Physiol Rev 89: 1269–1339, 2009;
doi:10.1152/physrev.00027.2008.

The Hepatic Microcirculation: Mechanistic Contributions and Therapeutic Targets in Liver Injury and Repair

BRIGITTE VOLLMAR AND MICHAEL D. MENGER

Institute for Experimental Surgery, University of Rostock, Rostock; and Institute for Clinical and Experimental Surgery, University of Saarland, Homburg-Saar, Germany

Vollmar B, Menger MD. The Hepatic Microcirculation: Mechanistic Contributions and Therapeutic Targets in Liver Injury and Repair. *Physiol Rev* 89: 1269–1339, 2009; doi:10.1152/physrev.00027.2008.—The complex functions of the

liver in biosynthesis, metabolism, clearance, and host defense are tightly dependent on an adequate microcirculation. To guarantee hepatic homeostasis, this requires not only a sufficient nutritive perfusion and oxygen supply, but also a balanced vasomotor control and an appropriate cell-cell communication. Deteriorations of the hepatic homeostasis, as observed in ischemia/reperfusion, cold preservation and transplantation, septic organ failure, and hepatic resection-induced hyperperfusion, are associated with a high morbidity and mortality. During the last two decades, experimental studies have demonstrated that microcirculatory disorders are determinants for organ failure in these disease states. Disorders include *1*) a dysregulation of the vasomotor control with a deterioration of the endothelin-nitric oxide balance, an arterial and sinusoidal constriction, and a shutdown of the microcirculation as well as *2*) an overwhelming inflammatory response with microvascular leukocyte accumulation, platelet adherence, and Kupffer cell activation. Within the sequelae of events, proinflammatory mediators, such as reactive oxygen species and tumor necrosis factor-α, are the key players, causing the microvascular dysfunction and perfusion failure. This review covers the morphological and functional characterization of the hepatic microcirculation, the mechanistic contributions in surgical disease states, and the therapeutic targets to attenuate tissue injury and organ dysfunction. It also indicates future directions to translate the knowledge achieved from experimental studies into clinical practice. By this, the use of the recently introduced techniques to monitor the hepatic microcirculation in humans, such as near-infrared spectroscopy or orthogonal polarized spectral imaging, may allow an early initiation of treatment, which should benefit the final outcome of these critically ill patients.

I. INTRODUCTION

The microcirculation of the liver is of utmost importance for the physiology and function of the whole organism. It guarantees the supply of the parenchymal tissue with oxygen and nutrients, serves as the gate for leukocyte entrance in hepatic inflammation, and is responsible for the clearance of toxicants and foreign bodies from the bloodstream. Historically, the microvasculature could only be studied by histological techniques, which lack information on dynamic processes. With the introduction of in vivo microscopy, however, it became possible to analyze flow and resistance of hepatic microvessels under physiological and pathological conditions. Further development in this technology and the in vivo application of fluorescent markers and epi-illumination techniques allow nowadays sophisticated analyses of mechanistic contributions of distinct blood and liver cells to the hepatic microcirculation during physiological regulation and to the microcirculatory dysfunctions in disease.

In clinical practice, acute liver dysfunction and failure represent life-threatening conditions that require immediate intervention. Causes for the deterioration of liver function are warm and cold ischemia and reperfusion (I/R) during liver resection and transplantation, generalized inflammation and sepsis in particular after endotoxin exposure, acetaminophen-induced hepatic intoxication, and the small-for-size syndrome, which is a mismatch between size and need, after extended hepatectomy or split liver transplantation. The small-for-size syndrome is additionally aggravated by an impaired process of liver regeneration. These disease states are in focus of interest in clinical practice of surgery, because they are still associated with a high morbidity and mortality.

Hepatic microvascular activation and microcirculatory dysfunctions have been shown to be determinants for the manifestation of these disease states. Accordingly, the mechanisms of activation and dysfunction are of pivotal interest, not only for the understanding of the disease, but also for the development of novel therapeutic strategies. In the following, this review will describe the morphology and physiology of the hepatic microcirculation. It will further focus on *1*) the deteriorations of the microcirculation in disease, *2*) the microcirculatory interactions with cellular activation and mediator response, *3*) the mechanisms of these interactions, and *4*) how this knowledge can be used to develop new treatment regimens. The cellular response includes the accumulation and activation of leukocytes, platelets, and Kupffer cells (KC), while the mediator response consists of proinflammatory cascades with release of cytokines, chemokines, and reactive oxygen species. The microcirculatory deteriorations are characterized by vasoconstriction, white blood cell and platelet endothelial adherence, shutdown of the sinusoidal circulation, and parenchymal tissue hypoxia, resulting in hepatocellular excretory dysfunction and organ failure. These microcirculatory dysfunctions are the major target for treatment strategies, which may be specific according to the mechanisms recognized, or unspecific when using pleiotropic drugs.

With this review we want to assist in improving the understanding of the physiology of the hepatic microcirculation and its pathology in disease. We hope that the delineation of the complex mechanisms of dysregulation may inspire the design and development of novel treatment approaches.

II. PHYSIOLOGY OF THE HEPATIC MICROCIRCULATION

A. Dual Blood Perfusion of the Liver

The liver constitutes 2.5% of the body weight and is, thus, the largest organ in the body. It receives ~25% of the

cardiac output via two inflows, the portal vein and the hepatic artery. Both vessels enter the liver at its hilus accompanied by the hepatic bile duct, lymphatics, and nerves. The portal vein is a valveless afferent vessel that drains the blood from the capillary system of the intestine, spleen, pancreas, omentum, and gallbladder and contributes to the liver's blood supply with ~75–80% of its total inflow. The remaining 20–25% is delivered by the hepatic artery (656, 858). Total hepatic perfusion amounts to ~1 ml·min^{-1}·g tissue^{-1}, and oxygen consumption by the liver accounts for 20% of total body oxygen consumption. In contrast to the well-oxygenated hepatic arterial blood, the portal vein carries partly deoxygenated, but nutrient-rich blood. Nevertheless, >50% of the hepatic oxygen requirements are provided by portal venous blood due to its high flow rate. Hence, hepatic oxygenation depends almost equally on both large afferent vessels. In addition to the existence of the two afferent vessels, the liver circulation includes an efferent system by way of the hepatic veins. The hepatic artery is a vessel of resistance, whereas the portal and hepatic veins are vessels of capacitance. Thus the liver is interposed in an arterial high-pressure and a venous low-pressure system.

The dual blood supply of the liver is a unique feature of the hepatic vasculature and distinctly determines the regulation and distribution of blood flow. There is an intimate relationship between the two vascular systems, termed the "hepatic arterial buffer response" (HABR), representing the ability of the hepatic artery to produce compensatory flow changes in response to changes in portal venous flow (Fig. 1). While Burton-Opitz observed an increase in hepatic arterial blood flow upon reduced portal venous inflow already in 1911 (76), the term HABR was stamped first in 1981 by Wayne Lautt (465). In addition to the intrinsic mechanism of classical arterial autoregulation, i.e., the myogenic constrictive response of the hepatic artery if arterial pressure rises, there exists a second intrinsic mechanism in that the hepatic artery dilates, if portal flow decreases, and the hepatic artery constricts, if portal flow increases (459). The increase in hepatic arterial blood flow is capable of buffering ~25–60% of the decreased portal flow (458, 464). Hereby, the hepatic artery is not regulated by the metabolic demand of the liver, because a hemodilution-induced reduction of oxygen content in the inflow and outflow vessels or a massive increase of oxygen demand do not cause arterial vasodilation (66, 464). Instead, hepatic arterial flow subserves the hepatic role as a regulator of blood levels of nutrients and hormones by maintaining blood flow and thereby hepatic clearance, as steady as possible (461, 462). Because the portal vein cannot control its blood flow, which is simply the sum of outflows of the extrahepatic splanchnic organs, there is no reciprocity of the HABR, i.e., alterations of the hepatic arterial perfusion do not induce compensatory changes of the portal vascular flow (465) or resistance (473).

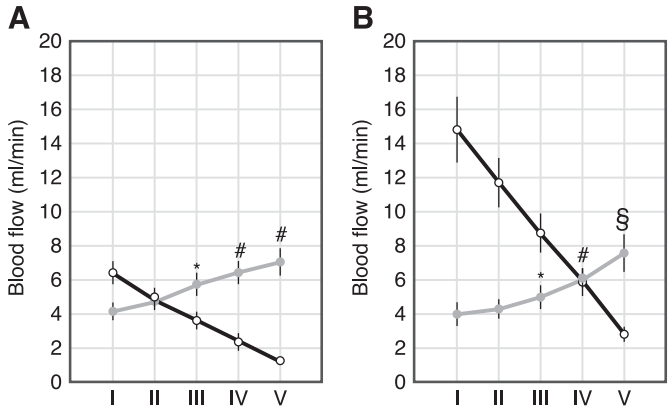

FIG. 1. Hepatic arterial buffer response in cirrhotic (*A*) and control livers (*B*). Upon reduction of portal venous blood flow (open circles) to 80% (II), 60% (III), 40% (IV), and 20% (V) of baseline (I), there is a constant increase of hepatic arterial blood flow (solid circles). Note the markedly diminished portal venous blood flow in the cirrhotic livers but the preserved buffer response of the hepatic artery. Values are means ± SE of triplicate measurements per animal ($n = 6$). §$P < 0.05$ vs. I, II, III, IV. #$P < 0.05$ vs. I, II, III. *$P < 0.05$ vs. I, II. [From Richter et al. (670).]

In contrast to potential mechanisms, including neural and myogenic control, which are considered unlikely (464, 465) or even disproved (12, 531), adenosine has been repeatedly advocated as the putative mediator in the space of Mall driving the communication between the hepatic artery and the portal vein. The space of Mall surrounds the hepatic arterial resistance vessels and portal venules and is contained within a limiting plate that separates this space from other fluid compartments. According to the wash-out hypothesis of adenosine, adenosine accumulates in or less adenosine is washed away from the space of Mall, if portal blood flow is reduced. Elevated adenosine concentrations lead to a dilation of the hepatic artery with a subsequent increase of hepatic arterial flow. There are several lines of evidence which suggest that adenosine largely mediates the HABR. First, adenosine produces dilation of the hepatic artery (458, 460). Second, portal venous application of adenosine increases hepatic arterial blood flow. Third, the adenosine receptor antagonists 3-isobutyl-1-methylxanthine (IBMX) (458) and 8-phenyltheophylline (8-PT) (70, 460, 672) reduce the HABR, while dipyridamole, an adenosine uptake antagonist, potentiates the magnitude of the HABR (458). Adenosine also activates hepatic sensory nerves to cause reflex renal fluid retention, thus increasing the circulating blood volume and maintaining the cardiac output and portal flow (463).

In addition to adenosine, other vasoactive substances, namely, nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S), might contribute to this regulatory mechanism; however, they have not extensively been studied in this context yet (85, 302). In addition, sensory innervation and sensory neuropeptides

seem to be involved in the HABR, which is partially mediated by activation of capsaicin-sensitive sensory fibers (47).

The intriguing arterial buffer response of the liver has been shown to operate not only under physiological conditions and prenatally (166), but is also maintained in cirrhotic livers (18, 572, 670) (Fig. 1). Decreased portal venous inflow to the liver leads to a decrease in oxygen supply (261, 670) and thus induces a compensatory increase of hepatic arterial blood flow. It has been shown that both adenosine and NO are main mediators involved in the vasodilation of the splanchnic circulation in cirrhosis (329, 330, 899). Adenosine is released from hypoxic tissues and mediates vasodilation by the adenosine A1 receptor through a NO-dependent pathway (973). The site of resistance of the hepatic arteries is located in the presinusoidal arterioles (782) where NO production is preserved, while in the sinusoidal and postsinusoidal areas deficiency of NO facilitates the effects of vasoconstrictors and thus contributes to the increased intrahepatic resistance in portal hypertension (504).

In liver transplants (144, 286, 749), HABR is also maintained. As increased flow in transplanted livers is predominantly carried through the portal vein, the intact HABR causes a reduction of the hepatic arterial flow, potentially harming organ integrity and function (286). Small-for-size grafts, as seen in split-liver transplantation, are associated with portal hypertension and, as a consequence of an intact buffer response, poor hepatic arterial flow and vasospasm. In severe cases, this leads to functional dearterialization, ischemic cholangitis, and parenchymal infarcts (144). Of note, the HABR-induced decrease of the hepatic arterial blood flow can successfully be counteracted. Splenic artery embolization reduces excessive portal vein flow and, thereby, ameliorates the overactive HABR (651).

B. Anatomy of the Hepatic Microvascular Bed

The anatomy of the hepatic microvascular bed, in particular the terminal distribution of the afferent vessels and the sinusoids, has been studied in detail by light microscopy, intravital fluorescence microscopy, and transmission and scanning electron microscopy (72, 367, 551, 619, 926).

In the portal tracts, branches of the hepatic artery, the hepatic portal vein, the main bile duct, and the main lymphatic vessels travel parallel to each other through the liver parenchyma. Of the structures present, the lymphatic vessels are often collapsed and inconspicuous, as are the autonomic nerves. Thus three structures are regularly visible with the consequence that portal tracts are often referred to as portal triads. In cirrhotic livers with deterioration of trans-sinusoidal macromolecular exchange, it has been shown that lymphatic drainage functions as a compensatory mechanism, guaranteeing the transport of macromolecules that are trapped extravascularly due to diffusion-barrier-induced hindrance of hepatocellular uptake. As a consequence, lymph vessels massively expand and gain visibility due to an increase of density and area within the portal tracts (875).

It is commonly understood that there is some form of communication between the portal venous and the hepatic arterial circulation (55, 72, 398, 541, 543, 601). After repeated branching, the terminal vessels, i.e., terminal hepatic arterioles and terminal portal venules with a diameter of 15–35 μm and a length of 50–70 μm (600), supply the blood to the hepatic sinusoids. At the transition of the terminal portal venule to the sinusoid, inlet sphincters are located and comprise large unfenestrated endothelial cells, covering the vascular lumen and being surrounded by a basement membrane and pericytes, but not smooth muscle cells (72).

In addition to that, the hepatic arterioles wind themselves around the portal venules sending short branches *1*) to the portal venules, i.e., arteriolo-portal anastomoses (Fig. 2), and *2*) to the capillaries of the peribiliary plexus, which nourish the bile duct and drain into the sinusoids via arteriosinus twigs. Within the periportal tissue at the periphery of the lobule, these twigs have a complete basement membrane and unfenestrated endothelium (72), still resembling capillaries. A short distance downstream into the parenchyma they loose their basement membrane, become fenestrated, and are true sinusoids. The terminal hepatic arteriole-derived capillaries further supply *3*) the portal venular wall as vasa vasorum and *4*) the connective tissue including the nerves of the portal tract (600, 601). With the use of enzyme histochemistry of alkaline phosphatase activity, the identification of endothelial cells of the arteriolar capillaries within the microvascular system allowed the distinct evaluation of the terminal distribution of the hepatic artery and its involvement in the control of hepatic sinusoidal blood flow (601). The shunting of blood via hepatic arteriolo-portal anastomoses has been shown to guarantee maintenance of nutritional microvascular supply and oxygen delivery in HABR in rats (672) (Fig. 2).

The hepatic sinusoids correspond to the capillary bed of the liver and represent the segment of the microcirculation in which supply of nutrients and removal of metabolic products takes place. Main sinusoids run straight between the liver cell cords over a length of ~250 μm and communicate with each other through shorter interconnecting sinusoids running across the liver cell cords. Sinusoidal diameters increase from ~7 μm in the periportal to ~15 μm in the pericentral area. Sinusoids are invested with a unique type of lining consisting of endothelial cells with flattened processes perforated by small fenestrae. These open fenestrations are arranged in

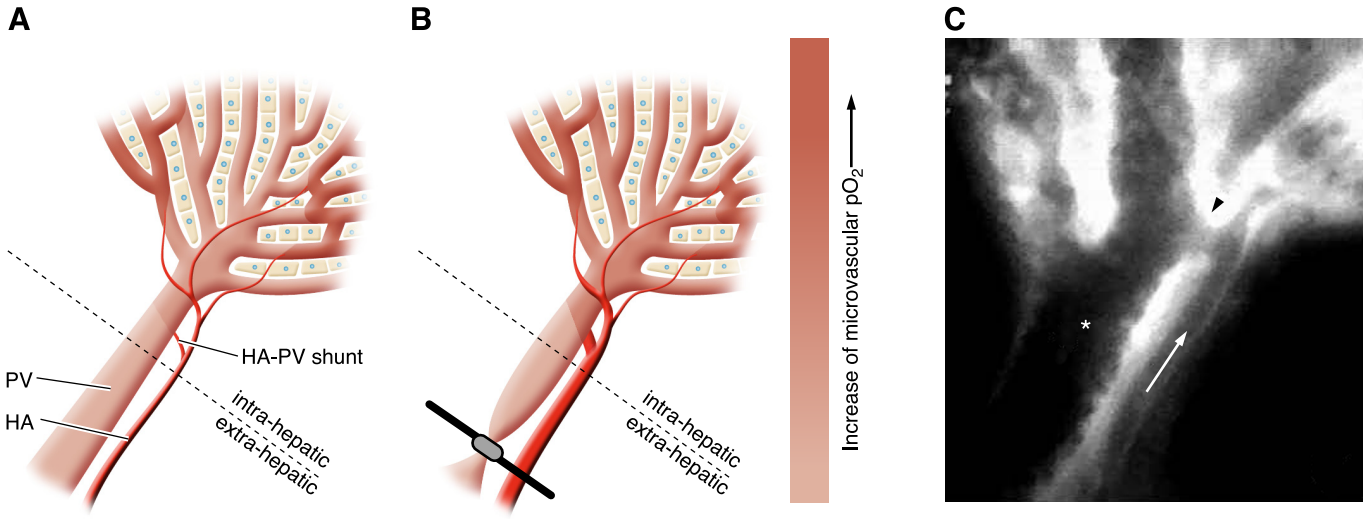

FIG. 2. Schematic representation of hepatic arterial (HA) and portal venous (PV) blood supply to sinusoids with indication of the hepatic arteriolo-portal venular (HA-PV) shunt. *A*: under normal conditions, all sinusoids are perfused with portal venous blood, while only some of them are additionally supplied directly by terminal hepatic arterioles. *B*: under conditions of reduced portal venous flow with induction of the hepatic arterial buffer response, preferential shunt perfusion leads to a disproportionally increased contribution of perfusion of sinusoids with hepatic artery-derived blood. This guarantees maintenance of oxygen supply despite an overall reduction of nutritive blood flow. *C*: intravital fluorescence microscopic image of the surface of a normal rat liver displaying the most terminal hepatic arteriole (white arrow) and portal venule (asterisk) running in parallel to each other. Note the hepatic arteriolo-portal venular shunt (arrowhead) located in the distal part of the terminal afferent vessels, but upstream from the sinusoidal network of the lobule. [From Richter et al. (672).]

clusters of 10–50 pores forming so-called "sieve plates" with a diameter of 150–175 nm and represent, apart from the absence of a basement membrane, the structural peculiarity of hepatic sinusoids (903). The sieve plates occupy ~6–8% of the endothelial surface and are not uniform in size or distribution throughout the length of the sinusoids (Fig. 3). There is a decrease in diameter but an increase of frequency from periportal to centrilobular zones, which results in higher centrilobular porosity (64, 902). These membrane-bound pores lack a diaphragm and a basal lamina, thus contrasting the fenestrae described in the kidney, pancreas, and brain (62). The fenestrae are dynamic structures that contract and dilate in response to alterations of sinusoidal blood flow and perfusion pressure. Furthermore, the fenestrae act as a selective sieving barrier to control the extensive exchange of material between the blood and the liver cells, and vice versa, contribute to the homeostatic control of the hepatic microcirculation. In addition, they exert scavenger function by their high receptor-mediated endocytotic capacity and clear the blood from many macromolecular waste products (748). The unique morphology of the liver sinusoidal endothelial cells (SEC) further permits interactions between lymphocytes and hepatocytes, which are accused to allow naive T-cells to interact with hepatocytes and thus to develop immune tolerance as lymphocytes pass through the liver (889). Meanwhile, innovations in correlative imaging techniques by using combined light, probe, laser, and various electron microscope techniques and their application in the hepatic endothelial cell model allow novel insights into the subcellular components and supramolecular structures of the liver sieve (reviewed in Ref. 63). They will help to further understand their biological relevance in various diseases, such as fibrosis, cirrhosis, atherosclerosis, and cancer (64).

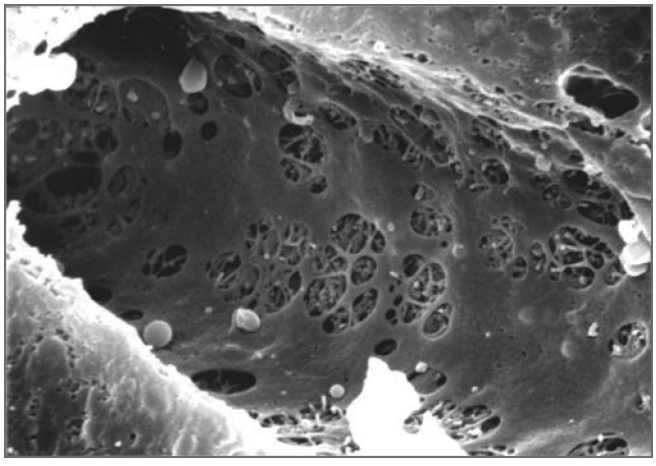

FIG. 3. Lumen of a hepatic sinusoid with the endothelial cell coating, displaying the typical fenestrations arranged as clusters and forming the so-called sieve plates. Freeze-fracture technique and scanning electron microscopy of the rat liver are shown. Magnification ×12,000.

A unique cellular component of the hepatic sinusoids is the fat- and vitamin A-storing perisinusoidal cell, known as stellate cell (211). External to the endothelium stellate

cells are located in the space of Disse, which is the space between the basal microvilli-rich surfaces of the hepatocytes and the sinusoidal lining cells. While the cell body of stellate cells is often found in recesses between hepatocytes, their perisinusoidal processes direct along the sinusoids with numerous fingerlike secondary branches, which encircle the sinusoidal tube (56). In addition to their well-known importance in retinol metabolism and as key actors in the hepatic fibrogenic response to injury, stellate cells have been strongly implicated to play a central role in the regulation of blood flow through hepatic sinusoids (681). This is not only based on the close relationship of these cells in a persinusoidal orientation within the space of Disse, but on the endowment with desmin, α-smooth muscle actin, and microfilaments and, thus, their remarkable capacity for cellular contraction (681).

In addition to the perisinusoidal stellate cells, the KC constitute a cellular component of the hepatic sinusoids, being anchored to the luminal site of the endothelium and, thus, exposed to the bloodstream. In contrast to stellate cells, which are distributed almost homogeneously throughout the different zones of the liver lobule (766, 873), the majority of KC is found in periportal regions where they are larger and have greater phagocytic activity than those located in the perilobular region (59, 60). This results in a zonal distribution with a specific kinetics of phagocytosis (861). KC are attached to the endothelium by cytoplasmic processes, which sometimes also anchor across the lumen to the opposite sinusoidal wall. By their large bodies protruding into the sinusoidal lumen, KC represent a flow hindrance and are considered as contractile cells contributing to blood flow regulation through sinusoids (21, 541) (Fig. 4).

