Wien Klin Wochenschr (2010) 122: 129–139
DOI 10.1007/s00508-010-1357-6

Printed in Austria

Wiener klinische Wochenschrift
The Middle European Journal of Medicine

Hypoxic hepatitis – epidemiology, pathophysiology and clinical management

Valentin Fuhrmann[1], **Bernhard Jäger**[1], **Anna Zubkova**[2], **Andreas Drolz**[1]

[1]Department of Internal Medicine 3, Division of Gastroenterology and Hepatology, Intensive Care Unit 13H1, Medical University Vienna, Vienna, Austria
[2]Department of Surgery, Klinikum Ansbach, Germany

Received January 4, 2010, accepted after revision March 8, 2010

Zusammenfassung. Hypoxische Hepatitis (HH) – auch unter den Bezeichnungen ichämische Hepatitis oder Schockleber bekannt – ist durch eine zentrilobuläre Leberzellnekrose und einen fulminanten Anstieg der Serumaminotransferasen als Folge von kardialem, zirkulatorischem oder respiratorischem Versagen charakterisiert. Dies ist die häufigste Ursache der akuten Leberschädigung mit einer Prävalenz von bis zu 10 Prozent an Intensivstationen. Kritisch kranke Patienten mit HH und der Notwendigkeit einer Vasopressorentherapie haben ein signifikant erhöhtes Mortalitätsrisiko. Die häufigsten HH auslösenden Ursachen sind erniedrigtes Herzauswurfvolumen und septischer Schock, wobei in der großen Mehrheit der Fälle eine multifaktorielle Ätiologie der HH zugrunde liegt. HH kann verschiedene Komplikationen wie spontane Hypoglykämie, respiratorische Insuffizienz als Folge des hepatopulmonalen Syndroms und Hyperammoniämie verursachen. HH bildet sich nach erfolgreicher Behandlung der zugrunde liegenden Ursachen zurück. Derzeit sind keine Therapieansätze etabliert, die spezifisch die Leberfunktion verbessern. Ein frühestmögliches Erkennen der HH, ihrer zugrunde liegenden Ursachen sowie die unverzügliche Einleitung entsprechender Therapiemaßnahmen sind von zentraler prognostischer Bedeutung. Diese Übersichtsarbeit vermittelt den heutigen Wissensstand hinsichtlich Epidemiologie, Pathophysiologie, sowie diagnostischen und therapeutischen Möglichkeiten der HH.

Summary. Hypoxic hepatitis (HH), also known as ischemic hepatitis or shock liver, is characterized by centrilobular liver cell necrosis and sharply increasing serum aminotransferase levels in a clinical setting of cardiac, circulatory or respiratory failure. Nowadays it is recognized as the most frequent cause of acute liver injury with a reported prevalence of up to 10% in the intensive care unit. Patients with HH and vasopressor therapy have a significantly increased mortality risk in the medical intensive care unit population. The main underlying conditions contributing to HH are low cardiac output and septic shock, although a multifactorial etiology is found in the majority of patients. HH causes several complications such as spontaneous hypoglycemia, respiratory insufficiency due to the hepatopulmonary syndrome, and hyperammonemia. HH reverses after successful treatment of the basic HH-causing disease. No specific therapies improving the hepatic function in patients with HH are currently established. Early recognition of HH and its underlying diseases and subsequent initiation of therapy is of central prognostic importance. The purpose of this review is to provide an update on the epidemiology, pathophysiology, and diagnostic and therapeutic options of HH.

Key words: Ischemic hepatitis, shock liver, acute liver failure, GOT, GPT.

Background

Hepatic dysfunction is a common finding in critically ill patients and is associated with poor outcome [1]. Serum aminotransferases serve as an indicator of hepatocellular damage and liver cell necrosis. Up to the mid-1990s viral and drug-induced hepatitis were considered the most frequent underlying diseases contributing to acutely and massively raised aminotransferase levels [2, 3]. However, several studies changed the clinical perception of acute hepatic injury: they concordantly identified hypoxic hepatitis (HH), also known as ischemic hepatitis or shock liver, as the most frequent cause of notably raised aminotransferases in hospital and in the intensive care unit [4–8].

This acute liver injury is mainly caused by insufficient oxygen uptake by the hepatocytes, leading to centrilobular liver cell necrosis. Several mechanisms lead to hepatic hypoxia: hepatic ischemia as a consequence of insufficient hepatic perfusion, insufficient oxygen extraction by the

Correspondence: Valentin Fuhrmann, MD, Associate Professor of Medicine, Department of Internal Medicine 3, Division of Gastroenterology and Hepatology, Intensive Care Unit 13H1, Medical University Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria, E-mail: valentin.fuhrmann@meduniwien.ac.at

liver, systemic arterial hypoxemia and passive venous congestion. Accordingly, this acute liver injury was renamed from "ischemic hepatitis" and "shock liver" to "hypoxic hepatitis", as decreased hepatic blood flow is not the sole mechanism of HH [6, 9].

The presence of HH has central prognostic impact on outcome: 30-day mortality in critically ill patients with HH is reported to be more than 50% [6, 7, 10]. Nevertheless, despite its frequent incidence, clinicians often ignore raised aminotransferase levels and do not put these abnormal parameters in the correct clinical context [4].

The purpose of this review is to provide an update on epidemiology and an insight into the pathophysiology of HH, and to discuss the diagnostic and therapeutic options.

Definition and diagnosis

Definition

HH is characterized by centrilobular liver cell necrosis as consequence of hypoperfusion with subsequent ischemia and passive congestion of the liver, severe systemic arterial hypoxemia, and/or impaired hepatic oxygen extraction [6, 8, 9, 11–13]. The main underlying conditions are low cardiac output and sepsis [6–8], although a recent prospective study has demonstrated that more than one underlying event causing HH was present in 74% of all patients [8].

Although the histopathological finding of centrilobular liver cell necrosis is the essential element of HH, liver biopsy is usually not required for diagnosis of HH. Furthermore, if the clinical criteria mentioned above are fulfilled, biopsy is inadvisable in many patients, as those suffering from HH frequently have abnormal coagulation and receive anticoagulant drugs (mainly as a consequence of their basic cardiac disease) [8, 14].

The diagnosis of HH is usually established using three simple criteria that are illustrated in Table 1.

HH can usually be delineated from other causes of massively raised aminotransferase levels in critically ill patients, as shown in Fig. 1. However, unclear cases require additional testing, such as imaging techniques, laboratory assessment (hepatitis serology, autoimmune markers, drug dose levels (e.g. acetaminophen), invasive assessment of hepatic hemodynamics, and liver biopsy.

Furthermore, HH needs to be separated from ischemic-like cholangiopathy [15], which can lead to secondary cholangitis and the necessity for liver transplantation. In contrast to the dual blood supply of the hepatic parenchyma, the biliary tree is exclusively supplied by the hepatic artery. Patients with ischemic-like cholangiopathy have mainly cholestatic liver injury and no or only mild increase of aminotransferase levels [15].

