Shock liver

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Shock liver describes a collecting pool of critically ill patients in whom the elevation of liver function tests or overt hepatic dysfunction is apparent. Different grades of shock liver affect about 50% of all intensive-care patients, varying from a mild elevation of serum aminotransferase and bilirubin levels in septic patients to an acute onset of high serum aminotransferases after haemodynamic shock. Abnormalities can subside within days or progressively deteriorate when persistent hepatic microcirculatory failure is present. Although hepatic injury in critically ill patients influences mortality rates it is underdiagnosed. The underlying pathophysiology involves changes in the portal and arterial blood supply as well as in microcirculation. Cross-talk between hepatocytes, Kupffer cells and endothelial cells, leading to an inflammatory response mediated primarily by tumour necrosis factor-α (TNF-α), is central to shock liver. The liver is a victim of shock inducers, and can also be the orchestrator of the inflammatory response syndrome (IRS). Hepatic injury by TNF-α is modulated by the prevalent pro-inflammatory or anti-inflammatory mediator profile elaborated by Kupffer cells. Kupffer cells additionally participate in the clearance of endotoxin, bacteria and inflammatory mediators and are thereby capable of preventing IRS. The hepatocyte undergoes dramatic alterations in synthetic activity, biliary transport, bile flow and glucose metabolism. Although standard determinations of aminotransferases, coagulation studies, glucose, lactate and bilirubin can detect hepatic injury they only partially reflect the cellular mechanisms driving shock liver. The management of shock liver is focused on the prevention of precipitating causes by controlling sepsis, circulation parameters and metabolism in addition to the cautious monitoring of therapeutic measures that can increase hepatic injury, which include intravenous nutrition, mechanical ventilation and catecholamine administration.

Key words: septic shock; haemodynamic shock; TNF-α; Kupffer cell; IRS; hepatic artery perfusion buffer.

The observation of elevated liver function tests or outright hepatobiliary dysfunction is common in critically ill patients. Liver dysfunction is diagnosed in over 50% of patients treated in intensive care units (ICU). This influences overall mortality and is therefore a parameter of great significance for the physicians involved1–4 (Figure 1). However, the presenting picture of hepatobiliary dysfunction is diverse; it ranges from acute elevations of serum aminotransferase levels, an acute or gradual decrease in liver synthesis, indicated by coagulation factor or albumin levels, a decrease in hepatic

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detoxification and transport shown by bilirubin elevations, to a mere mild elevation of liver enzymes.1,5,6 Interestingly, the timing of hepatic injury, and the onset of evidence of hepatic injury, can vary as well. An interval of several days after major surgery or trauma is possible before hepatic injury becomes apparent.1,7 These general considerations suggest that hepatobiliary dysfunction in the critically ill represents a complex syndrome from the point of view of clinical presentation and in the underlying pathophysiology.8 The high frequency of abnormalities in liver tests also indicates that the liver is a key player in critically ill patients.9

In practical terms, the designation ‘shock liver’ encompasses two important aetiologies of liver damage: (i) haemorrhagic shock, or failure of the macrocirculation due to other reasons, and (ii) septic shock. Shock liver can also result from multiple organ dysfunction and acute respiratory distress syndrome. In these conditions the liver plays a central pathophysiological role which can be appreciated only when the features of hepatic blood flow10 and anatomical structure, and the interplay of its diverse subsets of cells, are analysed.11 The liver has a dual supply of blood flow, one-third arising from the hepatic artery and two-thirds arising from the portal venous system.12 It is the only example in the human body in which two venous systems are connected in series. The mesenteric–splanchnic circulation is followed by the portal venous system and thereby combines the effects of splanchnic vasoconstriction, bacterial translocation in the intestine, and mesenteric arterial supply with the portal perfusion, which, in turn, influences total venous return to the heart. The liver therefore has only limited control over its venous blood flow.13 Most of the regulation occurs at the level of the hepatic artery, which has been designated the hepatic artery buffer response. It is the inverse change of hepatic artery flow as a response to changes in portal venous blood flow that maintains a constant overall hepatic blood supply. However, blood flow is only one side of the coin. Sixty percent of the liver mass consists of hepatocytes, but the presence of Kupffer cells, endothelial sinusoidal cells (dependent upon the state of inflammation)
and also neutrophils and mononuclear cells are an important functional part of the remaining liver mass.\textsuperscript{9,14} The liver harbours about 80\% of all macrophages in the human body as resident Kupffer cells. Kupffer cells not only play a role as scavengers of bacteria\textsuperscript{15} and endotoxin\textsuperscript{16}, and in the clearance of inflammatory cytokine mediators\textsuperscript{17}, but also secrete cytokines, leukotrienes, lysosomal enzymes and oxygen radicals\textsuperscript{18–23} (Figure 2). Cross-talk between the different cells present in the liver is therefore at the centre of the mechanisms leading to shock-induced hepatic injury. In view of this multiplicity, the central functional role of the liver becomes evident. On the one hand, it suffers from the effects of shock-inducing circumstances, such as sepsis or haemorrhage, which alter hepatic circulation parameters, oxygen supply and inflammatory responses at the cellular level. On the other hand, the liver is an orchestrator of injury as a direct result of the clearance and production of inflammatory mediators, the scavenging of bacteria, and the synthesis of acute-phase proteins. This balance defines the stage upon which the syndrome of shock liver develops.

