J Anesth (2013) 27:447–460
DOI 10.1007/s00540-012-1543-y

REVIEW ARTICLE

Resuscitation after hemorrhagic shock: the effect on the liver—a review of experimental data

Iosifina I. Karmaniolou · Kassiani A. Theodoraki · Nikolaos F. Orfanos · Georgia G. Kostopanagiotou · Vasileios E. Smyrniotis · Anastasios I. Mylonas · Nikolaos F. Arkadopoulos

Received: 15 October 2012 / Accepted: 5 December 2012 / Published online: 29 December 2012
© Japanese Society of Anesthesiologists 2012

Abstract The liver is currently considered to be one of the first organs to be subjected to the hypoxic insult inflicted by hemorrhagic shock. The oxidative injury caused by resuscitation also targets the liver and can lead to malfunction and the eventual failure of this organ. Each of the various fluids, vasoactive drugs, and pharmacologic substances used for resuscitation has its own distinct effect(s) on the liver, and the anesthetic agents used during surgical resuscitation also have an impact on hepatocytes. The aim of our study was to identify the specific effect of these substances on the liver. To this end, we conducted a literature search of MEDLINE for all types of articles published in English, with a focus on articles published in the last 12 years. Our search terms were "hemorrhagic shock," "liver," "resuscitation," "vasopressors," and "anesthesia." Experimental studies form the majority of articles found in bibliographic databases. The effect of a specific resuscitation agent on the liver is assessed mainly by measuring apoptotic pathway regulators and inflammation-induced indicators. Apart from a wide range of pharmacological substances, modifications of Ringer's Lactate, colloids, and pyruvate provide protection to the liver after hemorrhage and resuscitation. In this setting, it is of paramount importance that the treating physician recognize those agents that may attenuate liver injury and avoid using those which inflict additional damage.

Keywords Hemorrhagic shock · Liver · Resuscitation · Vasopressors · Anesthesia

I. I. Karmaniolou · G. G. Kostopanagiotou
2nd Department of Anesthesiology, Attikon Hospital–University of Athens Medical School, 1 Rimini Str, 12410 Chaidari, Greece

I. I. Karmaniolou (✉)
8 Lyndhurst Gardens, NW3 5NR London, UK
e-mail: zozefina_k@hotmail.com

K. A. Theodoraki
1st Department of Anesthesiology, Aretaieion Hospital–University of Athens Medical School, 76 Vasilisis Sofias Avenue, 11528 Athens, Greece

N. F. Orfanos · V. E. Smyrniotis · A. I. Mylonas · N. F. Arkadopoulos
4th Department of Surgery, Attikon Hospital–University of Athens Medical School, 1 Rimini Str, 12410 Chaidari, Greece

Introduction

Hemorrhagic shock (HS) is the major cause of death in trauma patients [1]. In addition, even among patients who initially survive HS, a percentage will subsequently die of multiple organ failure mainly due to ischemia/reperfusion injury [2]. The liver is among the organs most frequently affected by shock [3]. It has been reported that 20 % of patients in hypovolemic shock will exhibit some degree of liver dysfunction and that the morbidity related to inflammation-induced liver dysfunction is by no means negligible [2, 3]. Proper hepatic failure, as assessed by bilirubin levels, is certainly less common, but again not insignificant. As many as 5 % of patients who survive 24 h after hemorrhagic shock may ultimately suffer from hepatic failure, although in the majority of cases the condition is reversible [3].

Fluid resuscitation is the mainstay of the management of hemorrhagic shock. The amount and type of fluid is of particular importance, as is the timing of resuscitation. Although early resuscitation with aggressive fluid administration restores central hemodynamics, this treatment may cause further bleeding through elevation of the blood pressure and dislodgment of blood clots. In this setting,

different pharmacologic strategies can also be helpful. Late resuscitation, on the other hand, may cause or aggravate ischemia–reperfusion injury that particularly affects the liver.

The aim of this article is to review the impact of different resuscitation strategies on the liver, including different types of fluids and pharmacological agents. Two of the authors conducted a systematic literature search of MEDLINE using the terms "hemorrhagic shock," "liver," "resuscitation," "vasopressors," and "anesthesia." A manual review of references from each pertinent article was also carried out in order to identify additional related articles. Articles in languages other than English and editorials, letters, and case reports were excluded from the review. We mainly included studies published between 2000 and May 2012, although articles published before 2000 were included if they contained an important pathophysiologic mechanism. When studies were identified that involved the same substances and similar results, we included the most recent one in the review. Experimental studies were all included since they constituted the greatest source of information in the field.

Pathophysiology of liver dysfunction during hemorrhagic shock

Hemorrhagic shock-induced hepatic injury has two main components (Fig. 1). The primary injury takes place in the early phase of shock and is due to hypovolemia and subsequent ischemia, while the secondary injury is attributed to the reperfusion phase [2]. More specifically, massive blood loss leads to reduced oxygen delivery, mainly because of hemoglobin reduction, which is the principal determinant of the oxygen content of blood. Moreover, peripheral vasoconstriction also contributes to ischemia. At the cellular level, ischemia often results in membrane damage, loss of homeostasis ability, and hepatocyte necrosis. Conversely, apoptotic cell death occurs mainly during the restoration of the circulation and oxygen supply, as apoptosis is a process that depends on oxidative metabolism [4]. As a result, apoptosis is more associated with the reperfusion phase rather than the ischemic period. However, it is possible that signals resulting from ischemia initially share common pathways and finally culminate in either necrosis or apoptosis depending on the degree of resuscitation and the particular position of the hepatocyte within the acinus [5]. Thus, the distinction between the two components is not always that clear as they may coexist.

Liver dysfunction following HS and resuscitation is therefore a combination of ischemia and reperfusion injury. The extent of ischemia is determined by the duration and the depth of the shock, which also influences the degree of reperfusion injury. Depletion of cellular ATP due to ischemia results in the induction of inflammatory pathways and ultimately to necrosis. Specifically, hypoperfusion causes neutrophil adhesion and infiltration, activation of Kupffer cells, endothelial and hepatocyte damage, and

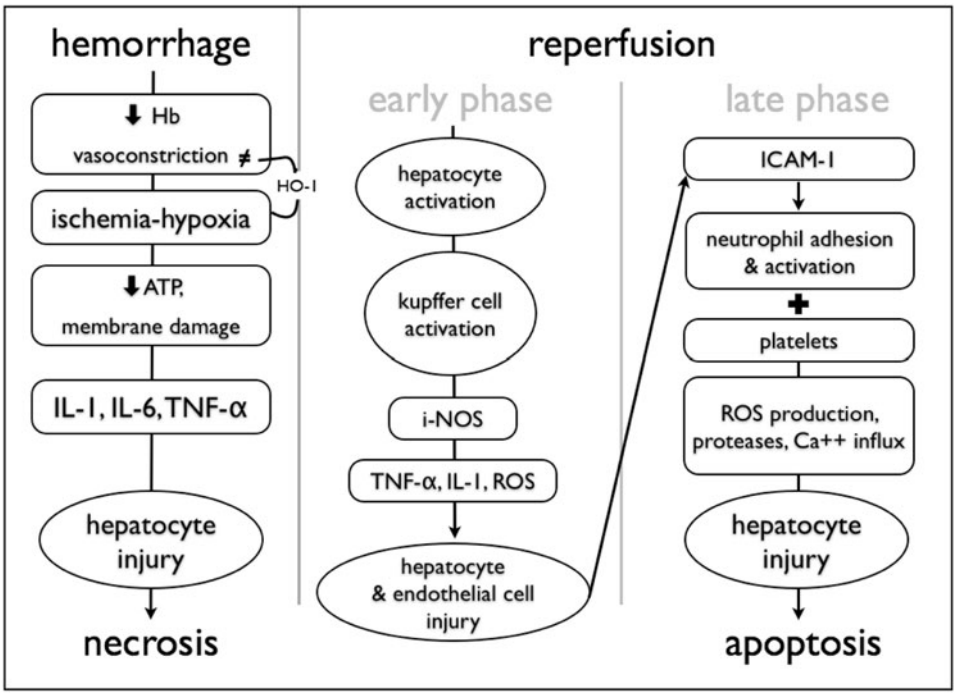

Fig. 1 Illustration of the pathophysiologic mechanisms that mediate hepatic damage after hemorrhagic shock and resuscitation. *Hb* Hemoglobin, *HO-I* heme-oxygenase-I, *IL* interleukin, *TNF* tumor necrosis factor, *I-NOS* inducible form of nitric oxide synthase, *ROS* reactive oxygen species, *ICAM* inter-cellular adhesion molecule-I

release of proinflammatory cytokines. Microcirculatory dysfunction within the liver, biliary stasis, and subsequent fibrosis also occur [6]. Inter-cellular adhesion molecule 1 (ICAM-1), which is expressed on endothelial cells, plays an important role in neutrophil adhesion and is found to be up regulated in hepatocytes in HS [7]. The degree of systemic inflammation depends on the balance between production of proinflammatory cytokines [interleukin (IL)-1, -6; tumor necrosis factor-alpha (TNF-α)] and anti-inflammatory ones (IL-4, IL-10), with the gut and liver being the major sites of cytokine production in this setting.