Table 1. Diagnostic criteria for hypoxic hepatitis

1. Clinical setting of acute cardiac, circulatory, or respiratory failure
2. Dramatic but transient increase in serum aminotransferase activity reaching at least 20 times the upper limit of normal
3. Exclusion of other putative causes of liver cell necrosis, such as viral or drug-induced hepatitis

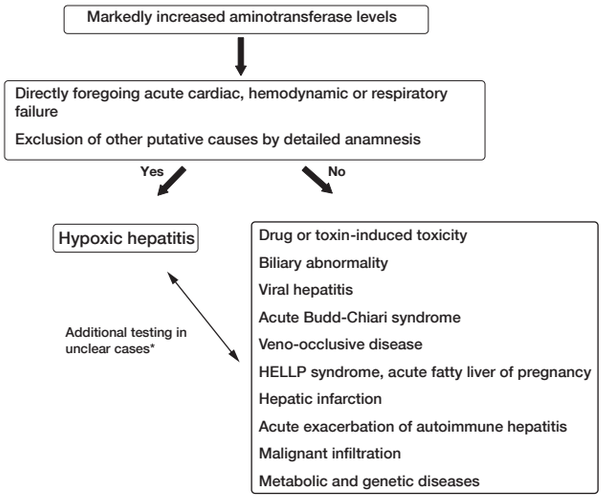

Fig. 1. HH can usually be simply delineated from other causes of massively raised aminotransferase levels. *Imaging techniques, laboratory assessment (hepatitis serology, autoimmune markers, drug dose levels, e.g. acetaminophen) liver biopsy or invasive assessment of hepatic hemodynamics are necessary in unclear cases

Laboratory assessment

Different aspects of the hepatic function can be characterized by several biomarkers [16]. The first step in evaluation is determination of the overall pattern of the abnormal liver function tests, which can be broadly divided into two categories: patterns predominantly reflecting hepatocellular injury (as in HH) and patterns predominantly reflecting cholestasis. Alkaline phosphatase is mainly elevated in cholestasis, whereas bilirubin can be elevated in both hepatocellular injury and cholestasis. In contrast, serum aminotransferases are classic markers of hepatocellular injury and necrosis. A British study prospectively investigated the etiology and outcome of patients with serum aspartate transaminases (AST) levels >400 U/l [4]. Ischemic and/or anoxic liver injury was the cause of the raised AST in about 50% of the patients and was associated with the highest mortality in the study population. Surprisingly, the cause of the AST rise was initially correctly diagnosed in fewer than 50% of the patients. Furthermore, the AST rise was apparently not noticed by the attending physician in 38% of the patients [4]. Ischemic liver injury was also the most frequent disease underlying extreme elevation of serum AST levels in another study [5]. Several authors have proposed that a dramatic but transient increase in serum aminotransferase activity reaching at least 20 times the upper limit of normal (normal range at the laboratory of the Medical University Vienna: AST < 35 U/l; alanine transaminase [ALT] <45 U/l) should be the minimal requirement for a diagnosis of HH [6, 11, 14, 17–19]. Histologic examination of the liver has revealed centrilobular liver cell necrosis in all patients who underwent liver biopsy and fulfilled these diagnostic criteria (Table 1) [6, 8]. Other authors have chosen a less restrictive cut off for diagnosing HH [7, 20–24]. Although centrilobular liver cell necrosis and HH also occur in patients with aminotransferase

activity less than 20 times the upper limit of normal, some authors consider liver biopsy for diagnostic clarification in such patients with suspected HH [25]. Data from a recently published small study examining liver histology in patients suffering from sepsis revealed centrilobular liver cell necrosis in 80% of the patients ($n = 15$), even though the median AST and ALT levels were below 20 times the upper limit of normal. In summary, we believe that there is now sufficient evidence to diagnose HH in patients with levels of aminotransferase activity reaching at least 20 times the upper limit of normal in a given clinical context. However, future studies need to clarify diagnostic approaches for HH in patients with aminotransferase levels below 20 times the upper limit of normal.

The typical pattern of transaminases during the course of HH is illustrated in Fig. 2. Initially there is a dramatic rise of both transaminases with leading AST and lactate dehydrogenase levels within 12–24 hours after the initiating event [13]. Usually the aminotransferase levels fall more than 50% within three days after stabilization and elimination of the underlying HH-causing condition. AST levels decline towards normal earlier than ALT levels during this recovery period because of the shorter half-life of AST [26].

Serum lactate levels are usually significantly increased in patients with HH. However, in a recent prospective study, peak serum lactate levels did not independently predict mortality in the multivariate regression analysis [8].

Serum albumin and markers of coagulation typically illustrate the synthetic function of the liver. Serum albumin levels appear unsuitable for illustration of hepatic synthetic function during a highly dynamic process such as HH as the half-life of albumin is too long. Furthermore, albumin functions as a negative acute-phase protein and its levels may be lowered due to malnutrition. In contrast, because of their shorter half-lives, markers of coagulation illustrate acute impairment of the synthetic function of the liver more accurately. The international normalized ratio (INR) and prothrombin time indicate either vitamin K deficiency or significant hepatocellular dysfunction. Lack of improvement of coagulation following parenteral administration of vitamin K indicates severe liver injury. An INR > 1.5 is a diagnostic criterion for acute liver failure [27]. We also recently outlined the prognostic importance of the degree of hepatic synthetic impairment in patients with HH: an INR > 2 is an independent risk factor for overall mortality [8].

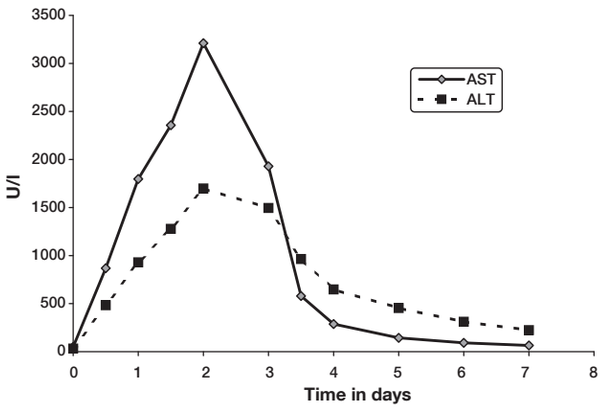

Fig. 2. Pattern of aminotransferase levels in 37 patients with hypoxic hepatitis (Fuhrmann, unpublished data). *AST* Serum aspartate transaminases level; *AIT* serum alanine transaminase level

Hepatic blood flow

Hepatic blood flow in patients with HH has been characterized by galactose clearance by several study groups [7, 9]. Hepatic extraction of galactose is almost 100% at the first passage. As body clearance is equal to hepatic clearance, systemic galactose clearance corresponds to hepatic blood flow [28, 29]. However, the galactose clearance method has limitations. First, it reveals appropriate results only if galactose extraction is complete at the first passage through the liver (intrahepatic portosystemic shunting). Second, measurement of hepatic blood flow by galactose clearance is appropriate only if the liver is the sole site of elimination [29]; extrahepatic elimination rate of galactose is discussed controversially [29, 30]. In addition, this method is frequently not available for clinical routine.

