHF patients should be monitored with peripheral arterial catheters. Vital signs, urinary output, arterial blood gases and central hemodynamic parameters should be continuously monitored. FHF patients are treated with standard supportive measures to correct electrolyte, metabolic, respiratory and hemodynamic abnormalities. Hypovolemia may exacerbate hypotension, and may reduce CPP, inducing brain ischemia. Systemic hypertension may also be deleterious by increasing ICP^[62]. In this case, β -blockers may be more useful than nitroprusside or calcium-channel inhibitors, because of their potential risk of brain blood vessel dilatation. Patient positioning and nursing is also

important in the care of FHF patients with intracranial hypertension. The head should be in the midline because neck rotation or flexion may compromise jugular venous drainage and increase ICP. Head and chest elevation may lower ICP by enhancing CSF drainage and maximizing cerebral venous output^[12]. However, the efficacy of this positioning in FHF patients is yet to be proven and further elevations to 40° and 60° may paradoxically increase ICP^[63]. Environmental stimulation should be maintained at a minimal level. Most of the FHF patients with encephalopathy grade III/IV are endotracheally intubated to provide airway protection and/or ventilation support. This ventilation may promote some ICP fluctuation. Moreover, positive end-expiratory pressure (PEEP) may increase ICP when mean airway pressures are increased and should be used carefully^[12]. Straining against the mechanical ventilator may increase intrathoracic pressure and reduce venous outflow from the head. Coughing, which is a frequent reflex to tracheal tube aspiration, should be avoided for the same reason. Therefore, if necessary, the patient is sedated and/or paralyzed with nondepolarizing neuromuscular blockers.

Specific treatment of intracranial hypertension in FHF patients is aimed at the culprit underlying pathophysiology, for example therapy to reduce brain volume or lower ICP by reducing intracranial blood volume and CBF.

Treatments to decrease brain volume

As hyperammonemia is considered responsible for the cytotoxic brain edema, it seems logical to try to reduce ammonia in FHF patients. There is no randomized study on the effects of lactulose in FHF. In a retrospective study, lactulose administration did not change the outcome of treated patients, and the routine use of lactulose is not recommended^[64]. The use of intravenous *mannitol* improved the survival and decreased the ICP level in a controlled trial^[8]. Mannitol (0.5 to 1 g/kg iv every 6 h, blood osmolality < 310 mosmol/L) increases blood osmolality, thereby inducing fluid movement from brain to blood. Therefore, the efficacy of mannitol depends on an intact BBB. The efficacy of mannitol to reduce ICP may be affected by acute renal failure and oliguria. In order to be able to use mannitol repeatedly, fluid can be taken off with *hemofiltration* (up to 500 mL), which by itself reduces ICP^[64]. *Hypertonic saline* has also been evaluated in a small controlled trial to prevent the occurrence of intracranial hypertension. Intravenous hypertonic saline (30%) to maintain serum sodium between 145-155 mmol/L was compared with an untreated group. The treated group suffered smaller increases of ICP^[65]. By extension, hyponatremia should be avoided in FHF patients.

Treatments to decrease cerebral blood flow and intracranial blood volume

Hyperventilation: In non-FHF patients, hyperventilation induces ICP reduction through vasoconstriction of the brain blood vessels^[12]. The duration of this ICP reduction varies, and ICP usually returns to baseline within hours of hyperventilation. In FHF patients, this effect of hyperventilation on intracranial hypertension is not clear^[7] but may help to restore cerebral blood flow

Table 1 Liver transplantation criteria in patients with fulminant hepatic failure

Clichy criteria (<i>Hepatology</i> 1991; 14: 49A)
Grade III or IV encephalopathy and
- Factor V level < 20% (patients younger than 30)
- Factor V level < 30% (patients older than 30)
King's College criteria (Modified from <i>Gastroenterology</i> 1989; 97: 439-445)
Paracetamol intoxication:
- pH < 7.3 or
- INR > 4 and serum creatinin > 300 µmol/L (> 34 mg/L) and grade III or IV encephalopathy
Other causes:
- INR > 4 or
- 3 of the following criteria:
- Age < 10 or > 40 yr
- Etiology: NonA nonB hepatitis, halothane hepatitis, idiosyncratic drug reactions
- Delay between jaundice and encephalopathy > 7 d
- INR > 3.5
- Bilirubin > 300 µmol/L (> 175 mg/L)

autoregulation^[66]. From these observations, it can be stated that hyperventilation may reduce ICP acutely but should not be used over a prolonged period^[64]. *Indomethacin* induces cerebral vasoconstriction through inhibition of the endothelial cyclooxygenase pathway, alterations in extracellular pH and reduction in cerebral temperature^[64]. *Indomethacin* has been shown to reduce ICP in an animal model^[67] and a small cohort of 12 patients^[68], and should be evaluated in a randomized controlled study before wider use. *Thiopental sodium* has also been studied in FHF patients. Its administration results in cerebral vasoconstriction possibly by inhibition of nitric synthase. There is only one small study in the literature involving 13 patients, that showed beneficial effects of thiopental on ICP but its efficacy and side effects have to be evaluated in further randomized studies^[69]. *Propofol* in a dose of 6 mg/kg per hour reduces CBF through metabolic suppression^[64] and was used in a small report^[70]. It could be the sedative of choice in FHF patients.