TNF-α contributes to hemodynamic instability and organ damage [8]. Increased production of vasoconstrictors and the increased sensitivity of the hepatic vasculature to endothelin may further compromise liver perfusion [9]. As a consequence, despite fluid resuscitation, the liver may still exhibit signs of hypoperfusion [10]. Interestingly, hypovolemic shock results in the induction of heme oxygenase 1 (HO-1), an enzyme that degrades heme to biliverdin, iron, and carbon monoxide (CO). As CO acts as a vasodilator on the hepatic vessels, the induction of HO-1 in HS has a protective effect in the liver [11, 12]. Hence, substances that act through induction of HO-1 seem to play a protective role in HS.

Hepatic injury can be accentuated during the reperfusion phase that occurs with volume replacement. Despite intravascular fluid restoration, liver vasoconstriction and subsequent hypoperfusion may persist together with tissue fluid sequestration. In this phase, the production of reactive oxygen species (ROS) further compromises liver function. The production and release of free radicals is partially attributable to the inducible form of nitric oxide synthase (iNOS) in the liver, which is upregulated in HS [13]. The influx of Ca^{2+} due to acidosis or its accentuated release from intracellular sites during reperfusion plays a major role in death after ischemia/reperfusion [14]. Finally, there is a growing body of evidence that platelets have a proinflammatory role in HS by interacting directly with leucocytes or by augmenting leukocyte function through direct interaction and subsequent release or surface expression of substances such as arachidonic acid and CD40 ligand that augment reperfusion injury [15]. More specifically, hepatic reperfusion injury can be distinguished as two different phases. The early reperfusion phase consists of the first 2 h of reperfusion and is mainly characterized by the activation of Kupffer cells, which causes the formation of ROS and cytokines, culminating in damage to both endothelial cells and hepatocytes [16]. This early period of reperfusion injury provides the basis for the subsequent late reperfusion phase, which mainly consists of neutrophil activation and the additional release of ROS as described above [17].

In this setting, the regulation of the inflammatory response through the type and amount of fluids administered for resuscitation and the pharmacologic strategies used are of paramount importance.

Impact of resuscitation fluids on the liver

Crystalloids

Resuscitation with crystalloid fluids has been the treatment of choice for HS for more than half a century. The most commonly used crystalloids are the lactated Ringer's solution (LR) and the normal saline (NS) (see Table 1 for abbreviations). Both of these have been studied thoroughly with regard to their hemodynamic properties, their effect on coagulation and acid–base homeostasis, their transition from the intravascular to the extracellular and intracellular space, and their effects on lungs and kidneys, whereas a relative paucity of information exists regarding their effects on the liver (Table 2).

The exact composition of the crystalloid fluid seems to play a pivotal role in regulating hepatic apoptosis. Racemic LR solution, which contains both the D- and L-isomers of lactate, is the crystalloid most widely used in the clinical setting. However, modifications of the classic LR have also been studied. These include bicarbonate Ringer's (BR), ketone Ringer's (KR), pyruvate Ringer's (PR), and L-lactated Ringer's (L-LR) which contains only the L-isomer of lactate. Conventional LR has been proven to possess hepatotoxic properties in animal models [18, 19]. In fact, in a short-term model, Ayuste et al. [19] found that the degree of liver apoptosis with LR, as measured both by nuclear DNA fragmentation and morphological parameters, was more accentuated in animals resuscitated with LR than in those not resuscitated at all. As there is no high incidence of complications in the clinical use of LR, these authors

Table 1 Abbreviated terms for crystalloid fluids

Abbreviation	Crystalloid fluids
BR	Bicarbonate Ringer's
HES	Hydroxyethyl starch
HSD	Hypertonic saline dextran
HSP	Hypertonic sodium pyruvate
HTS	Hypertonic saline 7.5 %
KR	Ketone Ringer's
L-LR	L-Lactate stereoisomer Ringer's
LR	Lactated Ringer's solution
NS	Normal saline solution
PR	Pyruvate Ringer's
REP	Ringer's ethyl pyruvate
β-HOB	β-Hydroxybutyrate

Table 2 Studies of resuscitation fluids

First author of published studies	Animal model	Shock depth/duration	Fluids compared[a]	Enzyme leakage	Inflammation	Oxidative stress	Apoptosis/ necrosis	Other results
Tawadrous [28]	Rat	40 mmHg/150 min	REP			↓		
Yang [92]	Mice	30 mmHg/120 min	REP		↓	↓		↑ Survival at 24 h
Shah [50]	Rat	33–36 ml/kg/150 min	LR fast rate	↑				↓ Survival at 72 h
			LR medium rate	↓				↑ MAP
			LR slow rate	↓↓				↑ MAP
Knudson [43]	Swine	40 mmHg/40 min	LR					
			HSD					
			HBOC-201			↓		↑ MAP
Shires [21]	Rat	40 mmHg/40 min	Plasma				↑↑↑↑	
			HTS				↑↑↑	
			NS				↑↑	
			LR				↑	
			BR				↓	
			KR				↓↓	
Sharma [29]	Rat	40 mmHg/60 min	HTS					
			β-HOB					
			HSP	↓		↓		↑ Mitochondrial resp
Mulier [24]	Swine	47–55 mmHg 90 min	LR			ND		ND mitochondrial respiration
			REP					
Hoppen [36]	Rat	45 mmHg/60 min	LR					
			HTS	↓↓				↑ Secretory function
Jaskille [18]	Rat	40 % total blood volume/ 75 min	DL-LR				↑	
			L-LR				↓	↑ Mitochondrial resp
			KR				↓	↑ Mitochondrial resp
			PR				↓↓	
Ayuste [19]	Swine	40 % total blood volume/ 30 min	NS	↓↓	↓↓		↓↓	
			LR	↑	↑↑↑		↑↑	
			L-LR	↑↑↑	↑↑		↓↓↓	
			KR	↓	↓		↓	
			HES	↑↑	↑		↑	
Johnson [44]	Swine	40 or 55 % total blood volume/ 20 min + uncontrolled HS group/15 min	HBOC-201		↑ Cholangiohepatitis			↑ Survival at 72 h in severe shock
			HES					
Tsai [33]	Rat	30–40 mmHg/60 min	Whole blood					
			L-LR					
			HES			↓	↓↓	↑ Survival
Deree [37]	Rat	35 mmHg/60 min	LR					
			HSPTX	↓	↓	↓↓	↓↓	↑ Survival

Table 2 continued

First author of published studies	Animal model	Shock depth/duration	Fluids compared[a]	Enzyme leakage	Inflammation	Oxidative stress	Apoptosis/ necrosis	Other results
Cai [31]	Rat	35–40 mmHg/30 min	HES					
			HES + ethyl pyruvate		↓		↓	↑ Survival
Sharma [30]	Rat	40 mmHg/60 min	HTS					
			LR					
			REP	↓	↓	↓	↓	↑ Mitochondrial resp
			HSP	↓↓	↓↓	↓↓	↓↓	↑↑ Mitochondrial resp

ND No difference, *HS* hemorrhagic shock, *MAP* mean arterial pressure

[a] *DL-LR or LR* D- and L-stereoisomer lactated Ringer's, *HSPTX* hypertonic saline 7.5 % with pentoxifylline, *HBOC-201* hemoglobin-based oxygen carrier; for other abbreviations, see Table 1

postulated that the adverse effects were probably dose-dependent. In agreement with this proposal, various other fluids, namely, NS, L-LR, KR, and hetastarch, were found to be superior to LR in terms of anti-apoptotic effects on hepatic tissue, even though lactate/pyruvate ratios in the liver, reflecting metabolic activity, did not exhibit statistically significant differences between groups. This latter finding is not necessarily conflicting as tissue ATP levels do not always reflect the degree of apoptosis. A similar study comparing LR, L-LR, KR, and PR yielded comparable results: the use of racemic LR increased the number of apoptotic cells, reduced the expression of antiapoptotic protein bcl-2, and reduced the hepatic ATP reserve [18]. When lactate was substituted with β-hydroxybutyrate (β-HOB) or pyruvate, forming KR and PR, respectively, apoptosis was further decreased. L-LR and KR improved hepatocellular ATP levels while PR and LR failed to replenish ATP reserve. Overall, modifications of LR would appear to exert protective effects on hepatic tissue during resuscitation.