The indocyanine green plasma disappearance rate (ICG-PDR) is an alternative method of assessing hepatic function during acute hepatic injury and HH [31, 32]. ICG is the most commonly used indicator in clinical measurement of hepatosplanchnic blood flow (sum of portal venous and hepatic arterial inflow into the liver) and is calculated by the quotient between ICG extraction and ICG

Table 2. Laboratory characteristics* in patients with hypoxic hepatitis

Variable	Henrion et al. [6]	Birrer et al. [7]	Fuhrmann et al. [8]
Number of patients	138	293	117
AST (U/l)	2155 (455–15400)	2288 (1768–2715)	2507 (701–27560)
ALT (U/l)	1645 (237–8590)	1803 (1493–2084)	1348 (135–12452)
LDH (U/l)	2750 (105–9040)	3545 (3224–3787)	2826 (324–27220)
Bilirubin (mg/dl)	2.1 (0.4–22.5)	2.2 (1.8–2.5)	2.6 (0.4–49.5)
PTT (%)	36 (6–89)	n.a.	31 (5–87)
Lactate (mmol/l)	5.6 (0.8–32)	5.5 (4.6–9.5)	9.5 (1.1–26)

*Peak laboratory characteristics of recent selected reports.
AST Serum aspartate transaminases; *ALT* serum alanine transaminases; *LDH* lactate dehydrogenase; *PTT* prothrombin time.

clearance, expressed as the ICG-PDR [33]. ICG is eliminated almost completely and unchanged by the liver into the bile without enterohepatic circulation. The ICG-PDR is routinely assessed noninvasively *via* transcutaneous pulse densitometry [31]. Preliminary data indicated that hepatic impairment assessed from the ICD-PDR in patients with HH is comparable to that in patients with end-stage cirrhosis [34]. In contrast to cirrhosis, the ICG-PDR improves rapidly after reversal of HH [34]. Future data should clarify the clinical relevance of the ICG-PDR in diagnosis and management of HH in comparison with conventional laboratory assessment.

Liver biopsy

The typical histological lesion in HH is centrilobular liver cell necrosis [35, 36]. However, the clinical diagnostic criteria of HH are usually sufficient for its diagnosis (see Table 1). Several authors reported centrilobular liver cell necrosis in all patients who had histological examination of the liver and fulfilled the clinical diagnostic criteria of HH as listed in Table 1 [6, 8]. However, in selected cases (as mentioned above in *Laboratory assessment)* liver biopsy may help to clarify the underlying etiology of an acute rise in aminotransferase levels. For safety reasons, transjugular liver biopsy seems to be the preferred route for sampling liver specimens (see also *Invasive assessment of hepatic hemodynamics* below) [37].

Invasive assessment of hepatic hemodynamics

Invasive assessment of hepatic hemodynamics may be necessary in selected cases of unclear hepatic impairment in the intensive care unit [38]. The free hepatic venous pressure and the wedged hepatic venous pressure were elevated in the majority of patients with cardiac hepatopathy – many of these patients fulfilled the criteria for HH – as a consequence of transmission of elevated right arterial pressure [38]. However, the hepatic venous pressure gradient (the difference between wedged and free hepatic venous pressure representing the gradient between the portal vein and the intraabdominal vena caval pressure) was normal in the vast majority of patients [38]. Apart from assessment of hepatic hemodynamics, hepatic vein catheterization offers the possibility of transjugular liver biopsy, a safe route for collection of liver specimens [37]. Furthermore, the intervention is usually not associated with postinterventional pain, because the liver capsule is not affected.

Imaging techniques

The typical sonographic findings in patients with HH are dilated liver veins as a consequence of passive congestion of the liver due to low cardiac output. However, there is a lack of studies investigating the value of ultrasound examination in the diagnosis and management of HH.

Computed tomography or magnetic resonance imaging are usually not necessary in diagnosis or management of HH, but may provide helpful information in selected cases [39].

Table 3. Conditions predisposing patients to HH in selected publications

Parameter	Henrion et al. [6]	Birrer et al. [7]	Fuhrmann et al. [8]*
Number of cases	142	293	117
Shock state, *n* (%)#	78 (55)	147 (50)	103 (88)
Acute heart failure, *n* (%)	20 (21)	41 (14)	
Cardiogenic shock, *n* (%)			56 (48)
Acute myocardial infarction, *n* (%)	18 (13)	87 (30)	30 (26)
Valvular heart disease, *n* (%)		253 (86)	25 (21)
Rhythmogenic heart disease, *n* (%)	43 (30)	81 (28)	32 (27)
Pericardial effusion, *n* (%)	7 (5)	3 (1)	9 (8)
Pulmonary embolism, *n* (%)	9 (6)	6 (2)	5 (4)
Cardiopulmonary resuscitation, *n* (%)			34 (29)
Septic shock, *n* (%)	19 (13)	52 (18)	37 (32)
Hemorrhagic shock, *n* (%)	5 (4)		5 (4)
Trauma, *n* (%)	3 (2)	9 (3)	0
Cardiomyopathy/chronic heart failure, *n* (%)	80 (58)	171 (58)	44 (38)
Liver cirrhosis, *n* (%)	5 (4)		17 (15)
COPD/chronic respiratory failure, *n* (%)	19 (13)	45 (15)	23 (20)
Pulmonary hypertension, *n* (%)			9 (8)

*84 patients (74%) had more than one factor contributing to HH.
#Defined as systolic blood pressure < 90 mmHg or necessity for vasopressor therapy.
COPD Chronic obstructive pulmonary disease.

Pathophysiology

Development of HH is usually the consequence of a multifactorial event of several distinct acute and chronic organ dysfunctions leading to centrilobular liver cell necrosis. The most frequent underlying conditions are low cardiac output and septic shock, as shown in Table 3 [6–8, 13]. Several mechanisms contribute to development of HH. Major underlying factors are reduced hepatic blood flow, hepatic ischemia and passive congestion of the liver (mainly found in low cardiac output and right ventricular failure), decreased oxygen extraction by the liver (as in sepsis), and severe systemic hypoxia (as reported in acute exacerbations of chronic respiratory failure and obstructive sleep apnea) [6–8, 13, 40]. In addition, increased oxygen consumption as in cases of hyperthermia, and hypovolemia as in hemorrhage (mainly in patients with liver cirrhosis and gastrointestinal hemorrhage) can also contribute to the occurrence of HH [6–8].

The liver's supply of blood and oxygen

The liver is the largest visceral organ in the human body and receives up to 25% of the entire cardiac output, approximately 20–25% *via* the hepatic artery and 75–80%

from the portal system [41, 42]. The hepatic artery receives a fixed percentage of cardiac output under physiological conditions and its blood flow correlates inversely with that in the portal vein [43, 44]. Because of this unique dual blood supply, the liver is usually protected against ischemia. The liver's oxygen consumption accounts for 20% of whole-body oxygen consumption [41]; however, the liver is able to extract as much as 95% of blood-oxygen in order to maintain an appropriate oxygen uptake [13, 42].

Regulation of hepatic perfusion

Blood flow in the hepatic artery varies inversely with blood flow in the portal vein, which seems to be the predominant regulatory mechanism of liver perfusion [45]. In contrast to most other organs of the human body, perfusion of the liver does not strictly follow principles of supply and demand, evidenced by the fact that hemodilution with subsequent decrease in oxygen delivery to the liver does not provoke the expected increase in hepatic blood flow [45]. A decrease in the oxygen content of arterial blood is compensated by increased oxygen extraction rather than by enhancement of hepatic arterial blood flow [46].

A common theory explaining the extraordinary properties of hepatic blood flow regulation has been established by Lautt [45]. According to this "adenosine washout theory", adenosine, which is presumably synthesized constantly and secreted into the space of Mall, serves as primary regulator of hepatic arterial blood flow. Thus, increase of portal venous flow may lead to a decrease of adenosine concentration in the space of Mall *via* outwash, which is immediately followed by hepatic arterial constriction and decrease of hepatic arterial blood flow. Conversely, reduction of portal venous flow may result in accumulation of adenosine, therefore causing dilation of the hepatic artery. This mechanism has also been referred to as the hepatic arterial buffer response [45]. However, there is no reciprocity, as the portal vein cannot control its blood flow (sum of outflow of the extrahepatic splanchnic organs) [41].