After flowing through the sinusoids, blood passes through outlet or efferent sphincters composed of SEC and is collected in small branches of hepatic veins (terminal central veins). Several of these terminal central veins may combine, increasing in diameter and reaching the sublobular vein and hepatic veins, which leave the liver on the dorsal surface and extend to the extrahepatic inferior vena cava (541). Thus the hepatic microcirculatory unit in principle consists of the two terminal afferent vessels, the network of sinusoids running between the liver cords and the efferent terminal hepatic venule. Although the organization of the liver into morphological and functional units is an ongoing matter of debate among anatomists, pathologists, and clinicians, the hexagonal hepatic lobule seems to be the most consistent concept with existing evidence (171, 517) and has displaced the unit termed "simple liver acinus," being first proposed by Rappaport (657, 658). The primary lobule, proposed by Matsumoto and Kawakami in 1982 (533), has gained acceptance as the functional unit of the liver over other conceptual views (657), because it is based on the vessel architecture and includes the classic lobule as a secondary feature (541). The classic lobule, comprising several cone-shaped primary lobules, is a polygonal structure featured by placing the terminal central vein in the center with portal tracts distributed along its periphery. In con-

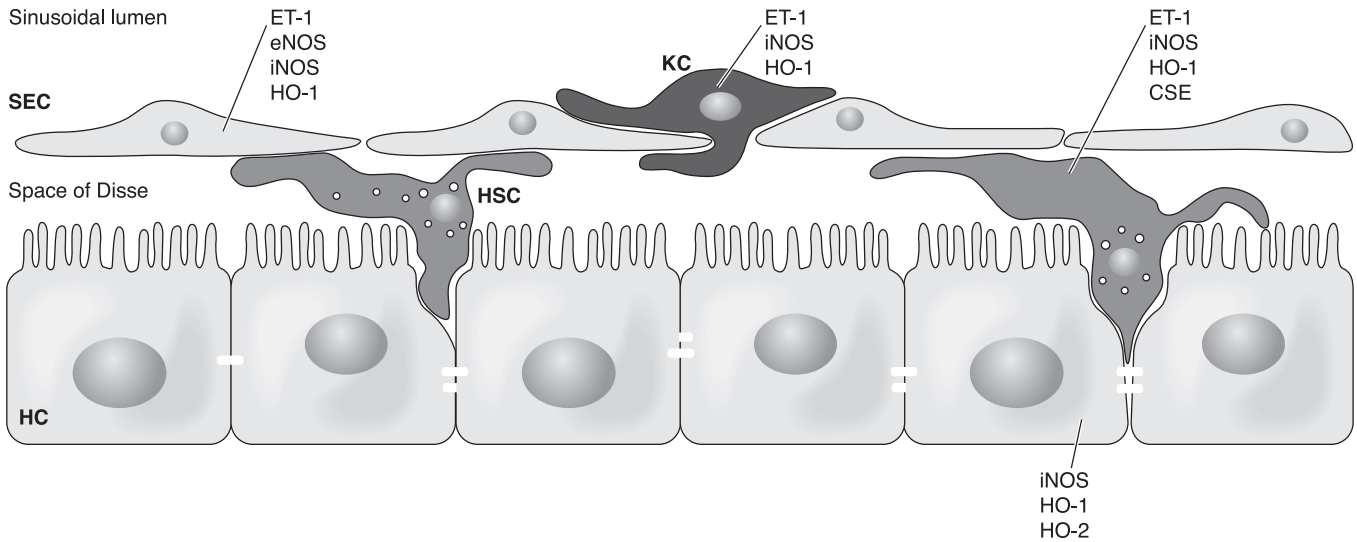

FIG. 4. Local regulators of the hepatic sinusoidal microcirculation. The sinusoid is composed of nonparenchymal contractile cells, such as hepatic stellate cells (HSC), sinusoidal endothelial cells (SEC), and Kupffer cells (KC), which serve as both sources and targets of endothelin (ET), nitric oxide synthase (NOS)-derived NO, heme oxygenase (HO)-derived CO and cystathionine-γ-lyase (CSE)-derived H_2S. In the normal liver, the primary source for NO is most likely the eNOS, which is expressed by the SEC. The cellular source of the vasodilative CO is primarily the hepatocellular HO-2 and to some extent the nonparenchymal cell-confined HO-1. H_2S is released from the CSE-expressing HSC. In contrast to the K_{ATP} channel opener H_2S, CO and NO exert vasorelaxation by the soluble guanylate cyclase-mediated increase of cGMP within HSC. Counteracting these vasodilative mediators, ET-1 is synthetized and released by SEC, HSC, and KC. While stimulation of ET_{B1} receptors on SEC may result in NO-dependent vasorelaxation, ET-1-mediated ligation of ET_A and ET_{B2} receptors on HSC causes vasoconstriction. HC, hepatocyte.

trast to pigs with considerable connective tissue, in tissue of most other species, including humans, the periphery of these lobules is not distinct and easily definable. Primary lobules were renamed as hepatic microvascular subunits, consisting of a group of sinusoids supplied by a single inlet venule and its associated termination of a branch of the hepatic arteriole, finally draining into a central venule. This functional substructure conforms to the basic idea of a microcirculatory unit and is also in line with the proposed gradient of hepatocellular metabolic heterogeneity along the sinusoidal path (806).

C. Regulation of the Hepatic Microvascular Blood Flow

As outlined above, the liver is morphologically and structurally multifaceted and has been considered second only to brain in its complexity. All vascular segments of the hepatic microvascular subunit, i.e., the afferent portal venules and hepatic arterioles, the sinusoids and the central venules, represent potential sites of regulation of blood flow. In addition to the presence of smooth muscle cells restricted to the afferent and efferent vessels and its branches, the sinusoids contain contractile cells, such as stellate cells, SEC and KC, which all are reported to be involved in the regulation of blood flow through sinusoids.

According to direct blood pressure measurements by micropuncture of hepatic microvessels, the blood pressure in the terminal hepatic arteriole is at least 300–400 mmH_2O and that in the terminal portal venule is 50 mmH_2O, while the sinusoidal pressure is estimated as low as 10–20 mmH_2O (583). More than 50 years ago, Knisely et al. (398) suggested the existence of sphincterlike specialized structures at the entrance to and at the exit from the sinusoids to maintain these steep blood pressure gradients from the portal-venous system, but in particular from the hepatic arteriolar system into the sinusoids (398). The existence of both inlet and outlet sphincters has been confirmed by a number of investigators (55, 927). However, others failed to find any evidence for such structures (657), which might, at least in part, be due to the fact that resistance sites in the portal, sinusoidal, and hepatic venous system are subject to species variations (171). In addition to the vagueness of the existence of hepatic sphincters, there is even more uncertainty about the constituting cellular components. While many studies failed to demonstrate smooth muscle cells or other contractile cells at these locations, electron microscopic studies in the dog have demonstrated branches of the hepatic veins that were equipped with peculiar, periodically arranged sphincter muscles (781). These contained tufts of smooth muscle cells most strongly disposed in the sublobular veins (100–250 μm in diameter), that reduced the luminal diameters of veins by 34% (7). In addition, double layered smooth muscle cells could be detected in the walls of the terminal hepatic venules of the rat liver by means of electron microscopy (700). Nonetheless, the structure, function, and regulation of intravascular sphincters and their role in controlling sinusoidal blood flow remain obscure.

In contrast, there is a large body of evidence that hepatic microvascular blood flow is regulated and redistributed at the level of the microcirculation (Fig. 4). This view is based on the fact that both stellate cells and endothelial cells can actively control various functions of the microvasculature. Since the description of acetylcholine-induced endothelial cell-dependent relaxation of blood vessels by Furchgott and Zawadski (216), the discovery of NO as endothelium-derived relaxing factor (614), the identification of the endothelium-constricting factor endothelin (ET) (292, 930) and the demonstration of another two vasodilatory gaseous molecules, i.e., CO (215, 489) and H_2S (306, 961), these endothelial mediators are known to delicately control vascular tone under both physiological and pathological conditions (Table 1).

Hepatic cellular sources of ETs are SEC, stellate cells, and KC (625, 678) (Fig. 4). Of the three isopeptides ET-1, ET-2 and ET-3, ET-1 is the one of predominant significance in vascular physiology, acting via the ET_A receptor, which results in a constriction of the effector cell. On the contrary, binding of ET to the ET_{B1} receptor on endothelial cells may result in a NO-dependent relaxation of adjacent vascular smooth muscle cells and pericytes, while ET_{B2} receptor stimulation induces cell contraction. In addition to the local generation of ET, the ET-dependent action strongly depends on the temporal and spatial distribution of ET receptor expression. This was found greatest on hepatic stellate cells, followed by SEC and KC (307) (Table 1). ET causes reversible and graded contraction of isolated stellate cells in culture (634, 680) and narrows the sinusoidal lumen in isolated perfused livers (679, 954) as well as in livers with intact afferent and efferent nerves upon systemic or intraportal infusion (38). Thereby, the ET-1-induced reduction of sinusoidal diameter was found colocalizing with the body of stellate cells, underlining that these liver-specific pericytes serve as contractile targets for ET (954). In addition to this intrasinusoidal site of action of ET, intraportal infusion of ET causes also an intense contraction of perivascular smooth muscle cells and protrusion of endothelial cells into the lumen of preterminal portal venules. This indicates that these microvascular segments can function as presinusoidal quasi-sphincters (365).

Based on the concept of a critical balance between vasoconstrictive and vasodilative agents, ET is counteracted by the vasodilating mediators NO and CO (621) (Table 1). Within the normal liver, the gaseous mole-

TABLE 1. *Vasoactive agents, their pathways, cellular source, and distribution in hepatic (patho)physiology*

Vasoactive Agent	Function	Enzyme System	Cellular Source and Distribution	Target Cell	Pathways	References
Thromboxane A_2	Vasoconstriction, platelet activation and aggregation, leukocyte adhesion	COX-1, COX-2	(S)EC, KC	(S)EC, platelet, leukocyte	TxA_2R	Yokoyama et al., 2005
Prostaglandin I_2	Vasodilation, inhibition of platelet aggregation	COX-1, COX-2	(S)EC	(S)EC, HSC	PGI_2R	Fennekohl et al., 1999; Yokoyama et al., 2005
Angiotensin II	Vasoconstriction	ACE	HSC	HSC	AT_1 subtype	Rothe and Maass-Moreno, 2000; Yokoyama et al., 2005; Bataller et al., 2000
Nitric oxide	Vasodilation	eNOS	(S)EC	VSMC, HSC	sGC	Suematsu et al., 1996; Shah et al., 1997; Pannen, 2002; Oda et al., 2003
	Vasodilation	iNOS	(S)EC, KC, VSMC, HSC, HC	VSMC, HSC	sGC	Suematsu et al., 1996; Pannen, 2002; Oda et al., 2003
Endothelin-1	Vasoconstriction		(S)EC, HSC, KC	VSMC, HSC, SEC, KC	ET_AR, $ET_{B2}R$	Rockey et al., 1998; Pannen, 2002; Oda et al., 2003; Housset et al., 1993
	Vasodilation		(S)EC, HSC, KC	(S)EC	$ET_{B1}R$	Pannen, 2002; Oda et al., 2003
Carbon monoxide	Vasodilation	HO-1	(S)EC, VSMC, KC, HSC, HC	VSMC, HSC	sGC	Suematsu et al., 1995; Suematsu et al., 1996; Pannen, 2002
		HO-2	HC	VSMC, HSC	sGC	Goda et al., 1998
Hydrogen sulfide	Vasodilation	CSE (CBS)	HSC, HC	VSMC	K_{ATP} channels	Fiorucci et al., 2005

(S)EC, (sinusoidal) endothelial cells; VSMC, vascular smooth muscle cells; KC, Kupffer cells; HSC, hepatic stellate cells; HC, hepatocytes; HO-1, inducible heme oxygenase; HO-2, constitutive heme oxygenase; sGC, soluble guanylate cyclase; eNOS, endothelial constitutive nitric oxide synthase (type III); iNOS, inducible nitric oxide synthase (type II); CSE, cystathionine γ-lyase; CBS, cystathionine β-synthase.

cule NO is predominantly synthesized by the constitutive NO synthase of endothelial cells (eNOS) of large resistance vessels but also of SEC (727) (Fig. 4). In arteriolar resistance vessels, abluminal NO release from endothelial cells acts in a paracrine fashion. NO diffuses into smooth muscle cells and reacts with the ferrous iron in the heme prosthetic group of the soluble guanylate cyclase (sGC) that increases the concentration of cGMP and activates a cell-signaling pathway, which results in smooth muscle relaxation (682, 816). Under basal conditions, NO regulates the vascular tone of the hepatic circulation in that either L-arginine or NO donors increase liver blood flow, which can be attenuated by NOS or cGMP inhibitors (563, 727, 951). Hereby, NO seems to serve as a potent vasodilator in the hepatic arterial circulation, but exerts only a minor vasodilatory effect in the portal venous bed. This is most probably due to the higher shear stress and shear stress-dependent NO release in the arterial compared with the venous bed (623). With the use of cultured SEC exposed to flow in a parallel-plate flow chamber, it has been shown that these cells respond to an increase of flow with an increased NO production (727). In line with this, NO is released from isolated perfused livers in a time- and flow-dependent manner (727). Because the hepatic sinusoids contain no smooth muscle layer, it is tempting to speculate that basal and flow-dependent NO release regulates vessel resistance by modulating stellate cells, whose perisinusoidal location is ideal to regulate sinusoidal diameter through contraction and relaxation. This view is supported by the fact that adenoviral gene vector-based expression of neuronal NOS (nNOS) in SEC, stellate cells, and hepatocytes increases NO production and inhibits ET-1-induced contractility of perisinusoidal stellate cells in normal livers (944).

In addition to biliverdin and iron, the second gaseous molecule CO is released through the physiological catabolism of the heme molecule by the microsomal enzyme heme oxygenase (HO). HO consists of two distinct isoenzymes termed HO-1 and HO-2. Under physiological conditions, HO-1, the inducible form, is only found in KC, while the constitutive form HO-2 is distributed to parenchymal cells (Fig. 4, Table 1). There is convincing evidence for the physiological significance of extrasinusoidal CO-mediated mechanisms for microvascular relaxation and that CO derived from HO-2 in hepatocytes contributes to active relaxation of

the sinusoids (234). By using dual-color digital microfluorography, Suematsu et al. (765) could demonstrate after functional blockade of HO-1 by zinc protoporphyrin IX an inhibition of baseline CO generation, an increase of resistance, a discrete pattern of constriction in sinusoids, and a reduction of the sinusoidal perfusion velocity. Because the major sites of constriction corresponded to local sinusoidal segments colocalized with hepatic stellate cells, CO is proposed to function as an endogenous modulator of hepatic sinusoidal perfusion through a relaxing mechanism involving stellate cells (765). Furthermore, CO maintains portal venous vascular tone in a relaxed state, while there is no intrinsic CO-mediated vasodilation in the hepatic artery (623).

In contrast to CO and NO, much less is reported about the role of H_2S in the regulation of hepatic microvascular blood flow. H_2S is a gaseous neuromodulator that exerts potent vasodilatory effects in both the systemic and the splanchnic circulation (201, 202). In normal livers, H_2S treatment, from either exogenous (NaHS supplementation) or endogenous (L-cysteine supplementation) sources, reverses the norepinephrine-induced increase of portal pressure (201). Unlike NO, H_2S is not produced by SEC, as they express none of the two H_2S-generating enzymes [cystathionine-γ-lyase (CSE) and cystathionine-β-synthetase (CBS)], but is released from the CSE-expressing stellate cells (201) (Fig. 4, Table 1). The fact that H_2S released by normal rat livers is not modified by an increased shear stress underscores that sites different from that of SEC are involved in the synthesis of H_2S (201). This is in line with the observation that modulation of intrahepatic resistance by H_2S is not dependent on NO (201). Although endothelial dysfunction caused by hyperhomocysteinemia comprises defective NO bioavailability, homocysteine-induced impairment of NO release can be reversed by H_2S in a NO-independent manner, indicating that NO and H_2S exert additive effects in the liver microcirculation (154).

In aggregate, the major site of blood flow regulation through sinusoids is recognized to reside in the sinusoids themselves, where the most pronounced blood pressure drop occurs in the liver. The interplay of the cellular components and all mediator systems is extraordinary complex. NO and CO may exert synergistic vasodilatory effects due to their common stimulation of sGC. Furthermore, NO may either attenuate or enhance HO-1 gene expression (301, 571). NO and CO can functionally antagonize the vasoconstrictive effects of ET (767). NO limits the ET-1 release from endothelial cells (71) and is capable of terminating ET signaling (235). Finally, NO is a physiological modulator of the endogenous production of H_2S by increasing the expression and activity of CSE (961).

D. Changes of the Microcirculation During Development and Ageing

The anatomy and morphology of the hepatic microvascular bed underlies distinct changes during postnatal development and ageing. Corrosion cast procedures and scanning electron microscopy in neonatal rats revealed the development of a simple capillary network directly pouring into the portal vein towards a peribiliary vascular plexus being composed of arteries and veins in the outer layer and of capillary vessels in the inner layer (272). In parallel, the intrahepatic biliary tree matures within the first 4 wk of newborn rats. The hepatic artery gradually develops. One-day-old animals show small branches of the hepatic artery ending in sinusoids or capillary plexuses around portal vein branches near the hilus. After 4 wk, branches appear up to the peripheral portal networks (272). Survey of the rat liver architecture by in vivo fluorescence microscopy demonstrates a progressive growth of the lobular areas with a proportional increase of postsinusoidal venules from early juvenile to adult (867). In weanling rat livers, lower sinusoidal resistance due to shorter sinusoidal pathways is countered by the smaller caliber of the sinusoids so that overall sinusoidal resistance seems to be not age dependent (160). In addition, age does not affect sinusoidal density and dispersion number, because 24-mo-old rats are reported to present a sinusoidal perfusion rate above 98%, similarly as observed in juvenile rats (867, 888). On the contrary, a 14% reduction in the number of perfused sinusoids with a 35% decrease of sinusoidal blood flow is reported for 27-mo-old senescent mice that might be due to species differences or different age groups (327). In addition to microhemodynamics, age also affects the endocytotic capacity of sinusoidal endothelial cells in mice (327) and rats (471). The age-related thickening and defenestration of the liver sinusoidal endothelial cell, as well as the sporadic deposition of collagen and basal lamina in the extracellular space of Disse, known as "pseudocapillarization" (470) further impair the hepatic clearance capacity in the elderly (471). In addition, loss of fenestrations hampers transfer of lipoproteins from blood to hepatocytes and might explain the impaired hepatic lipoprotein metabolism with old age (469).

III. TECHNIQUES FOR THE STUDY OF THE HEPATIC MICROCIRCULATION

Measuring blood flow to the liver is fundamental for the understanding of the organ's physiology and pathophysiology. However, it comprises several challenges due to the fact that the liver blood supply is dual, the ratio of portal venous to hepatic arterial flow is not constant, and the direct access to the vessels is difficult. In the follow-

ing, quantitative techniques that are frequently applied in experimental research and clinical settings are addressed.

A. Radioactive, Colored, and Fluorescent Microspheres Technique

The microspheres technique is relatively simple and extraordinarily accurate, if appropriately applied. Typically, carbonized insoluble plastic microspheres, labeled with radioactive gamma nuclides, such as ^{141}Ce, ^{51}Cr, ^{85}Sr, ^{95}Nb, and ^{46}Sc, can be used (126, 857). The method is based on the indicator fractionation principle. A known number of radioactive microspheres is injected into the left ventricle, and a reference sample is simultaneously withdrawn from a peripheral artery using a pump. The injected radioactive microspheres are trapped in the various vascular beds in the body in proportion to the fraction of the cardiac output supplying the individual vascular bed. Upon removal of the organ, radioactivity in the organ samples is assessed by a gamma scintillation counter as radioactive counts per minute (CPM). Organ blood flow (Q) is then calculated as follows: Q = organ radioactivity × reference blood flow/reference blood radioactivity.

With the use of this technique, only hepatic arterial blood flow can be measured, while portal venous flow must be estimated by adding the separate flows to the splanchnic organs that drain into the portal vein (858).

For the technique to work, the microspheres must be trapped on the first circulation, be evenly distributed, and should have no effect on the liver blood flow and function. In general, 15-μm-diameter microspheres satisfy both the conditions of distribution similar to red blood cells and the absence of significant nonentrapment (125, 857). Compared with larger microspheres, 15-μm-diameter microspheres are distributed more like red blood cells, obstruct less the vascular bed, are less variable in size, and can be given in significantly greater numbers, enhancing the statistical precision of the measurements (291). Only a small number of 15-μm microspheres fail to be trapped in the liver (142, 890). Uniform mixing of the microspheres already at the aortic root is best achieved by injection into the left atrium (dog, sheep, pig) (268) or the left ventricle (rodents) (126, 857). Evenness of microsphere mixing can easily be assessed by comparison of the number of spheres per gram tissue in the left and right cerebral hemisphere or the left and right kidney, which should not differ by >10%. Calculation of the number of spheres injected should consider that 384 microspheres must be present in the portion of the organ studied to have a distribution variability within 10% of the mean distribution at the 95% confidence level (291). The more microspheres injected, the higher the precision of measurement is, but also the risk for deterioration of the systemic or regional circulation.

Although the microspheres technique is still regarded as the gold standard to assess nutritive organ perfusion (ml per min and g tissue), the technique requires postmortem removal of organs and, thus, has no clinical application. The additional limitations of radiation and environmental pollution had meanwhile been overcome by the fabrication of fluorescent or colored microspheres (242, 641) (Fig. 5). By simultaneous blood flow measurement with radionuclide-labeled and colored microspheres, it was shown that the techniques produced comparable values of liver blood flow (39). Currently, the fluorescent microspheres technique seems to be the most promising nonradioactive microspheres technique, because the use of nonradioactive microspheres saves money, facilitates the use of microspheres in chronic animal experiments, and, using histological techniques, allows the assessment of particle distributions in subunits of organs (642). The fluorescent microspheres technique has a high sensitivity and a good spectral separation. Thus the number of microspheres injected can be as small as that used for radioactive microspheres, and at least six labels can be measured simultaneously. In addition, the relatively large volume in which fluorescence is measured

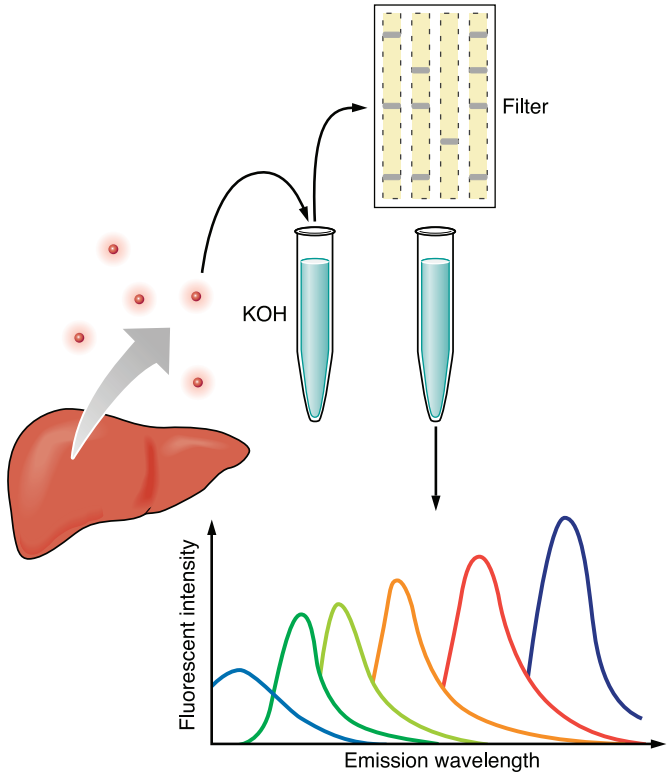

FIG. 5. Microspheres technique for the determination of hepatic arterial blood flow. Upon entrapment of colored or fluorescent microspheres within the liver, the organ is removed and cut into small pieces for subsequent digestion with potassium hydroxide. After microfiltration, the dyes are extracted from the microspheres with a known volume of solvent. Spectrometry allows for separation of the various colors and their concentration.

(~1–3 ml) enables the use of time-saving microsphere isolation techniques and further automation of the quantification process (using either automized spectrometry or FACS analysis) (642) (Fig. 5).

B. Hydrogen, Xenon, and Indocyanine Green Clearance Technique

Inert gas clearance has been used for more than 30 years to measure hepatic blood flow (507). Injection of a saline solution of ^{133}Xe is usually made via the portal vein, and the resulting hepatic clearance is monitored with a Geiger-Müller tube, scintillation crystal, or gamma camera (368, 507, 532). Accuracy of flow measurement is critically dependent on the knowledge of the partition coefficient of the gas used. The fact that the gas partition coefficient remains unaffected by liver diseases makes the technique an attractive tool for the measurement of hepatic hemodynamics in humans.

Beside portal venous application, there are reports introducing the intrasplenic (445) and the hepatic intraparenchymal application of ^{133}Xe for measurement of hepatic blood flow (352, 491). Nowadays, nonradioactive gases, like hydrogen (H_2) or xenon, are commonly administered with the respiration gas. They distribute instantaneously until the tissue reaches saturation. Then the supply of the gases is turned off, and their clearance rates are determined polarographically through platinum electrodes placed on or into the liver to a depth of 3–6 mm (783). The H_2 clearance technique has been successfully applied in various experimental models for the study of liver blood flow in rats, dogs and pigs (304, 436, 584, 783, 790). In clinical practice, the temporal changes in radiographic enhancement produced by xenon gas inhalation are measured by sequential computer tomography and then the time-dependent xenon concentrations within the various tissue segments are used to achieve local liver blood flow maps (263, 264, 735).

Next to the measurement of the products of liver synthesis, a second approach of assessing liver function is to monitor hepatic clearance function using sulfobromophthalein or indocyanine green (ICG). In addition to serving as an objective test of hepatocellular function (75), ICG clearance has been considered to represent a valid method for determination of hepatic perfusion. In support of this view, simultaneous use of the radioactive microspheres technique, the laser Doppler flowmetry, and the ICG clearance method have revealed similar values for hepatic blood flow in an experimental setting of hemorrhagic shock and resuscitation (884, 885). Of interest, hepatic ICG clearance can be measured directly using near-infrared spectroscopy (see sect. III*E*). By this, significant positive correlations can be obtained between hepatic ICG rate of uptake and both hepatic blood flow and microcirculation (172). In addition, ICG uptake measured directly by NIRS is sensitive to assess reduced liver microvascular blood flow in cirrhosis, and its excretion correlates with the degree of liver parenchymal dysfunction (356). Of interest, ICG clearance is also inversely correlated with the collagen content of the liver (846), indicating that the reduction of the microcirculation is part of the manifestation of the disease.