Compared to NS, resuscitation with LR requires less volume and is associated with less dilutional coagulopathy and increased survival in swine [20]. Shires et al. compared the apoptotic effect of NS, LR, hypertonic saline 7.5 % (HTS), plasma, BR, and KR and concluded that BR and KR induced the lowest apoptosis among all solutions studied [21]. Unexpectedly, liver apoptosis in the LR group was lower than that in the HTS group which is not in agreement with the effect in other tissues studied [22, 23]; the authors postulated the cause to be a technical error. The novel BR used in this experiment is believed to decrease apoptosis by balancing the membrane potentials and decreasing overall cellular destruction.

Pyruvate-containing solutions

Special attention should be given to pyruvate, as several studies have proved its value as either an additive in balanced salt resuscitation solutions or as an independent agent. In particular, pyruvate, an intermediate molecule in glucose metabolism, serves as a potent antioxidant and ROS scavenger [24], and its antioxidant action has been substantiated in hepatocellular cultures [25]. Unfortunately, it has a very poor stability in aqueous solutions where it forms 2,4-dihydroxy-2-methylglutarate, a substance that is poisonous to mitochondria; consequently, its clinical use has not gained popularity [26]. In an attempt to overcome this toxicity problem, Sims et al. [27] used a derivative of pyruvate, ethyl pyruvate, in a calcium + potassium-containing balanced salt solution, i.e., Ringer's ethyl pyruvate (REP). Shortly thereafter, Tawadrous et al. [28] confirmed the positive effect of REP in reducing the oxidative stress for hepatocytes as compared to conventional LR. Compared to hypertonic saline and hypertonic β-HOB, hypertonic sodium pyruvate has a protective effect on the liver by lowering alanine transaminase (ALT), aspartate transaminase (AST), and iNOS levels and by improving mitochondrial respiration [29]. This protective effect has been attributed to the excellent antioxidant action of pyruvate [29]. The same investigators also compared the infusion of low-volume hypertonic sodium pyruvate (HSP) with REP, HTS, NS, and LR. HSP was found to possess better metabolic, antioxidant, and antiapoptotic properties than REP and the other fluids used. However the anti-inflammatory effects HSP and REP were comparable, as shown by their reduction of TNF-α and IL-6 levels in the liver and serum. HSP is likely to be a better resuscitation medium than REP

as it mitigates elevations in ALT, AST, caspase-3 activity, a marker of apoptotic cell death, and malondialdehyde (MDA) levels in addition to increasing ATP levels in hepatocyte mitochondria [30]. MDA is a product of lipid peroxidation, and increases in its level imply impairment of normal mitochondrial membrane structure; consequently, it is used as a marker of oxidative stress. Cai et al. [31] have supplemented 6 % hydroxyethyl starch with 50 mM ethyl pyruvate and compared it to plain starch in awake hemorrhage. Although both solutions attenuated the elevation of liver TNF-α, starch with ethyl pyruvate additionally prevented high serum TNF-α levels. On the contrary, a study on liver tissue energetics and tissue perfusion, assessed by nuclear magnetic spectroscopy and near-infrared reflectance spectroscopy, did not confirm a superiority of REP over LR [24]. However, this is not in conflict with the concept that pyruvate acts mainly through its antioxidant capacity and not through its energetic properties.

Low-volume resuscitation

The classic resuscitation strategy with high-volume crystalloids has recently been brought into question. Hypertonic crystalloids and colloids, or a combination of the two, have gained attention due to certain improved attributes, i.e., they are more effective in expanding the plasma volume, restoring hemodynamic parameters, and improving microcirculation [32]. A study comparing hydroxyethyl starch (HES) with blood and LR in a resuscitation model of hemorrhaged rats demonstrated that both shed blood and that HES reversed the NF-κB-mediated inflammatory process caused by HS when low volumes were infused [33]. Based on their measurements of glutathione, a molecule that is pivotal in the cellular defense against oxidative stress, these authors concluded that HES did cause oxidative stress for hepatocytes [33]. Both colloids and hypertonic fluids have also been studied in combination with adjunctive substances with the aim of improving resuscitation results. For example, Wu et al. [34] used a murine model to study the effects of a Na^+/H^+ exchanger inhibitor (BIIB513) in combination with low-volume resuscitation with HES (15 ml kg^{-1}). These authors reported that Na^+/H^+ exchanger activation resulted in intracellular Na^+ and Ca^{2+} overload, thus contributing to cell death. Hetastarch alone improved hemodynamic parameters, but failed to restore plasma TNF-α, ICAM-1, AST, ALT, and myeloperoxidase (MPO) activity in the liver, while the addition of the inhibitor further raised mean arterial pressure (MAP) towards baseline and also attenuated the inflammatory response [34].

HTS, which is known to possess an anti-inflammatory action by suppressing neutrophils [35], has also been investigated as a low-volume resuscitation strategy. Hoppen et al. [36] found that HTS reduced ALT and total bilirubin levels and increased bile flow. Its hepato-protective effect was attributed to improved microvascular perfusion due to low-volume resuscitation. Compared with LR, the co-administration of HTS and pentoxifylline attenuates histologically proven liver injury and elevates transaminases, i-NOS, and pro-inflammatory cytokines [37].

The combination of colloid and hypertonic solutions seems to further improve outcome. In two consecutive animal experiments, Corso et al. [38, 39] concluded that hypertonic saline dextran (HSD) improved hepatic microvascular perfusion by roughly 4 % more than dextrane alone and by 6 % more than LR; this improvement was statistically significant, although it might be relatively small to be biologically important. The arterial ketone body ratio and bile flow were also measured as an index of the functional reserve of the liver, and both were found to be improved with the use of HSD. In the second experiment, leukocyte adherence and stagnation in hepatic sinusoids and venules were studied, and both were found to be reduced in the dextran group and further minimized in the HSD group [38, 39].

An older study comparing recombinant human serum albumin, plasma-derived 5 % albumin, and LR found no differences in hepatic energy metabolism or blood pyruvate and lactate levels between the three treatment groups [40]. In another study, a laboratory-constructed conjugate of human albumin with bovine hemoglobin conferred 100 % survival rate (same as whole blood) and better liver histology compared to LR, 5 % human albumin in LR, and stroma free hemoglobin [41].

Lastly, plasma resuscitation, especially lyophilized plasma, reduces inflammation markers in blood, but studies focusing specifically on hepatic tissue are lacking [42].

Hemoglobin-based solutions

Hemoglobin-based oxygen-carrying (HBOC) solutions constitute another relatively novel resuscitation strategy currently under investigation. Knudson et al. [43] compared HBOC-201 to conventional LR and HTS dextran in a swine HS model. Although HBOC-201 was the most effective fluid in restoring MAP to baseline levels, liver PO_2 was lower with HBOC-201 than with the other fluids test, although the difference did not reach statistical significance [43]. While HBOC-201 seems to favor overall survival in severe uncontrolled HS, it has been associated with hepatobiliary hyperplasia, cholestasis, and neutrophilic cholangiohepatitis. Furthermore, AST and alkaline phosphatase are higher with HBOC treatment than with 6 % hetastarch in LR [44]. Interestingly, these manifestations

were more obvious when HS was moderate, but with increasing severity of the HS, the difference between HBOC and hetastarch-LR resuscitated swine was less pronounced [44]. York et al. [45] also reported elevation of liver enzymes when resuscitating swine with HBOC-201 in comparison to LR or blood. HBOC-201 hepatotoxicity has been well documented [46] and constitutes a problem, especially for patients with pre-existing liver diseases.

Hypotensive resuscitation

A resuscitation practice that has gained attention in recent years is the so-called "controlled" or "hypotensive" or "slow" resuscitation. This concept is in conflict with the current trauma resuscitation approach that recommends rapid volume resuscitation in order to restore arterial blood pressure to normal values [47]. However, slow—as opposed to aggressive—resuscitation would allow compensatory hemostatic mechanisms to work and would minimize the risk of clot dislocation, hemodilution, loss of platelets, and coagulant factors while restoring some intravascular volume. On the other hand, a great delay in providing adequate resuscitation could aggravate ischemia/reperfusion injury and decrease survival. Li et al. [48] studied and compared different target MAPs and different durations of permissive hypotension in a rat model of liver injury. Resuscitation was achieved with whole blood and LR at a ratio of 1:2. According to their findings, the ideal resuscitation MAP seems to be 50–60 mmHg, as a MAP of >80 mmHg or <40 mmHg augments hepatic damage, worsens mitochondrial function, and reduces survival rates. However, this "permissive hypotension" should not exceed 90 min in duration because severe liver damage can occur after this critical point.