**CRITERIA FOR HEPATIC DYSFUNCTION**

The criteria for hepatic dysfunction (Table 1) have been described mainly in studies that include critically ill patients and therefore represent a mix of cases with sepsis, trauma, post-operative hepatic injury or other reasons for circulatory dysfunction.\textsuperscript{1–3,5–7,24,25} The diagnosis of shock liver relies primarily on laboratory parameters which include hyperbilirubinaemia or clinical jaundice\textsuperscript{25}, an increase in serum aspartate

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**Figure 2.** Functional role of Kupffer cells in shock liver. The Kupffer cell accounts for about 15\% of all hepatic cells. As a response to septic shock it elaborates pro-inflammatory cytokines (left) and anti-inflammatory cytokines (right) in addition to TNF-\(\alpha\). TNF-\(\alpha\) is responsible for hepatic injury in shock liver, but this action is modulated by the co-existing profile of inflammatory modulators, which can serve to attenuate or aggravate hepatic cellular injury.
aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP), an increase in serum lactate dehydrogenase (LDH), and a decrease in albumin or coagulation factor levels. In septic shock, aminotransferase (AST, ALT) levels are usually mildly elevated and are disproportionately lower than bilirubin levels. Hepatic injury is most likely to be more prevalent among ICU patients than generally assumed. It can occur 6–8 days after surgery, after pulmonary failure, and even over 1 week after the onset of septic shock in patients without pre-existing hepatic disease. Because of the degree and timing, mild hyperbilirubinaemia without jaundice frequently goes unnoticed and, additionally, reduces the awareness of hepatic injury. In this situation the alteration in prothrombin time without bilirubin elevation may be an early marker of liver injury. When even mild elevations of liver function tests are taken into account, hepatic injury appears to be as frequent as kidney and lung failure. It is therefore desirable to quantify hepatic injury in critically ill patients to allow for an assessment of prognosis and hepatic cellular injury. Several scores have been used that are based on AST and bilirubin, jaundice, bilirubin and prothrombin time, LDH, AST and bilirubin. The main pitfall with these scoring systems is the fact that the most severe laboratory values are employed, and that the duration of hepatic injury is not incorporated. In addition, pre-existing hepatic disease, such as cirrhosis, is not appreciated in these scores. In one study, a mortality rate of 100% was observed in cirrhotic patients on ventilation for septic shock, and therefore cirrhosis in shock clearly alters prognosis.

Finally, the question remains whether standard laboratory parameters are capable of reflecting critical hepatic functions that influence prognosis, such as the beneficial synthesis of acute-phase proteins, endotoxin clearance, cytokine clearance, bacterial scavenging versus oxygen radical release, and the reduction of gluconeogenesis and biotransformation, which lead to increased cellular injury. From a practical point of view biochemical tests should include ALT, AST, gamma glutamyltransferase (γGT), alkaline phosphatase, bilirubin, prothrombin time, glucose and lactate. Even mild alterations as long as 1 week after the injury are indicative of hepatic injury.