Experimental studies have shown that the blood flow measured by the H_2 gas method was only 39% of the calculated blood flow by the ICG method. This indicates that the H_2 gas clearance technique may be a method that assesses hepatic arterial liver perfusion rather than total hepatic blood flow (243). Moreover, ICG clearance is thought to assess only 30% of the blood flow, which was measured electromagnetically by direct placement of flow probes around the hepatic artery and portal vein (138). This may be due to a significant amount of shunting of electromagnetically measured blood flow which is not detected by the ICG method. Overall, these results underline the challenge to accurately assess liver blood flow, which is mainly due to the dual blood supply and the particular interrelation of these two vascular systems.

C. Multiple Indicator Dilution Technique

The description of the indicator dilution principle to calculate flow and volume goes back to Stewart in 1894 (760) and is discussed with respect to its theoretical foundation by Meier and Zierler (549). In brief, an indicator is injected into an organ with one inflow and one outflow. Observations of the concentration C as a function of time t of the indicator in the outflow permits the calculation of flow (F), i.e., $F = q_0/C(t) \times dt$, where q_0 is the amount of indicator injected. Typically, the technique comprises the combination of diffusible substances apt to leave the capillaries together with the inclusion of a vascular reference substance (660). Goresky (239) introduced this method to the study of the circulation in the liver and described a linear method to calculate sinusoidal and extravascular volumes (Fig. 6). Due to the specific anatomy of the hepatic sinusoids with lack of a basement membrane and the presence of fenestrae, extravascular substances such as albumin and sucrose are freely diffusible, establishing the pattern of flow-limited multiple dilution curves as opposed to the barrier-limited pattern (238). The technique allows calculating not only volumes of distribution, but also to study transport of hormones, drugs, organic and anorganic ions, bile acids, and metabolic substances (240, 618, 715, 895).

Although over the last three decades there has been major progress made in the field of modeling the liver for investigating the kinetic behavior of substrates, drugs, and metabolites (812), the multiple indicator dilution

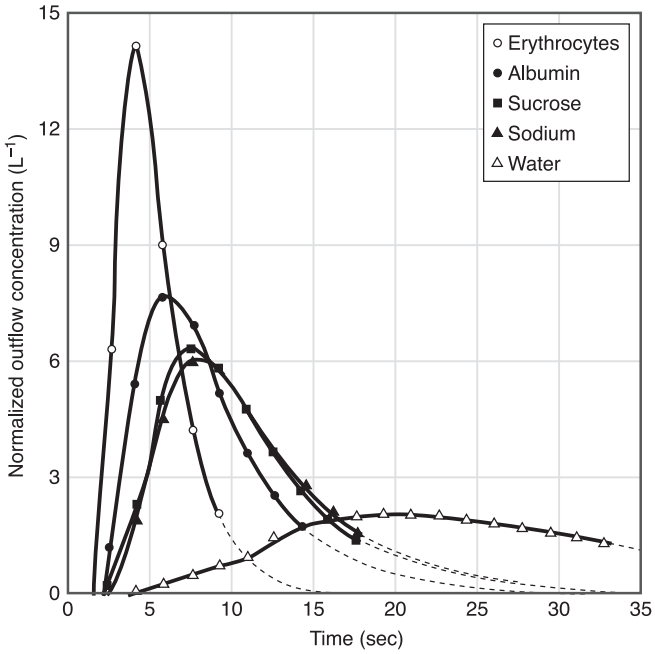

FIG. 6. Multiple indicator dilution technique for assessment of liver blood flow. Displayed are outflow profiles for ^{51}Cr-labeled erythrocytes (white dot), Evans blue as an indicator for albumin (black dot), [^{14}C]sucrose (black square), $^{22}Na^{+}$ (black triangle), and ^{3}HOH (white triangle) in the liver of an anesthetized dog. Broken lines represent monoexponential extrapolation of data to correct for recirculation. [From Goresky (239).]

technique is not universalized. Surprisingly, relatively few studies have investigated this method which, for instance, is ideally suited to probe the permeability properties of hepatic sinusoids and to assess receptor-binding kinetics within the hepatic microcirculation (87, 148, 308, 311, 853). By means of multiple indicator dilution technique, Dupuis et al. (164), investigating the hepatic binding of tracer ^{125}I-labeled ET-1, could demonstrate that there is both substantial clearance and production of ET-1 by the intact liver and that ET-1 clearance is mediated by the ET_B receptor with the presence of reversible, nonspecific ET-1 binding at the liver surface. As an extension of the latter observation, it was demonstrated that ET-1 markedly decreases extravascular albumin space in both controls and cirrhosis (659) and that cirrhosis reduces ET-1 clearance probably by capillarization of hepatic sinusoids and reduced access to ET_B receptors. This contributes to the increase of circulating ET-1 levels in chronic liver disease (817).

D. Laser Doppler Flowmetry

The Doppler effect, named after Christian Doppler, is the change in frequency and wavelength of a wave for an observer moving relative to the source of the waves (669). Laser Doppler flowmetry is an established technique for the real-time measurement of microvascular red blood cell perfusion in tissue, including the liver (14). The technique relies on the assessment of the Doppler shift in wavelengths of reflections from particles moving with the flow. It works by illuminating the tissue under investigation with low-power laser light from a solid-state diode laser operating at ~780 nm, which is guided to the measurement site via an optical fiber. Two identical adjacent fibers receive backscattered light from the tissue which is then transmitted to independent photodetectors (14). This back-scattered portion consists of light scattered from the static tissue matrix which has not been Doppler shifted and a spectrally broadened component resulting from interactions with moving cells. Optical mixing of these components at the photodetector surface produces an electrical signal containing the Doppler shift information. The readout signal is defined as microvascular perfusion (red blood cell flux) = number of cells moving in the tissue sampling volume × mean velocity of these cells.

Red blood cell flux is dependent from hematocrit and red blood cell velocity. It has been shown to respond linearly to velocity-mediated flow changes, while increases in tissue red blood cell concentrations are underestimated (14). The ease of operation and the continuous and real-time measurements with a high degree of spatial resolution are considerable advantages of laser Doppler flowmetry over other techniques (797, 897). However, the major limitation of the technique is that laser Doppler devices do not assess absolute blood flow, as different tissues present with different optical properties, but, instead, provide measurement of arbitrary blood perfusion units (BPU). Moreover, the actual sampling volume and the depth at any tissue site cannot be assessed, which definitely limits its quantitative use. Furthermore, baseline values are very variable and, thus, results should be expressed in general as changes relative to baseline (859).

However, comparison between laser Doppler flowmetry and intravital fluorescence microscopy revealed a significant correlation between red blood cell flux and sinusoidal perfusion rate, indicating a reliable assessment of the hepatic microperfusion by this noninvasive technique (405, 637, 798, 864). In line with this, it has been shown that the laser Doppler signal primarily depends on flow in the sinusoids, and not on flow in the efferent portal venules and central veins (798). In addition, a strong correlation between the laser Doppler flowmetry signal and the total liver blood flow (14) and the portal venous and hepatic arterial flow (23) have been demonstrated. In addition to the analysis of the hepatic microcirculation, the laser Doppler technique may also be used to study flow in larger blood vessels, such as the inflow or outflow vasculature of the liver. Accordingly, laser Doppler flowmetry probes were successfully placed onto the hepatoduodenal ligament for measurement of portal ve-

nous inflow changes upon extended hepatectomy (169, 231).

E. Near-Infrared Spectroscopy

Near-infrared (650–1,100 nm) spectroscopy (NIRS) is a relatively new, noninvasive technique that uses the principles of light transmission and absorption and that allows a continuous monitoring of changes in intravascular (hemoglobin) and mitochondrial (cytochrome aa_3) oxygenation in relatively large tissue samples of 2–6 cm^3 (199, 488). The technique depends on the relative transparency of biological tissue to light in the near-infrared region of the spectrum. In contrast to light at visible wavelengths of 450–700 nm, which is strongly reduced in tissue and which can only penetrate a maximum distance of a few millimeters, absorption of light by the tissue chromophores is significantly lower at near-infrared wavelengths of 700–1,000 nm. Sensitive detectors can assess light that has transversed up to 80 mm of tissue (44). There are three main compounds in the liver whose near-infrared absorption characteristics vary with their oxygenation status, i.e., oxyhemoglobin, deoxyhemoglobin, and cytochrome oxidase. The application of NIRS to monitor liver oxygenation has been extensively validated and allows to compute absolute changes in oxyhemoglobin, deoxyhemoglobin, and cytochrome oxidase in micromoles per liter of hepatic tissue (174, 175, 931).

NIRS-assessed cytochrome oxidase (intracellular oxygenation) has been shown to correlate with intracellular β nucleoside triphosphate under graded hypoxia of rat livers (718). It further correlates with the parameters of hepatocellular injury to a higher degree than HbO_2 (extracellular oxygenation) (173). Thus NIRS-assessed cytochrome oxidase reflects cellular ATP metabolism (718). Application of NIRS optodes across the right hepatic lobe of piglets in endotoxemic shock indicates significant correlations between the perfusion parameters and the NIRS readings. This is reflected by a simultaneous decrease of oxyhemoglobin readings and liver oxygen delivery, liver blood flow, and cardiac output. Vice versa, deoxyhemoglobin readings highly correlate with mixed venous lactate and with hepatic vein lactate (577, 578). In humans, intraoperative NIRS is used to determine hemoglobin and cytochrome oxidase content as parameters of perfusion and oxygenation in hepatic tissue (604). NIRS enables quantification of the congestion and impairment of mitochondrial redox state in the anterior segment of a right lobe liver graft caused by deprivation of the middle hepatic vein tributaries (561, 604). In addition, measurement of hepatic ICG uptake by NIRS reveals impairment of sinusoidal perfusion in the veno-occlusive regions of living donor livers (278). Thus NIRS might represent a valuable tool for assessing the indication for venous reconstruction in living-donor liver transplantation and split donor liver transplantation.

F. In Vivo Fluorescence Microscopy

The first detailed description of intravital microscopy dates back to the middle of the second last century, when Waller described the passage of leukocytes through microvessels in the frog tongue (878). Later, because of its ease of exposure and its high translucency, the mesentery was acknowledged as a suitable object for the study of microvascular morphology and function (975). Advanced optical imaging in combination with video technology has not only improved imaging quality at up to 1,000-fold magnification using both trans- and epi-illumination technique, but has also considerably widened the spectrum of intravital microscopy, being applied in almost all organs of the body, including the liver (550, 553).

Knisely (399, 400) was the first who reported on a method of illuminating living structures of the liver for microscopic study. He presented the use of properties of fused quartz for conducting light by internal reflection from one end of a rod of this material to the other end (399). During the following 20 years, ~6,000 animals have been analyzed to establish the basic concepts of the living anatomy and certain aspects of the physiology and pathology (for review, see Ref. 55). Of this number, about two-thirds have been frogs, while the other third constituted of rats, mice, bats, guinea pigs, rabbits, dogs, and monkeys. In 1948, Knisely, Bloch, and Warner (397) reported on the regulation of blood flow through the frog liver and presented a schematic drawing of the frog liver lobule, displaying vascular structures, which all could be reidentified and confirmed by subsequent studies. Using also the fused quartz rod transillumination method, Irwin and MacDonald (323) reported on the transillumination of the lower edge of livers of anesthetized guinea pigs, particularly emphasizing the obstacles of this approach. By means of intratracheal insufflation of oxygen and specific surgical exposure of the liver, they overcame the respiration-associated movement of the liver as the factor limiting the resolution of the optical system and provided the first quantitative data on diameters of the various intrahepatic vessels (323). In 1955, Bloch (55) added a few modifications, achieving a twofold increase of magnification. Although the basic concept of the vascular pattern of liver lobules was derived from these transillumination studies, the technique is restricted to the thin edges and boundaries of the liver, because only these tissue portions allow enough light to transmit for visualization of microscopic blood vessels. As a consequence, the number of microvascular segments accessible for intravital microscopic studies is strictly limited. Accordingly, the description of leukocyte adherence (661) and phagocytosis (54)

has been only qualitative in nature. Even in case of quantitative analysis of the transilluminated liver (415, 661, 662), results should be interpreted with caution, because the areas within the liver periphery present with a considerable extent of nonperfused sinusoids already under baseline conditions (167) and cannot be considered representative for the liver microcirculation in general.

With the introduction and use of fluorescent markers, the spectrum of hepatic in vivo microscopy could be widened from the transillumination approach to the epi-illumination technique (Fig. 7). Moreover, the availability of an enormous number of different fluorescent markers for ex vivo and in vivo staining has extended the possibilities of intravital microscopy from purely morphological analysis to the study of complex physiological and pathological events. Apart from all changes in microhemodynamics, i.e., sinusoidal perfusion, sinusoidal diameter, blood cell velocity and flux, as well as volumetric blood flow, various cellular and molecular aspects can be studied (Fig. 7). The quantitative analysis of the hepatic microcirculation includes the perfusion of the terminal afferent vessels, the sinusoids and the postsinusoidal venules, as visualized after intravenous administration of sodium fluorescein (859) or fluorescein isothiocyanate (FITC)-labeled macromolecular substances, such as albumin (112) and dextran (123, 124, 556, 761) (Fig. 7*A*). Depending on the molecular weights of the individual compounds and on the differences in secretion rates exhibited by hepatocytes in different acinar zones, the kinetics of distribution of the fluorescence across the lobule markedly differ (731). While sodium fluorescein with a molecular weight of 371 almost freely diffuses from the intravascular sinusoidal towards the extravascular space, there is significant intravascular retention of FITC-dextrans with calculated effective diffusion coefficients, being 2.5 times larger for dextrans with <66,000 molecular weight compared with dextrans of 156,000 molecular weight. In addition to analysis of perfusion, the use of high-molecular-weight dextrans is further suited to study the macromolecular trans-sinusoidal exchange capacity of the liver, which is typically limited upon fibrosis- and cirrhosis-associated deposition of extracellular matrix and thus increased diffusion hindrance (875).

The quality of sinusoidal blood flow can be quantitatively assessed by determining the sinusoidal perfusion rate or the functional density of sinusoids. The sinusoidal perfusion rate reflects the number of perfused sinusoids in percentage of all sinusoids. The functional sinusoidal density represents the length of red blood cell perfused sinusoids per square centimeter area of observation. The recording and assessment of these two parameters, however, are time-consuming. A more easily applicable and time-sparing procedure is the usage of the nuclear marker bisbenzimide (H33342; 2 μmol/kg iv) with near ultraviolet epi-illumination to assess hepatic microvascular perfusion failure by planimetric analysis of faint hepatocellular staining in areas of nonperfused sinusoids (870). Application of bisbenzimide further allows for the visualization of hepatocyte distribution in vivo and can be used for detailed morphological analysis of proliferating hepatocytes undergoing either hyperplasia or hypertrophy (6).

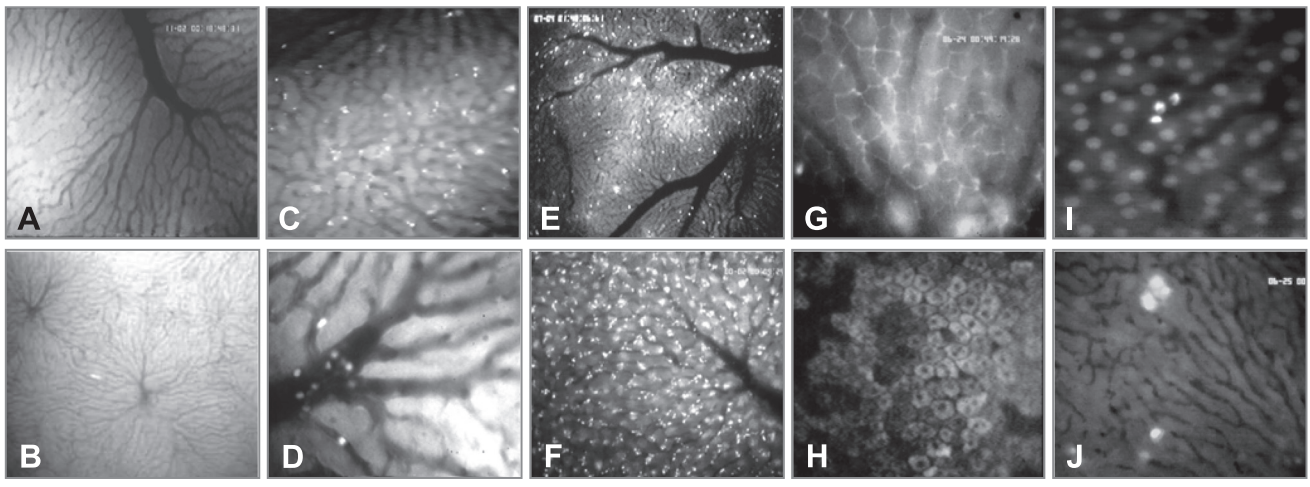

FIG. 7. Intravital fluorescence microscopy of the rat liver in epi-illumination technique. This high-resolution real-time technique allows to visualize the hepatic sinusoidal perfusion (*A*) and parenchymal NADH autofluorescence (*B*), platelet (*C*) and leukocyte (*D*) adhesive interaction, Kupffer cell phagocytic activity (*E*) and hepatic stellate cell-associated vitamin A distribution (*F*), biliary canalicular secretion (*G*) and hepatocellular transport (*H*), as well as apoptotic (*I*) and necrotic cell death (*J*). *A*: blue light epi-illumination and sodium fluorescein. *B*: hepatic autofluorescence upon near ultraviolet epi-illumination. *C*: blue light epi-illumination and ex vivo BCECF-stained platelets. *D*: green light epi-illumination and in vivo acridine orange-stained leukocytes. *E*: blue light epi-illumination and yellow-labeled latex beads. *F*: near ultraviolet light epi-illumination and vitamin A autofluorescence. *G* and *H*: blue light epi-illumination and sodium fluorescein. *I*: near ultraviolet light epi-illumination and bisbenzimide. *J*: green light epi-illumination and propidium iodide. Magnification: *B* and *E*, ×100; *A*, *C*, *D*, *F*, *G*, *I*, ×200; *H*, *J*, ×400.

Intravital fluorescence microscopy further allows estimating hepatocellular transport after application of sodium fluorescein or FITC-labeled bile salts. Along with the differences in secretion rates exhibited by hepatocytes in different acinar zones, the sinusoid-to-bile transport times markedly differ among fluorescent compounds and can be used for the study of hepatocyte function and biliary secretion by imaging hepatocellular brightness (Fig. 7*H*) and the accumulation of the fluorescent dye within the fine canalicular network (731) (Fig. 7*G*). In addition to that, intra-arterial injection of fluorescently labeled latex particles allows for the assessment of the phagocytic activity of the KC in that calculation of the clearance of beads from the circulating blood (fraction of nonadherent particles over time) nicely reflects KC phagocytosis (508, 636, 707, 747, 861, 871) (Fig. 7*E*). Most recently, fluorescent-labeled liposomes consisting of phosphatidylcholine and phosphatidylserine have been described as a useful research tool to intravitally stain and to clearly delineate KC using both confocal laser scanning microscopy and in vivo microscopy (891).

In addition, the intravenous application of acridine orange and rhodamine-6G allows for the in vivo staining of leukocytes and platelets and, thus, for the quantitative analysis of the flow behavior along the microvascular path (347, 406) and the interaction of these cells with each other and with the endothelial lining of the microvasculature (380, 474, 551, 865) (Fig. 7*D*). There is evidence for a zonal gradient of leukocyte velocity in the liver sinusoids, with increasing velocity from zone 1 to zone 3 due to the wider diameters, the lower resistance, and the less tortuous path in zone 3 (406). In addition to in vivo staining, circulating blood cells, in particular platelets, can also be isolated and stained ex vivo (874). For this purpose, dyes, such as bis-carboxyethylcarboxyfluorescein (BCECF) and calcein, are used, providing an appropriate bright staining of the cells (168) (Fig. 7*C*). Moreover, ex vivo FITC-stained erythrocytes are used for the determination of red cell velocity and can be stored at 4°C after addition of citrate-phosphate dextrose (1.4:10) up to 5 days. Prior to microscopy, cells are diluted 1:1 in saline and are visible as single bright dots (969).

Another potential of in vivo fluorescence microscopy is to monitor NADH fluorescence of liver parenchymal tissue (74, 770, 856) (Fig. 7*B*). Chance and co-workers (95, 96) pioneered the fluorescence property of NADH as an indicator of mitochondrial redox state and, in the presence of sufficient substrate and phosphate, as an indicator of cellular oxygen. NADH is a naturally occurring intracellular fluorophore and one of the main means of transfer energy from the tricarboxylic acid cycle to the respiratory chain in the mitochondria (317). Inhibition of the respiratory chain due to inadequate oxygen supply is reflected by increased intracellular NADH levels. Upon ultraviolet epi-illumination of tissue, NADH, unlike NAD^+, fluoresces in blue (317). Experimental studies in rats undergoing hemorrhagic shock and resuscitation revealed significant correlations between NADH fluorescence and both hepatic tissue oxygenation and hepatic bile flow (856). A further approach to study the metabolic state of the liver by intravital microscopy is the intravenous administration of the oxygen-sensitive fluorescent dye tris(1,10-phenanthroline)ruthenium(II) chloride hydrate [$Ru(phen)_3^{2+}$] (628). In contrast to NADH, reflecting the mitochondrial redox state and the activity of the mitochondrial electron transport chain, $Ru(phen)_3^{2+}$ fluorescence is directly dependent on the tissue Po_2. Thus the simultaneous use of both fluorimetric methods may provide important information about mechanisms of tissue hypoxia with differentiation between oxygen supply and oxygen utilization deficits (628).

In addition to the diffuse NADH autofluorescence of parenchymal tissue, stellate cells are easily visualized by ultraviolet epi-illumination because of the autofluorescence of stored vitamin A (766, 870) (Fig. 7*F*). Under continuous near-ultraviolet excitation, there are multiple patchy activities along the sinusoids and terminal hepatic venules, which correspond to the fat-storing intracellular droplets of stellate cells. These fluorescent activities show a rapid photobleaching phenomenon and can completely be eliminated by a vitamin A-deficient diet-induced depletion of intrahepatic retinoid contents. Vice versa, repeated administration of vitamin A significantly enhances the patchy fluorescent activities (766, 863). Moreover, it has been shown that hepatic stellate cell-associated area of ultraviolet vitamin A-autofluorescence increases with age and significantly correlates with increasing tissue concentrations of vitamin A metabolites (867). Thus intravital fluorescence microscopy enables the in vivo assessment of stellate cells, which are uniformly distributed throughout the liver under physiological conditions. In contrast, there is a striking redistribution and accumulation of stellate cells in fibrous septa upon CCl_4 exposure of rats, which is associated with a subsequent loss of the vitamin-A storing function due to their transformation into myofibroblast-like cells (873).

More recent developments further allowed extending the microcirculatory analyses with the intravital microscopic assessment of cell viability, differentiating between apoptotic and necrotic cells. Apoptotic cell death can be determined in vivo after staining the nuclei of hepatocytes by bisbenzimide (H33342; 2 μmol/kg iv) using a near-ultraviolet filter system (330–380/>415 nm) (Fig. 7*I*). Characteristic signs of cell apoptosis which can be detected by the H33342 staining are condensation, fragmentation, and margination of nuclear chromatin. These can be analyzed quantitatively, providing the number of apoptotic cells per square millimeter observation area (176, 705). To distinguish from apoptotic cell death, propidium iodide can be applied for staining of necrotically

damaged hepatocytes (68, 784, 964) (Fig. 7*J*). By combining propidium iodide for assessment of necrotic cell death with rhodamine-123 for assessment of mitochondrial depolarization, it could be shown that hepatocytes taking up rhodamine-123 fail to exclude propidium iodide, indicating that depolarization precedes cell death (964).

Fluorescent pH-sensitive probes, such as BCECF, allow for the in vivo measurement of liver tissue pH, although spectra may considerably vary depending on the blood content of the illuminated area and the time range in which the measurement is performed (151). With the use of digitized video microscopy and single, cultured rat hepatocytes, quantification of cytosolic pH and vesicular pH is reported by ratio imaging of the pH-sensitive BCECF fluorescence and FITC-dextran fluorescence (713). In addition, digital imaging fluorescence microscopy allows for assessment of changes in cytosolic free calcium by fura 2 loading of hepatocytes (792). In conclusion, due to the high versatility, we feel that intravital fluorescence microscopy is the most ideal tool *1*) to analyze complex biological interactions and dynamic hepatic disease mechanisms and *2*) to develop and test novel prophylactic and therapeutic approaches aimed at the disruption of microcirculatory and microvascular pathology in liver diseases.