Other mediators involved in regulatory processes of mesenteric and hepatic blood flow are norepinephrine, epinephrine, agents originating from the renin-angiotensin-aldosterone sytem, endothelins and nitric oxide (see *Disturbances in mesenteric blood distribution during critical illness* below) [47–50].

Disturbances in mesenteric blood distribution during critical illness

Several different agents such as norepinephrine and epinephrine contribute to systemic vasoconstriction during hypovolemic or cardiogenic shock. Catecholamines are known to decrease microcirculatory blood flow in the gastrointestinal tract and reduce regulation of hepatic blood flow [51, 52]. Furthermore, they induce an inflammatory response syndrome and dysfunction of human hepatocytes [53]. The prognostic impact of catecholamines in patients with HH is therefore not surprising: the dose of norepinephrine was found significantly higher in patients dying from HH [8]. Furthermore, HH was an independent prognostic factor only in critically ill patients requiring vasopressor support [10].

Nitric oxide attenuates experimental norepinephrine-induced vasoconstriction [49]. A recent clinical study demonstrated that inhaled nitric oxide reduced reperfusion-induced hepatic cell death and improved liver function tests in patients undergoing liver transplantation [54]. The impact of nitric oxide on the course of HH needs to be evaluated in future studies.

During shock, the mesenteric blood flow is basically affected by angiotensin (AT) II, one of the most potent endogenous vasoconstrictors. The mesenteric ischemia may be worsened by hyperresponsiveness to AT II during shock, which may be attributable to an overproportional increase of AT II in the mesenteric circulation during ischemia and an increased affinity of mesenteric AT II receptors under these conditions [47, 55]. Accordingly, several experimental studies have demonstrated attenuation of hepatic microcirculation and improvement of ischemia reperfusion injury after AT-converting enzyme inhibition and AT II receptor antagonism, respectively [56, 57]. Further, results obtained from animal models suggest that the hepatic arterial buffer response is compromised by ischemia during shock [58].

Clinical studies have revealed significantly decreased hepatic blood flow in patients with congestive heart failure and low cardiac output compared with patients without hemodynamic or cardiac impairment [9]. Furthermore, a much more pronounced reduction of hepatic blood flow was observed in patients with congestive heart failure and HH [7, 9].

Hepatic ischemia/reperfusion injury and HH

Several mechanisms that have been described in experimental models of hepatic ischemia/reperfusion (I/R) injury are also involved in pathophysiological processes during HH [59]. Reactive oxygen species can injure cells both directly *via* oxidation of proteins, lipids or DNA and indirectly through initiation of inflammatory cascades, subsequently causing hepatocyte damage [60, 61]. Oxidative stress, which is commonly deemed a major contributor to I/R injury, has also been demonstrated in patients with HH [61]. Furthermore, exaggerated immune reaction as described in I/R injury may also aggravate ischemic cell damage in HH [48, 60, 62]. Henrion et al. hypothesize that not only ischemia but also reperfusion may cause centrilobular liver damage in patients suffering from HH [59]. Although a frequent finding, prolonged shock is not mandatory for occurrence of HH [6–8]. Whether reperfusion or a short unrecognized period of hypotension causes the hypoxic liver injury in patients without apparent clinical signs of shock remains a matter of debate. Midzonal necrosis that is found occasionally in liver histology as pattern of hepatocellular injury after shock may be another indicator of reperfusion injury in HH [59, 63–65]. Nevertheless, the role of reperfusion injury in HH needs to be clarified in detail in future studies.

Other factors contributing to HH

It should be emphasized that reduction of hepatic blood flow and ischemia of the liver is an important but not the sole mechanism responsible for the observed hypoxic liver injury [6]. Hemodynamic shock is not a mandatory requirement for the occurrence of HH [6–8].

Severe systemic hypoxia resulting from acute exacerbation of chronic respiratory failure has been reported as the central underlying mechanism of HH in 17 patients [12], all of whom had a PaO_2 below 45 mmHg, most of them below 40 mmHg. Oxygen delivery (a hemodynamic combination of cardiac index and oxygen saturation) was comparably low in patients with HH due to low cardiac output and patients with HH due to hypoxia. Low oxygen delivery was caused by a low cardiac index in patients with underlying heart disease. In contrast, hypoxia was the only cause of low oxygen delivery despite high cardiac output in patients with acute-on-chronic respiratory insufficiency [12]. Other authors have reported occurrence of HH after severe hypoxemia caused by obstructive sleep apnea [8, 66, 67].

In contrast to low cardiac output, septic shock is usually characterized by increased systemic and hepatic blood flow. HH in septic shock is mainly the consequence of increased oxygen demand at the hepatocyte level combined with disturbances of oxygen metabolism, due to decoupling of the respiratory chain resulting in subsequent ATP depletion [6, 7]. This occurs after continuous progression of septic shock to severe multiorgan failure despite exhausting the therapeutic options of intensive care. Increased oxygen consumption (e.g. in hyperthermia) and hypovolemia mainly due to hemorrhagic shock have also been deemed potential causes of development of HH [6–8].

The liver as victim and offender in HH

A multitude of factors apparently contribute to damage of the liver and may hinder recovery of the acute hepatic injury in HH. However, the liver can also conduct injury of other organs, mainly as a consequence of induction of the inflammatory response syndrome [68]. Liver injury may aggravate hypoxia and respiratory insufficiency by induction of the hepatopulmonary syndrome and acute respiratory distress syndrome [11, 69]. Experimental data have demonstrated that I/R injury of the liver contributes to renal and myocardial injury [70, 71]. Furthermore, myocardial damage is frequently observed in acute liver failure [72]. Features of systemic inflammation, progression to multiple organ dysfunction and functional immunoparesis play a pivotal role in the pathogenesis and outcome of acute hepatic injury [73, 74]. In summary, the liver seems to be not only a victim but also an offender in critical illness in patients with HH.

Clinical presentation

Patients with HH are frequently of advanced age: the median age was about 70 years in several reports [6–8]. About 70% of reported cases of HH have been observed in male patients [6–8]. In general, typical clinical signs of liver injury are uncommon in patients with HH. Jaundice was found in 10–15% of all patients with HH and occurred mainly in the late course of the disease [6, 7]. The prevalence of hepatomegaly was about 50% in two case series [6, 38]. Splenomegaly and varices are rarely observed in patients with HH [6]. However, many patients reveal signs of cardiac insufficiency, which is the main underlying condition of HH in most reports [6–8]. Apart from low cardiac output, right ventricular failure is also frequently found in patients with HH [8, 40]. Right upper abdominal pain as a consequence of the congested and enlarged liver, hepatojugular reflux, shortness of breath, weakness and ankle edema can be observed [6, 7].

In older reports the presence of shock was a prerequisite condition of HH, where the term shock liver was frequently used [19, 36]. However, several studies demonstrated that a systemic state of shock, defined as systemic arterial blood pressure < 90 mmHg and/or the necessity for vasoactive drugs, occurred only in 50–90% of all patients with HH [6–8].