HEPATIC BLOOD FLOW DURING SHOCK

The understanding of hepatic and splanchnic blood flow during septic shock or sepsis is based upon a number of human studies and a wealth of experimental animal models.
One of the main problems with human data is the fact that portal venous blood for haemodynamic study is not available and therefore the accurate pathophysiological picture has to be extrapolated from animal data which may not always reflect the human situation. The majority of data regarding hepatic blood flow in humans is based on indocyanine green (ICG) clearance measurements calculated on the basis of the principle of Fick.\textsuperscript{12,28} When endotoxin is injected into voluntary subjects hepatosplanchnic blood flow increases within 1 hour.\textsuperscript{29} In septic patients with hyperdynamic circulation hepatosplanchnic flow also increases. However, the analysis of patients with and without sepsis shows similar results so that hepatosplanchnic perfusion appears to remain stable, regardless of aetiology, at a ratio of about 25% of cardiac output.\textsuperscript{30} An important point beyond the mere analysis of flow is oxygen consumption. The use of hepatosplanchnic oxygen is higher in septic compared to non-septic patients,\textsuperscript{31} and it almost doubles in volunteers injected with endotoxin.\textsuperscript{29} Interestingly, the administration of noradrenalin (norepinephrine), which is commonly given in severe sepsis, leads to an increase of oxygen delivery,\textsuperscript{32} although noradrenaline is known to lead to a reduction in hepatosplanchnic flow.\textsuperscript{33} This may be explained by a reduced responsiveness of the mesenteric circulation during sepsis. The increase of oxygen use is likely to be the result of an increased substrate delivery to the liver and an increase in hepatic glucose production and metabolism.\textsuperscript{34} A critical factor for adequate oxygen delivery to, and uptake by, the liver appears to be the oxygen saturation gradient between mixed venous and hepatic venous blood. While oxygen delivery is adequate in most septic patients, those with a high gradient between mixed venous and hepatic vein oxygen pressure exceeding 10% may not meet the actual hepatic oxygen demand and are at risk for hepatic injury.\textsuperscript{35} Hepatic flow during shock situations is also regulated by the hepatic artery buffer response, which is capable of ensuring hepatic blood flow by dilatation of the hepatic artery down to a systemic mean arterial pressure of 50 mmHg. In animal models this regulation is primarily observed in haemorrhagic shock,\textsuperscript{36} but is altered in septic shock.\textsuperscript{37} When endotoxin is administered, the decrease in portal flow due to an increase in intrahepatic resistance\textsuperscript{38} does not lead to an increase in hepatic arterial blood flow. Although, overall, hepatic blood flow increases, due to an increase in cardiac output, the regulation between arterial and venous flow is impaired in sepsis. This regulation may put the liver at risk for ischaemic injury. In the intensive care setting of patients on mechanical ventilation the increase in intrathoracic pressure additionally contributes to a reduction in hepatic flow. Combined with the pathophysiological mechanisms described, mechanical ventilation represents a risk factor for hepatic cellular injury.

**HEPATIC MICROCIRCULATION DURING SHOCK**

The classical case for ischaemia includes trauma, blood loss and major surgery requiring circulation support. In these instances hepatic microcirculation decreases below a critical threshold and leads to cellular ischaemia, which is the most important initial event for hepatic injury and dysfunction. Endothelin levels rise in haemorrhagic hypotension and lead to profound vasoconstriction in vascular beds, including those of the liver. This process can be antagonized by the synthesis of nitric oxide by endothelial cells. However, it is also important to recognize that hepatocellular dysfunction can arise in the absence of microcirculatory changes. In one study the application of endotoxin and tumour necrosis factor (TNF) induced cellular dysfunction in
the absence of microcirculatory changes detected by colloidal carbon infusion and laser Doppler flowmetry. This finding may explain the clinical observation of the late appearance of biochemical signs of hepatic injury in some patients, in particular during sepsis.

HEPATIC CELL FUNCTIONS DURING SHOCK

The cross-talk between hepatic cells, which ultimately leads to the release of radical oxygen species and enzymes, is at the centre of hepatic injury in shock situations. Three types of hepatic cell are relevant in this respect: Kupffer cells, hepatocytes and endothelial cells.