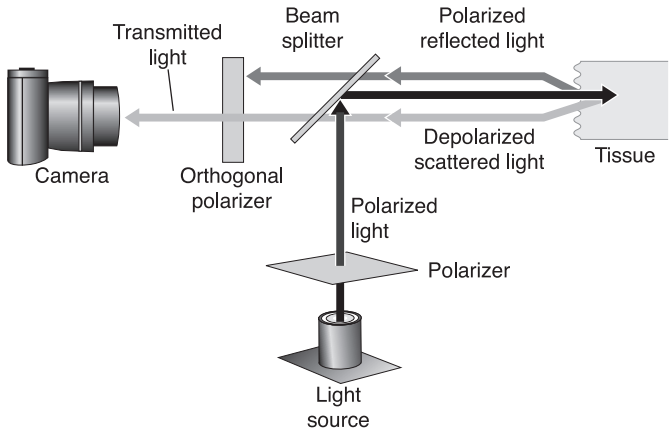

FIG. 8. Schematic representation of the technique of orthogonal polarized spectral (OPS) imaging. Light passes a spectral filter to isolate the wavelength region and is then linearly polarized and reflected toward the target tissue by a beam splitter. By means of a focusing objective lens, a region of ~1 mm in diameter of the target tissue is illuminated. The identical lens collects the remitted light, which forms the image of the illuminated region upon the charge-coupled device camera. Hereby, the orthogonal polarizer in front of the camera increases efficacy in that one orthogonal polarization state is reflected while the other is transmitted.

G. Orthogonal Polarized Spectral Imaging

In orthogonal polarized spectral (OPS) imaging, the tissue is illuminated with linearly polarized light and imaged through a polarizer oriented orthogonally to the plane of the illuminating light (Fig. 8). The OPS technique delivers images of the microcirculation that are comparable to those achieved with intravital fluorescence microscopy (252, 449), but without the use of fluorescent dyes. In rats undergoing hepatic I/R, OPS imaging has been shown to allow accurate quantification of the sinusoidal perfusion rate, vessel diameter, and venular red blood cell velocity. There was a significant correlation of microcirculatory parameters between OPS and in vivo fluorescence microscopic imaging (449). For optimal imaging with the OPS technique, a wavelength at which oxy- and deoxyhemoglobin absorb equally (548 nm, isobestic point) is chosen. As a consequence, blood vessels of the microcirculation can be visualized as in intravital transillumination microscopy (252). OPS imaging relies on the absorbance of hemoglobin to create contrast and, thus, is dependent on the presence of red blood cells within the microvessels to be visualized. The power of the system is sufficient to resolve a single red blood cell and individual capillaries with a diameter of ~5 μm.

Apart from the fact that OPS imaging is useful for the quantitative determination of local hematocrit using the optical density approach in epi-illumination, this noninvasive, small and easily portable, hand-held imaging technology represents a new diagnostic tool for the study of human microvascular physiology and pathology. With the application of OPS imaging in four different regions of interest of the left and right liver lobes in 11 healthy individuals before partial liver resection for living-donor liver transplantation (Fig. 9), OPS imaging could for the first time demonstrate in vivo human physiological values of sinusoidal red blood cell velocity of 0.97 ± 0.43 mm/s, mean sinusoidal diameters of 8.8 ± 0.9μm, sinusoidal volumetric blood flow of 58.2 ± 9.6 pL/s, intersinusoidal distance of 22.6 ± 2.5 μm, and functional sinusoidal density of 391 ± 30 cm^{-1} (648). In the setting of hepatic I/R, OPS imaging further proved to be a valuable tool to assess the deterioration of the hepatic microcirculation, which represents a determinant for graft dysfunction (646, 647, 709) (Fig. 9*D*). Using this technology, liver surgeons will be able to monitor development and progression of microcirculatory disorders as well as effects of treatment on the hepatic microcirculation.

H. Sidestream Dark-Field Imaging

Sidestream dark-field (SDF) imaging is the successor of OPS imaging. It consists of a light guide, surrounded by diodes, emitting 530 nm light. This is absorbed by the hemoglobin of red blood cells, allowing their observation as dark cells in the microcirculation. The diodes at the tip of the guide are optically isolated from the inner image-conducting core, and pump light deep into the tissue,

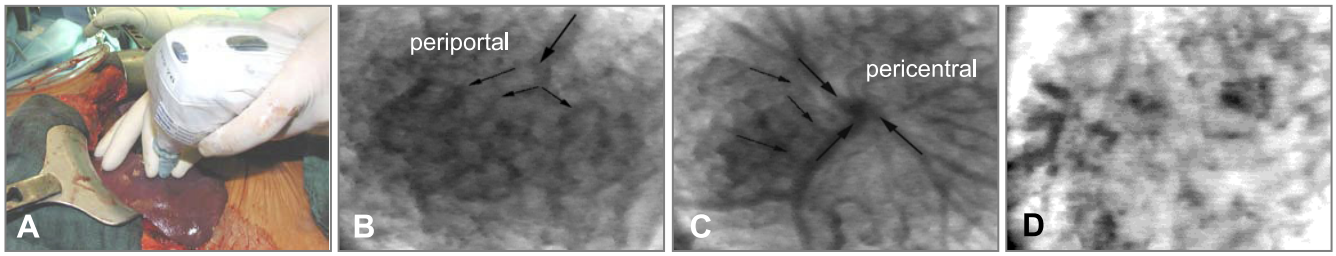

FIG. 9. OPS imaging for assessment of human hepatic microcirculation. *A*: the OPS probe is positioned on the liver surface of a healthy individual before partial liver resection for living-donor liver transplantation. The OPS probe is equipped with a sterile cap and is easily held by hand for imaging. Representative OPS images of the hepatic microcirculation before liver resection (*B* and *C*), displaying the blood flow direction (arrows) from periportal to pericentral sinusoids. *D* illustrates the human hepatic microcirculation upon transplantation, revealing the I/R-induced sinusoidal perfusion failure. *B–D* magnification ×465. [From Puhl et al. (648).]

illuminating the microcirculation from within. This dark-field illumination applied from the side avoids tissue surface reflections and thus enables very clear images of the microcirculation with visualization of not only red, but also white blood cells (318). So far, there is one application of SDF imaging to study rat liver microcirculation, revealing a mean functional sinusoidal density of 402 ± 15 cm^{-1}, a sinusoidal diameter of 10.2 ± 0.5 μm, and a mean postsinusoidal venular diameter of 34 ± 13 μm (93).

IV. MICROVASCULAR INFLAMMATION IN LIVER INJURY

A. Kupffer Cell Activation, Oxidative Stress, and Mediator Release

The hepatic macrophage population significantly contributes to the innate immunity, in particular by its initial and rapid response to potentially dangerous stimuli. Together with the SEC they form the reticuloendothelial system of the liver. They constitute the first macrophage population of the body to come in contact with bacteria, bacterial endotoxins, and microbial debris derived from the gastrointestinal tract and transported via the portal vein to the liver. This strategic location with the predominant site in the periportal segment of the hepatic sinusoids suggests a central role of KC in regional and systemic defense (Fig. 10).

KC are found to be distributed over zone 1 (periportal), zone 2 (midzonal), and zone 3 (pericentral) of the rat liver lobule in a ratio of 4:3:2. The periportal KC are larger and show higher lysosomal enzyme activities on a per cell basis with large and heterogeneous lysosomes, and higher endocytic activity than those located in midzonal and pericentral segments of the sinusoids (746). In line with the fact that the functional heterogeneity of KC is related to their position in the liver lobule, periportal KC display low expression levels of MHC class II molecules and show highest production of tumor necrosis factor-α (TNF-α) and prostaglandin E_2 (PGE_2), while pericentral (smaller) KC are more active in Ia antigen expression and elaborate more IL-1, representing important components of the immune response (328).

KC have three complex functions: *1*) phagocytosis of particulate matter and uptake of macromolecules, *2*) presentation of antigens, and *3*) release of soluble mediators (52). For the clearance of blood, KC are endowed with a variety of receptors, facilitating their function as sentinel cells. Scavenger receptors, including the scavenger recep-

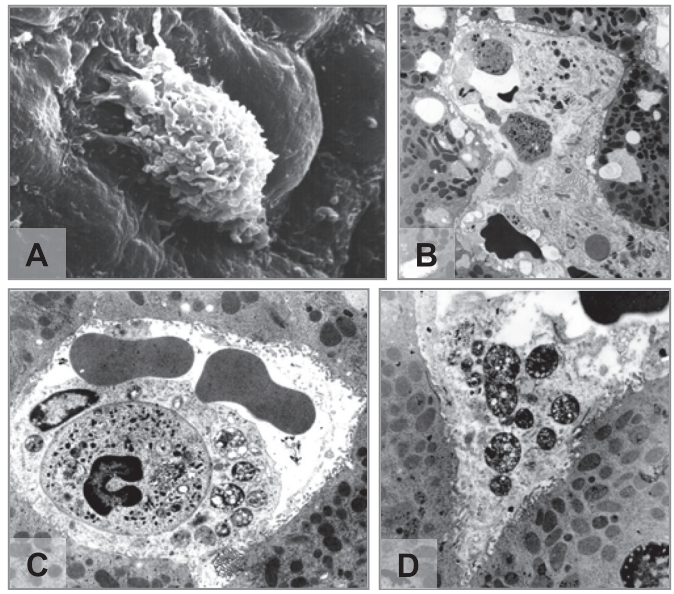

FIG. 10. Scanning (*A*) and transmission (*B*) electron micrographs of hepatic Kupffer cells in rat livers upon endotoxin exposure. The activated Kupffer cell, being attached to the luminal surface of the sinusoidal endothelium, presents an irregular surface with numerous microvilli (*A*). Further early signs of activation are an irregular shape, variable-sized vacuoles, and enrichment of lysosomes and phagolysosomes (*B*). Intrasinusoidally accumulated platelets and leukoyctes are in direct contact with the Kupffer cell surface (*B*) and might be ingested (*C*). Initial overactivation of Kupffer cells results in severe cell injury with disintegration of cell membranes, focal cytoplasmic lesions, and large phagolysosomes ("autolysis", *D*). Magnification: *B*, ×3,200; *C* and *D*, ×8,000. [From Vollmar et al. (871).]

tor cystein-rich (SRCR) superfamily members, are expressed on KC from an early stage of ontogeny and are involved not only in the lipid metabolism (847) but also in the bactericidal action by binding and endocytosis of endotoxin (579, 844, 849). CD163, also well known as ED2 antigen in rats, is a member of the SRCR family class B and functions as a scavenger receptor for hemoglobin-haptoglobin complexes (635), thereby protecting tissue from free hemoglobin-mediated oxidant injury (422). In addition to the CD11/CD18 receptor of KC, being reported to contribute to the clearance of lipopolysaccharide (LPS) from blood by recognition of the lipid A part of LPS (319, 907), the pattern recognition receptors (PRRs) CD14 and Toll-like receptor 4 (TLR4), in combination with the adaptor protein MD2, are essentially involved in the endotoxin-associated KC activation (674, 763, 823). KC are chronically exposed to higher concentrations of endotoxin than circulating peripheral blood monocytes. Therefore, it seems plausible that protective mechanisms have evolved to avoid the inadvertent activation of KC while maintaining scavenger function. For example, KC have relatively low CD14 expression, which however can be upregulated upon various stimuli, including endotoxin (536, 764, 968). Thus changes in CD14 expression can be hypothesized to represent the underlying mechanism that determines the liver and the KC sensitivity to LPS toxicity. Moreover, it has been shown that high hepatic arginase activity, resulting in low arginine concentrations locally in the liver, limits the reactivity of KC towards endotoxin via an arginine-specific and PGE_2-dependent depression of TNF-α release (81). This may reflect an evolutionary adaptation by KC to their local hepatic environment and strategic anatomic position in the portal circuit, which is optimal for removal of endotoxin and, thus, for protection of the host (81). In line with this, binding of LPS to scavenger receptors does not result in KC activation and production of TNF-α. Even more, studies in scavenger receptor type A knock out mice implied that scavenger receptors can downregulate proinflammatory cytokine production by competing for endotoxin and thus protect the host against lethal endotoxic shock (289). In addition to the scavenger receptors, there is a more recently identified class of PRRs, i.e., the nucleotide-binding oligomerization domain (Nod) molecules, Nod1 and Nod2, which serve as intracellular ligands for LPS (321). So far, the contribution of these molecules in the innate immune response against pathogen infection and in susceptibility to liver injury is not completely understood (633, 764).

Aside from LPS, the endotoxins of Gram-negative intestinal bacteria, β-glycans from bacteria and fungi, and the complement factors C3a and C5a are the most prominent and important activators of KC (52). The transfer of LPS to the LPS receptor CD14 and its TLR coreceptor is facilitated by the acute-phase protein LBP (LPS binding protein), which is produced by hepatocytes and can increase as much as 100-fold during an acute phase response (45). At the same time, LBP participates in neutralization of LPS by transfer to high-density lipoproteins (913), and LBP-deficient mice exert exquisite sensitivity to pathogen challenge, indicating that the critical function of LBP in vivo is to protect animals from bacterial infections (188). In contrast, ethanol administration leads to a significant increase of endotoxin levels in serum and LBP and CD14 mRNA expression in liver tissue, thereby sensitizing the liver to endotoxin-induced tissue injury (974). In line with this, knocking out LBP protects against alcohol-induced liver injury, most likely by blocking the downstream signaling pathway due to reduced availability of LBP (833).

LPS can activate KC directly (763) or indirectly by triggering complement activation, which results in the release of potent anaphylatoxins C3a and C5a and the stimulation of their receptors (219). Subsequently, G protein-enhanced activity of phospholipase C leads to an activation of protein kinase C and the opening of L-type calcium channels with activation of NADPH oxidase and PLA-mediated eicosanoid production (52). Activated complement seems to be responsible for the priming of KC, for the production of reactive oxygen species (ROS) and, thus, for the increased vulnerability of the liver to second hits, such as endotoxin exposure (333, 497).

In addition to neutrophils, KC represent the major source for vascular ROS, in particular upon I/R (333, 335, 336) (Fig. 11). There is a 10-fold increase of plasma oxidized glutathione (GSSG) and a 9-fold higher spontaneous superoxide formation of KC after 60 min of hepatic no-flow ischemia and 90 min of reperfusion (335). In addition, endotoxin has been shown to enhance dose-dependently the release of glutathione (GSH) and its oxidation to GSSG through complement activation (342). Moreover, animals pretreated with KC activating agents, such as retinol, galactosamine (Gal) or propionibacterium acnes, and subjected to I/R reveal enhanced GSSG as an indicator of an increased oxidative stress formation (336). Vice versa, inactivation of KC with gadolinium chloride or methyl palmitate significantly attenuates the postischemic increase of plasma GSSH levels. This strongly indicates that KC are the main source of intravascular oxidative stress. However, it has been shown that lipid peroxidation by these intravascular ROS is not the primary cause of parenchymal cell injury, but may be important as a damaging mechanism for the nonparenchymal cells of the liver, in particular the endothelial cells, which are located close to the sources of the ROS, i.e., the KC (530). Electron microscopic studies confirmed the selective damage of hepatic SEC by ROS, demonstrating a dose-dependent formation of large intracellular gaps and a reduction of the diameter of the remaining endothelial fenestrations. This was shown to have major implications for specific pro-

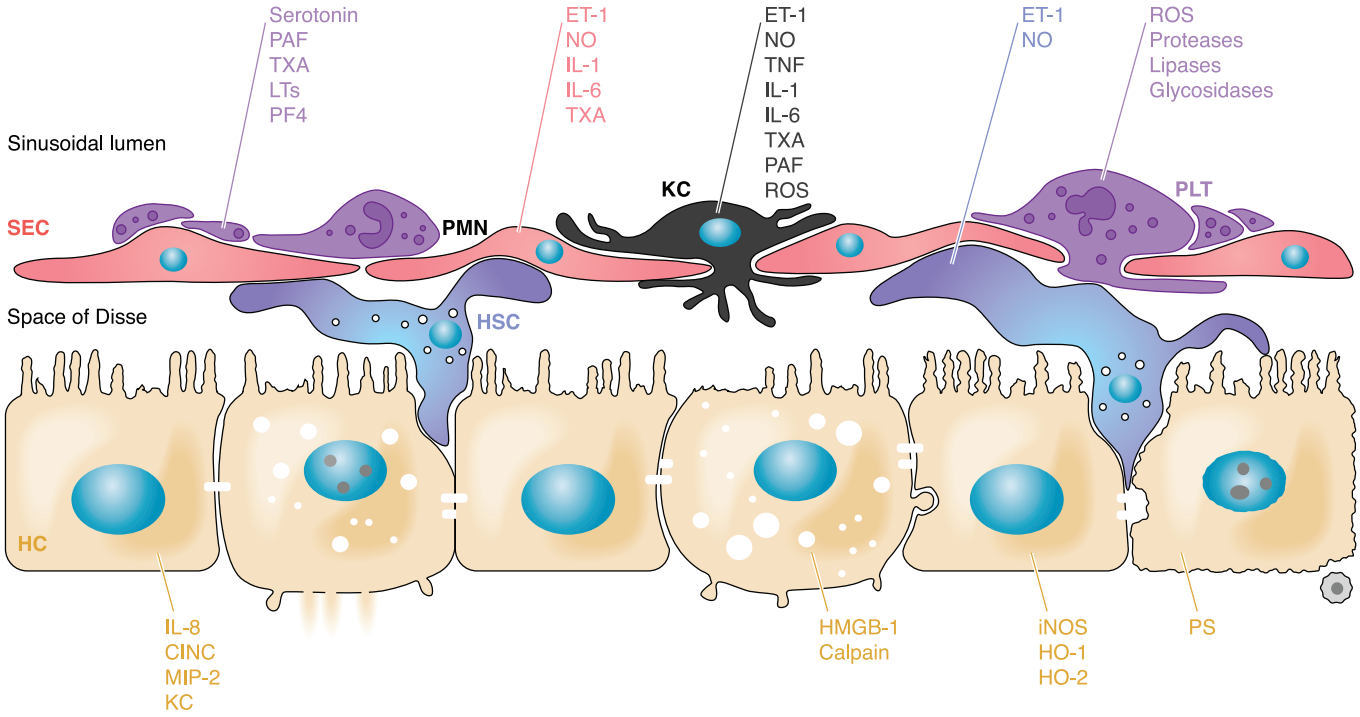

FIG. 11. Cellular mechanisms of microvascular inflammation in liver injury. Injurious stimuli and stress signals cause an activation of sinusoidal endothelial cells (SEC), Kupffer cells (KC), leukocytes (PMN), and platelets (PLT) with release of an armamentarium of aggressive mediators, enhancing the intrahepatic accumulation of inflammatory cells. PMN, PLT, and SEC can interact and bind to each other, leading to further adhesion and accentuation of mediator release. Upregulation of adhesion molecules allows the firmly attaching PMN to migrate towards chemotactic signals (IL-8, CINC, MIP-2, and KC), being released by intact but stress-exposed hepatocytes. Tissue-infiltrating PMN exert direct hepatotoxicity by reactive oxygen species (ROS) and hydrolytic enzyme release. Hepatocytes undergo either necrosis, apoptosis, or mixed aponecrosis, depending on the severity of insult and their intracellular ATP stores. Apoptotic and necrotic hepatocytes can further attract PMN by either surface exposure of phosphatidylserine (PS) or leak of high-mobility group box-1 (HMGB-1).

cesses, such as ageing, cirrhosis and hepatotoxic injury (115).

Although ROS are able to cause cell destruction by lipid peroxidation, in most cases, ROS are more likely to modulate signal transduction pathways by affecting redox-sensitive enzymes, organelles (e.g., mitochondria), and transcription factors (137, 344). Thus ROS can directly induce or regulate apoptotic and necrotic cell death. In addition, ROS can have indirect effects by supporting protease activity through inactivation of antiproteases and modulation of inflammatory mediator formation and adhesion molecule expression (137).

Upon activation, KC release not only ROS, but also an array of inflammatory mediators, such as cytokines, eicosanoids, platelet-activating factor (PAF), nitrogen species, proteases, and chemokines (844) (Fig. 11). The constitutive transcription of TNF-α mRNA in KC allows the rapid and transient release of this so-called "first" cytokine upon LPS-activation of KC (251). This is regularly followed by the secretion of IL-1 and IL-6 (506). In many models of liver injury, TNF-α levels are elevated and correlate with injury (92, 170, 447, 956). Vice versa, inhibition of TNF-α activity by soluble TNF receptors, TNF or TNF-receptor knockout can attenuate liver injury, protect hepatic morphology, and decrease mortality (212, 764, 828). Though one best studied pathway is the production of TNF-α and the greatest attention has been paid to the role of this cytokine in liver injury, the pathogenic contribution of other proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-17, and IL-18 (134, 786, 826, 827, 933), and anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13 (371, 503, 940, 941), is not less important.

It is far beyond the scope of this review to address in detail the complex network of cytokines, as several positively and negatively acting regulatory loops as well as distinct priming functions are possible. Nonetheless, there is a large body of evidence that it is not just the marked elevation of one distinct proinflammatory cytokine or the limited release of a specific anti-inflammatory cytokine that results in global liver injury. Instead, it is the global mismatch and the imbalance of pro- and anti-inflammatory substances that cause a disease (91, 213, 316). Moreover, it has been recognized that KC function as mediator of damage, but protect during processes of regeneration and repair (675). Strategies, such as application of gadolinium chloride or liposome-encapsulated dichloromethylene bisphosphonate (Cl_2-MBP), which inhibit, deplete, or modulate KC (11, 273, 288, 313), were

effective to protect against liver injury upon toxin exposure (17, 82, 421) and endotoxemia (4, 288, 376, 468, 762, 871) (Fig. 10) as well as warm and cold I/R (429, 594, 823, 956).

On the other hand, there is clear indication that KC can mediate protection in that their depletion increases liver injury after hepatectomy (640). Moreover, KC are demonstrated to be mandatory for sufficient restoration of liver tissue upon hepatectomy (5). Due to the fact that KC-derived hepatoprotective factors, such as IL-10 and cyclooxygenase-derived mediators, such as PGE_2 are also upregulated in response to hepatic damage, KC may also serve important regulatory functions in pathophysiological states of the liver and may help to protect against exacerbation of liver injury. This view is based on the fact that intravenous injection of liposome-encapsulated clodronate almost completely eliminates KC and, by this, significantly increases susceptibility to acetaminophen-induced liver injury when compared with mice pretreated with empty liposomes (357). Along with the observation that 60 min but not 20 min of hepatic warm ischemia followed by reperfusion causes depression of KC phagocytic activity (861), activation of KC by muramyl dipeptide restored KC activity and reduced plasma transaminases and liver tissue necrosis 6 h after a 90-min period of warm hepatic ischemia (255).

Taken together, the currently available data on the role of KC in mediating hepatotoxicity support the idea of an initially protective response which in case of overstimulation develops to turn into damage (675) (Fig. 10, *B* and *D*). This threshold hypothesis of KC activation paved the way for strategies modulating rather than inhibiting the KC-associated innate immune response, including heat shock protein induction (36, 714) and application of glutathione (706), CpG-oligodeoxynucleotides (CpG-ODNs) (747), granulocyte-colony stimulating factor (G-CSF) (866), glycine (916), or statins, to name a few (555).

B. Leukocyte Recruitment Within the Hepatic Microvasculature

In response to the exposure to KC-dependent inflammatory mediators, both endothelial cells and leukocytes become activated, and the leukocytes accumulate within the hepatic vasculature. The substances known to trigger intrahepatic leukocyte accumulation include TNF-α (118, 395, 904), IL-1α and -β (80, 182), IL-8 (740), PAF (723), activated complement factors (427, 904), cytokine-induced neutrophil chemoattractant (957), and CXC chemokines, such as macrophage inflammatory protein-2 (27, 477) and others (see also Ref. 337). These mediators increase the leukocytic expression of CD11b/CD18, a member of the β-2 integrin family of adhesion molecules, as well as the induction of E-selectin, P-selectin, and intercellular adhesion molecule-1 (ICAM-1) on endothelium (244). Although these first steps of priming, activation, and recruitment of leukocytes are vital for host defense and removal of cell debris, leukocytes also mediate inflammation-associated tissue injury (244). In line with this, leukocyte recruitment has also been shown to be of paramount importance for the development of liver injury in hepatic I/R (869, 950), endotoxemia (168, 705), acute liver failure (170, 472), alcohol-, toxin-, or drug-induced liver disease (499) and biliary cholestasis (453, 454).

Before transendothelial migration and infiltration into tissue, leukocytes need to interact with the vascular endothelium. The recruitment is dependent on a multistep process, involving the sequential engagement of adhesion molecules. These include selectins with their corresponding ligands for primary leukocyte-endothelial cell interaction and the family of β-2 integrins, which react with endothelial ICAMs to cause a secondary firm leukocyte-endothelial interaction (554). In this multistep sequence, selectin-mediated rolling of leukocytes along the endothelial lining of the microvasculature is a prerequisite for later firm attachment and subsequent transendothelial migration. For this, inflammatory mediators and chemotactic factors play an essential part in initiating, propagating, and directing these dynamic processes (Fig. 11). Although the current knowledge about the molecular and humoral mechanisms, underlying the trafficking of leukocytes to inflammation sites, applies also to leukocyte-dependent liver injury, specific aspects of how leukocytes behave within the individual segments of the hepatic microvasculature still need to be addressed.