Similarly, in another study in rats resuscitated with NS, apoptosis in the liver was more pronounced when the target MAP was 80 mmHg compared to 40 mmHg. Higher blood pressure was also associated with increased blood loss [49]. The detrimental effects of rapid LR resuscitation had already been confirmed by Shah et al. [50] in terms of both survival and hepatic dysfunction measured by plasma ornithine carbamoyltransferase. On the contrary, Talving et al. [51] found a comparable survival at 100 min in swine resuscitated with HTS dextran when the infusion was delayed either for 20 min or for 40 min after HS. Even though portal vein and hepatic artery blood flow were increased in the delayed resuscitation group, there was no statistically significant effect on mortality.

Direct peritoneal resuscitation

A novel resuscitation strategy, denoted direct peritoneal resuscitation (DPR), has been recently studied as an alternative or in combination to conventional fluid resuscitation. DPR is a process by which the small intestine is exposed to peritoneal dialysis solution during resuscitation from HS. Peritoneal resuscitation initiated at the start of intravenous (i.v.) fluid administration improves effective liver blood flow, as measured by galactose clearance [6]. Additionally, it is associated with minimal or no hepatic injury and normal ALT and AST levels [6]. Another important aspect of DPR is that it prevents the formation of tissue edema caused by conventional resuscitation alone as assessed by dry/wet weight ratios [6, 52, 53]. DPR increases the production of the anti-inflammatory cytokine IL-10 from the liver [52] and reduces the levels of TNF-α and IL-6 in the liver and portal blood. The overall beneficial effect of DPR seems to be attributed to better gut and liver perfusion, which is related to attenuation of the inflammatory cascade following HS and resuscitation. More recently, DPR has also been applied in clinical practice, in trauma patients in particular, with the favorable result of lower intra-abdominal complication rates [54].

Vasoactive substances

Vasoactive substances are also widely used in HS resuscitation. The hepatic artery possesses α_1-adrenergic receptors, which cause vasoconstriction, as well as β_2-adrenergic, dopaminergic (D_1) and cholinergic vasodilating receptors. The portal vein has only α_1-adrenergic and D_1 receptors. Among the vasoactive substances having an effect on the liver, the most thoroughly studied agents are vasopressin, noradrenaline (norepinephrine), and dobutamine.

As previously described, HS causes the hepatocellular induction of HO-1, which contributes to the maintenance of liver blood flow and hepatocellular integrity. Dobutamine preconditioning seems to offer a protective effect through activation of this pathway [55]. Arginine vasopressin (AVP) raises blood pressure by acting on V1 vasoconstricting receptors and seems to be more effective in maintaining MAP in uncontrolled HS than noradrenaline [56]. Concerns have been raised that by diverting blood flow away from the splanchnic bed to the heart and brain, AVP may contribute to gut necrosis, translocation, and subsequent sepsis and death [57]. However, studies have shown only a transient decrease of liver blood flow 2.5 min after AVP administration, with restoration 10 min later, and a significantly higher portal vein blood flow with AVP compared to noradrenaline [58, 59]. Moreover, this effect is attributed, as discussed, to a decrease in portal vein blood flow, while it is important that hepatic artery flow is maintained. Stadlbauer et al. [60] demonstrated that AVP administration (0.4 U/kg) during HS caused by liver

trauma in pigs resulted in less blood loss and increased long-term survival (7 days) compared to fluid resuscitation with LR + plus gelatin, with the disadvantage that organ blood flow was not measured. It has also been confirmed in small animal models that 0.1 U/kg AVP, unlike noradrenaline, increases blood flow in the liver, as measured through a Doppler flowmeter, and ameliorates hepatic mitochondrial function. However, the precise mechanisms need to be investigated. Even though in previous models AVP seemed to be the better choice over noradrenaline when each agent was the only agent administered, in this study these favorable effects seemed to be more accentuated with the combined administration of AVP and noradrenaline [61]. Lastly, angiotensin II release during HS is at least partially responsible for extracellular signal-related kinase (ERK1/2) elevation in the liver. ERK1/2 is a kinase with an established role in stress-signaling; as a result, the modulation of angiotensin II levels through the inhibition of angiotensin converting enzyme may play a protective clinical role by improving perfusion [62]. The greatest limitation of the aforementioned studies is that the impact on long-term survival could not always be estimated. The researchers focused mainly on short-term survival and the effects on liver blood flow without thorough investigation on hepatic cellular function.

Impact of anesthetic agents on the liver during resuscitation

Most trauma patients will require anesthesia for definite surgical control of bleeding. This usually takes place concomitantly or shortly after fluid resuscitation. Various agents used in anesthetic practice have been investigated for their effect on the liver during hemorrhage and resuscitation. In an experimental study in conscious rats, post-shock treatment with low-dose propofol (1 mg/kg/h for 48 h) decreased AST, ALT, lactate dehydrogenase, creatine phosphokinase, TNF-α, and IL-10 levels, while it also attenuated hepatic cell necrosis [63]. Overall, low-dose propofol was associated with increased survival rate. In this same study, high-dose propofol (10 mg/kg/h for 48 h) produced adverse results, possibly due to a greater reduction in blood pressure [63]. In a similar experiment model in hypertensive rats subjected to the withdrawal of 40 % of blood volume, high-dose propofol (10 mg/kg/h) given in continuous infusion for 48 h conveyed greater liver protection than low-dose propofol (1 mg/kg/h), but in contrast the former also increased IL-10 levels [64]. This discrepancy should be addressed in future studies. It has been postulated that the beneficial effect of propofol can be attributed to its anti-inflammatory properties. Combining the results of hypertensive and normotensive animals it could be postulated that the protective effect of propofol is evident as long as hypotension is not accentuated with its use. Limitations such as the absence of temperature monitoring were also highlighted in the above-mentioned studies.

Volatile anesthetics influence hepatic blood flow through their varying effects on the hepatic artery and the portal vein. Halothane is well-known for its hepatotoxicity under certain circumstances. Takahashi et al. compared the effects of isoflurane and halothane on the rat liver during HS at 40 mmHg for 50 min, using these two agents for both the induction and maintenance of anesthesia [65]. Overall, halothane was associated with greater increases in AST, greater intracellular acidosis, and a reduction in ATP content, as assessed by ^{31}P nuclear magnetic resonance spectroscopy. Taken together, these changes suggest an impairment of the oxygen supply to the liver and a possible correlation with hepatocyte damage. The same investigators compared the continuous administration of ketamine and isoflurane. Between the two agents, isoflurane was again superior to ketamine as the decrease in ATP/Pi (inorganic phosphate), reflecting that phosphoenergetic state of hepatic cells was more marked in the ketamine group, with limitations involving the use of spectroscopy in rat liver [64]. Similarly, hepatic necrosis was found in rats anesthetized with ketamine/diazepam and ketamine/xylazine (an α-2 agonist), while it was not present in the animal group anesthetized with isoflurane [67]. In the ketamine/xylazine group distention of Disse spaces was found. On the contrary, a study comparing ketamine and isoflurane mainly focusing on the lung demonstrated lower TNF-α mRNA production in the ketamine group, even though serum IL-6, IL-8, and TNF-α were equal in the two groups [68]. In a pig model of ischemia/reperfusion injury not due to hemorrhagic shock and resuscitation, but caused by portal triad clamping, isoflurane and sevoflurane were found to exert a comparable effect on the liver judged mainly by plasma α-glutathione-*S*-transferase (α-GST) concentration, which is a very sensitive index of liver injury [69]. Emulsified isoflurane preconditioning, a recent formulation of isoflurane mixed with intralipid, was found to confer hepatic protection during HS of 50 % of blood volume loss for 70 min [70], expressed by reduced MDA activity, increased superoxide dismutase (SOD) in liver mitochondria, and by reduced apoptosis in the emulsified isoflurane preconditioned group. SOD is an enzyme, which protects the mitochondria against cytotoxic reactions. However, as in most experimental studies, there was a lack of correlation with the clinical assessment of organ dysfunction.