Encephalopathy is frequently found in patients with HH, although in most of the cases the encephalopathy is based on the underlying diseases contributing to the HH (e.g. cerebral malperfusion due to shock, hypoxic brain damage after cardiopulmonary resuscitation) and not on hepatic encephalopathy itself [75].

Natural history and prognosis

The incidence of HH varies depending upon the underlying setting. About 20 years ago Hickman et al. documented HH in 0.16% of all inpatient admissions [18]. According to the literature, HH is a rare finding on normal wards, with a reported incidence of less than 1‰ [20]. Most cases of HH are reported in critically ill patients in the intensive care unit. Henrion et al. observed an incidence of 0.9% in the intensive care unit during a 10-year observation period [6]. However, the incidence of HH seems to depend on the type of intensive care unit. A much higher proportion of HH can be expected in patients undergoing cardiovascular surgery and in cardiac care units, where the incidence increases up to 22% in patients with decreased cardiac output [9]. However, most of the published epidemiological findings have been from small or retrospective studies or are now more than 15 years old and may therefore not represent the current status of this disease. We recently performed a prospective epidemiological study at three medical intensive care units in the Medical University Vienna. The incidence of HH was more than 11% in these critically ill patients [10]. The 118 admissions with HH had a significantly higher simplified acute physiology score 2 (a well established prognostic score in critically ill patients [76]), a significantly longer stay in the intensive care unit and significantly increased intensive care unit mortality in comparison with all other admissions ($n = 948$) to the intensive care units during the 22-month observation period [10]. Multivariate regression analysis revealed that the presence of HH was a strong and independent risk factor for mortality in our collective of patients admitted to the

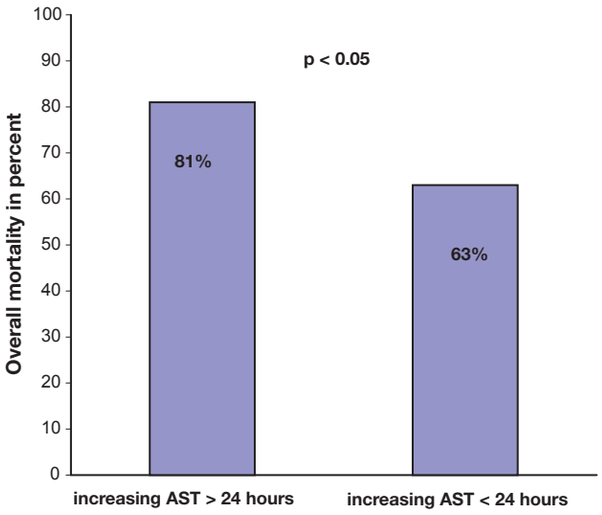

Fig. 3. Overall mortality in patients with hypoxic hepatitis ($n = 117$) depending on the duration of liver injury [8]. AST > 24 hours increasing serum aspartate transaminases levels for more than 24 hours as indicator of prolonged onset of hypoxic hepatitis in contrast to AST < 24 hours

intensive care unit: patients requiring vasopressor therapy and suffering from HH had an increased mortality risk nearly five times higher [10]. The intensive care unit mortality of patients with HH was about 55% [7, 8]. Others have reported a 30-day mortality rate of 52% [6]. In two studies the one-year survival rate was only 25% [6, 7].

The majority of critically ill patients develop HH within one day after admission to the intensive care unit [6, 8]. Although HH predicts poor prognosis, only a minority of patients die from liver disease itself. The leading causes of death in patients with HH are the underlying HH-causing diseases such as septic and cardiogenic shock [8]. The natural course and outcome of HH appear to depend on several factors. First, the extent and duration of liver injury have central prognostic importance in patients with HH. An INR > 2 is an independent risk factor for mortality in these patients [8]. Patients suffering from HH with increasing AST levels for more than 24 hours had a significant higher mortality rate, as illustrated in Fig. 3 [8]. This increased mortality rate in patients with prolonged liver injury may be a consequence of the inability to stabilize the underlying HH-causing disease. In addition, HH itself may also trigger aggravation of organ failure, as suggested in several studies [69, 70]. Second, the underlying disease contributing to development of HH has an important prognostic impact on outcome. Septic shock was found an independent predictor for mortality in a prospective series of patients with HH [8]. Third, vasopressor therapy and a systemic state of shock aggravate hepatic damage, impact on hepatic recovery and worsen outcome. Shock is found in 50–90% of patients with HH (Table 3). Mortality was significantly higher in patients receiving more than one vasopressor [8]. Furthermore, patients who died during the course of HH required significantly higher doses of norepinephrine than did the survivors [8]. Lastly, the presence of HH was an independent risk factor for mortality in an intensive care population only in patients requiring vasopressor support, but not in patients without vasopressor therapy [10].

Sepsis was the most frequent underlying cause of death in patients with HH [8]. However, in contrast to patients suffering from acute liver failure, cerebral edema usually does not contribute to mortality during the course of HH [8, 77]. Although there is only limited information available, cerebral edema seems to occur infrequently and not as a consequence of the acute liver injury but as a consequence of the underlying disease (e.g. hypoxic brain damage after cardiopulmonary resuscitation) in patients with HH [75].

Management

Treatment of the underlying disease

In general, treating HH means treatment of the underlying disease: patients with HH suffering from cardiogenic shock due to acute myocardial infarction require urgent therapy in the cardiac catheterization laboratory, percutaneous coronary intervention and/or surgery [78]. In general, low cardiac output should be treated with positive inotropic agents and hypotensive patients should receive fluid resuscitation and vasopressor support as early as possible. Patients with septic shock need therapy according the guidelines of the Surviving Sepsis Campaign [79]. Hypoxia should be treated by administration of oxygen and by mechanical ventilation if necessary. Accordingly, all other underlying disease entities should be causally treated (a selection of the most frequent underlying causes of HH is given in Table 3). Early correct diagnosis and subsequent initiation of adequate therapy are of central prognostic importance: the longer the underlying diseases remain unstabilized and the longer the progression of the acute hepatic injury continues, as indicated by increasing transaminases, the worse the outcome (Fig. 3) [8].

Hepatopulmonary syndrome

An important issue in management of HH is the management of its complications. A frequently observed complication of HH is the hepatopulmonary syndrome [11], defined as abnormality of gas exchange due to the intrapulmonary vasodilation in the patient's liver disease [80]. The hepatopulmonary syndrome is of central prognostic importance in patients with liver cirrhosis, where patients have a 2.5-times increased mortality risk [81, 82], and is a frequent finding in such patients with a prevalence of 5–32% [83]. We have demonstrated that the hepatopulmonary syndrome occurs in patients with HH with an incidence of 46% [11]. Patients with HH had worse gas exchange in the first days after the occurrence of hepatopulmonary syndrome. However, intrapulmonary vasodilation and hepatopulmonary syndrome resolved during follow-up after normalization of hepatic function. Outcome did not differ between patients suffering from HH with and without hepatopulmonary syndrome.

Hypoglycemia

Glucose monitoring is a routine measure in critically ill patients. Patients with acute liver failure are at increased risk of hypoglycemia [27]. Accordingly, several studies have reported increased incidence of spontaneous hypoglycemia also in patients with HH [8, 20]. Blood glucose levels should be monitored at regular intervals to avoid spontaneous hypoglycemic events. On the other hand, an increased incidence of hyperglycemia has also been reported in patients with HH [6, 14]. Consequently, tight glycemic control is warranted in patients with HH. The recently published recommendation of the US Acute Liver Failure Study Group that blood glucose levels should be maintained at <150 mg/dl seems to be a rational managing goal while further clinical data are missing [27].