Using intravital fluorescence microscopy, a considerable number of animal studies have demonstrated that in most experimental models of hepatic injury (I/R, shock/resuscitation, endotoxemia, acute liver failure, etc.), a particular fraction of leukocytes sequestered in the hepatic vasculature is localized in sinusoids (105, 127, 128, 168, 382, 384, 395, 453, 865, 868, 887). With the assumption that leukocyte-endothelial cell interaction requires selectin-mediated rolling, leukostasis in sinusoids may not involve adhesions molecules, because sinusoidal lining cells express little E-selectin, if any (183), and do not express P-selectin, neither physiologically nor in inflammation, I/R, or rejection (341, 759, 876). In line with this, leukocyte rolling in sinusoids has never been reported (865). This further implies that leukocyte accumulation in sinusoids is mostly independent from the function of the classical adhesion molecules. Accordingly, leukocyte recruitment in sinusoids is not diminished in P-selectin-deficient mice, P-/E-selectin double-deficient mice, and P-/E-selectin double-deficient mice with antibody-induced L-selectin blockade (905). In the absence of selectins, vascular adhesion protein-1 (VAP-1) (443, 444, 545) and liver- or lymph node-specific ICAM-3-grabbing nonintegrin (L-SIGN) (31) have

been shown to be expressed by SEC. However, their role in leukocyte sequestration in liver injury has not yet been analyzed. Most recently, spinning disk intravital microscopy revealed that constitutive expression of hyaluronan is restricted to liver sinusoids, and blocking CD44-hyaluronan interactions selectively reduces leukocyte adhesion in sinusoids of endotoxemic mice. This indicates that the CD44-hyaluronan interaction represents a dominant mechanism for leukocyte sequestration in inflamed liver sinusoids (542).

Currently, the prevailing view is that leukocytes become physically trapped in inflamed liver sinusoids. Leukocytes, with a mean diameter of 10–12 μm, need to force themselves in their passage through narrow hepatic sinusoids presenting with a spherical diameter ranging from 5 to 12 μm. Due to this mismatch in size, leukocytes, while passing, compress the endothelial lining cells and the underlying space of Disse. As a result of this endothelial massage, fluid in the space of Disse is pushed downstream, and upon passage of the leukocyte, the space of Disse resumes its original shape with, thus, suction of fresh fluid into the space of Disse, contributing to the physiological process of hepatic transport and exchange (902). Activated leukocytes show a rapid decrease in their deformability or, conversely, an increase of cell stiffness due to polymerization of soluble G-actin to filamentous F-actin at the cell periphery (158, 208, 906). This leukocytic increase in both rigidity and viscosity hampers leukocyte traveling though the liver and supports cell sequestration. In addition to the high tortuosity of sinusoids, promoting lowering of leukocyte flow velocity and leukocyte stasis (406), additional mechanical factors might further hinder sinusoidal leukocyte trafficking and promote intrasinusoidal leukostasis. These include endothelial cell swelling, interstitial edema, but also protrusion of blebs and activated KC (237, 540, 861). Moreover, sinusoidal diameter reduction due to a misbalance of vasodilating and vasoconstricting mediators are known to increase flow hindrance and, thus, aggravating leukocyte sequestration (37, 616, 837). In support of this view, increased leukocyte stasis in sinusoids of postischemic livers can be attenuated by an ET_A receptor antagonist (835, 836). Conversely, HO-1 inhibition significantly reduces sinusoidal diameters and volumetric blood flow, resulting in a significantly increased number of stationary leukocytes (912). However, it is hard to clearly decipher whether the entrapment of leukocytes is due to changes in resistance conditions or due to classical mediator-stimulated expression of adhesion molecules on the endothelial cells (320), which might endorse leukocyte recruitment.

In contrast to the mechanical trapping of leukocytes in sinusoids, leukocytes accumulate in postsinusoidal venules via interactions, like rolling and firm adhesion, which are mediated by specific adhesion molecules, i.e., L-/P-/E-selectin, β-2 integrins, and ICAMs (401, 694, 860). Rolling interaction of leukocytes in postsinusoidal venules is thought to involve selectins, because postsinusoidal rolling is reduced by anti-P- and anti-L-selectin monoclonal antibodies in mice transfected with TNF-α or IL-1β containing adenoviral vectors (626) and also in P-selectin knockout mice with concanavalin-A-induced hepatitis (519). In adenovirus-activated mice, which exhibit profound liver injury with almost exclusive recruitment of leukocytes in postsinusoidal venules, but not in sinusoids, inhibition of both P-selectin, α-4 integrin, and E-selectin is necessary to completely block leukocyte rolling and subsequent adhesion (485). In both warm and cold rat liver ischemia models, the role of selectins has been demonstrated by the fact that a soluble P-selectin glycoprotein ligand-1 (PSGL-1) decreases hepatocyte injury, leukocyte adhesion, and subsequent migration, resulting in a significant increase of liver graft survival (163). In addition, CD18 antiserum can also protect against LPS/ranitidine-induced liver injury, suggesting that leukocyte activation is required for tissue injury (147).

ICAM-1 is constitutively expressed on SEC and KC, but expression can markedly be increased by inflammation-associated mediator release, including hepatocytes and stellate cells (285, 605, 696). For example, there is a strong relationship among ICAM-1 expression, TNF-α, plasma endotoxin, and inflammatory changes in alcoholic liver disease (412, 585). The cytokines TNF-α and IL-1 are considered the main mediators responsible for upregulation of ICAM-1 mRNA in the inflamed liver (182) and have been shown to be major inducers of soluble ICAM-1 formation in vivo (332). In addition, IL-2 causes organ-specific TNF-α and RANTES production with increased ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) expression, which may facilitate lymphocytic infiltration and cause liver dysfunction (15). In warm and cold hepatic I/R, anti-ICAM-1 antibody application does not affect sinusoidal leukostasis, but effectively inhibits postischemic leukocyte adherence to the venular endothelial lining (117, 587, 666, 860). However, only warm ischemic livers benefit from anti-ICAM-1 blockade with attenuation of tissue injury (117, 581, 587, 860). On the contrary, sequestration of leukocytes in endotoxemic livers has been shown to be independent of β-2 integrins (334) and ICAM-1 (334, 872), suggesting other receptor-ligand interactions which mediate endotoxin-induced leukocyte adhesion to the vascular endothelium.

The inflamed liver develops a vicious circle involving mediators, not only recruiting leukocytes, but also priming them for an enhanced release of ROS. In line with this, inhibition of platelet activating factor, blockade of xanthine oxidase, and induction of leukopenia reduces leukocyte accumulation and hepatocellular injury (925). This vicious circle in turn increases adhesiveness of leukocytes by mobilization of secretory granules, leading to enhanced expression of CD11b/CD18 and shedding of

L-selectin (337). Despite this stimulated inflammatory microenvironment, activated leukocytes logging within the hepatic vasculature are considered not to cause damage, but need an additional chemotactic signal from the parenchymal tissue, which triggers extravasation and attack on target cells, i.e., hepatocytes (Fig. 11).

C. Leukocyte Transendothelial Migration and Parenchymal Cell Killing

After firm adhesion to the endothelial lining, the leukocytes with their extending pseudopodia migrate between adjacent endothelial cells into the subendothelial tissue and the adjacent interstitial compartment. This complex event, termed diapedesis, is dependent on an array of cellular processes, including adhesion molecule expression and activation, cytoskeletal reorganization, and alteration of membrane fluidity. In contrast to other organs, only a limited number of studies have addressed the importance and contribution of different adhesion molecules and chemotactic stimuli in the emigration of leukocytes from the vascular space of the liver. Nevertheless, it became clear that the liver does not follow the simple paradigm of the inflammatory cell recruitment with *1*) selectin-mediated leukocyte rolling, *2*) subsequent integrin activation, *3*) integrin-mediated firm adhesion, and *4*) β-2 integrin and immunoglobulin-dependent diapedesis, as typically established. In mesentery and cremaster muscle leukocyte rolling, adhesion and transendothelial migration occur almost exclusively in postcapillary venules (425, 495). In the liver, the primary site of leukocyte migration into parenchymal tissue, i.e., sinusoids or postsinusoidal venules, is still an unresolved question (105, 865). Extravasation has been shown from all microvascular segments of the liver, including hepatic postsinusoidal venules (384, 865), but the hepatic sinusoids seem to play an undisputable greater role than capillaries in other organs. This is most probably due to the unique type of endothelium, being discontinuous and fenestrated, and lacking basal lamina and tight junctions. Of importance, the sinusoidal endothelium also fails to express E- and P-selectin, and CD34 and VE-cadherin (716, 759). However, it constitutively expresses ICAM-1 (759) and VAP-1 (521, 545), and VCAM-1 upon stimulation, though lower than the endothelium of other vessels (759).

In vitro and in vivo studies provide good evidence that the β-2 integrins CD11a/CD18 and CD11b/CD18 and the counterreceptors ICAM-1 and VCAM-1 on endothelial cells can mediate transendothelial migration (337, 693, 848, 860, 917). In addition, junctional adhesion molecule-A (JAM-A), a receptor expressed on endothelial tight junctions, leukocytes, and platelets, is shown to be upregulated in hepatic venules and to serve as an endothelial receptor of leukocyte transmigration in warm liver ischemia (384). On the other side, there are some reports challenging the clear-cut role of these adhesion molecules for invading leukocytes (401). In particular, when there is extensive endothelial damage, e.g., cold I/R (221, 309, 564) or degradation of membrane constituents by leukocyte-released proteases (78, 192), the access of leukocytes to the parenchyma might become independent from cell adhesion molecules. For example, matrix metalloproteinase (MMP)-9 inhibition attenuates postischemic rolling and adherence of leukocytes in hepatic postsinusoidal venules, CD4+ T cell accumulation in sinusoids, and neutrophil transmigration (383). The relevance of matrix degrading substances for mediating injury is underlined by studies which demonstrate protection against liver damage by a specific neutrophil elastase inhibitor (751) or by MMP deficiency (269). Moreover, MMPs have been shown responsible for sinusoidal endothelial gap formation, allowing initial contact of leukocytes with damaged hepatocytes (326).

Aside from adhesion molecules which serve as tracks for leukocyte movement, chemotactic factors represent the driving force for leukocyte migration. One of the most potent and specific chemoattractants for leukocytes are the CXC chemokines (505), e.g., IL-8, MIP-2, KC, or CINC, being released by hepatocytes in response to TNF-α, IL-1, and endotoxin (155, 369, 482, 687, 737, 811, 957). Excessive CXC chemokine formation in parenchymal cells can recruit leukocytes into the hepatic vasculature (190, 510, 740), induce migration, and cause injury (510) (Fig. 11). The pivotal role of chemokines for leukocyte extravasation and leukocyte cytotoxicity in the liver is convincingly demonstrated by the attenuation of hepatic leukocyte recruitment and leukocyte-mediated injury after neutralizing or inhibiting CXC chemokines in models of hepatic I/R (118, 370, 477), endotoxemia (687, 957), agonistic Fas antibody-induced liver injury (190), and acute Gal/LPS-induced liver failure (830). At the same time, there is evidence that the importance of chemokines may markedly vary between different experimental models used, pharmaceutical approaches applied, and pathophysiological situations present. In fact, immunoneutralization of chemokines is ineffective against endotoxin-induced recruitment of leukocytes in the liver (28), while endotoxin-induced transmigration and extravascular tissue accumulation is dependent of CXC chemokines in Gal/LPS-exposed mice (482). Finally, Dorman et al. (155) have disproved a pathophysiological role of the CXC chemokines MIP-1 and KC in the hepatic injury process after Gal/LPS exposure. This is based on the fact that *1*) the time course of CXC chemokine formation did not correlate with leukocyte extravasation; *2*) only Gal/LPS caused leukocyte extravasation, although LPS and Gal/LPS induced a similar CXC chemokine response; *3*) chemokine neutralization had no effect on leukocyte extravasation and injury; and *4*) wild-type and CXCR2 knock-out mice

showed comparable leukocyte extravasation and liver injury (155).

Hepatocytes are recognized as important attractors to control guided transmigration of leukocytes. In mice which display agonistic Fas antibody-induced hepatocellular apoptosis, hepatic induction of CXC chemokines is associated with leukocytic infiltration of the hepatic parenchyma (190). It has further been shown that parenchymal apoptotic cell death coincides with leukocyte transmigration in mice with Gal/endotoxin-induced liver injury (467). Detailed in vivo high-resolution multifluorescence microscopy studies have shown that leukocytes frequently colocalize with apoptotic hepatocytes in endotoxemic livers and that these colocalizing leukocytes are the consequence of hepatocyte apoptosis, because intrahepatic leukocyte adherence is markedly inhibited upon blockade of hepatocellular apoptosis by the pancaspase inhibitor zVAD-fmk (168). The fact that in endotoxemic animals inhibition of hepatocellular apoptosis by p53 blockade also reduces intrahepatic leukocyte accumulation further supports the view that apoptotic hepatocytes are capable of recruiting leukocytes (705). Apoptotic hepatocytes might attract leukocytes by specific surface modifications, such as the exposure of phosphatidylserine. Thus diannexin, a 73-kDa homodimer of human annexin V, binds to phosphatidylserine and, by modulating leukocyte and platelet trafficking and EC activation, it suppresses vascular inflammation and decreases apoptosis in rat cold I/R injury (730). Likewise, necrotic hepatocytes can signal by the leak of intracellular messengers, such as high-mobility group box 1 (824) (Fig. 11). Also, calpain is reported to leak out of necrotic hepatocytes into the extracellular milieu and to hydrolyze proteins in the plasma membrane of neighboring cells, leading to progression of injury (547). Experimental intervention with calpain inhibitors substantially mitigates progression of liver injury initiated by toxicants, thereby preventing acute liver failure and toxicant-induced animal death (547).

Although there are a variety of potential mechanisms of leukocyte-dependent hepatotoxicity discussed, two major concepts are under the principal focus of investigation. In cytosolic granules, leukocytes possess a large number of hydrolytic enzymes (192), of which many have been shown responsible for cytotoxicity to isolated hepatocytes (298). These include the classical proteases, lipases, and glycosidases, but also very specialized proteins, such as bactericidal/permeability-increasing protein, defensine, and bactenecins. All of these enzymes can induce membrane damage, cell growth arrest, and activation of other hydrolytic enzymes in target cells (298). For example, analysis of conditioned medium from α-naphthylisothiocyanate-treated leukocytes indicates the presence of both cathepsin G and elastase activities, which causes hepatocellular damage in vitro (294). The clear involvement of leukocytic proteases in cell killing has been shown among others *1*) by the protective effect of a neutrophil elastase inhibitor or antileukoproteinase in lethal acute liver failure and in endotoxin-induced liver injury after partial hepatectomy (170, 437, 830), *2*) by the attenuation of liver I/R injury through an urinary trypsin inhibitor (484, 924), and *3*) by the reduction of liver fibrin deposition, plasma PAI-1 concentration, and parenchymal injury after LPS/ranitidine exposure (147).

In addition, leukocyte-associated oxidant stress has been implied as common mechanism of liver injury. Oxidant stress is considered the condition in which the cellular levels of ROS exceed the neutralizing capacity of nonenzymatic and enzymatic capacities. Most recently, novel approaches to deliver antioxidative enzymes, such as polylipid nanoparticles (PLNP) (282), liposomes (910), or adenoviral-mediated gene transfer (967) have been shown to protect against I/R and endotoxemic liver injury. Despite the ability of antioxidants to block liver damage (908), the relevance of ROS for direct cell killing has likely been overestimated (344). The very high antioxidant capacity of the liver, including catalase and superoxide dismutase (SOD), can neutralize and detoxify extremely high intracellular oxidant stress without adverse effects. The amount of lipid peroxidation, as assessed by highly sensitive and specific gas chromatographic-mass spectrometric analysis of hydroxy-eicosatetraenoic acids (HETES) and F2-isoprostanes is one order of magnitude below that which would be necessary to cause direct cell killing (339, 530). Instead, oxidant-induced liver injury is more likely to be mediated by the direct effects of ROS on signal transduction pathway activities through oxidation of kinases and phosphatases (137). There is specific focus directed towards the mitogen-activated protein kinases (MAPK), the extracellular signal-related kinase 1/2 (ERK1/2), the c-Jun NH_2-terminal kinase (JNK), and the nuclear factor κB (NF-κB) pathways, which play different and complex roles in an often cell-specific manner. For example, ERK1/2 and JNK, but not p38 MAPK, are activated by the liver toxicant toosendanin. Inhibition of ERK1/2 activation sensitizes hepatocytes for death and increases the activity of caspase-9 and -3 in response to toosendanin. In contrast, inhibition of JNK attenuates toosendanin-induced cell death (960). Acetaminophen-induced liver injury involves JNK activation, due to increased ROS generated by GSH-depleted mitochondria, and translocation of activated JNK to mitochondria where JNK induces mitochondrial permeability transition (MPT) and inhibits mitochondria bioenergetics (270).

Altogether, leukocyte-mediated oxidant stress may induce mitochondrial dysfunction in hepatocytes and, thus, enhance proneness of cells to undergo apoptosis or oncotic necrosis (591). Inhibition of acetaminophen-induced phosphorylation of JNK prevents downstream Bcl-2 and Bcl-xL inactivation and protects from mitochondrial permeabilization and cytochrome *c* release (456). In

addition, JNK inhibition in vivo markedly reduces mortality in acetaminophen hepatotoxicity, but not in acute carbon tetrachloride-mediated or anti-Fas antibody-mediated hepatic injury, with a significant reduction in hepatic necrosis and apoptosis (287). Comparable effects for JNK inhibition, i.e., a decrease of hepatic necrosis and apoptosis, have been shown for livers exposed to cold storage and transplantation (832).

D. Platelet Adhesive Interactions

In addition to leukocytes, platelets and their intrahepatic adhesion and accumulation have also been implicated in inflammatory liver injury (130, 168, 380, 582). However, their contribution to the injury is far less studied. Decades ago, first studies have reported about histomorphological changes within hepatic sinusoids of endotoxemic livers, such as swelling of KC, accumulation of leukocytes and, in particular, the deposition of platelets and fibrin clumps (296, 539, 540). After a bolus dose of endotoxin, time course analysis of circulation of autologous indium 111-labeled platelets revealed initial hepatic sequestration, resulting in a marked peripheral thrombocytopenia (266, 754).

Although platelets are anuclear, they possess a cellular machinery comparable to that of leukocytes in many aspects. In addition to the cytoskeleton which allows platelets to move, they release an armamentarium of proinflammatory and procoagulant mediators upon activation, such as thromboxane A_2 (TxA_2), leukotrienes, serotonin, platelet factor 4, and platelet-derived growth factor (PDGF). Due to their potential to modulate leukocyte functional response (689), platelets have been accused of aggravating endothelial damage and leukocyte activation and recruitment to the site of injury. In support of this view, coculture experiments with human leukocytes and platelets revealed a marked elevation of superoxide anion production through a P-selectin-dependent mechanism when thrombin-activated platelets were used (576). P-selectin is found in the α-granules of resting platelets and in Weibel-Palade bodies of endothelial cells, rapidly occurs on the surface upon cellular activation and recognizes lineage-specific carbohydrate ligands on both monocytes and leukocytes. Thus leukocytes, platelets, and endothelial cells can interact and bind with each other (Fig. 12), leading to further adhesion of leukocytes and platelets with accentuated ROS generation (452, 576).

Leukocytes cultured in the presence of platelets show a dramatic inhibition of apoptosis compared with leukocytes cultured alone (16). Thus adherent platelets might significantly prolong life span of leukocytes and, thus, their capacity for oxidative burst and release of proteolytic substances. Accordingly, interference with platelet sequestration by inhibition of PSGL-1 and GP1b,

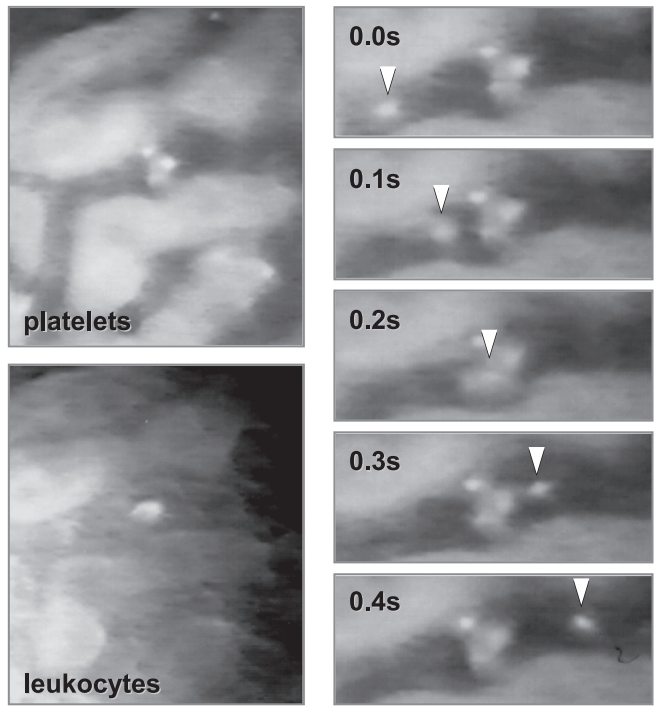

FIG. 12. Intravital fluorescence microscopic images, displaying the cellular passage through hepatic sinusoids. *Left panels* illustrate the identical images studied by different filter sets, demonstrating the colocalization of stagnant platelets and leukocytes. *Right panel* shows a time series of identical images, representing just a higher magnification of the image of the *left panel*. Note that the cluster of adherent cells forms an intrasinusoidal hindrance, which, however, can still be easily passed by an additional inflowing platelet (arrowhead).

P-selectin deficiency, or induction of thrombocytopenia induces protection in normo- and hypothermic postischemic, endotoxemic, and cholestatic liver injury (163, 168, 453, 526, 822, 829, 918). Hereby, endothelial, but not platelet, P-selectin expression seems critical for postischemic platelet-endothelial cell interactions (379). Vice versa, in mice rendered neutropenic with an anti-neutrophil serum, sepsis-induced leukocyte and platelet recruitment is attenuated (743). In an isolated perfused rat liver model, it has been shown that platelets adhere to SEC via sialyl Lewis-X [sLe(x)] oligosaccharide and induce cellular apoptosis (136, 741). The presence of platelets after cold storage and rewarming aggravates liver injury, as assessed by increased release of transaminases (136). After cold I/R of livers with freshly isolated leukocytes and platelets, a synergism of platelets and leukocytes in inducing endothelial cell apoptosis could be found, which was completely abrogated by gadolinium chloride- or pentoxifylline-induced KC blockade. This highlights the need of activated leukocytes, platelets, and KC for full expression of the injury (742). In line with this, animals that were depleted for KC by liposome-encapsulated Cl_2-MBP and subjected to 20 min of warm ischemia and 120 min of reperfusion showed that platelet adherence in sinusoids

is suppressed, and, as a consequence, sinusoidal perfusion failure, endothelial cell damage, and serum alanine aminotransferase (ALT) levels are significantly attenuated (582). Vice versa, microvascular and hepatocellular injury upon antigen-independent I/R is found aggravated after activation of the endothelium by CD4+ T cells and recruitment of platelets (382). Activated platelets even contribute to cytotoxic T-lymphocyte-mediated liver immunopathology, such as viral hepatitis (314).

Although this triangular interaction seems to be a major mechanism in reperfusion injury (629), there are also controversial data, showing that neither inhibition of platelet function by clopidogrel nor platelet depletion by repetitive anti-CD41 injections leads to a reduction of postischemic liver injury (596). Instead, studies in platelet-depleted animals indicate that platelets are critically involved in repair after liver injury and in liver regeneration via serotonin-mediated mechanisms (479, 595). Nonetheless, it has to be taken into account that platelet-derived serotonin may at the same time increase oxidative stress and mitochondrial toxicity in nonalhoholic steatohepatitis and aggravate viral hepatitis (446, 595).

E. Sinusoidal Cell Plugging

The close interrelationship between intraorgan leukocyte accumulation and microvascular injury has given rise to the concept that cells stagnant in capillaries might contribute to the manifestation of perfusion failure and subsequent hypoxic tissue injury. Compelling support for the concept of nutritive perfusion failure induced by leukocytic capillary plugging is provided by studies demonstrating that leukocyte depletion and prevention of leukocyte adherence is associated with a marked reduction of nonperfused capillaries in reperfused myocardium, brain, and skeletal muscle (141, 178, 353).