Kupffer cells

In the rabbit model an injection of endotoxin leads to a rapid clearance by hepatic uptake into Kupffer cells and also into hepatocytes. Kupffer cells are capable of efficiently clearing bacterial cells, endotoxin and cytokine mediators from the blood, thereby preventing entry into the systemic circulation. This activity is supported by the clearance activity of the lung and the spleen. By this action, Kupffer cells are capable of limiting the magnitude of a systemic inflammatory response. A reduction in Kupffer cell function may therefore lead to a spillover of bacteria and endotoxin, as well as inflammatory mediators, and can contribute to the development of an inflammatory response syndrome (IRS). In addition, Kupffer cells are macrophages which, after endotoxin stimulation, can elaborate pro-inflammatory mediators, including tumour necrosis factor-alpha (TNF-α), interleukin (IL) 1α-β, IL-8, granulocyte-colony stimulating factor (G-CSF), IL-12, IL-18 and granulocyte-macrophage colony stimulating factor (GM-CSF). The pro-inflammatory cytokines can be counteracted by the production of anti-inflammatory mediators, including IL-4, (IL-6), IL-10, transforming growth factor-beta (TGF-β), tumour necrosis factor (TNF) soluble receptors, and IL-1

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
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<tbody>
<tr>
<td><strong>Hepatocytes</strong></td>
<td></td>
</tr>
<tr>
<td>Acute-phase proteins [α1-antitrypsin, coeruloplasmin, α2-macroglobulin etc.]</td>
<td>Biotransformation, CYP activity</td>
</tr>
<tr>
<td>Amino acid uptake</td>
<td>Hepatobiliary transport</td>
</tr>
<tr>
<td>Glycogenolysis</td>
<td>Bile flow</td>
</tr>
<tr>
<td>Gluconeogenesis (early shock)</td>
<td>Gluconeogenesis (late shock)</td>
</tr>
<tr>
<td><strong>Kupffer cells</strong></td>
<td></td>
</tr>
<tr>
<td>Production of TNF-α, IL-1, IL-1-ra, IL-6</td>
<td>Endotoxin uptake (relative)</td>
</tr>
<tr>
<td>Reactive oxygen intermediates</td>
<td>Cytokine clearance (relative)</td>
</tr>
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<td></td>
<td>Bacterial product uptake (relative)</td>
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</tbody>
</table>

Table 2. Alterations in hepatocyte and Kupffer cell functions in shock liver situations (based on animal experiments of septic shock).

CYP, cytochromes P450; TNF, tumour necrosis factor; IL, interleukin; ra, receptor antagonist.
Kupffer cells are capable of producing ample amounts of TNF-\(\alpha\), which, in human subjects, accounted for a relevant proportion of systemic TNF-\(\alpha\) levels. \(^{29}\) TNF-\(\alpha\) leads to the production of hepatic acute-phase proteins in addition to hepatic nitric oxide production, and thereby to an increase in protein synthesis \(^{41}\) (Table 2). These effects are positive actions of TNF-\(\alpha\); however, an increase in TNF-\(\alpha\) levels also leads to an increase of anticoagulant activity of endothelial cells, the activation of neutrophils, and (with interferon-gamma) an increase in expression of adhesion molecules. \(^{42}\) Hepatic injury is increased by the adhesion of neutrophils to the sinusoidal endothelial cells and the resulting radical oxygen species. The balance of the different actions initiated by Kupffer cells is crucial for the development of hepatic injury in shock situations (Figure 2). Evidence for this hypothesis is provided in animal models. The application of methyl palmitate \(^{43}\) or gadolinium chloride \(^{44}\), which inactivate Kupffer cells, has been shown to lead to a reduction in hepatic injury. Furthermore, acute-phase proteins \(^{45}\) and IL-10 \(^{46}\) have been shown to protect against hepatic damage during sepsis. Whether these results are reproducible in humans, and have therapeutic implications, is currently not known.