Hyperammonemia

The American Association for the Study of Liver Diseases considers acute ischemic liver injury as a potential cause of acute liver failure [84]. Acute liver failure is usually defined as the onset of hepatic encephalopathy and coagulopathy within 26 weeks of jaundice in patients without preexisting liver disease [27]. However, the incidence of acute liver failure in patients with HH is unknown for several reasons. First, there are few prospective studies in the field of HH. Second, it is difficult to diagnose hepatic encephalopathy in patients with HH: many suffer from encephalopathy for several reasons such as sepsis and septic encephalopathy [85], cerebral malperfusion as a consequence of shock, or brain damage after cardiopulmonary resuscitation. Furthermore, hepatic encephalopathy is graded clinically according to clinical severity from 1 (lack of awareness, shortened attention span) to 4 (coma) [86]. The degree of hepatic encephalopathy is difficult to judge in many patients with HH as they are frequently analgosedated for non-hepatic reasons prior to the development of HH (Table 3). This is significantly different compared with patients suffering from primary acute hepatic injury for other reasons, such as paracetamol intoxication, where the primary organ injury occurs in the liver [87]. However, preliminary data suggest that hyperammonemia is a common finding also in patients with HH [75]. Elevated arterial ammonia levels were found associated with prolonged duration of HH and increased mortality. However, cerebral edema was not a frequent consequence of hyperammonemia in HH [75]. Recently, a randomized controlled study demonstrated no efficacy of L-ornithine L-asparate in acute liver failure [88]. Thus, because of the lack of data on HH, we cannot recommend targeted therapeutic interventions, apart from treating the underlying disease in patients with HH and hyperammonemia.

The liver as a therapeutic target

There is no strong clinical evidence that any liver-specific therapy improves outcome, including n-acetylcysteine or other antioxidants. There is consensus agreement that HH is not an indication for liver transplantation [84].

However, several studies have provided data for future therapeutic options. Naschitz et al. reported improvement of outcome in patients with nonhypotensive cardiogenic shock accompanied by renal and hepatic injury after administration of dopamine [89–91]. Others observed in a small retrospective study that patients ($n = 28$) receiving calcium-channel blockers and/or antiarrhythmic drugs had a higher mortality risk [92] and suggested that this may be a consequence of decreased clearance of hepatic drugs and altered cardiac sensitivity. Nevertheless, these results of old, small and retrospective studies have methodological limitations and must be interpreted with caution.

MARS

Many toxins that are produced during liver failure are hydrophobic, small and are transported by serum albumin. Functional disturbances in the antioxidant function are described in patients with liver failure [61, 93], where albumin is incapable of binding and effectively removing waste products for metabolism and excretion. Albumin-bound substances can be dialyzed through a normal dialysis membrane if clean albumin is the molecular acceptor in the dialysate. The most commonly used systems are the molecular adsorbent recirculating system (MARS) and single-pass albumin dialysis [94]. Studies have suggested that MARS therapy improved the hemodynamic situation in patients with acute and acute-on-chronic liver failure [95]. Several groups observed an increase in arterial pressure, systemic vascular resistance index, a decrease in portal pressure and improvement of renal blood flow [95–100]. MARS may therefore be a therapeutic option of potential interest in patients with HH. In a prospective single-center study, 27 patients suffering from hypoxic liver injury following cardiogenic shock after surgery were randomized to MARS therapy or placebo [101]. Survival, which was chosen as the primary end point of the study, did not differ significantly between the two groups although it was higher in the MARS group (50% *vs.* 34%). Thus, the routine use of MARS therapy cannot be recommended according to currently available data. Future randomized controlled studies investigating the efficacy of MARS are required to clarify the therapeutic impact of albumin dialysis in patients with HH.

Summary

In the intensive care unit population, HH is by far the most common cause of acute liver injury. Patients suffering from HH have a significantly increased mortality risk. Outcome is influenced by the underlying disease, its overall severity, and the degree and duration of hepatic impairment. Consequently, early diagnosis and subsequent adequate therapy of the HH-causing basic disease appear to be of central importance in these patients. Liver transplantation is not a therapeutic option in patients with HH.

Conflict of interest
The authors declare that there is no conflict of interest.