In postischemic liver tissue, Koo et al. (413) reported an increased incidence of microvascular plugging by leukocytes, causing complete cessation of blood flow in "some" sinusoids. Ferguson et al. (197) demonstrated that at the whole organ level leukocyte accumulation appears to correlate well with microvascular damage, while when the data are analyzed on the basis of 0.05 mm^2 microscopic fields on the surface of the liver, there is no difference in leukocyte accumulation in areas with sinusoidal blood flow compared with areas that were devoid of perfused sinusoids (197). More detailed analysis of leukocyte flow dynamics in individual sinusoids of postischemic rat livers revealed that leukocytes become stagnant in sinusoids and alter sinusoidal blood flow, but do not necessarily occlude the sinusoidal lumen (868) (Fig. 12). The tortuous path of the proximal segments of the sinusoids (406) as well as the lobular distribution of KC (746) and the peculiar junctional site of contractile stellate cells at the transition of terminal portal venules to the sinusoids (599) are accused of causing the zonal gradient of leukocyte flow behavior with more tethering interactions in periportal and midzonal than pericentral segments (868). This steep gradient of stagnant leukocytes located at bifurcations, with the highest fraction in the periportal and the lowest fraction in the pericentral sinusoids, further indicates a substantial impact of the hepatic angioarchitecture on leukocyte flow behavior. Of utmost interest, however, is the analysis that stagnant leukocytes increase hindrance, as given by the reduction of velocity and number of leukocytes passing sinusoids with stagnant leukocytes (Fig. 12). However, they do not necessarily cause cessation of blood flow. In nonischemic livers, only 3% of the sinusoids with leukostasis simultaneously show perfusion failure, and in postischemic livers, this fraction increases but does not exceed 30%, while >70% of sinusoids with stagnant leukocytes still conduct blood flow (868) (Fig. 12). Thus sinusoidal leukostasis per se does not necessarily determine hepatic perfusion failure. In line with this, it has been shown that large amounts of leukocytes can accumulate in the liver without causing tissue damage, indicating that leukocytes do not contribute to hepatic reperfusion injury passively by plugging of sinusoids, but need an additional stimulus to produce injury (955).

V. MICROVASCULAR DYSFUNCTION IN LIVER INJURY

A. Sinusoidal Endothelial Cell Activation

Along with KC, the hepatic sinusoidal endothelium participates in host defense mechanisms and blood flow regulation and represents a major target for injury in the early phase of inflammation. The SEC are secretory and have the capacity to produce immunoregulatory and proinflammatory cytokines, such as IL-1, IL-6, and interferon (193, 748, 901). In addition, they produce eicosanoids, particularly TxA_2 and PGE_2, as well as important regulators of vascular tone, including NO and ET (901). By forming a thin and continuous layer, the sinusoidal endothelium represents the only structural barrier, separating the hepatic parenchyma from blood constituents passing the liver. However, as SEC are fenestrated and lack tight junctions and an underlying basement membrane, they do not represent a barrier in the same sense that vascular endothelial cells do in other organs. Nonetheless, they still act as a functional barrier. It became appreciated that intact microvascular function requires the finely tuned and integrated activity of the distinct sinusoidal cell populations, i.e., KC, SEC, and stellate cells (757). In line with this, cell morphological changes in the hepatic sinusoid with old age are increasingly recog-

nized as determinants for impaired metabolism of drugs, adverse drug interactions, and susceptibility to toxins (327).

The site of KC activation and leukocyte adhesion is the sinusoid. The release of ROS is the predominant proinflammatory action during the early innate immune response. Although SEC are well-known for their capacity to release ROS, particularly upon in vitro exposure to endotoxin, the amount of ROS release in vivo is far less (756). Thus SEC are targets rather than significant sources of ROS in the sinusoid. Even more, the SEC have been recognized as antioxidant, being of essential importance for the intercellular oxidant balance with the prooxidant KC (757). As an important adaptive response to oxidative stress during the innate immune response of SEC (757), they regulate the pentose cycle with induction of glucose-6-phosphate (G-6-P) dehydrogenase, the key enzyme of the hexose monophosphate shunt (HMS). It has been shown that the glucose transporter GLUT-1, Mn- and CuZn-dependent SODs (Mn-SOD, CuZn-SOD), and Se-dependent glutathione peroxidase (Se-GPX) are simultaneously upregulated in endothelial cells, allowing accelerated elimination of ROS released from activated sinusoidal phagocytes (758).

Injurious stimuli, such as endotoxin and ethanol, induce similar morphological and functional changes in SEC. Livers from alcohol-fed animals are characterized by massive loss of sieve-plate architecture of the sinusoidal endothelium, which is virtually replaced with a meshwork of enlarged openings with diameters frequently exceeding 1 micron (699). LPS administration further accentuates these alcohol-associated alterations of the sinusoidal lining (699). The fact that reduced fenestration and hyaluronan uptake, being a means for assessing the functional state of SEC, are preventable by elimination of KC, underlines the importance of intercellular communication in the liver (140). Inflammation-induced sinusoidal endothelial gap formation precedes leukocyte adhesion and is shown to be dependent from MMPs, as a MMP-2/-9 inhibitor reduces gap formation by lowering TNF-α production (326). Morphological changes, such as gap formation, are of major pathological implication, because gaps facilitate the contact of leukocytes with hepatocytes (326).

Furthermore, harmful substances, like alcohol and endotoxin, upregulate ICAM-1 expression on SEC, which further primes the sinusoid as site for inflammatory leukocyte adhesion and transmigration (585). Alcohol-associated malondialdehyde-acetaldehyde (MAA)-modified proteins have demonstrated an increase in adhesion molecule expression and the secretion of proinflammatory cytokines and chemokines by SEC, with endotoxin being a cofactor in this scenario (165). SEC are highly responsive to the exposure of endotoxin with TLR4-dependent activation of p38 MAP kinase and the transcription factors AP-1 and NF-κB (99). The expression of ICAM-1 on SEC correlates with TNF-α mRNA expression and plasma endotoxin concentrations (585). This further demonstrates the complex interplay between cellular, humoral, and molecular events. In line with this, endotoxemia induces a sublobular pattern of leukocyte margination, which is consistent with the concept of cell adhesion regulation by inflammatory mediators released from endotoxin-stimulated KC (37). Vice versa, dexamethasone suppresses TNF-α production by endotoxin-stimulated KC and decreases ICAM-1 expression and leukocyte adhesion on SEC (693).

Along with ICAM-1, VCAM-1 is upregulated by inflammatory stimuli either directly or by mediators released from stimulated KC, resulting in increased adhesion of leukocytes to the endothelial surface (848). In addition, SEC have been shown to recruit leukocytes via VAP-1, which is increasingly induced in inflammatory liver disease and liver allograft rejection (444, 521). Thereby, complex mechanisms regulate VAP-1 to induce adhesion, with *1*) direct binding of leukocytes to endothelial VAP-1 protein, *2*) indirect enzyme-dependent activation of other endothelial adhesive pathways, and *3*) activation of leukocytes by VAP-1 ligand occupancy (444). In addition to leukocyte adhesion, substrate binding to VAP-1 results in SEC activation, which can be abrogated by treatment with the enzyme inhibitor semicarbazide. VAP-1-mediated SEC activation is rapid; dependent on NK-κB, phosphatidylinositol-3 kinase, and MAPK pathways; and leads to upregulation of the adhesion molecules E-selectin, ICAM-1, and VCAM-1 and secretion of the chemokine CXCL8 (444). Moreover, stabilin-2, known as hyaluronic acid (HA) receptor for endocytosis (HARE; also designated FEEL-2) (274), is shown to be involved in lymphocyte adhesion to the hepatic sinusoidal endothelium via the interaction with α-M beta-2 integrin (358).

In addition to the proadhesive function of activated SEC, they also exert a procoagulant microenvironment. Endotoxin decreases protein S antigen and mRNA levels in SEC via MEK/ERK signaling and NF-κB activation by involving membrane-bound CD14 and TLR4 (281). Thrombomodulin antigen and activity levels are significantly decreased in SEC isolated from endotoxin-treated rats, and thrombomodulin expression in cultured SEC isolated from normal rats is also reduced after treatment with endotoxin and TNF-α in vitro. Accordingly, recombinant thrombomodulin is capable of attenuating increased levels of serum fibrin degradation products, fibrin deposition within liver sinusoids, injury of SEC, and liver dysfunction after endotoxin exposure (431). Also, urine thrombomodulin administration prevents intrasinusoidal fibrin depositions and attenuates posthepatectomy liver dysfunction in endotoxin-challenged cirrhotic rats (359). The localization of endotoxin in KC and SEC correlates with the incidence of sinusoidal thrombosis both temporarily and spatially within the septic liver tissue (787), which,

among many other factors, explains the prothrombotic state in sepsis. In addition to endotoxin, also alcohol and alcohol-associated MAA-modified proteins initiate a profibrogenic response by inducing the expression of the fibronectin EIIIA isoform by SEC (808).

Taken together, upon activation SEC exert proinflammatory and proadhesive as well as procoagulant properties, which can substantially contribute to aggravation of injury.

B. Sinusoidal Vasomotor Dysfunction

Hepatic injury is caused by several mechanisms, including inflammation and microcirculatory dysfunction. The latter involves the action of potent vasoactive mediators. ETs, TxA_2, angiotensin II, and catecholamines are proposed as vasoconstrictors, whereas NO, CO, and prostaglandins are indicated as vasodilators that counteract the effect of the vasoconstrictors. Under physiological conditions, the influence of these vasoactive mediators on intrahepatic blood flow is rather small and their effects are balanced. Any adverse stimulus, however, may lead to an upregulation of constrictor or dilator influences at all microvascular segments of blood flow regulation. These are mostly matched neither for time nor for space and may therefore cause a dysbalance of vasomotor activity and vasotonus. Thus the maintenance of a critical balance seems to be an attractive concept for an adequate regulation of hepatic blood flow, aiming at limiting microcirculatory dysfunction-associated liver injury (625). Although there are innumerable mediators, particular emphasis is given on the intimate relationship of the ET/ET-receptor system and the enzyme systems which liberate the vasoactive gaseous molecules NO and CO, i.e., NOS and HO (625) (Fig. 13).

ROS, endotoxins, cytokines, hypoxia, and vascular shear stress can induce ET gene expression (688). Because all of these mediators play an essential role in I/R, endotoxemia, and sepsis, drug-induced toxicity, and liver resection, increased generation and plasma concentra-

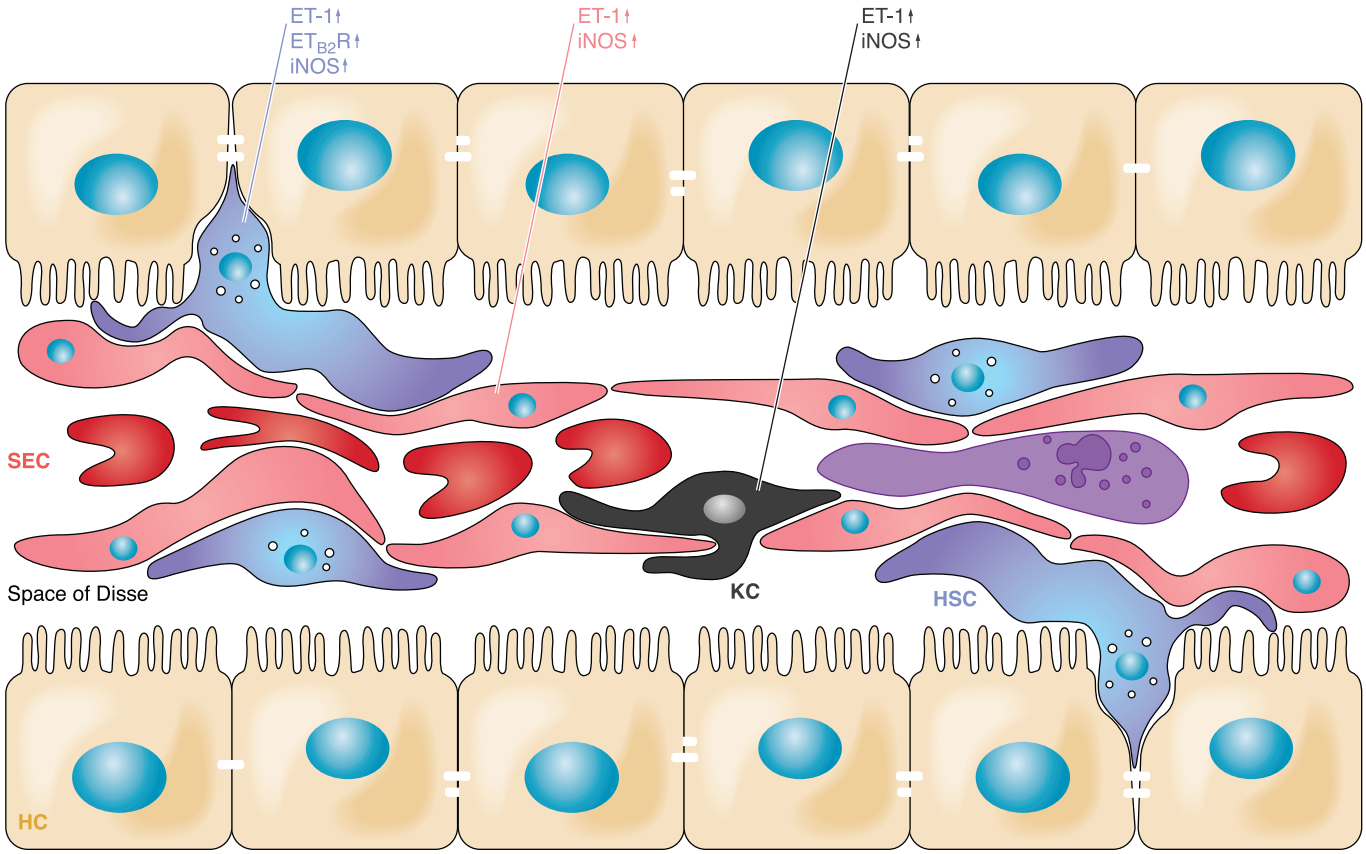

FIG. 13. Consequences of vasomotor control dysfunction in inflammatory liver injury. The dysbalance between the vasoconstrictive ET-1 and the vasodilative gaseous molecules NO and CO with a shift towards the ET system is due to *1*) an increased ET-1 production by stellate cells (HSC), Kupffer cells (KC) and endothelial cells (SEC), and *2*) an increased expression and sensitivity of ET_{B2} receptor on HSC. The increased expression of iNOS further stimulates ET-1 production, most probably through the excessive NO release and, thus, reactive nitrogen species formation. The consequence of this ET-1-dominated loss of balance of vasomotor control is a contraction of HSC, which reduces the diameters of the hepatic sinusoids, resulting in an increase of vascular resistance and a hindrance of blood flow. The narrowing of the sinusoidal lumen does not necessarily result in obstruction by blood cells; however, red blood cells and, in particular, leukocytes have to squeeze to pass the HSC-induced constrictions.

tions of ET are reported in endotoxemia and endotoxin shock (184, 206, 218, 324, 389, 606, 736, 753, 946), postischemic reperfusion (389, 753), hemorrhagic shock (496, 664), prehepatic portal hypertension (939), and acute liver failure (931). In addition, substantial changes of the pattern of ET receptor expression can be observed, including an upregulation of ET and a downregulation of the ET_A receptor expression in hepatic I/R (35, 389, 753, 937), endotoxemia (40, 389, 753), portal vein ligation (939), and other conditions of major inflammatory stimulation. Under these pathological conditions, ET-1 may also induce vasodilation by ET_{B1} receptor stimulation on SEC, attenuating its own vasoconstrictive effects mediated via ET_A and ET_{B2} receptors on hepatic stellate cells (625). This implies a self-restricting process, because in the absence of this ET-mediated vasodilatory effect, the extent of I/R-induced liver injury has been found even larger (623). As net result of these molecular and humoral events, the hepatic microcirculation is sensitized to ET-1. The enhanced response of hemorrhagic shock- and resuscitation-primed livers to ET-1 leads to a greater increase of portal driving pressure, total portal resistance, and zero-flow pressures and to a more pronounced decrease of portal flow and sinusoidal diameters (624). Comparably, microvascular hyperresponsiveness to ET-1 has been described in endotoxin-pretreated livers (622) or in livers during polymicrobial sepsis (40). These enhanced ET-1 responses occur at sinusoidal and presinusoidal levels and may contribute to microvascular dysfunction and liver injury.

The vasoconstrictive effects of ET can functionally be antagonized by the vasoactive gaseous monoxides NO and CO (767) (Fig. 13). CO has paracrine effects on endothelial cells, provoking an increase of endothelial cGMP content and a decrease of ET-1 and PDGF expression (569). In parallel, ET-1 secretion from endothelial cells is reduced in the presence of NO donors (71, 562). Although these close interactions might imply that the vasoactive mediators could neutralize each others' effects, there is a large body of evidence that an imbalance of the expression of stress-induced vasoactive mediators is responsible for the alterations of the liver microcirculation and the subsequent tissue injury. Microcirculatory injury in small-for-size liver grafts is related to an upregulation of ET-1 and inducible NOS (iNOS), leading to a deterioration of intracellular homeostasis, as reflected by the downregulation of HO-1 (487). Ischemia and endotoxemia are reported to induce mRNA encoding ET-1 (2.5- and 6-fold), HO-1 (2- and 2.5-fold), and iNOS (6.4- and >24-fold) (753). In addition, HO-1 (16-fold) and ET-1 (9-fold) mRNA, but not iNOS, are found upregulated in hemorrhagic shock-exposed rat livers (663, 664). Increased endogenous production of NO counteracts ET-1-induced increases in sinusoidal resistance, providing protection in models of I/R (620). In support of this, NO donors and ET-receptor blockers protect the postischemic liver microcirculation by maintaining the ET-NO balance (560, 717, 837). I/R injury might also benefit from blockade of excessive iNOS expression, decreasing NO and hydroxyl radical production (490). In sepsis, iNOS and eNOS seem to be differently regulated. eNOS is thought to protect the liver microcirculation, while the strong upregulation of iNOS might contribute to microvascular dysfunction and hepatic injury (184, 527). This view is further underscored by the fact that the administration of arginine together with a selective iNOS inhibitor during the early phase of sepsis restores plasma arginine, reduces oxidative stress by maintaining NO derived from constitutive NOS, and attenuates neuroendocrine stress responses (915). In contrast, unselective inhibition of NOS activities aggravates liver injury (785).

Comparably to eNOS, HO-1 upregulation confers cytoprotection in many models of organ and tissue injury (691, 912) and CO ameliorates hepatobiliary dysfunction caused by heme overloading in endotoxemic livers (438). Accordingly, HO-1 deficiency exhibits a heightened and dysregulated inflammatory response to endotoxin (814). Of interest, the cytoprotection of the HO-1 metabolite bilirubin is mediated at least in part through the inhibition of iNOS expression, underlining the close interaction of these mediators controlling sinusoidal vasotonus (886). Loss of the delicate equilibrium between NO, CO, and ET induces vasoconstriction and narrowing of the sinusoidal lumen, compromising blood flow, tissue oxygenation, and cell trafficking (Fig. 13).

Furthermore, vasoregulatory imbalances and increased intrahepatic resistance play a central role in the pathophysiology of portal hypertension in cirrhotic livers. The imbalance between the hyperresponsiveness and overproduction of vasoconstrictors (mainly ET-1 and cyclooxygenase-derived prostaglandins) and the hyporesponsiveness and impaired production of vasodilators (mainly NO) is responsible for the increased vascular tone in the sinusoidal and postsinusoidal space (729). Multiple derangements of eNOS-derived NO production are proposed to contribute to impaired sinusoidal relaxation and increased resistance (260, 677, 728). Enhanced expression and interaction of inhibitory protein caveolin binding to eNOS contribute to impaired NO production, reduced NOS activity, and vasoconstriction in the intact cirrhotic liver (728, 936). Higher levels of the NO synthesis inhibitor amino acid asymetric dimethylarginine (ADMA) (440, 567, 817), reduced phosphorylation of the major eNOS activator Akt (568), and increased expression of the Akt activity inhibiting G protein-coupled receptor kinase-2 (GRK2) by sinusodial endothelial cells (498) are thought to further impair eNOS function and NO availability in cirrhosis. In addition, hepatic stellate cells as the target cells for NO action are described to exert a blunted NO response due to defects in the GC signaling pathway and cGMP cascade

(161, 631). Moreover, cirrhotic livers show impaired vasodilation to mediators such as CO and H_2S (201, 260).

Apart from decreased response to vasodilators, vasoconstrictive systems, such as ET receptors and ET-1 levels as well as COX-1-dependent TxA_2 synthesis and 5-lipoxygenase-derived eicosanoids, are upregulated and increased in cirrhotic livers, thereby also contributing to the increase of vascular tone (38, 113, 245, 246). The imbalance in vasoreactivity is primarily mediated by the hepatic stellate cells which, in cirrhosis, undergo activation, thus enhancing their contractility (224, 679). Hereby, smooth muscle like Ca^{2+}-dependent contraction patterns as well as calcium-independent mechanisms participate in the contractile function of activated hepatic stellate cells (441). Studies, demonstrating the correction of the hyperresponsiveness to vasoconstrictors by Rho kinase inhibitors, imply a causal role of the RhoA/Rho kinase pathway for the increased vasoconstrictor sensitivity and the elevated intrahepatic resistance of cirrhotic livers (966). Most recently, adenosine has been shown to be a physiological inhibitor of the Rho pathway in hepatic stellate cells. Thus loss of adenosine-induced contraction of hepatic stellate cells might contribute to the substantial functional benefit seen in patients with cirrhosis in the presence of adenosine-induced hepatic arterial dilatation (972). Treatment with nitroflurbiprofen, a NO-releasing cyclooxygenase inhibitor, seems to be a particularily interesting approach to counteract the imbalance in vasoreactivity, because nitroflurbiprofen improves portal hypertension in cirrhotic rats by inhibition of the hyperresponsiveness to vasoconstrictors through the inhibition of COX and by the supply of NO to the intrahepatic circulation (442).

C. Sinusoidal Perfusion Failure and Hypoxic Cell Injury

Sinusoidal perfusion failure is discussed as a key factor in the pathogenesis of tissue injury in warm I/R (73, 382, 859), cold preservation and transplantation (403, 548, 667), shock and resuscitation (428, 683, 864), endotoxemia (483, 743, 747), acute liver failure (170, 472, 616), bile duct ligation (4, 453), and drug-induced hepatotoxicity (34, 654). Several mechanisms are well established to contribute to sinusoidal perfusion failure, including sinusoidal narrowing caused by SEC edema (98, 864) or stellate cell-mediated vasoconstriction (38, 113, 620). In addition, structural peculiarities of the sinusoid, including diameter, tortuosity of path, branching pattern and number, size and activity of KC with the regional differences between periportal and pericentral areas, predispose to flow heterogeneities within the liver. These cause a gradient of perfusion failure, which is most pronounced in the periportal segment of the sinusoids (68, 864). Upon entrapment of activated leukocytes, sinusoidal flow velocity decreases due to increased hindrance (868), further inducing perfusion heterogeneity and perfusion deficits. In addition, inflammation- and injury-associated adherence of leukocytes in outflow venules may alter sinusoidal perfusion due to an increase of blood viscosity (104) and, hence, vascular resistance (65). Furthermore, perfusion failure in sinusoids is thought to be caused by sluggish blood flow, intravascular hemoconcentration, and procoagulant conditions (552).

Among others, sinusoidal perfusion failure is particularly dependent on the nature of the injurious stimuli, on the animal and strain of species used, and on the time point of assessment but can amount to 40–60% in models of severe liver injury, such as reperfusion upon 24 h of cold storage (403) or Gal/endotoxin exposure for induction of fulminant liver failure (472). Microcirculatory failure in the liver after stress is characterized by perfusion heterogeneity, resulting in a mismatch between oxygen and nutrient supply and demand. The impaired nutritive blood flow accompanied by reduced oxygen availability decreases cellular levels of high-energy phosphates and contributes to early and late hepatocellular injury and dysfunction. In line with this, regression analyses demonstrated significant correlations between microcirculatory disorders and hepatocellular disintegration or liver dysfunction (859, 862) as well as between reduced blood oxygenation index and increased transaminases (241). Lobular microvascular dysfunction is thought to occur along with parenchymal injury, supporting a functional perfusion deficit-injury relationship, and vice versa. This underlines the determinant role of an intact microcirculation for the adequate organ integrity and function (552). However, in case of direct cytotoxic effects of injurious stimuli, such as TNF-α (883) or endotoxin (170), or in case of remote organ injury (68), hepatocyte death can occur without concomitant sinusoidal perfusion failure. Accordingly, hypoxic hepatitis has been allocated to differing reasons, i.e., decreased hepatic blood flow (venous congestion, heart failure), systemic hypoxemia (respiratory failure), and oxygen utilization failure (sepsis) (289).