Various pharmacologic resuscitation strategies

Since HS-related mortality remains quite high, numerous other pharmacologic interventions are currently being

investigated, mainly in animal models, in an effort to improve outcome. Pharmacological resuscitation is usually combined with conventional fluid resuscitation, as no one specific medication alone seems to be capable of supporting the circulation. Pharmacologic resuscitation strategies include the use of either substances currently used in clinical practice for the treatment of conditions other than HS or agents that are being used only experimentally (Table 3). Statins represent an example of the first category. Fluvastatin pre-treatment, administered together with vitamin K and before volume replacement with normal saline, has yielded promising results in rats by diminishing AST and ALT levels and improving the liver injury scores [71]. Simvastatin pretreatment for 6 days before shock induction was found to ameliorate hepatic injury by regulation of the microcirculation via induction of HO-1 and to enhance eNOS expression [72]. Moreover, HO-1 overexpression prevents the interaction of leukocytes with the endothelium, thus reducing the inflammatory response. In this study, resuscitation was achieved with shed blood plus LR [72]. Deferoxamine, a well-studied iron chelator and oxygen-free radical scavenger, improves liver function and blood flow in doses of 100 mg/kg, as assessed by lidocaine metabolism. The protective effect is much more pronounced when combined with starch 15 ml/kg instead of LR [73]. Rosiglitazone, an anti-diabetic agent of the thiazolidinedione class, also displays an anti-inflammatory effect. When given intravenously during shock establishment (before resuscitation with NS) it reduces AST, ALT, and serum TNF-α and IL-6 levels compared to fluid

Table 3 Impact of pharmacological resuscitation strategies on the liver

First author (references)	Species	Substance	Administration timing	Outcome
Rana [73]	Rats	Deferoxamine + starch (7.5 mg/kg)	Post-HS	Improved hepatic metabolism and blood flow
Kuebler [79]	Ovariectomized rats	Progesterone	Post-RS	↓ AST, ALT, ↓ serum TNF-α, IL-6, ↓ MPO
Gundersen [82]	Rats	Hydrocortisone	Post-HS	↓ Serum IL-6, non-significant ↑ IL-10, ↓ TNF-α unaffected leukocyte infiltration, ALT, AST, α-GST
Dhar [85]	Rats	Crocetin	Post-HS	↓ Liver mitochondrial damage (↑ bcl-2, ↓ cytochrome-c) ↓ caspase-3, ↑ ATP, ↑ survival 90 min
Mathes [77]	Rats	Melatonin	Pre-HS	↑ Hepatic perfusion, ↑ redox state, ↓ hepatocellular injury
Liu [91]	Rats	Sirtinol	Post-HS	↓ ALT, ↓ liver (MPO, IL-6, ICAM-1)
Lee [71]	Rats	Fluvastatin + Vit K	Pre-HS	↓ AST, ALT ↓ serum TNF-α, IL-10, ↓ liver injury score
Roesner [84]	Swine	FX06	Post-RS	↓ Serum IL-6, no difference (IL-1b, total hepatic blood flow), ↓ AST, restored tpO_2 ↓ MPO
van den Berg [88]	Rats	Synthetic beta subunit of HCG	Post-HS	↓ serum and liver TNF-α, IL-6, ↓ neutrophil infiltration
Shah [86]	Rats	Adrenomedullin + ABP-1	Post-HS	↓ AST, ALT, ↓ serum TNF-α, ↑ survival on day 1
Huang [87]	Rats	Astringinin	Post-HS	↓ AST, ALT, ↓ MPO, ↓ IL-6, ICAM-1, ↓ hepatic injury
Liu [76]	Rats	Ondansetron	Post-HS	↓ AST, ALT, ↓ MPO, ↓ ICAM-1, ↓ IL-6, TNF-α
Chai [93]	Rats	Hydrogen sulfide	Post-HS	↓ AST, ALT, ↑ survival at 24 h, ↓ serum MDA, ↑ SOD, ↓ MPO
Zaets [83]	Rats	Recombinant factor XIII	Post-RS	↑ Liver microvascular blood flow
Kan [94]	Mice	Flutamide	Post-HS	↓ α-GST, MOP, lipid peroxidation, apoptosis, iNOS
Zuckerbraun [95]	Mice	Carbon monoxide (CO)	Post-HS	↑ Serum IL-10, maintenance of ATP levels in hepatocytes
Schmidt [96]	Rats	Dihydralazine	Post-HS	↓ AST, ALT, ↑ portal + hepatic microvascular blood flow
Yang [97]	Rats	Glutamine	Post-HS	↓ apoptosis, ↑ survival, restoration of hepatic ATP

RS Resuscitation, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TNF-α* tumor necrosis factor-α, *IL* interleukin, *MPO* myeloperoxidase, *α-GST* α-glutathione-*S*-transferase, *bcl-2* B cell lymphoma-2, *ICAM-1* inter-cellular adhesion molecule 1, tpO_2 tissue oxygen pressure, *SOD* superoxide dismutase

resuscitation alone [74]. Ciglitazone, another thiazolidinedione, studied in rats resuscitated with shed blood, reduces liver apoptosis through a peroxisome proliferator-activated receptor-gamma activation pathway, a receptor known to control glucose homeostasis and lipid metabolism [75]. Ondansetron, a well-known 5-HT3 receptor antagonist, attenuates the elevation of transaminases caused by HS when administered i.v. during resuscitation with LR and also reduces hepatic MPO activity and ICAM-1 (thus regulating neutrophil adhesion on the endothelial cells) through a p38 mitogen-activated protein kinase (MAPK) pathway [76]. Melatonin in combination with NS resuscitation has also been found to possess similar anti-inflammatory effects in the liver, lung, and small intestine. Furthermore, pretreatment seems to improve hepatic perfusion and redox state [77, 78]. Gender dimorphism has been identified with reduced hepatocellular damage and improved overall survival of female animals after HS. In this regard, the administration of sex hormones can influence outcome of male animals [79, 80]. As previously described, excessive NO production mitigates hemorrhage-related hepatic damage, so in this regard selective inhibition of the iNOS pathway by various pharmacological agents, either widely used, such as sodium nitroprusside, or not, attenuates liver injury [13, 81]. On the contrary, hydrocortisone does not seem to display a protective effect on hepatic tissue. Although it possesses anti-inflammatory activity, it did not manage to reduce leukocyte infiltration in the liver or reduce AST, ALT, and plasma α-GST levels when administered before resuscitation in rats [82]. Finally, recombinant factor XIII administered in high doses improves hepatic microvascular blood flow in controlled HS, with the limitation that the monitoring period in the study was only 3 h; consequently, the long-terms effects of this factor are still unknown [83].

A significant number of substances used only in experimental animal models have been found to exert a protective effect on the liver when administered as adjuncts to resuscitation. As such, the fibrin-derived peptide $B\beta_{15–42}$ (namely FX06) reduces neutrophil accumulation in the liver, as well as in other tissues, and lowers plasma IL-6 levels at 5 h [84]. Crocetin 2–4 mg/kg restores ATP levels in hepatic cells after HS and decreases caspase-3 activity [85]. Adrenomedullin, a peptide found in endocrine tissues, together with its binding protein, also exerts a beneficial impact on liver resuscitation [86]. Combined with LR fluid resuscitation, it protects the liver through downregulation of proinflammatory cytokines, such as TNF, and concomitant upregulation of anti-inflammatory IL-10, even though the exact mechanisms underlying this regulation have not yet been elucidated. Astringinin, a resveratrol analogue with antioxidant properties [87], and synthetic human chorionic gonadotropin-related peptides also mitigate HS-induced hepatic damage [88]. Resveratrol acts via an estrogen receptor-related pathway [89]. Finally, the potential therapeutic role of histone deacetylase inhibitors, a class of agents involved in DNA transcription regulation, such as valproic acid [90], sirtinol [91], or trichostatin A [90] has also been addressed and yielded promising results.

Treatment options in relation to the phase of shock/resuscitation

The interventions described herein can be applied at different time points. It would be prudent to divide therapeutic management strategies into those that can be applied before or concomitantly with shock induction, those that can be applied before resuscitation, and those which could be helpful even if applied after the conventional resuscitation process. Fluids have only been studied when given after the induction of HS as they constitute the major means of resuscitation. The only decision to be made is on the type and the amount of fluid to be given, as thoroughly discussed above, taking into consideration the beneficial impact of hypotensive or delayed resuscitation. The same post-shock timing applies for DPR and vasoconstricting agents. Most of the anesthetic agents are also administered after the shock for discrete periods of time, with the exception of propofol, which has been studied as infusion for 48 h after shock establishment, and emulsified isoflurane, the only agent so far to be proved useful as preconditioning.

Regarding pharmacological interventions, the division in relation to time of administration is more distinct (Table 3). Substances as fluvastatin and melatonin can be given before shock, while others, such as rosiglitazone, can be administered before conventional resuscitation. Substances such as adrenomedullin can be combined well with fluid resuscitation. It is important to emphasize that some agents can help even when given after classic fluid resuscitation, such as progesterone and recombinant factor VIII.

Unfortunately, there is insufficient clinical data on the issue of hepatoprotective strategies during resuscitation to make recommendations on their use in humans at this time. However, the data currently available from experimental studies could provide a rough guide and more importantly serve as useful material for future research.

Future directions: conclusions

In conclusion, the liver is undoubtedly one of the organs most vulnerable to hemorrhage and subsequent resuscitation. To date, no large-scale clinical trials exist to evaluate the effects of various resuscitation strategies, particularly on the hepatic tissue. In view of the existing, mainly

experimental evidence it would appear that hypertonic solutions and colloids offer some degree of protection in terms of apoptosis when compared to LR. The addition of pyruvate to resuscitating fluids seems to confer greater antiapoptotic properties than conventional fluids alone. In addition, permissive hypotension for a discrete period of time offers further protection.