References

1. Kramer L, Jordan B, Druml W, et al (2007) Incidence and prognosis of early hepatic function in critically ill patients – a prospective multicenter study. Crit Care Med 35: 1099–104
2. Kaplan M (1993) Laboratory tests. In: Schiff L (ed) Diseases of the liver. JB Lippincott, Philadelphia, pp 108–44
3. McIntyre N, Rosalki S (1991) Biochemical investigations in the management of liver disease. In: McIntyre N, Benhamou JP, Bircher J, et al (eds) Oxford textbook of clinical hepatology. Oxford University Press, Oxford, pp 293–309
4. Whitehead N, Hawkes ND, Hainsworth I, et al (1999) A prospective study of the causes of notably raised aminotransferase of liver origin. Gut 45: 129–33
5. Johnson R, O'Connor C, Kerr RM (1995) Extreme serum elevations of aspartate aminotransferase. Am J Gastroenterol 90: 1244–5
6. Henrion J, Schapira M, Luwart R, et al (2003) Hypoxic hepatitis. Clinical and hemodynamic study in 142 consecutive cases. Medicine (Baltimore) 82: 392–406
7. Birrer R, Takuda Y, Takara T (2007) Hypoxic hepatopathy: pathophysiology and prognosis. Intern Med 46: 1063–70
8. Fuhrmann V, Kneidinger N, Herkner H, et al (2009) Hypoxic hepatitis: underlying conditions and risk factors for mortality in critically ill patients. Intensive Care Med 35: 1397–405
9. Henrion J, Descamps O, Luwaert R, et al (1994) Hypoxic hepatitis in patients with cardiac failure: incidence in a coronary care unit and measurement of hepatic blood flow. J Hepatol 21: 696–703
10. Fuhrmann V, Kneidinger N, Herkner H, et al (2008) Impact of hypoxic hepatitis on mortality at the intensive care unit. Hepatology 48[Suppl 4]: A320
11. Fuhrmann V, Madl C, Mueller C, et al (2006) Hepatopulmonary syndrome in patients with hypoxic hepatitis. Gastroenterology 131: 69–75
12. Henrion J, Minette P, Colin L, et al (1999) Hypoxic hepatitis caused by acute exacerbation of chronic respiratory failure: a case-controlled, hemodynamic study of 17 consecutive cases. Hepatology 29: 427–33
13. Ebert E (2006) Hypoxic liver injury. Mayo Clin Proc 81: 1232–6
14. Gitlin N, Serio K (1992) Ischemic hepatitis: widening horizons. Am J Gastroenterol 87: 831–6
15. Gelbmann C, Rümmele P, Wimmer M, et al (2007) Ischemic-like cholangiopathy with secondary sclerosing cholangitis in critically ill patients. Gut 102: 1221–9
16. American Gastroenterological Association (2002) American Gastroenterological Association medical position statement: evaluation of liver chemistry tests. Gastroenterology 123: 1364–6
17. Gibson P, Dudely FJ (1984) Ischemic hepatitis: clinical features, diagnosis and prognosis. Aust N Z J Med 14: 822–5
18. Hickman P, Potter J (1990) Mortality associated with ischemic hepatitis. Aust N Z J Med 20: 32–4
19. Rawson J, Achord JL (1985) Shock liver. South Med J 78: 1421–5
20. Fuchs S, Bogomolski-Yahalom V, Paltiel O, et al (1998) Ischemic hepatitis: clinical and laboratory observations of 34 patients. J Clin Gastroenterol 26: 183–6
21. Pauwels A, Levy VG (1993) Ischemic hepatitis in cirrhosis: not so rare, not always lethal. J Clin Gastroenterol 17: 88–9
22. Kamiyama T, Miyakawa H, Tajiri K, et al (1996) Ischemic hepatitis in cirrhosis: clinical features and prognostic implications. J Clin Gastroenterol 22: 126–30
23. Rashed K, McNabb WR, Lewis RR (2002) Ischemic hepatitis in the elderly. Gerontology 48: 245–9
24. Raman J, Kochi K, Morimatsu H, et al (2002) Severe ischemic early liver injury after cardiac surgery. Ann Thorac Surg 74: 1601–6
25. Henrion J, Schapira M, Heller F (1996) Ischemic hepatitis: the need for precise criteria. J Clin Gastroenterol 23: 305–6
26. Dufour R, Lott J, Nolte F, et al (2000) Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. Clin Chem 46: 2027–49
27. Stravitz R, Kramer A, Davern T, et al (2007) Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. Crit Care Med 35: 2498–508
28. Keiding S (1987) Hepatic clearance and liver blood flow. J Hepatol 4: 393–8
29. Henderson J, Kutner MH, Bain RP (1982) First-order clearance of plasma galactose: the effect of liver disease. Gastroenterology 83: 1090–6
30. Keiding S (1988) Galactose clearance measurements and liver blood flow. Gastroenterology 94: 477–81
31. Sakka S, Reinhart K, Meier-Hellmann A, et al (2000) Comparison of invasive and noninvasive measurements of indocyanine green plasma disappearance rate in critically ill patients with mechanical ventilation and stable hemodynamics. Intensive Care Med 26: 1553–6
32. Sakka S, von Hout N (2006) Relation between indocyanine green (ICG) plasma disappearance rate and ICG blood clearance in critically ill patients. Intensive Care Med 32: 766–9
33. Uusaro A, Ruokonen E, Takala J (1995) Estimation of splanchnic blood flow by the Fick principle in man and problems in the use of indocyanine green. Cardiovasc Res 30: 106–12
34. Kneidinger N, Fuhrmann V, Kitzberger R, et al (2007) Assessment of liver function via indocyanine green clearance. Intensive Care Med 33[Suppl 2]: O188
35. Bynum T, Boitnott JK, Maddrey WC (1979) Ischemic hepatitis. Dig Dis Sci 24: 129–35
36. Arcidi J, Moore GW, Hutchins GM (1981) Hepatic morphology in cardiac dysfunction. A clinicopathologic study of 1000 subjects at autopsy. Am J Pathol 104: 159–66
37. Kalambokis G, Manousou P, Vibhakorn S, et al (2007) Transjugular liver biopsy – indications, adequacy, quality of specimens, and complications – a systematic review. J Hepatol 47: 284–94
38. Myers R, Cerini R, Sayegh R, et al (2003) Cardiac hepatopathy: clinical, hemodynamic, and histologic characteristics and correlations. Hepatology 37: 393–400
39. Kahn J, Haker KM, Petrovic LM, et al (2000) Radiographic findings of ischemic hepatitis in a cirrhotic patient. J Comput Assist Tomogr 24: 887–9
40. Seeto R, Fenn B, Rockey DC (2000) Ischemic hepatitis: clinical presentation and pathogenesis. Am J Med 109: 109–13
41. Vollmar B, Menger MD (2009) The hepatic microcirculation: mechanistic contributions and therapeutic targets in liver injury and repair. Physiol Rev 89: 1269–339
42. Naschitz J, Slobodin G, Lewis RJ, et al (2000) Heart diseases affecting the liver and liver diseases affecting the heart. Am Heart J 140: 111–20
43. Bonnet F, Richard C, Glaser P, et al (1982) Changes in hepatic flow induced by continuous positive pressure ventilation in critically ill patients. Crit Care Med 10: 703–5
44. Lautt W (1995) The 1995 Ciba-Geigy Award Lecture: intrinsic regulation of hepatic blood flow. Can J Physiol Pharmacol 74: 223–33
45. Lautt W (2007) Regulatory processes interacting to maintain hepatic blood flow constancy: vascular compliance, hepatic arterial buffer response, hepatorenal reflex, liver regeneration, escape from vasoconstriction. Hepatol Res 37: 891–903
46. Schiltholt J, Shiraishi T (1970) Die Wirkung einer allgemeinen Hypoxie, Hypocapnie und Hypercapnie auf die Durchblutung der Leber und des Splanchniucusgebietes des narkotisierten Hundes. Pfluegers Arch 318: 185–201
47. Ceppa E, Fuh KC, Bulkley GB (2003) Mesenteric hemodynamic response to circulatory shock. Curr Opin Crit Care 9: 127–32
48. Jaeschke H (2003) Molecular mechanism of hepatic ischemia-reperfusion injury and preconditioning. Am J Physiol Gastroinest Liver Physiol 284: G15–26