D. Sinusoidal Endothelial Capillarization

In addition to alterations in vasoreactivity, vascular remodeling represents an important component contributing to increased intrahepatic resistance in portal hypertension. Different anatomic lesions have become apparent as important structural changes to the vascular compartment, including fibrosis, sinusoidal collapse, defenestration of sinusoidal cells (capillarization), hepatocyte enlargement, and formation of a basement membrane in the space of Disse, all narrowing the sinusoid (598, 853, 873). In addi-

tion, the result is a reduced access of plasma and plasma-dissolved substances to hepatocytes due to their limited diffusion in the extravascular space. With the use of the multiple indicator dilution curve technique, it was shown that capillarization of SECs plays a lesser role than collagenization of the space of Disse in the reduced exchange between sinusoids and hepatocytes in thioacetamide-induced cirrhotic rat livers (308). Moreover, capillarization of hepatic sinusoids is described to occur only in very limited regions of the cirrhotic parenchyma and seems to be less relevant for functional consequences in cirrhotic livers than the markedly smaller areas occupied by sinusoids per unit of parenchyma and the sinusoid/hepatocyte interfaces disposable for metabolic exchanges (609). Sinusoids of cirrhotic livers further lack features of zonation, thereby contributing to the development and progression of liver failure (609).

VI. MODES OF CELL DEATH IN LIVER INJURY

A. Microcirculatory Determinants for Parenchymal and Nonparenchymal Cell Death

As outlined above, liver tissue exposed to various stress stimuli is characterized by deteriorations of the microcirculation. It is generally accepted that microcirculatory disturbances lead to insufficient energy supply, alteration of mitochondrial redox state (232, 838), subsequent decline of hepatic tissue oxygenation (173, 241), and impaired ATP regeneration (214, 522, 523, 655). The strong dependency between an intact microcirculation and the viability of both parenchymal and nonparenchymal cells is indirectly evidenced by numerous studies that demonstrate a cytoprotective effect by implementation of therapeutic strategies improving the liver microcirculation (100, 552, 755). These strategies comprise hemodilution, vasoactive agents, ROS scavenging drugs, immunomodulatory substances, and antiadhesive compounds (373, 466, 803, 963).

The degree of microvascular shutdown during postischemic reperfusion can be modulated in that sinusoidal shutdown is largely avoided with flow-controlled reperfusion. In contrast, pressure-controlled reperfusion may result in early and severe microcirculatory shutdown, correlating well with the manifestation of hepatocyte death (109). This underlines again the dependency of tissue injury from microcirculatory disturbances. In line with this, an improvement of the hepatic microcirculation by application of ET-receptor antagonists (35, 152, 560, 834, 835), NO and L-arginine supplementation (8, 152, 734, 785), and PGE_2 or prostacyclin (PGI_2) (813, 815) results in an attenuation of hepatocellular injury.

In addition to the perfusion failure-associated impairment of oxygen supply to tissue, activated endothelial cells, leukocytes, and platelets within the injured vasculature release extracellular nucleotides (e.g., ATP, UTP, ADP), which bind to specific cell-surface type 2 purinergic receptors. This process is suggested to further drive vascular inflammation and thrombosis (41). In turn, ectonucleoside triphosphate diphosphohydrolases (NTPDases, i.e., CD39) hydrolyze extracellular nucleotides and, therefore, potentially regulate nucleotide-mediated signaling. This limits the activation of platelet- and leukocyte-expressed P2 receptors and, thus, the generation of adenosine to reverse inflammatory events. The vascular protective activity of NTPDase1, which is expressed in hepatic arteries, portal veins, and hepatic central veins (159), is rapidly inhibited by oxidative reactions, as observed in liver I/R injury (for review, see Ref. 41). Also, endotoxin-induced cholestatic liver injury is associated with a decrease of the NTPDase activity (970), potentially increasing the procoagulatory status of the microvasculature during endotoxemia.

The implication of leukocytes for microvascular injury is unequivocal, but the relative contribution of microvessel obstruction versus adhesion and transendothelial migration versus release of toxic mediators is still a matter of debate. In the isolated perfused liver, nonactivated oxidatively quiescent leukocytes stick in the liver but have no significant effect on either perfused sinusoids or dead hepatocytes, while activated leukocytes cause damage (955). However, detailed spatial analysis disproved a correlation between leukocyte accumulation and microvascular damage on the individual level of sinusoids (197). This supports the observation that stagnant leukocytes increase flow resistance, but do not significantly contribute to perfusion failure of the individual sinusoid (868). On the basis of whole liver upon I/R, linear regression estimates reveal significant correlations between transaminases and bile flow as indicators of hepatocellular integrity and function with the number of adherent leukocytes in postsinusoidal venules, but not of stagnant leukocytes in sinusoids (859). On the other hand, it has been shown that in endotoxemic shock only leukocytes from the sinusoids actually transmigrated at a time when parenchymal cell injury occurs (105). In a remote model of liver injury, i.e., limb I/R, however, the number of stationary leukocytes within both sinusoids and postsinusoidal venules correlated with plasma ALT activities (911).

Substantial differences are described in the vulnerability of the different liver cell types to damage, in particular upon cold I/R. Here, a huge discrepancy could be observed between viability of parenchymal cells and nonparenchymal cells. In addition, there is a qualitative difference between warm and cold preservation injury, with relatively selective damage to hepatocytes or sinusoidal lining cells, respectively (315, 544). For example, after prolonged cold storage in Euro-Collins solution, most

parenchymal cells remained viable (>90%), while severe damage to nonparenchymal cells of up to 40% was observed (79, 525).

B. Apoptosis, Oncotic Necrosis, Secondary Necrosis, and Aponecrosis

True apoptotic and necrotic cells can be differentiated on the basis of morphological and biochemical characteristics. It is a widely accepted way to define necrotic cell death by demonstrating a lack of apoptotic features. The classical morphology of an apoptotic cell includes cell shrinkage, chromatin condensation, fragmentation and margination, and apoptotic body formation. A swollen cell with evidence for vacuolization, karyolysis, and karyorrhexis is considered to undergo oncotic necrosis. Biochemically, necrotic cell death presents with acute metabolic disruption and ATP depletion, ion dysregulation, and activation of degradative enzymes, finally resulting in plasma membrane rupture and release of cell contents. These features contrast those of apoptosis, representing a cellular differentiation program, leading to resorption of the cell without significant impairment of cellular metabolism (364). In distinction to cell apoptosis, the molecular mechanisms underlying oncotic necrosis are poorly understood, which might be due to the fact that necrosis is still believed to be an uncontrollable and passive form of cell death (364, 387). However, there is meanwhile preliminary evidence that cell necrosis can also be a physiological and regulated, i.e., programmed event (290, 643, 644, 775). In aggregate, it has been recognized that both modes of cell death share common features and pathways, challenging the past view that apoptosis and necrosis are fundamentally different processes. In particular, the MPT, initially described as a reversible Ca^{2+}-induced permeabilization of the mitochondrial inner membrane, resulting in simultaneous changes, like increased permeability, induction of ATPase, uncoupling of oxidative phosphorylation, and loss of respiratory control (312), is regarded to play a causative role in necrotic, but also in apoptotic cell death (388, 407, 476, 649) (Fig. 14).

It has been hypothesized that cellular ATP levels might be an important factor in determining the cell death pathway secondary to a harmful insult, an apoptotic pattern when ATP levels are high and a necrotic pattern when ATP levels are low (139, 340, 388, 476, 649). Thus it is thought that the severity of injury is a main determinant for the mode of cell death in that if the insult is severe enough to damage most of the mitochondria, cellular ATP levels will drop and oncotic necrosis occurs. Is the insult less severe or even moderate, enough mitochondria are left intact to maintain cellular ATP levels, allowing apoptosis but preventing necrotic cell death (476, 592) (Fig. 14). The dependency of induction of either necrotic or apoptotic cell death on the oxidative metabolism of the cell was nicely demonstrated by data in a graded model of hemorrhagic shock in rats, suggesting that prolonged low flow/hypoxia induces ATP depletion and pericentral necrosis, while restoration of oxygen supply and ATP levels

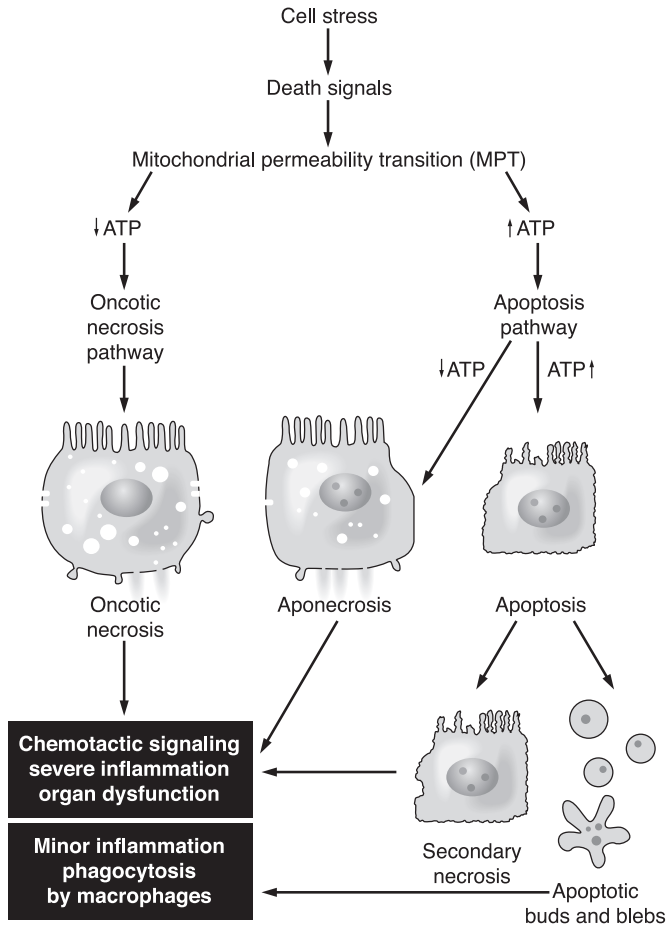

FIG. 14. Apoptotic and necrotic hepatocellular death in response to stress signals. Injurious stress causes mitochondrial permeability transition (MPT) with mitochondrial swelling and lysis, which represents a causative mechanism of acute necrotic cell death. MPT also precedes mitochondrial cytochrome *c* release, which is followed by a cascade of caspase activation, resulting in apoptotic cell death. The important factor in directing the cell death pathway secondary to the insult-induced MPT is the cellular ATP availability. The apoptosis pathway requires ATP, and intracellular ATP prevents the onset of the oncotic necrosis pathway. The characteristics of apoptotic cell death are condensation, fragmentation, and margination of the nuclear chromatin and shrinkage of the cell without damage of the plasma membrane. When MPT depletes ATP, necrotic cell death occurs, which is characterized by cytoplasmic vacuolization and cell swelling as well as plasma membrane blebbing and disruption. Of note, if ATP depletion develops during progression of apoptosis, the cell undergoes aponecrosis. This mixed form of cell death exhibits features of both apoptosis and oncotic necrosis. Apoptotic cells may break up into a cluster of apoptotic bodies, which are removed by neighboring cells or macrophages without a marked inflammatory response. In contrast, oncotic necrotic hepatocytes as well as aponecrotic and secondary necrotic hepatocytes serve as strong chemoattractants for leukocytes, aggravating inflammation and organ dysfunction.

after shorter periods of low-flow ischemia propagates pericentral apoptosis (627).

In addition to the severity of the insult, the mode of the insult is also known to influence the nature, kinetics, and extent of the individual cell death. However, there is still constant discussion on which is the predominant pathway in most forms of liver disease. For example, in pig livers subjected to 180 min of warm ischemia, the frequency of apoptotic cells was reported to be only 2.6%, but that of necrotic cells 37% at 24 h after reperfusion (546). This is well in accordance with reports on rat livers exposed to 60 or 120 min of warm ischemia, demonstrating <1% apoptotic hepatocytes and increasing numbers of necrotic hepatocytes up to 57% over 24 h of reperfusion (257). These results challenge data of others, indicating 30 and 50% apoptotic hepatocytes in rat livers after 60 min of warm ischemia and 24 h of reperfusion (404). These controversies on apoptosis and necrosis become even more complex, surveying cold versus warm ischemia and the susceptibility of SEC versus parenchymal cells in normal or steatotic livers (457, 719, 793). In the aggregate, however, warm ischemic-reperfusion injury is thought to preferentially occur through oncotic necrosis (257), while both apoptosis and necrosis contribute to cold preservation injury of the liver (176, 340).

In hepatotoxin-induced injury models, using Gal (90, 391), dimethylnitrosamine (565), acetaminophen (345, 407), carbon tetrachloride (565), alcohol (30), microcystin-LR (153, 894, 896), and endotoxin (22), cytotoxicity has predominantly been related to apoptotic cell death, although necrotic tissue injury is also reported (227, 560, 909). The generation of reactive intermediate metabolites from the metabolism of hepatotoxins, and the generation of ROS during the inflammatory reaction account for the stimulation of a variety of pathways leading to cell death. These include covalent binding, disordered cytosolic calcium homeostasis, depletion of GSH and methione pools (22), reduced activities of SOD and catalase (30), onset of MPT (153, 896) and, finally, lipid peroxidation (30).

In line with in vitro data, demonstrating that apoptosis and necrosis result from low and high concentrations of the hepatotoxin 7H-dibenzo(c,g)carbazole (DBC) and are dependent upon intracellular ATP levels (597), it became common view that ATP plays a pivotal role in directing apoptotic and necrotic cell killing (476). In proportion of MPT-associated injury of mitochondria and, thus, the extent of ATP depletion, progression of apoptosis is supervened by cell lysis in a pattern of secondary necrosis (27, 771, 772) (Fig. 14). In contrast to primary oncotic necrosis, secondary necrosis is unequivocally preceded by apoptotic hallmarks. For example, carbon tetrachloride and Gal are shown to cause apoptosis in the liver by activating caspase-3, which is released to the plasma by secondary necrosis, indicated by a concomitant rise in glutamate-oxaloacetate transaminase (GOT) (771, 772). In support of this, secondary necrotic tissue injury, as assessed by the release of transaminases, can be completely prevented by inhibiting the onset of early apoptosis (27, 176).

Given the shared triggers, overlapping pathways, and common signaling events, the terms *necrapoptosis* (475, 476) or *aponecrosis* (205) have been established, describing a syncretic process of cell death sharing characteristics of both apoptosis and necrosis (101, 176, 388) (Figs. 14 and 15). Because necrotic cell death intervenes if ATP depletion occurs during the progression of the cell towards apoptosis, the term *aponecrosis* seems to be superior to the term *necrapoptosis*. Classic apoptosis and necrosis may represent only extremes of a continuum of intermediate forms of aponecrotic cell demise. Aponecrosis has been shown to be responsive to both antiapoptotic and antinecrotic strategies, including MPT inhibition (475, 934, 964), p53 and caspase inhibition (176, 705), application of IL-6 (772) and antioxidants (424, 934), as well as upregulation of Bcl-xL (220). This also underlines the idea of the existence of a mixed form of cell death (Fig. 15).

C. Cell Death and Secondary Inflammatory Tissue Injury

Cellular oncotic necrosis with rupture of the plasma membrane and release of cell content represents a source of multiple mediators (118, 608), which are best known for their capacity to attract leukocytes. Dying hepatocytes serve as chemoattractants for primed leukocytes, guiding them during their migration. In cholestatic liver injury, more than 50% of all accumulated leukocytes are found extravasated and colocalized with foci of oncotic hepatocytes (259). In postischemic reperfused livers, Colletti et al. (118) described *1*) a coincident increase in hepatic neutrophil sequestration, elevated serum ALT levels, and hepatic production of epithelial neutrophil activating protein; *2*) a significant suppression of epithelial neutrophil activating protein by immunization against TNF-α; and *3*) an attenuation of intrahepatic neutrophil sequestration and ALT release upon neutralization of epithelial neutrophil activating protein. Moreover, livers benefit from the deficiency of chemoattractants, show reduced leukocyte infiltration and, thus, attenuated leukocyte-dependent secondary tissue injury (947). In addition, inhibition or deficiency of MMPs, which are critically involved in the degradation of extracellular matrix, decreases inflammatory cellular recruitment, because MMPs promote transmigration and are required for the motility of interstitially migrating leukocytes (383, 745). Leukocytes aggravate local injury by their release of ROS, which diffuse into neighboring hepatocytes, cause mitochondrial dysfunction, and trigger MPT-dependent oncotic necrosis (277, 337, 591). This view is further supported by the fact that

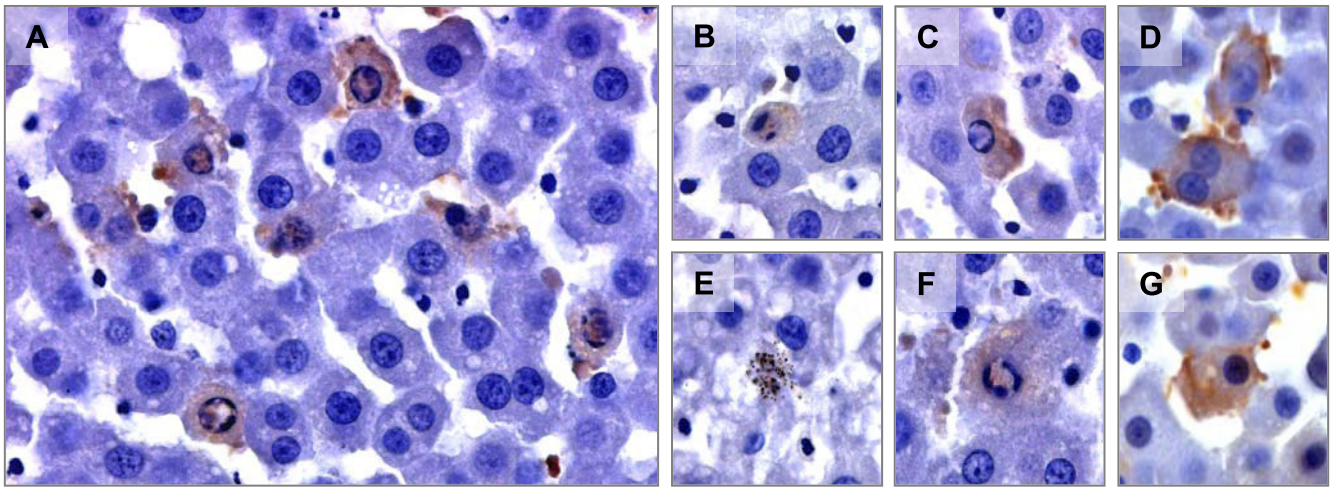

FIG. 15. Cleaved caspase-3 immunohistochemistry of liver specimens, which underwent cold storage and reperfusion. Note the staining of individual contiguous cells rather than groups of cells (*A*). *B* and *E* show caspase-3-positive cells with the classical signs of apoptotic death, i.e., nuclear fragmentation and cell shrinkage. Of interest, however, the caspase-3-positive cell in *E* displays also marked vacuolization, which is a characteristic of oncotic necrosis. Accordingly, cells in *C* and *F* display apoptotic characteristics, such as caspase-3 staining and nuclear condensation and margination; however, these are not associated with cellular shrinkage. Furthermore, cells may express caspase-3, but may lack nuclear changes and shrinkage, and may show, instead, characteristics of oncotic necrosis, such as plasma membrane blebbing (*D*, *G*). These cells sharing features of both apoptosis and necrosis are termed aponecrotic. *A–G* magnification ×500. [From El-Gibaly et al. (176).]

glutathione peroxidase-deficient mice are more susceptible to neutrophil-mediated hepatic parenchymal cell injury, because they cannot adequately encounter intracellular oxidant stress (338). In addition to ROS, proteases released by invading leukocytes (192) are involved in the pathway of leukocyte-dependent aggravation of tissue injury (Fig. 11), as given by the efficacy of protease inhibitors to attenuate liver injury (133, 147, 170, 271, 417, 923).

In addition to the acceleration and aggravation of necrotic tissue injury by infiltrating leukocytes, hepatocellular damage itself may contribute to sustain the detrimental inflammatory response by the release of high mobility group box-1 (HMGB-1) (704). In cytotoxic T-cell-mediated liver inflammation, this nuclear protein is translocated to the cytoplasm of hepatocytes surrounding necroinflammatory foci. It is further supposed to be released into the extracellular space by hepatocytes and responsible for recruitment of antigen nonspecific cells (744). HMGB-1, released from stressed and necrotic cells, has been shown to be a late mediator in systemic inflammation (879), but to act also as an early mediator following I/R injury (825, 892).

In contrast to the paradigm that apoptotic cell death does not induce an inflammatory response (377, 512), apoptotic hepatocytes, like necrotic ones, have been shown to exert chemotactic signals, triggering transmigration of primed leukocytes and sustaining the cell-dependent inflammatory response in severe endotoxemia (467) (Fig. 11). Colocalization of leukocytes with apoptotic hepatocytes in endotoxemic livers can be blocked by pancaspase inhibition, which confirms the causative role of apoptotic cells to provoke recruitment of leukocytes (168). Infection of hepatocytes in culture with *Listeria monocytogenes* induces cell death by apoptosis with release of neutrophil chemoattractants. Accordingly, *Listeria monocytogenes*-infected mice livers present with apoptotic hepatocytes and recruited leukocytes (684). Similarly as shown for endotoxemia, repression of hepatocyte apoptosis by administration of the caspase inhibitor zVAD-fmk results in an attenuation of neutrophil infiltration and liver injury upon warm I/R (401). Fas ligation on hepatocytes with induction of cell apoptosis has been demonstrated to induce hepatic chemokine expression, which in turn causes leukocyte inflammation of the liver (190). In analogy to antigen-independent unspecific inflammatory liver diseases, cytotoxic T-cell-induced parenchymal apoptotic cell death is aggravated by the intrahepatic recruitment of antigen nonspecific cells. This contributes to the formation of necroinflammatory foci scattered throughout the liver parenchyma (362).

Apoptotic hepatocytes synthesize and release peptide mediators that recruit inflammatory cells and aggravate inflammation-dependent injury. This fact explains the discrepancy between the small number of apoptotic cells and the large protection observed with caspase inhibitors (131, 132, 401). In addition to leukocytes, KC might also promote the inflammatory response upon hepatocellular apoptosis. Activated KC are shown to frequently colocalize with apoptotic hepatocytes (170). They release cytokines and express death ligands upon phagocytosis, which further promotes hepatocyte apoptosis in a feed-forward loop (83) (Fig. 11). In line with data from experimental work, a positive correlation can be observed between hepatocyte apoptosis, hepatic fibrosis,

and inflammatory activity in patients with nonalcoholic steatohepatitis (194). Accordingly, colocalization of apoptotic hepatocytes with neutrophils found in alcoholic hepatitis underlines the relevance of apoptosis-dependent transmigration of leukocytes also in human pathophysiology (971).

VII. MICROCIRCULATORY AND MICROVASCULAR MECHANISMS OF LIVER REPAIR

A. Role of Platelets, Leukocytes, and Kupffer Cells

Platelets are recognized for their physiological functions that extend well beyond their role in hemostasis. There is a true body of evidence that platelets which are found activated and sequestrated in the hepatic microvasculature are not innocent bystanders in this process. In fact, platelets actively contribute to the pathogenesis of organ damage and organ dysfunction upon I/R as well as in endotoxemia, steatosis, and cholestasis (136, 191, 453, 582, 629, 741, 742). Contrasting their critical involvement in inflammation, platelets may serve as regenerative cells themselves. This view comes from abundant data, connecting platelets to the repair of vascular injury and to the progenitor cell biology (448). For hepatocytes, it has been shown that platelets and platelet-derived serotonin can act as potent comitogens and induce DNA synthesis in primary cell cultures through the serotonin S2 receptor (29, 189). Also, growth factors, like vascular endothelial growth factor (VEGF), insulin-like growth factor I (IGF-I), and hepatocyte growth factor (HGF), contribute to platelet-induced hepatocyte proliferation (534). Of interest for clinical use, freeze-dried platelets sufficiently maintain their storage of peptide mediators and growth factors and preserve their proliferative action on hepatocytes identical to that of fresh platelets (305). In line with these in vitro results, thrombocytopenia (GPIb-α antibody) or impaired platelet activity (clopidogrel application) have been shown to result in failure of cellular proliferation in a mouse model of liver regeneration (479). In thrombocytopenic animals as well as in mice deficient for tryptophan hydroxylase-1, i.e., the rate-limiting enzyme for the synthesis of peripheral serotonin, it has been demonstrated that a serotonin agonist can reconstitute liver proliferation. This underlines the predominant role of serotonin for hepatocellular regeneration upon both resection and postischemic tissue injury (479, 596).

Depletion or modulation of platelet, leukocyte, and KC function has been convincingly shown to ameliorate inflammation and to protect the liver from subsequent endotoxemic, cholestatic, and postischemic as well as hepatotoxin-induced injury (see sect. IV). However, it is well established that hepatic inflammation is also part of the normal healing process (322). Livers from ICAM-1-deficient mice exhibit impaired regeneration upon two-third resection. This is associated with a dramatic decrease of leukocyte recruitment and TNF-α and IL-6 tissue levels, which can be reconstituted by IL-6 supplementation (720). As physiological liver regeneration is not associated with markedly enhanced leukocyte-endothelial cell interaction (6), the availability of leukocytes and their cross-talk with KC rather than their activation per se seem to be mandatory for an adequate regeneration.