Apart from fluid resuscitation, various pharmacologic strategies seem to offer promising results. Future studies should focus on cytoprotective pathways associated with heat shock proteins and nitric oxide. Moreover, substances used in similar settings and readily available in clinical practice, such as *N*-acetylcysteine, statins, L-carnitine or various combinations, could also be studied. Overall, even though the results of experimental trials on resuscitation means and strategies provide us with some guidelines with respect to liver protection, more clinical studies will be needed so that these results can be extrapolated to humans and be helpful in clinical practice, especially for patients with pre-existing compromised liver function. Moreover, the exact correlation between apoptosis and organ damage/failure in practice has to be thoroughly addressed.

References

1. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma. 2006;60:S3–11.
2. Heckbert SR, Vedder NB, Hoffman W, Winn RK, Hudson LD, Jurkovich GJ, Copass MK, Harlan JM, Rice CL, Maier RV. Outcome after hemorrhagic shock in trauma patients. J Trauma. 1998;45:545–9.
3. Helling TS. The liver and hemorrhagic shock. J Am Coll Surg. 2005;201:774–83.
4. Leist M, Single B, Castoldi AF, Kuhnle S, Nicotera P. Intracellular adenosine triphosphate (ATP) concentration: a switch in the decision between apoptosis and necrosis. J Exp Med. 1997;185:1481–6.
5. Paxian M, Bauer I, Rensing H, Jaeschke H, Mautes AE, Kolb SA, Wolf B, Stockhausen A, Jeblick S, Bauer M. Recovery of hepatocellular ATP and "pericentral apoptosis" after hemorrhage and resuscitation. FASEB J. 2003;17:993–1002.
6. Hurt RT, Zakaria el R, Matheson PJ, Cobb ME, Parker JR, Garrison RN. Hemorrhage-induced hepatic injury and hypoperfusion can be prevented by direct peritoneal resuscitation. J Gastrointest Surg. 2009;13:587–94.
7. Matsutani T, Kang SC, Miyashita M, Sasajima K, Choudhry MA, Bland KI, Chaudry IH. Liver cytokine production and ICAM-1 expression following bone fracture, tissue trauma, and hemorrhage in middle-aged mice. Am J Physiol Gastrointest Liver Physiol. 2007;292:G268–74.
8. Lee CC, Chang IJ, Yen ZS, Hsu CY, Chen SY, Su CP, Chiang WC, Chen SC, Chen WJ. Delayed fluid resuscitation in hemorrhagic shock induces proinflammatory cytokine response. Ann Emerg Med. 2007;49:37–44.
9. Yokoyama Y, Baveja R, Sonin N, Nakanishi K, Zhang JX, Clemens MG. Altered endothelin receptor subtype expression in hepatic injury after ischemia/reperfusion. Shock. 2000;13:72–8.
10. Krejci V, Hiltebrand L, Banic A, Erni D, Wheatley AM, Sigurdsson GH. Continuous measurements of microcirculatory blood flow in gastrointestinal organs during acute haemorrhage. Br J Anaesth. 2000;84:468–75.
11. Rensing H, Bauer I, Peters I, Wein T, Silomon M, Jaeschke H, Bauer M. Role of reactive oxygen species for hepatocellular injury and heme oxygenase-1 gene expression after hemorrhage and resuscitation. Shock. 1999;12:300–8.
12. Kubulus D, Mathes A, Pradarutti S, Raddatz A, Heiser J, Pavlidis D, Wolf B, Bauer I, Rensing H. Hemin arginate-induced heme oxygenase 1 expression improves liver microcirculation and mediates an anti-inflammatory cytokine response after hemorrhagic shock. Shock. 2008;29:583–90.
13. Kan WH, Hsu JT, Schwacha MG, Choudhry MA, Raju R, Bland KI, Chaudry IH. Selective inhibition of iNOS attenuates trauma-hemorrhage/resuscitation-induced hepatic injury. J Appl Physiol. 2008;105:1076–82.
14. Siesjo BK. Calcium and cell death. Magnesium. 1989;8:223–37.
15. Tweardy DJ, Khoshnevis MR, Yu B, Mastrangelo MA, Hardison EG, Lopez JA. Essential role for platelets in organ injury and inflammation in resuscitated hemorrhagic shock. Shock. 2006;26:386–90.
16. Jaeschke H, Farhood A. Neutrophil and Kupffer cell-induced oxidant stress and ischemia–reperfusion injury in rat liver. Am J Physiol. 1991;260:G355–62.
17. Jaeschke H. Reactive oxygen and mechanisms of inflammatory liver injury. J Gastroenterol Hepatol. 2000;15:718–24.
18. Jaskille A, Koustova E, Rhee P, Britten-Webb J, Chen H, Valeri CR, Kirkpatrick JR, Alam HB. Hepatic apoptosis after hemorrhagic shock in rats can be reduced through modifications of conventional Ringer's solution. J Am Coll Surg. 2006;202:25–35.
19. Ayuste EC, Chen H, Koustova E, Rhee P, Ahuja N, Chen Z, Valeri CR, Spaniolas K, Mehrani T, Alam HB. Hepatic and pulmonary apoptosis after hemorrhagic shock in swine can be reduced through modifications of conventional Ringer's solution. J Trauma. 2006;60:52–63.
20. Todd SR, Malinoski D, Muller PJ, Schreiber MA. Lactated Ringer's is superior to normal saline in the resuscitation of uncontrolled hemorrhagic shock. J Trauma. 2007;62:636–9.
21. Shires GT, Browder LK, Steljes TP, Williams SJ, Browder TD, Barber AE. The effect of shock resuscitation fluids on apoptosis. Am J Surg. 2005;189:85–91.
22. Jaskille A, Alam HB, Rhee P, Hanes W, Kirkpatrick JR, Koustova E. D-lactate increases pulmonary apoptosis by restricting phosphorylation of bad and eNOS in a rat model of hemorrhagic shock. J Trauma. 2004;57:262–9. Discussion 69–70.
23. Deb S, Sun L, Martin B, Talens E, Burris D, Kaufmann C, Rich N, Rhee P. Lactated ringer's solution and hetastarch but not plasma resuscitation after rat hemorrhagic shock is associated with immediate lung apoptosis by the up-regulation of the Bax protein. J Trauma. 2000;49:47–53. Discussion 53–5.
24. Mulier KE, Beilman GJ, Conroy MJ, Taylor JH, Skarda DE, Hammer BE. Ringer's ethyl pyruvate in hemorrhagic shock and resuscitation does not improve early hemodynamics or tissue energetics. Shock. 2005;23:248–52.
25. Borle AB, Stanko RT. Pyruvate reduces anoxic injury and free radical formation in perfused rat hepatocytes. Am J Physiol. 1996;270:G535–40.
26. Willems JL, de Kort AF, Vree TB, Trijbels JM, Veerkamp JH, Monnens LA. Non-enzymic conversion of pyruvate in aqueous solution to 2,4-dihydroxy-2-methylglutaric acid. FEBS Lett. 1978;86:42–4.