49. Ming Z, Han C, Lautt WW (1999) Nitric oxide mediates hepatic arterial vascular escape from norepinephrine-induced constriction. Am J Physiol Gastroinest Liver Physiol 277: G1200–6
50. Koeppel TA, Kraus T, Thies JC, Gebhard MM, Otto G, Post S (1997) Effects of mixed ETA and ETB-receptor antagonist (Ro-47-0203) on hepatic microcirculation after warm ischemia. Dig Dis Sci 42: 1316–21
51. Mehrabi A, Golling M, Kahfi A, et al (2005) Negative impact of systemic catecholamine administration on hepatic blood perfusion after porcine liver transplantation. Liver Transpl 11: 174–87
52. Krejci V, Hiltebrand LB, Sigurdsson GH (2006) Effect of epinephrine, norepinephrine, and phenylepinephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis. Crit Care Med 34: 1456–63
53. Aninat C, Seguin P, Descheemaeker P-N, et al (2008) Catecholamines induce an inflammatory response in human hepatocytes. Crit Care Med 36: 848–54
54. Lang JTX, Chumley P, Crawford JH, Isbell TS, Chacko BK, et al (2007) Inhaled NO accelerates restoration of liver function in adults following orthotopic liver transplantation. J Clin Invest 117: 2583–91
55. Yilmaz E, Vahl AC, vanRij GL, et al (1999) The renin-angiotensin system in swine during hypovolaemic shock combined with low-flow ischaemia of the sigmoid colon. Cardiovasc Surg 7: 539–44
56. Masuko H, Jin MB, Horiuchi H, et al (2001) Protective effect of angiotensin II type I receptor antagonist, CV-11974, on ischemia and reperfusion injury of the liver. Transplantation 71: 1034–9
57. Anthuber M, Farkas S, Rihl M, et al (1997) Angiotensin-converting enzyme inhibition by enalapril: a novel approach to reduce ischemia/reperfusion damage after experimental liver transplantation. Hepatology 25: 648–51
58. Jakob S, Tenhunen JJ, Heino A, et al (2002) Splanchnic vasoregulation during mesenteric ischemia and reperfusion in pigs. Shock 18: 142–7
59. Henrion J, Descamps O, Luwaert R, et al (2000) Ischemia/reperfusion injury of the liver: pathophysiologic hypotheses and potential relevance to human hypoxic hepatitis. Acta Gasteroenterol Belg 63: 336–47
60. Casillas-Ramirez A, Mosbah IB, Ramalho F, et al (2006) Past and future approaches to ischemia-reperfusion lesion associated with liver transplantation. Life Sci 79: 1881–94
61. Biasi F, Lanfranco G, Capra A, et al (1994) Oxidative stress in the development of human ischemic hepatitis during circulatory shock. Free Radic Biol Med 17: 225–33
62. Massip-Salcedo M, Rosello-Catafau J, Prieto J, Avila MA, Peralta C (2007) The response of the hepatocyte to ischemia. Liver Int 27: 6–16
63. Bywaters E (1948) Anatomical changes in the liver after trauma. Am J Pathol 26: 19–39
64. Lambert R, Allison BR (1916) Types of lesions in chronic passive congestion of the liver. Bull Johns Hopkins Hosp 27: 350–6
65. DeLaMonte S, Arcidi JM, Moore GW, Hutchins GM (1984) Midzonal necrosis as a pattern of hepatocellular injury after shock. Gastroenterology 86: 627–31
66. Mathurin P, Durand F, Ganne N, et al (1995) Ischemic hepatitis due to obstructive sleep apnea. Gastroenterology 109: 1682–4
67. Henrion J, Colin L, Schapira M, Heller F (1997) Hypoxic hepatitis caused by severe hypoxemia from obstructive sleep apnea. J Clin Gastroenterol 24: 245–9
68. Szabo G, Romics L, Frendl G (2002) Liver in sepsis and systemic inflammatory response syndrome. Clin Liver Dis 6: 1045–66
69. Peralta C, Perales J, Bartrons R, et al (2002) The combination of ischemic preconditioning and liver BCL-2 overexpression is a suitable strategy to prevent liver and lung damage after hepatic ischemia-reperfusion. Am J Pathol 160: 2111–22
70. Nielsen V, Tan S, Baird MS, et al (1997) Xanthine oxidase mediates myocardial injury after hepatoenteric ischemia-reperfusion. Crit Care Med 25: 1044–50
71. Jiang H, Meng F, Li W, et al (2007) Splenectomy ameliorates acute multiple organ damage induced by warm ischemia reperfusion in rats. Surgery 141: 32–40
72. Parekh N, Hynan LS, Lemos JD, et al (2007) Elevated troponin I levels in acute liver failure: is myocardial injury an integral part of acute liver failure? Hepatology 45: 1489–95
73. Leber B, Mayrhauser U, Rybczynski M, et al (2009) Innate immune dysfunction in acute and chronic liver disease. Wien Klin Wochenschr 121: 732–44
74. Antoniades C, Berry P, Wendon J, et al (2008) The importance of immune dysfunction in determining outcome in acute liver failure. J Hepatol 49: 845–61
75. Fuhrmann V, Drolz A, Kneidinger N, et al (2009) Hyperammonemia in patients with hypoxic hepatitis. Gut 58[Suppl 2]: P0450
76. LeGall J, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 270: 2957–63
77. Ostapowicz G, Fontana R, Schiodt F, et al (2002) Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 137: 947–54
78. Babaev A, Frederick PD, Pasta DJ, et al (2005) Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. JAMA 294: 448–54
79. Dellinger R, Levy MM, Carlet JM, et al (2008) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 34: 17–60
80. Rodriguez-Roisin R, Krowka MJ, Herve P, et al on behalf of the ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee (2004) Pulmonary-Hepatic vascular Disorders (PHD). Eur Resp J 24: 861–80
81. Schenk P, Schöniger-Hekele M, Fuhrmann V, et al (2003) Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. Gastroenterology 125: 1042–52
82. Fallon M, Krowka MJ, Brown RS, et al (2008) Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. Gastroenterology 135: 1042–52
83. Rodriguez-Roisin R, Krowka MJ (2008) Hepatopulmonary syndrome – a liver-induced lung vascular disorder. N Engl J Med 358: 2378–87
84. Polson J, Lee WM (2005) American Association for the Study of Liver Disease AASLD position paper. The management of acute liver failure. Hepatology 41: 1179–97
85. Zauner C, Gendo A, Kramer L, et al (2002) Impaired subcortical and cortical sensory evoked potential pathways in septic patients. Crit Care Med 30: 1136–9
86. O'Grady J (2005) Acute liver failure. Postgrad Med J 81: 148–54
87. Kramer L (2004) Acute liver failure. Wien Klin Wochenschr 116: 67–81
88. Acharya S, Bhatia V, Sreenivas V, et al (2009) Efficacy of L-ornithine L-aspartate in acute liver failure: a double blind, randomized, placebo-controlled study. Gastroenterology 136: 2159–68
89. Naschitz J, Yeshurun D (1987) Compensated cardiogenic shock: a subset with damage limited to liver and kidneys. The possible salutary effect of low-dose dopamine. Cardiology 74: 212–8
90. Ander D, Jaggi M, Rivers E, et al (1998) Undetected cardiogenic shock in patients with congestive heart failure presenting to the emergency department. Am J Cardiol 82: 888–91
91. Menon V, Slater JN, White HD, et al (2000) Acute myocardial infarction complicated by systemic hypoperfusion without hypotension: report of the SHOCK trial registry. Am J Med 108: 374–80
92. Potter J, Hickman PE (1992) Cardiodepressant drugs and the high mortality rate associated with ischemic hepatitis. Crit Care Med 20: 474–8

93. Oettl K, Stadlbauer V, Petter F, et al (2008) Oxidative damage of albumin in advanced liver disease. Biochem Biophys Acta 1782: 469–73
94. Mitzner S, Klammt S, Stange J, et al (2006) Albumin regeneration in liver support – comparison of different methods. Ther Apher Dial 10: 108–17
95. Mitzner S, Stange J, Klammt S, et al (2001) Extracorporeal detoxification using the molecular adsorbent recirculating system for critically ill patients with liver failure. J Am Soc Nephrol 12: S75–82
96. Stefoni S, Coli L, Bolondi L, et al (2006) Molecular adsorbent recirculating system (MARS) application in liver failure: clinical and hemodepurative results in 22 patients. Int J Artif Organs 29: 207–18
97. Laleman W, Wilmer A, Evenepoel P, et al (2006) Effect of the molecular adsorbent recirculating system and Prometheus devices in systemic haemodynamics and vasoactive agents in patients with acute-on-chronic liver failure. Crit Care 10: R108
98. Schmidt L, Wang LP, Hansen BA, et al (2003) Systemic hemodynamic effects of treatment with the molecular adsorbent recirculating system in patients with hyperacute liver failure: a prospective controlled trial. Liver Transpl 9: 290–7
99. Sen S, Loock J, Peszynski P, et al (2005) Albumin dialysis reduces portal pressure acutely in patients with severe alcoholic hepatitis. J Hepatol 43: 142–8
100. Hetz H, Faybik P, Berlakovich G, et al (2006) Molecular adsorbent recirculating system in patients with early allograft dysfunction after liver transplantation. Liver Transpl 12: 1357–64
101. Banayosy A, Kizner L, Schueler S, et al (2004) First use of molecular adsorbent recirculating system technique on patients with hypoxic liver failure after cardiogenic shock. ASAIO J 50: 332–7