Liver transplantation

LT has emerged as the most important advance in the treatment of FHF^[58,71-74]. To date, transplantation of a functioning graft is the best treatment to achieve control of brain edema and intracranial hypertension. For this reason, every FHF patient should be referred to a transplant center and listed for LT if transplant criteria are met (Table 1)^[75,76]. However, some FHF patients in Grade IV encephalopathy may develop severe cerebral injury or brain death during the perioperative period, and these complications are believed to be secondary to perioperative ICP elevation or CPP reduction. For example, in a study from Paul Brousse's group, 13 patients among 116 (11.2%) who underwent LT for FHF developed brain death during or after the procedure, and 2 others suffered from neurological sequelae^[74]. It was demonstrated that during LT, the dissection phase and the graft reperfusion are particularly at risk of ICP elevation, and that the anhepatic phase seems to be more favorable with ICP normalization^[47,48].

FUTURE PROSPECTS IN THE TREATMENT OF INTRACRANIAL HYPERTENSION OF FHF

Hypothermia

The effects of moderate hypothermia (32-34°C) on ICP in FHF patients are currently being investigated. In rat models of FHF, hypothermia lowered brain edema measured by a gravimetric technique, and prolonged survival^[77,78]. Several reports have demonstrated that hypothermia causes a significant decrease of ICP in FHF patients^[79,80]. Hypothermia could be a very efficient therapy for patients with uncontrolled intracranial hypertension^[81] and a multicenter, randomized, controlled trial should be conducted to definitively assess the role of hypothermia in FHF patient management.

Liver assist systems

For more than 50 years, many research groups have attempted to support patients in acute liver failure as a bridge to LT or to recovery of adequate native liver function. Development of such a system presents a unique challenge as it has to reproduce an array of complex liver functions. Moreover, the results of this system have to be evaluated in very sick and unstable patients, in whom large, randomized, controlled trials are very difficult. Plasma exchange, plasmapheresis, blood exchange, hemodialysis, hemofiltration, cross-circulation, and cross-hemodialysis have all been tried without any benefit to patient survival^[82]. *Ex vivo* whole (animal and/or human) liver perfusion might be promising in small series, but is limited by several drawbacks that are beyond the scope of this review^[82]. Recent advances in semipermeable membranes and hollow-fiber technologies, as well as improved techniques of hepatocyte isolation, have allowed the development of new liver support systems, that may be classified as non-biological blood detoxification systems and liver assist systems with biological components^[82]. Two systems have achieved relatively large use in humans. The Molecular Adsorbents Recirculating System (MARS), which is based on the selective removal of albumin-bound toxins from the blood, is commercially available. In a small, randomized trial MARS was shown to improve survival of patients suffering from acute-on-chronic liver failure^[83], but controlled clinical data for the use of MARS in FHF patients is lacking, especially its effect on ICP. Recently, it was demonstrated that MARS may attenuate (but not normalize) ICP in a pig model with ischemic liver failure^[84]. MARS has still to prove its value in FHF patients in controlled trials.

Multiple liver assist systems with biological components have been tried, in order to construct a liver support that may provide not only detoxification, but also biotransformation and missing liver synthetic function^[82]. A lot of systems were based on isolated or cultured hepatocytes and liver tissue slices placed in a variety of perfusion bioreactors^[82]. Only one system has completed a controlled trial, the bioartificial liver (BAL). The BAL design is based both on a detoxification part and on a cartridge containing porcine hepatocyte and is explained elsewhere^[82]. The BAL has shown some

efficacy to decrease ICP in FHF patients^[85] and in patients suffering from acetaminophen-induced liver failure^[86]. However a controlled, randomized trial did not show any improvement in survival in the BAL treated group^[87] and the Circe company that produced the BAL, has stopped its activity. In conclusion, despite years of scientific efforts, there is no (bio)artificial system that has proved its efficacy on ICP control. The MARS seems promising but has still to prove its role on ICP in FHF patients.

Hepatocyte transplantation

Transplantation of isolated hepatocytes has been shown to provide metabolic support and improve survival in various experimental models of acute liver failure including 90% hepatectomy^[88,89], D-galactosamine^[90], acetaminophen^[91] and ischemic models^[92]. Hepatocyte transplantation has also been shown to improve chronic encephalopathy, induced by an end-to-side portocaval shunt in rats^[93]. In a pig model of ischemic liver failure, the intrasplenic transplantation of hepatocytes allowed the transplanted animal to maintain normal ICP, compared to the treated group^[46].

In two clinical reports, 12 patients were transplanted with a very small number of hepatocytes (0.01%-0.4% of the liver mass) which were infused either intraperitoneally or intrasplenically^[94,95]. Although both studies reported improvement in neurologic status and survival of the transplanted patients, the limited number of patients and the lack of appropriate controls do not allow reliable conclusions to be reached. More experiments in large animal models are needed in order to investigate the "neuro-protective" potential of transplanted hepatocytes. In addition, three major problems need to be solved before clinical application of hepatocyte transplantation can be established: (1) how to harvest and store the maximum number of functional hepatocytes from human liver (e.g. hepatic resection specimens, organs rejected for transplantation, *etc*); (2) how to safely perform transplantation of a significant amount of hepatocytes (at least 5% of the liver mass) considering the anatomic limitations and the severe metabolic disturbances of FHF patients (e.g. coagulopathy); (3) how to determine the optimal timing of hepatocellular transplantation in the course of FHF.

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