27. Sims CA, Wattanasirichaigoon S, Menconi MJ, Ajami AM, Fink MP. Ringer's ethyl pyruvate solution ameliorates ischemia/reperfusion-induced intestinal mucosal injury in rats. Crit Care Med. 2001;29:1513–8.
28. Tawadrous ZS, Delude RL, Fink MP. Resuscitation from hemorrhagic shock with Ringer's ethyl pyruvate solution improves survival and ameliorates intestinal mucosal hyperpermeability in rats. Shock. 2002;17:473–7.
29. Sharma P, Walsh KT, Kerr-Knott KA, Karaian JE, Mongan PD. Pyruvate modulates hepatic mitochondrial functions and reduces apoptosis indicators during hemorrhagic shock in rats. Anesthesiology. 2005;103:65–73.
30. Sharma P, Mongan PD. Hypertonic sodium pyruvate solution is more effective than Ringer's ethyl pyruvate in the treatment of hemorrhagic shock. Shock. 2010;33:532–40.
31. Cai B, Brunner M, Wang H, Wang P, Deitch EA, Ulloa L. Ethyl pyruvate improves survival in awake hemorrhage. J Mol Med (Berl). 2009;87:423–33.
32. Chiara O, Pelosi P, Brazzi L, Bottino N, Taccone P, Cimbanassi S, Segala M, Gattinoni L, Scalea T. Resuscitation from hemorrhagic shock: experimental model comparing normal saline, dextran, and hypertonic saline solutions. Crit Care Med. 2003;31:1915–22.
33. Tsai MC, Chen WJ, Ching CH, Chuang JI. Resuscitation with hydroxyethyl starch solution prevents nuclear factor kappaB activation and oxidative stress after hemorrhagic shock and resuscitation in rats. Shock. 2007;27:527–33.
34. Wu D, Dai H, Arias J, Latta L, Abraham WM. Low-volume resuscitation from traumatic hemorrhagic shock with Na^+/H^+ exchanger inhibitor. Crit Care Med. 2009;37:1994–9.
35. Rhee P, Wang D, Ruff P, Austin B, DeBraux S, Wolcott K, Burris D, Ling G, Sun L. Human neutrophil activation and increased adhesion by various resuscitation fluids. Crit Care Med. 2000;28:74–8.
36. Hoppen RA, Corso CO, Grezzana TJ, Severino A, Dal-Pizzol F, Ritter C. Hypertonic saline and hemorrhagic shock: hepatocellular function and integrity after six hours of treatment. Acta Cir Bras. 2005;20:414–7.
37. Deree J, Loomis WH, Wolf P, Coimbra R. Hepatic transcription factor activation and proinflammatory mediator production is attenuated by hypertonic saline and pentoxifylline resuscitation after hemorrhagic shock. J Trauma. 2008;64:1230–8. Discussion 38–9.
38. Corso CO, Okamoto S, Leiderer R, Messmer K. Resuscitation with hypertonic saline dextran reduces endothelial cell swelling and improves hepatic microvascular perfusion and function after hemorrhagic shock. J Surg Res. 1998;80:210–20.
39. Corso CO, Okamoto S, Ruttinger D, Messmer K. Hypertonic saline dextran attenuates leukocyte accumulation in the liver after hemorrhagic shock and resuscitation. J Trauma. 1999;46:417–23.
40. Nakatani T, Sakamoto Y, Ando H, Kobayashi K. Effects of fluid resuscitation with recombinant human serum albumin solution on maintaining hepatic energy metabolism in hemorrhagic shock rabbits. Res Exp Med (Berl). 1996;196:317–25.
41. Lu XL, Zheng CY, Xiao D, Wang YQ, Suo XY, Yu PZ, Xu YH, Ma TM, Su ZG. Conjugate of bovine hemoglobin and human serum albumin as a candidate for blood substitute: characteristics and effects on rats. Artif Cells Blood Substit Immobil Biotechnol. 2005;33:83–99.
42. Spoerke N, Zink K, Cho SD, Differding J, Muller P, Karahan A, Sondeen J, Holcomb JB, Schreiber M. Lyophilized plasma for resuscitation in a swine model of severe injury. Arch Surg. 2009;144:829–34.
43. Knudson MM, Lee S, Erickson V, Morabito D, Derugin N, Manley GT. Tissue oxygen monitoring during hemorrhagic shock and resuscitation: a comparison of lactated Ringer's solution, hypertonic saline dextran, and HBOC-201. J Trauma. 2003;54:242–52.
44. Johnson T, Arnaud F, Dong F, Philbin N, Rice J, Asher L, Arrisueno M, Warndorf M, Gurney J, McGwin G, Kaplan L, Flournoy WS, Apple FS, Pearce LB, Ahlers S, McCarron R, Freilich D. Bovine polymerized hemoglobin (hemoglobin-based oxygen carrier-201) resuscitation in three swine models of hemorrhagic shock with militarily relevant delayed evacuation—effects on histopathology and organ function. Crit Care Med. 2006;34:1464–74.
45. York GB, Eggers JS, Smith DL, Jenkins DH, McNeil JD, Mueller D, Josephs JD, Kerby JD. Low-volume resuscitation with a polymerized bovine hemoglobin-based oxygen-carrying solution (HBOC-201) provides adequate tissue oxygenation for survival in a porcine model of controlled hemorrhage. J Trauma. 2003;55:873–85.
46. Sprung J, Kindscher JD, Wahr JA, Levy JH, Monk TG, Moritz MW, O'Hara PJ. The use of bovine hemoglobin glutamer-250 (Hemopure) in surgical patients: results of a multicenter, randomized, single-blinded trial. Anesth Analg. 2002;94:799–808.
47. Xiao N, Wang XC, Diao YF, Liu R, Tian KL. Effect of initial fluid resuscitation on subsequent treatment in uncontrolled hemorrhagic shock in rats. Shock. 2004;21:276–80.
48. Li T, Zhu Y, Hu Y, Li L, Diao Y, Tang J, Liu L. Ideal permissive hypotension to resuscitate uncontrolled hemorrhagic shock and the tolerance time in rats. Anesthesiology. 2011;114:111–9.
49. Lu YQ, Cai XJ, Gu LH, Wang Q, Huang WD, Bao DG. Experimental study of controlled fluid resuscitation in the treatment of severe and uncontrolled hemorrhagic shock. J Trauma. 2007;63:798–804.
50. Shah KJ, Chiu WC, Scalea TM, Carlson DE. Detrimental effects of rapid fluid resuscitation on hepatocellular function and survival after hemorrhagic shock. Shock. 2002;18:242–7.
51. Talving P, Riddez L. A pilot study on early versus delayed hypertonic saline dextran resuscitation in a porcine model of near-lethal liver injury: early hemodynamic response and short-term survival. J Surg Res. 2006;136:273–9.
52. Garrison RN, Conn AA, Harris PD, el Zakaria R. Direct peritoneal resuscitation as adjunct to conventional resuscitation from hemorrhagic shock: a better outcome. Surgery. 2004;136:900–8.
53. Zakaria el R, Matheson PJ, Flessner MF, Garrison RN. Hemorrhagic shock and resuscitation-mediated tissue water distribution is normalized by adjunctive peritoneal resuscitation. J Am Coll Surg. 2008;206:970–80.
54. Smith JW, Garrison RN, Matheson PJ, Franklin GA, Harbrecht BG, Richardson JD. Direct peritoneal resuscitation accelerates primary abdominal wall closure after damage control surgery. J Am Coll Surg. 2010;210:658–64, 664–7.
55. Raddatz A, Kubulus D, Winning J, Bauer I, Pradarutti S, Wolf B, Kreuer S, Rensing H. Dobutamine improves liver function after hemorrhagic shock through induction of heme oxygenase-1. Am J Respir Crit Care Med. 2006;174:198–207.
56. Morales D, Madigan J, Cullinane S, Chen J, Heath M, Oz M, Oliver JA, Landry DW. Reversal by vasopressin of intractable hypotension in the late phase of hemorrhagic shock. Circulation. 1999;100:226–9.
57. Prengel AW, Lindner KH, Wenzel V, Tugtekin I, Anhaupl T. Splanchnic and renal blood flow after cardiopulmonary resuscitation with epinephrine and vasopressin in pigs. Resuscitation. 1998;38:19–24.
58. Raedler C, Voelckel WG, Wenzel V, Krismer AC, Schmittinger CA, Herff H, Mayr VD, Stadlbauer KH, Lindner KH, Konigsrainer A. Treatment of uncontrolled hemorrhagic shock after liver trauma: fatal effects of fluid resuscitation versus improved outcome after vasopressin. Anesth Analg. 2004;98:1759–66.