**Hepatocytes**

During septic shock the hepatocyte fulfils a dual role. It is involved in implementing effects of the inflammatory response as well as undergoing fundamental metabolic changes \(^{47}\) (Table 2). The metabolic changes include an increase in the elaboration of acute-phase proteins, mediated to a large extent by IL-6. Plasma concentrations of C-reactive protein, \(\alpha\)-1-antitrypsin, fibrinogen, prothrombin, haptoglobin etc. are increased, while hepatic production of albumin, high-density lipoprotein, transferrin and antithrombin is decreased. The synergistic effects of TNF-\(\alpha\), IL-1 and IL-6 appear to regulate this activity and indicate the key role that Kupffer cells play in the changes affecting the hepatocyte. \(^{48,49}\) The up-regulated synthesis of proteins is further shown by an increased uptake of glutamine \(^{50}\) and arginine \(^{51}\) into the hepatocyte. In addition, the activity of glycogenolysis and gluconeogenesis increases \(^{52,53}\). The up-regulated production of acute-phase proteins (APP) leads to a modulation of inflammatory action, for example, by \(\alpha\)-1-antitrypsin, that can inactivate extracellular elastase, as well as by coeuroplasmin and \(\alpha\)-2-macroglobulin, which contribute to the inactivation of reactive oxygen species and cytokines. This limits endotoxin and TNF-\(\alpha\)-induced hepatic injury. Glucose metabolism is significantly altered. The initial up-regulation of gluconeogenesis is impaired by the inhibition of the rate-limiting enzyme phosphoenolpyruvate carboxykinase by endotoxin. \(^{53}\) In rats with peritonitis this has been shown to lead to hypoglycaemia which is frequently observed in severe hepatic dysfunction in ICU patients. One of the major functions of the hepatocyte is biotransformation, which is found to be impaired during sepsis \(^{54,55}\), leading to a reduced activity of cytochrome P450s. Together with a reduced hepatobiliary transport rate and bile flow \(^{56}\), this results in the impaired elimination of endobiotic and xenobiotic compounds. Reduced hepatobiliary transport in the ICU patient is shown clinically by an increase in bilirubin concentration; this can be observed even in the absence of marked elevations in levels of aminotransferase. The cellular and molecular changes occurring in the hepatocyte during septic shock are reflected in the elevation of mitochondrial (AST), cytoplasmic (ALT) or bile-duct (AP, \(\gamma\)GT)-expressed enzymes, by the reduction in detoxification and transport activity (bilirubin), cell death (LDH), or alterations in key metabolic pathways (serum glucose, lactate).
Endothelial cells

The fenestrated endothelial cells of the hepatic sinusoids are not attached to a basal lamina. They are highly endocytotic and can produce thromboxane and prostaglandins in addition to the spontaneous production of IL-1 and IL-6, which is increased during exposure to endotoxin. Endothelial cells can therefore contribute to the pro-inflammatory actions, although the elaboration of small amounts of nitric oxide has also been shown. Nitric oxide may promote systemic antimicrobial activity by inhibiting leukocyte adhesion to hepatic endothelial cells and by reducing superoxide anions. The increased expression of vascular adhesion molecule-1, E-selectin, P-selectin and intracellular adhesion molecule-1 leads to the extravasation of neutrophils. This process plays a major role in the protection against infection. However, this neutrophil adhesion and activation can also drive hepatic injury. Experimental evidence suggests that TNF-α-mediated multi-organ damage can be attenuated by neutrophil depletion, suggesting that neutrophils may be one of the main effectors of hepatic injury in (septic) shock.

PRO-COAGULATION ACTIVITY

One of the most frequent features of shock is an increase in pro-coagulant activity. In septic shock the acute-phase response leads to considerable changes in the balance of coagulation factors (Table 2). The increase in α1-antitrypsin and α2-macroglobulin inhibits protein C. C4-binding protein is increased, lowering the levels of free protein S. In addition, the synthesis of antithrombin is decreased, tissue factor expression is increased, and hepatic production of thrombin-activatable fibrinolytic inhibitor enhancing fibrinolysis is increased. The up-regulation of acute-phase proteins therefore inhibits the protein C pathway and leads to increased binding of protein S, moving the balance towards coagulation. Low-level synthesis of antithrombin also contributes to pro-coagulatory activity and is associated with a higher rate of fatal outcome of hepatic injury. The alterations of coagulation are an indicator of the complex mechanisms observed during the syndrome of shock liver and reflect the considerable alterations in hepatocyte biosynthesis.

CLINICAL IMPLICATIONS

Based on the haemodynamic, cellular, immunological and molecular mechanisms described, as well as the laboratory features in critically ill patients, hepatic dysfunction can be divided into a rapid primary liver dysfunction and a late-onset secondary liver dysfunction. The rapid primary dysfunction is typically the result of an acute episode of shock, haemorrhage, resuscitation, low-output septic shock or surgery in which reduced perfusion is the initiating event. In this situation lactate clearance, gluconeogenesis, glycogenolysis and protein synthesis are reduced, and high levels of hepatic enzymes occur in the serum. Usually, the situation normalizes within a few days after the event. A late-onset form of hepatic injury is usually present, secondarily to septic episodes, in which most of the liver functions are retained and a multitude of inflammatory processes initiated by Kupffer cell function lead to local tissue inflammation and an attenuated, and often lower, elevation of serum liver enzymes or of serum bilirubin levels. This form of shock liver is frequently missed in clinical
routine. It is further complicated by the fact that medical treatment strategies—including mechanical ventilation, total parenteral nutrition, administration of drugs such as catecholamines—contribute to hepatic injury under these aggravating circumstances. Because hepatic injury influences mortality rates\(^1\)–\(^4\),\(^6\), the timely awareness of hepatic injury is clinically important (Figure 1).

### Table 3. Role of hepatic cellular subpopulations for the critically ill patient.

<table>
<thead>
<tr>
<th>Type of cell</th>
<th>Partial function</th>
<th>Role for the ICU patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatocyte</strong></td>
<td>Acute-phase proteins: C-reactive protein: (\alpha_1)-antitrypsin, (\alpha_2)-macroglobulin, coeruleoplasmin</td>
<td>Reduction of oxidative damage, attenuation of IRS</td>
</tr>
<tr>
<td></td>
<td>Glycogen cycle enzymes</td>
<td>Lactate metabolism</td>
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<td></td>
<td>Glycolysis</td>
<td>Acid–base balance</td>
</tr>
<tr>
<td></td>
<td>Gluconeogenesis</td>
<td>Glucose metabolism</td>
</tr>
<tr>
<td></td>
<td>Phase I biotransformation (cytochromes P450), biliary transport and bile flow</td>
<td>Reduced biotransformation, reduced detoxification and elimination, drug toxicities</td>
</tr>
<tr>
<td></td>
<td>C4-binding protein elevation, reduced antithrombin, inhibition of protein C by</td>
<td>Pro-coagulatory activity, microcirculation altered</td>
</tr>
<tr>
<td></td>
<td>(\alpha_1)-antitrypsin and (\alpha_2)-macroglobulin</td>
<td></td>
</tr>
<tr>
<td><strong>Kupffer cell</strong></td>
<td>Bacterial clearance</td>
<td>Reduction of IRS</td>
</tr>
<tr>
<td></td>
<td>Endotoxin clearance</td>
<td>Contribution to immunocompetence</td>
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<td></td>
<td>Cytokine and mediator clearance</td>
<td></td>
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<tr>
<td></td>
<td>Tumour necrosis factor-(\alpha)</td>
<td>Main mediator of hepatocellular injury</td>
</tr>
<tr>
<td></td>
<td>Pro-inflammatory cytokines (see Fig. 2)</td>
<td>Increased hepatic injury, increase of IRS, attraction of neutrophils</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory cytokines (see Fig. 2)</td>
<td>Attenuation of hepatic injury</td>
</tr>
<tr>
<td><strong>Endothelial cell</strong></td>
<td>Endocytosis</td>
<td>Clearance function</td>
</tr>
<tr>
<td></td>
<td>IL-1, IL-6, prostanoids, thromboxane</td>
<td>Pro-inflammatory action</td>
</tr>
<tr>
<td></td>
<td>Vascular cellular adhesion molecule I, E selectin, P selectin, intracellular</td>
<td>Attraction of neutrophils, oxidative damage, alteration of microcirculation</td>
</tr>
<tr>
<td></td>
<td>adhesion molecule I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nitric oxide</td>
<td>(?) prevention of neutrophil adhesion, (?) increased systemic antimicrobial activity of neutrophils</td>
</tr>
<tr>
<td><strong>Neutrophil</strong></td>
<td>Adhesion, extravasation, antimicrobial activity</td>
<td>Oxidative tissue damage, promotion of IRS</td>
</tr>
</tbody>
</table>
TREATMENT OF SHOCK LIVER