59. Voelckel WG, Raedler C, Wenzel V, Lindner KH, Krismer AC, Schmittinger CA, Herff H, Rheinberger K, Konigsrainer A. Arginine vasopressin, but not epinephrine, improves survival in uncontrolled hemorrhagic shock after liver trauma in pigs. Crit Care Med. 2003;31:1160–5.
60. Stadlbauer KH, Wagner-Berger HG, Raedler C, Voelckel WG, Wenzel V, Krismer AC, Klima G, Rheinberger K, Nussbaumer W, Pressmar D, Lindner KH, Konigsrainer A. Vasopressin, but not fluid resuscitation, enhances survival in a liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs. Anesthesiology. 2003;98:699–704.
61. Li T, Fang Y, Zhu Y, Fan X, Liao Z, Chen F, Liu L. A small dose of arginine vasopressin in combination with norepinephrine is a good early treatment for uncontrolled hemorrhagic shock after hemostasis. J Surg Res. 2011;169:76–84.
62. McCloskey CA, Zuckerbraun BS, Gallo DJ, Vodovotz Y, Billiar TR. A role for angiotensin II in the activation of extracellular signal-regulated kinases in the liver during hemorrhagic shock. Shock. 2003;20:316–9.
63. Lee CJ, Subeq YM, Lee RP, Wu WT, Hsu BG. Low-dose propofol ameliorates haemorrhagic shock-induced organ damage in conscious rats. Clin Exp Pharmacol Physiol. 2008;35:766–74.
64. Lee CJ, Lee RP, Subeq YM, Lee CC, Peng TC, Hsu BG. Propofol protects against hemorrhagic shock-induced organ damage in conscious spontaneously hypertensive rats. Biol Res Nurs. 2009;11:152–62.
65. Takahashi K, Shigemori S, Nosaka S, Morikawa S, Inubushi T. The effects of halothane and isoflurane on the phosphoenergetic state of the liver duringhemorrhagic shock in rats: an in vivo 31P nuclear magnetic resonance spectroscopic study. Anesth Analg. 1997;85:347–52.
66. Takahashi K, Nosaka S, Morikawa S, Inubushi T. Hepatic energy metabolism during ketamine and isoflurane anaesthesia in haemorrhagic shock. Br J Anaesth. 1998;80:782–7.
67. Bahrami S, Benisch C, Zifko C, Jafarmadar M, Schochl H, Redl H. Xylazine-/diazepam-ketamine and isoflurane differentially affect hemodynamics and organ injury under hemorrhagic/traumatic shock and resuscitation in rats. Shock. 2011;35:573–8.
68. Englehart MS, Allison CE, Tieu BH, Kiraly LN, Underwood SA, Muller PJ, Differding JA, Sawai RS, Karahan A, Schreiber MA. Ketamine-based total intravenous anesthesia versus isoflurane anesthesia in a swine model of hemorrhagic shock. J Trauma. 2008;65:901–8. Discussion 908–9.
69. Ishida H, Kadota Y, Sameshima T, Nishiyama A, Oda T, Kanmura Y. Comparison between sevoflurane and isoflurane anesthesia in pig hepatic ischemia–reperfusion injury. J Anesth. 2002;16:44–50.
70. Zhang L, Luo N, Liu J, Duan Z, Du G, Cheng J, Lin H, Li Z. Emulsified isoflurane preconditioning protects against liver and lung injury in rat model of hemorrhagic shock. J Surg Res. 2010;171:783–90.
71. Lee CC, Lee RP, Subeq YM, Lee CJ, Chen TM, Hsu BG. Fluvastatin attenuates severe hemorrhagic shock-induced organ damage in rats. Resuscitation. 2009;80:372–8.
72. Relja B, Lehnert M, Seyboth K, Bormann F, Hohn C, Czerny C, Henrich D, Marzi I. Simvastatin reduces mortality and hepatic injury after hemorrhage/resuscitation in rats. Shock. 2010;34:46–54.
73. Rana MW, Shapiro MJ, Ali MA, Chang YJ, Taylor WH. Deferoxamine and hespan complex as a resuscitative adjuvant in hemorrhagic shock rat model. Shock. 2002;17:339–42.
74. Yang FL, Subeq YM, Lee CJ, Lee RP, Peng TC, Harn HJ, Hsu BG. Rosiglitazone protects against severe hemorrhagic shock-induced organ damage in rats. Med Sci Monit. 2011;17:BR282–9.
75. Zingarelli B, Chima R, O'Connor M, Piraino G, Denenberg A, Hake PW. Liver apoptosis is age dependent and is reduced by activation of peroxisome proliferator-activated receptor-gamma in hemorrhagic shock. Am J Physiol Gastrointest Liver Physiol. 2010;298:G133–41.
76. Liu FC, Liu FW, Yu HP. Ondansetron attenuates hepatic injury via p38 MAPK-dependent pathway in a rat haemorrhagic shock model. Resuscitation. 2011;82:335–40.
77. Mathes AM, Kubulus D, Pradarutti S, Bentley A, Weiler J, Wolf B, Ziegeler S, Bauer I, Rensing H. Melatonin pretreatment improves liver function and hepatic perfusion after hemorrhagic shock. Shock. 2008;29:112–8.
78. Yang FL, Subeq YM, Lee CJ, Lee RP, Peng TC, Hsu BG. Melatonin ameliorates hemorrhagic shock-induced organ damage in rats. J Surg Res. 2011;167:e315–21.
79. Kuebler JF, Yokoyama Y, Jarrar D, Toth B, Rue LW 3rd, Bland KI, Wang P, Chaudry IH. Administration of progesterone after trauma and hemorrhagic shock prevents hepatocellular injury. Arch Surg. 2003;138:727–34.
80. Mizushima Y, Wang P, Jarrar D, Cioffi WG, Bland KI, Chaudry IH. Estradiol administration after trauma-hemorrhage improves cardiovascular and hepatocellular functions in male animals. Ann Surg. 2000;232:673–9.
81. Anaya-Prado R, Toledo-Pereyra LH, Guo RF, Reuben J, Ward PA, Walsh J. The attenuation of hemorrhage-induced liver injury by exogenous nitric oxide, L-arginine, and inhibition of inducible nitric oxide synthase. J Invest Surg. 2003;16:247–61.
82. Gundersen Y, Vaagenes P, Reistad T, Opstad PK. Modest protection of early hydrocortisone treatment in a rat model of volume-controlled haemorrhage. Acta Anaesthesiol Scand. 2003;47:1165–71.
83. Zaets SB, Xu DZ, Lu Q, Feketova E, Berezina TL, Malinina IV, Deitch EA, Olsen EH. Recombinant factor XIII mitigates hemorrhagic shock-induced organ dysfunction. J Surg Res. 2011;166:e135–42.
84. Roesner JP, Petzelbauer P, Koch A, Tran N, Iber T, Vagts DA, Scheeren TW, Vollmar B, Noldge-Schomburg GE, Zacharowski K. Bbeta15-42 (FX06) reduces pulmonary, myocardial, liver, and small intestine damage in a pig model of hemorrhagic shock and reperfusion. Crit Care Med. 2009;37:598–605.
85. Dhar A, Cherian G, Dhar G, Ray G, Sharma R, Banerjee SK. Molecular basis of protective effect by crocetin on survival and liver tissue damage following hemorrhagic shock. Mol Cell Biochem. 2005;278:139–46.
86. Shah KG, Jacob A, Rajan D, Wu R, Molmenti EP, Nicastro J, Coppa GF, Wang P. Resuscitation of uncontrolled traumatic hemorrhage induced by severe liver injury: the use of human adrenomedullin and adrenomedullin binding protein-1. J Trauma. 2010;69:1415–21;discussion 1421–2.
87. Huang YS, Liu FC, Li AH, Lau YT, Yu HP. Astringinin-mediated attenuation of the hepatic injury following trauma-hemorrhage. Chin J Physiol. 2011;54:183–9.
88. van den Berg HR, Khan NA, van der Zee M, Bonthuis F. JN IJ, Dik WA, de Bruin RW, Benner R. Synthetic oligopeptides related to the [beta]-subunit of human chorionic gonadotropin attenuate inflammation and liver damage after (trauma) hemorrhagic shock and resuscitation. Shock. 2009;31:285–91.
89. Yu HP, Hsu JC, Hwang TL, Yen CH, Lau YT. Resveratrol attenuates hepatic injury after trauma-hemorrhage via estrogen receptor-related pathway. Shock. 2008;30:324–8.
90. Lin T, Chen H, Koustova E, Sailhamer EA, Li Y, Shults C, Liu B, Rhee P, Kirkpatrick J, Alam HB. Histone deacetylase as therapeutic target in a rodent model of hemorrhagic shock: effect of different resuscitation strategies on lung and liver. Surgery. 2007;141:784–94.
91. Liu FC, Day YJ, Liou JT, Lau YT, Yu HP. Sirtinol attenuates hepatic injury and pro-inflammatory cytokine production following trauma-hemorrhage in male Sprague-Dawley rats. Acta Anaesthesiol Scand. 2008;52:635–40.

92. Yang R, Gallo DJ, Baust JJ, Uchiyama T, Watkins SK, Delude RL, Fink MP. Ethyl pyruvate modulates inflammatory gene expression in mice subjected to hemorrhagic shock. Am J Physiol Gastrointest Liver Physiol. 2002;283:G212–21.
93. Chai W, Wang Y, Lin JY, Sun XD, Yao LN, Yang YH, Zhao H, Jiang W, Gao CJ, Ding Q. Exogenous hydrogen sulfide protects against traumatic hemorrhagic shock via attenuation of oxidative stress. J Surg Res. 2012;176:210–9.
94. Kan WH, Hsieh CH, Schwacha MG, Choudhry MA, Raju R, Bland KI, Chaudry IH. Flutamide protects against trauma-hemorrhage-induced liver injury via attenuation of the inflammatory response, oxidative stress, and apopotosis. J Appl Physiol. 2008;105:595–602.
95. Zuckerbraun BS, McCloskey CA, Gallo D, Liu F, Ifedigbo E, Otterbein LE, Billiar TR. Carbon monoxide prevents multiple organ injury in a model of hemorrhagic shock and resuscitation. Shock. 2005;23:527–32.
96. Schmidt R, Baechle T, Hoetzel A, Loop T, Humar M, Roesslein M, Geiger KK, Pannen BH. Dihydralazine treatment limits liver injury after hemorrhagic shock in rats. Crit Care Med. 2006;34:815–22
97. Yang R, Martin-Hawver L, Woodall C, Thomas A, Qureshi N, Morrison D, Van Way C 3rd. Administration of glutamine after hemorrhagic shock restores cellular energy, reduces cell apoptosis and damage, and increases survival. J Parenter Enter Nutr. 2007;31:94–100