Hepatic injury due to shock is the consequence of a multitude of mechanisms which include haemorrhage, major surgery, respiratory failure, repeated infection or shock, the persistent failure of microcirculation, the overactivation of systemic inflammatory responses and also an unwanted side-effect of the intensive-care treatment strategy. The awareness of situations predisposing to severe hepatic injury is crucial for the prevention of mortality associated with hepatic dysfunction. Therapeutic efforts are therefore aimed at a timely elimination of the precipitating events leading to shock liver. This involves the stabilization of circulation parameters and cardiac output, the control of infection, the conscientious monitoring of mechanical ventilation as well as of the administration of catecholamines, in addition to metabolic monitoring to prevent hypoglycaemia and lactic acidosis. In future, detailed knowledge of the mechanisms underlying hepatic injury during shock (Table 3) may lead to the possibility of modulating the functions of neutrophils or Kupffer cells in order to establish a causative treatment strategy for this generally underdiagnosed condition in critically ill patients.

Practice points

- shock liver can be the consequence of haemorrhage, trauma, major surgery, hypodynamic septic shock, hyperdynamic septic shock, and persistent failure of the microcirculation for any reason. In critically ill patients it is present in about 50% of all patients to varying degrees
- in septic shock the liver (i) clears bacterial products and endotoxin, and, via Kupffer cells, (ii) produces significant amounts of inflammatory mediators. Therefore, the liver is (i) an orchestrator of disease, which can lead to an overwhelming inflammatory response syndrome, and (ii) a victim of extrahepatic circumstances of disease
- even mild elevations of the liver enzymes AST, ALT, γGT and AP, and bilirubin, as well as altered values of prothrombin time in the absence of aminotransferase abnormalities, indicate hepatic injury in critically ill patients. Hepatic injury influences overall mortality
- shock liver can occur, and lead to biochemical abnormalities, following an interval of several days to over a week
- shock liver secondary to septic shock—either as an overwhelming infection or as repeated septic episodes—usually leads to a mild elevation of serum liver enzymes with a disproportionate elevation in serum bilirubin levels. In septic patients the hepatic artery buffer response is not effective in maintaining adequate hepatic blood flow, so that careful monitoring of circulation parameters is required
- shock liver can be the consequence of, or aggravated by, medical treatment modalities, in particular mechanical ventilation, leading to alterations in hepatic blood flow, the administration of drugs, such as catecholamines, and total intravenous nutrition
- the treatment of shock liver implies the optimization of circulation and infection parameters, of glucose and acid–base homeostasis, and the cautious monitoring of medical treatment modalities
Research agenda

Although a wealth of animal experimental studies have been published, key mechanisms in shock liver remain enigmatic:

- the actuarial haemodynamics during shock liver in humans are difficult to assess in the absence of portal venous blood analyses. This would elucidate differences in hepatic blood supply in shock liver of different aetiologies such as in sepsis, haemorrhage, mechanical ventilation, and after surgery, etc.
- Kupffer cell and neutrophil-mediated oxygen radical injury is at the centre of the mechanisms leading to shock liver. TNF-α has been identified as a major mediator of hepatic injury. Future research will be required to identify strategies able to influence TNF-α activity as well as the inflammatory mediator profile required to lead to hepatotoxicity. In this way, causal treatment strategies for shock liver can emerge
- the diversity of biochemical abnormality, ranging from profiles found in hepatitis to those of subclinical cholestasis, indicates that parameters for the diagnosis of shock liver are insufficient. Classical enzymes only partially reflect the events and mechanisms influencing macrocirculation of the liver, microcirculation and cross-talk between Kupffer cells, hepatocytes and endothelial cells. The development of surrogate markers for the diagnosis and staging of shock liver is an important research goal

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