KC promote the resolution of fibrosis by leukocyte-dependent secretion of MMP-8 (275, 276). Vice versa, it is reported that KC inactivation during liver repair impairs collagen metabolism, inhibits the resolution of fibrosis, and supports the persistence of inflammatory cell infiltrates (685). These repair processes are crucially dependent on the balance of growth factors in aid of HGF (146, 513, 580, 928). In addition, depletion of KC in the regenerating liver alters the pattern of vasoregulatory gene expression, thereby limiting intrahepatic hyperperfusion as an important trigger of proliferation (5). In contrast, dysbalance of vasoactive mediators in postischemic reperfused livers is reported to be KC independent (390). These discrepant data might at least in part be attributed to the fact that marked differences exist between the action of the used KC-targeting substances, inducing either depletion, inhibition, or modulation of KC. Treatment with gadolinium chloride or dextran sulfate, which inhibit KC function, decreases acetaminophen toxicity in mice (455, 557). On the other hand, treatment of mice with Cl_2-MBP, which completely depletes livers from KC, increases toxicity of acetaminophen (357).

Moreover, the importance of nonparenchymal cells, i.e., KC but also hepatic stellate cells and endothelial cells, in the process of liver regeneration and repair is further supported by data demonstrating activation of KC and hepatic stellate cells upon transplantation of hepatocytes which partly plug the liver microvasculature. This reflects the engagement of KC and hepatic steallate cells in the local host defense and in the initiation of liver repair mechanisms owing to ischemia-related cell damage (900). Furthermore, endothelial cells are mandatory for angiogenesis within the regenerating tissue mass. This is indicated by the fact that acting via induction of endothelial cell apoptosis angiogenesis inhibitors cause a cessation of the regenerative process (247).

B. Kupffer Cell-Leukocyte Interaction

Although a dysregulated or overwhelming activation of KC and leukocytes is well known to contribute to an exaggeration of tissue inflammation (see sect. IV), physiological functions of these cells facilitate the elimination of invading organisms and represent the first line of defense. Recent reports on the underlying mechanisms in-

dicate that both cell types are complementary in the bacterial elimination process and that KC may play a less significant role in resolving systemic infections (250). While KC initially bind most organisms taken up in the liver on their extracellular surface by the interaction of lectins with the bacterial carbohydrate residues (602), leukocytes internalize and kill these organisms (250). The obligatory requirement of leukocytes in bacterial killing has been established by experiments in leukocyte-depleted animals, demonstrating a sharp decline in the capacity to kill gram-positive and gram-negative organisms trapped in the liver (120, 845, 851). In addition, blockade of the ICAM-1-CD11b/CD18 interaction using specific antibodies, which inhibit the accumulation of leukocytes, decreases the elimination of bacteria (249). These results have established the paradigm that those complementary adhesion molecules, beyond modulating leukocyte traffic and adhesion in the liver, facilitate the accumulation of bactericidal leukocytes at the surface of KC (249, 250). Thereupon, leukocytes eradicate the organisms and are ingested and destroyed by KC (250) (Fig. 10*C*). Because ICAM-1 is also expressed on other cells than KC, such as SEC and hepatocytes, these cells might effectively contribute in the fight against bacterial load. Accordingly, hepatocytes have been described as nonprofessional phagocytes (248).

The phagocytosis of leukocytes by KC is crucial for limiting inflammation, because by this elimination leukocyte-dependent production of toxic metabolic compounds and degradative enzymes is inhibited. The binding of apoptotic leukocytes or leukocytes expressing surface changes that enable their recognition (732) seems to involve, among other receptors with broad, lipid-binding capacity, a phosphatidylserine specific receptor (186), the α-4 beta-3 integrin (the vitronectin receptor) and CD36 complex (703). These three molecules probably constitute a single, large receptor complex (185). In addition, carbohydrate-specific receptors are active on KC (492). Upon binding, the cells are ingested by phosphatidylserine receptor-mediated macropinocytosis (303). In consequence, phosphatidylserine blockade by annexin V results in inhibition of phagocytosis by KC (732). There is considerable controversy on the consequence of ingestion of apoptotic leukocytes by KC. There are reports about the release of either anti-inflammatory cytokines (434) or proinflammatory cytokines (435, 831). This might be due to the markedly different in vitro settings chosen, but also due to the predominant receptor being involved (187) and to the stage of apoptosis the cells are, as an even silent cleanup of very early apoptotic cells by macrophages is reported (433). If the timing for phagocytosis is retarded, inflammation might occur through unbalanced production of proinflammatory cytokines. This may explain that in mice with bile duct ligation engulfment of apoptotic bodies by KC promotes death ligand and cytokine expression and, thus, inflammation (83). However, there are also contrasting data demonstrating also in bile duct-ligated animals an abrogation of cholestatic liver injury by KC via IL-6 release (226).

C. Microvascular Blood Flow and Shear Stress

The maintenance of an adequate hepatic blood flow is crucial for homeostasis (463). One mechanism that acts to maintain hepatic blood flow constant per liver mass is the HABR. In addition to physiological conditions, the HABR has been described to be also maintained in cirrhotic livers of animals and humans (18, 572, 670) and after liver transplantation (286). Of interest, this response is lost upon brain death (236), under increased intraabdominal pressure (CO_2 pneumoperitoneum) (671), and during endotoxemia (25, 262, 708). The fact that NO (262, 789) but also terlipressin (24) restore the HABR during endotoxemia reflects the temporal and spatial complexity in the misbalance of expression of vasoconstrictive and vasodilative mediators (see sect. v). Restoration of the HABR is shown to prevent subsequent hepatic damage in the course of endotoxemia (789).

In case of supranormal portal blood flow, as it occurs upon extended liver resection or small-for-size split liver transplantation, an intact HABR, though of principal benefit, may cause diminished arterial flow and is accused of significantly contributing to the life-threatening small-for-size syndrome with graft failure (144, 749). In line with this, pharmacological strategies to increase hepatic arterial blood flow (85) and maneuvers reducing the portal hyperperfusion and preventing hepatic artery constriction (57, 231, 325, 420, 501, 796, 819) have been shown to improve the postoperative clinical course after extended hepatectomy. Evaluation of posttransplant biopsies of small-for-size syndrome livers has revealed poor hepatic arterial flow and vasospasm, which resulted in functional dearterialization, ischemic cholangitis, and parenchymal infarcts (144). Beside the arterial hypoperfusion-related hypoxic sequelae (676, 749), portal hyperperfusion in small-for-size livers leads to portal vein and periportal sinusoidal endothelial disintegration and denudation (144). This is associated with the development of fused fenestrae and microvilli protruding into the vascular lumen (61), seriously impairing the postoperative recovery of these livers (325, 518). Liver biopsies from right lobe live donor liver recipients reveal ET-1 overexpression, together with downregulation of HO-1 and heat shock protein 70 (518), underlining the pivotal role of misbalanced vasoactive mediators in the pathogenesis of the small-for-size syndrome (615). In line with this, the hepatic regenerative capacity is found deteriorated by ischemic preconditioning of reduzed size livers, most probably due to the preconditioning-associated vasodilation and

thus aggravation of hyperperfusion (169). Vice versa, splenectomy-associated reduction of portal venous blood flow diminishes shear stress-induced liver injury and positively influences postoperative regeneration (231).

Aside from harmful effects of excessive portal hyperperfusion, the hyperperfusion-associated increase of intravascular shear stress is one of the main factors contributing to cell proliferation (593, 701, 702, 810, 880). Physical stimuli are converted into chemical signals with production of endothelium-derived relaxing factors, among those NO and prostaglandins are the best-studied candidates (77, 204). In plasma of partially hepatectomized rats, various growth factors, cytokines, and hormones have been detected, causing proliferation of cultured hepatocytes. This proliferation could be blocked by the NOS inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) and restored by L-arginine (880). From in vivo models of partial hepatectomy there is convincing evidence for a shear stress-related release of NO and prostaglandins. These molecules most probably trigger the liver regeneration cascade, because proliferation is inhibited by NOS antagonists and because this inhibition is reversed by NO donors or the prostaglandins PGE_2 and PGI_2 (85, 711, 712).

Patients with small, but not with large, liver grafts show an immediate increase of portal pressure, reflecting an increased sinusoidal shear stress, which accelerates liver regeneration through immediate induction of IL-6 and HGF (612). The relevance for appropriate shear stress in liver regeneration is reflected by genome expression analysis. These studies demonstrate differentially expressed genes in livers with a high portal pressure, which have functions related to apoptosis, NO metabolism, and oxidative stress, whereas differentially expressed genes in the livers with low portal pressure potentially regulate the cell cycle (570).

Wall shear stress regulates adaptive vessel growth and angiogenesis, which is of essential importance during the resection-induced restoration of new liver tissue mass. Initial mechanisms, such as the recruitment of all sinusoids and the increase of sinusoidal diameters preserve the functional vessel area after resection, guaranteeing an adequate oxygen supply to tissue (5, 855). Concomitantly, growth factor-driven endothelial cell proliferation with new vessel formation takes place and dictates the regenerative process (247).

D. Gaseous Molecules NO, CO, and H_2S

Beyond the pure vasoactive property of NO, this gaseous molecule is a potentially important paracrine mediator in many organs, including the liver (682). With the advent of mice selectively deficient in the various isoforms of NOS, the role that NO plays in liver injury and repair can be examined much better than the different and often very unspecific NOS inhibitors allowed. Consistent with the concept that excessive production of NO through inflammation-associated upregulation of the inducible NOS aggravates liver injury and that basal levels of NO deduced from the constitutive NOS mediates rather protection, postischemic liver injury is significantly enhanced in eNOS-deficient but not in iNOS-deficient mice (295, 374, 794). Comparably, eNOS deficiency increases necrapoptosis and fails to improve hepatic microcirculation upon cold storage and reperfusion (807). Accordingly, iNOS-deficient mice have been found less sensitive to the hepatotoxic effects of acetaminophen than wild-type mice (223). The liver-selective NO donor V-PYRRO/NO mediates protection by reduction of oxidative stress, inhibition of TNF-α and TNF-related apoptosis, and possibly by maintenance of hepatic microcirculation to prevent congestion (493, 494). Moreover, TNFR1(−/−) mice have been shown significantly more sensitive to the hepatotoxic effects of acetaminophen, most supposedly due to a more rapid and prolonged induction of iNOS in the liver (222). There is the hypothesis that the use of iNOS inhibitors is only beneficial in the presence of a functioning eNOS system, as some NO is needed to maintain adequate organ function (135). This view is deduced from data demonstrating that liver injury in endotoxemic animals with unspecific NOS blockade profit from simultaneous infusion of a liver-selective NO donor (611).

Generalized vasodilation and hypotension in endotoxemia is attributed to an overproduction of NO and CO by inducible NOS and HO-1. In addition, the most recently recognized gaseous molecule H_2S is overproduced in vascular tissue of septic animals and is shown to play a proinflammatory role with regulation of severity of sepsis and associated organ injury (310, 480, 953). In endotoxic stress-exposed livers, the expression and activity of both H_2S-synthesizing enzymes CSE and CBS is found increased (119). Furthermore, H_2S acts as an important endogenous regulator of leukocyte activation and trafficking by upregulating hepatic expression of the adhesion molecules ICAM-1, P-selectin, and E-selectin (952). However, the role of H_2S as proinflammatory mediator is not unambiguous. Antiadhesive properties of H_2S are also reported (520, 948). For example, Zanardo et al. (948) have shown that H_2S donors inhibit aspirin-induced leukocyte adherence in mesenteric venules. In addition, antiapoptotic properties of H_2S against leukocytes might cause prolongation of their life span, potentially enhancing the resolution of inflammatory processes (673).

While for each gaseous mediator, i.e., NO, CO, and H_2S, an immense spectrum of effects is reported, the scenario becomes even more complex, considering the multifaceted interrelation of the molecules and their synthesizing enzyme systems with each other. There is first evidence for the formation of a novel nitrosothiol gener-

ated by the reaction between H_2S and NO (898). NO can regulate endogenous production of H_2S by increasing vascular CSE expression (961) and, vice versa, H_2S enhances the NO-associated vessel relaxation (306). H_2S upregulates synthesis of CO through induction of HO-1 (650). Furthermore, H_2S is shown to inhibit NO production and NF-κB activation in LPS-stimulated macrophages through a mechanism that involves the action of HO-1 and CO (603). This most dynamic interplay between H_2S, the NO pathways, and the CO systems almost precludes a prognosis on the net effect of these mediators in liver disease.

VIII. MEASURES TARGETING HEPATIC MICROVASCULAR DISORDERS

A. Antioxidative, Antiadhesive, and Anti-Inflammatory Approaches

One target to prevent inflammatory liver diseases is enhancement of the capacity of endogenous redox defense, because ROS play a pivotal role as cytotoxic and signaling mediators in the pathophysiology of tissue injury. Important sources of ROS formation are KC and invading leukocytes via NADPH oxidase-dependent superoxide generation. In addition, ROS can also be generated intracellularly in every liver cell type after stimulation with cytokines (337, 344). The fact that oxidant-induced liver injury is not only the result of passive interaction of ROS with cellular macromolecules, like the peroxidation of lipid membranes, but in particular of the active modulation of cell signaling cascades by affecting antioxidant enzymes, transcription factors, and intracellular organelles (137), the strategies to augment the antioxidant defense systems are manyfold.

The application of radical scavengers (SOD, NAC, tocopherol, and allopurinol) has been proven to be beneficial in experimental and human settings of warm and cold I/R by inhibiting inflammatory leukocyte accumulation (403, 408, 524, 573), microvascular perfusion failure (403, 408, 414, 573), lipid peroxidation (850), and graft dysfunction (809) (Table 2). These salutary effects of radical scavengers have also been shown for endotoxemic livers (914) and steatotic livers subjected to I/R (217) as well as in conjugation with hydroxyethyl starch as antioxidative resuscitation upon hemorrhagic shock (33). Finally, the University of Wisconsin and HTK preservation solution enriched with antioxidative agents are widely established tools in experimental and clinical settings of liver transplantation (195, 639, 769).

Inhibitors of NADP oxidase, such as diphenylene iodonium, reduce the formation of superoxide anions and liver injury associated with hemorrhagic shock and resuscitation, most probably by the downregulation of the transcription factor AP-1 (3). They also prevent the neutrophil-derived oxidant stress in endotoxemia, which includes the formation of hypochlorous acid by myeloperoxidase (258). NADPH oxidase inhibitors further attenuate early alcohol-induced liver injury by inhibiting free radical formation via NADPH oxidase, thereby preventing NF-κB activation and TNF-α mRNA expression in the liver (411). In contrast to that, leukocytic NADPH oxidase-dependent oxidative stress seems to play a minor role in acetaminophen-induced toxicity (129). Next to NADPH oxidase, which is thought to be responsible for ROS production during later time periods of reperfusion (613), Rac1-regulated oxidase has been reported to mediate the production of injurious ROS, which contribute to apoptotic and necrotic cell death after I/R. Targeted inhibition of this oxidase, which is distinct from the phagocyte NADPH oxidase, should provide a new avenue for in vivo therapy, aimed at protecting organs at risk from I/R injury (613) (Table 2).

Prevention of inflammatory liver injury can further be achieved by increasing the extracellular antioxidant capacity by infusion of GSH to counteract extracellular and vascular oxidant stress (49, 51, 143). Upon postischemic GSH treatment, intravital fluorescence microscopy has demonstrated an almost complete restoration of sinusoidal blood flow, paralleled by a reduction of inflammatory leukocyte adherence in sinusoids and postsinusoidal venules, resulting in reduced necrotic tissue injury and improved rat survival (706). Micronutrients like selenium are observed to enhance the endogenous antioxidant capacity of the cells by increasing the activity of SOD and the GSH content (177). Accordingly, selenite supplementation significantly improves postischemic hepatic microcirculation by acting as a radical scavenger and by preserving the antioxidative capacity of the liver (949). This is supported by in vitro results on the organoselenium ebselen, which has been shown to be a potent inhibitor of NADPH oxidase in KC (882). Of interest, ebselen also protects against ET-1-mediated microcirculatory disturbances and cell damage in alcoholic liver injury (610). Furthermore, glutamine or alanyl-glutamine dipeptide are beneficial in supporting hepatic microcirculation and can protect against postischemic necrotic liver injury by enhancing GSH content (355, 778) (Table 2).

With the idea that inhibition of ROS has not only beneficial but also detrimental effects, because ROS are important in bactericidal defense and may trigger cell signals that are critical for hepatocellular proliferation, therapeutic strategies aim at increasing the resistance of hepatocytes against these reactive species and at targeting of downstream factors specific for the death effects of ROS (137). Heat shock proteins are considered to effectively mediate resistance against subsequent injurious stimuli. Heat shock protein 32, better known as HO-1, is among the most interesting molecule, exerting cytoprotective mechanisms activated during cellular stress (821).

TABLE 2. *Agents targeting the hepatic microcirculation, their site of action, and their mechanisms of inhibiting hepatic injury*

Agent Family	Family Members	Mechanism of Inhibition of Hepatic Injury	Liver Injury	References
Radical scavengers and antioxidants	Superoxide dismutase	Inhibition of intrahepatic leukocyte accumulation	I/R	Marzi et al., 1992; Müller et al., 1996; Kondo et al., 1999
		Attenuation of sinusoidal perfusion failure	I/R	Marzi et al., 1992; Müller et al., 1996; Kondo et al., 1999; Koo et al., 1992
	Deferoxamine-conjugated hydroxyethyl starch	Inhibition of intrahepatic leukocyte accumulation	Shock/resuscitation	Bauer et al. 1999
		Attenuation of sinusoidal perfusion failure	Shock/resuscitation	Bauer et al. 1999
		Inhibition of lipid peroxidation	Shock/resuscitation	Bauer et al. 1999
	N-acetyl-cysteine	Inhibition of leukocyte accumulation	I/R	Koeppel et al., 1996
		Attenuation of sinusoidal perfusion failure	I/R	Koeppel et al., 1996
			I/R in steatosis	Fusai et al., 2005
		Increase of portal flow	I/R in steatosis	Fusai et al., 2005
	Tocopherol	Inhibition of lipid peroxidation	I/R	Vardareli et al., 1998
	Allopurinol	Inhibition of leukocyte accumulation	I/R	Müller et al., 1996
			Endotoxemia	Xiang et al., 2003
		Attenuation of sinusoidal perfusion failure	I/R	Müller et al., 1996
			Endotoxemia	Xiang et al., 2003
		Reduction of hepatocyte apoptosis	Endotoxemia	Xiang et al., 2003
		Reduction of CXC chemokine expression	Endotoxemia	Xiang et al., 2003
	NADPH oxidase inhibitors	Downregulation of AP-1	Shock/resuscitation	Abdelrahman et al., 2005
		Prevention of NFκB activation	Alcohol	Kono et al., 2001a
		Prevention of TNF expression	Alcohol	Kono et al., 2001a
	Rac1-oxidase inhibitors	Suppression of NFκB activation	I/R	Ozaki et al., 2000
		Reduction of necrotic cell death	I/R	Ozaki et al., 2000
		Reduction of apoptotic cell death	I/R	Ozaki et al., 2000
	Glutathione	Inhibition of intrahepatic leukocyte accumulation	I/R	Schauer et al., 2004
		Attenuation of sinusoidal perfusion failure	I/R	Schauer et al., 2004
		Improvement of hepatic circulation	I/R	Bilzer et al., 1999b
		Detoxification of KC-derived hydrogen peroxide	I/R	Bilzer et al., 2002
	Glutamine	Increase of hepatic microvascular blood flow	I/R	Szijártó et al., 2007b
		Regulation of the Bcl-2 to Bax protein ratio	I/R	Jia et al., 2006
Micronutrients	Selenium	Preservation of hepatic antioxidative capacity	Pesticide	El-Khawaga, 2005
			I/R	Zapletal et al., 2008
		Amelioration of hepatic microcirculatory dysfunction	I/R	Zapletal et al., 2008
Heat shock proteins and metabolites	Heme oxygenase 1	Antioxidant function		Maines, 2005; Tsuchihashi et al., 2004
		Maintenance of hepatic microcirculation	I/R of steatotic livers	Yamagami et al., 2003
			I/R	Wunder et al., 2004
			SIRS	McCarter et al., 2004b
		Anti-inflammatory action		Maines, 2005; Tsuchihashi et al., 2004
		Antiapoptotic action		Maines, 2005; Tsuchihashi et al., 2004
	Carbon monoxide	Augmentation of hepatic iNOS expression	Endotoxic shock	Sarady et al., 2004
		Antiapoptotic action	Endotoxic shock	Sarady et al., 2004; Hoetzel et al., 2007
	Bilirubin and biliverdin	Reduction of adhesion molecule expression	I/R	Vachharajani et al., 2000

TABLE 2—*Continued*

Agent Family	Family Members	Mechanism of Inhibition of Hepatic Injury	Liver Injury	References
Anticoagulants	Activated protein C	Reduction of adhesion molecule expression	I/R	Kuriyama et al., 2009
		Reduced production of TNF-α	I/R	Kuriyama et al., 2009
		Antiapoptotic action	I/R	Kuriyama et al., 2009
		Reduction of CINC mRNA expression	I/R	Yamaguchi et al., 1997a
		Inhibition of intrahepatic fibrin deposition	Resection of cirrhotic livers	Yoshikawa et al., 2000
	Antithrombin III	Release of PGI_2	I/R	Okano et al., 1996
		Improvement of ATP recovery	I/R	Okano et al., 1996
		Improvement of hepatic microvascular blood flow	I/R	Okano et al., 1996; Maksan et al., 2000
		Inhibition of intrahepatic leukocyte accumulation	Cirrhosis	Maksan et al., 2005; Hisama et al., 1996
		Reduction of CINC production	I/R	Yamaguchi et al., 1997a; Hisama et al., 1996
	Heparin	Inhibition of intrahepatic leukocyte accumulation	I/R	Yamaguchi et al., 1997a; Hisama et al., 1996
		Reduction of CINC production	I/R	Yamaguchi et al., 1997a; Hisama et al., 1996
	Aprotinin	Inhibition of intrahepatic leukocyte accumulation	I/R	Maksan et al., 2000
	Hirudin	Reduction of intrahepatic leukocyte infiltration	I/R, endotoxemia	Kubes et al., 2002
Antiapoptotic agents	PARP inhibitors	Preservation of hepatic microcirculation	I/R	Szijártó et al., 2007a
			I/R	Khandoga et al., 2004
			Shock/resuscitation	Roesner et al., 2006
	Caspase inhibitors	Preservation of endothelial cell integrity	I/R	Natori et al., 1999
			Liver failure	Natori et al., 2003; Wanner et al., 1999
		Reduction of intrahepatic leukocyte infiltration	Endotoxemia	Eipel et al., 2004
			Liver failure	Wanner et al., 1999
		Attenuation of sinusoidal perfusion failure	Endotoxemia	Eipel et al., 2004
			Liver failure	Wanner et al., 1999
	Caspase siRNA	Reduction of intrahepatic leukocyte infiltration	I/R	Contreras et al., 2004
Adhesion molecule antibodies	sLe(x) oligosaccharide	Prevention of platelet adhesion	I/R	Sindram et al., 2000; Khandoga et al., 2002a
	Anti-ICAM-1 antibody	Prevention of leukocyte adhesion	I/R	Vollmar et al., 1995b
	Anti-P-selectin antibody	Prevention of platelet and leukocyte adhesion	Endotoxemia	Klintman et al., 2004
Vasoactive drugs	See Table 1			
Pleiotropic agents	Statins	Prevention of lipid peroxidation and anti-inflammation	Bile duct ligation	Demirbilek et al., 2007
		Antiapoptosis by induction of HO-1 expression	I/R	Lai et al., 2008
		Immunomodulation	Endotoxemia	Kruger, 2006
	Erythropoietin (EPO)	Reduction of hepatocellular apoptosis	Acute liver failure	Le Minh et al., 2007
		Reduction of cytokine release	Acute liver failure	Le Minh et al., 2007
			I/R	Yilmaz et al., 2004
		Reduction of intrahepatic leukocyte infiltration	Acute liver failure	Le Minh et al., 2007
		Reduction of sinusoidal perfusion failure	Acute liver failure	Le Minh et al., 2007
		Reduction of oxidative stress	I/R	Sepodes et al., 2006; Yilmaz et al., 2004
		Reduction of caspase activity	I/R	Sepodes et al., 2006; Hochhauser et al., 2008
		Decrease of JNK phosphorylation Decrease of IκB degradation	I/R	Hochhauser et al., 2008

TABLE 2—*Continued*

Agent Family	Family Members	Mechanism of Inhibition of Hepatic Injury	Liver Injury	References
	L-Glycine	Downregulation of TLR4 signaling		Xu et al., 2008
		Modulation of KC response		Neyrinck et al., 2005
		Inhibition of lipid peroxidation		Deters et al., 1997; Zhong et al., 1996
		Reduction of intrahepatic leukocyte infiltration		Yamanouchi et al., 2007
		Upregulation of antiapoptotic genes		Zhang et al., 2000
		Prevention of sinusoidal endothelial cell apoptosis		
		Inhibition of ligand-gated chloride channel		Zhong et al., 2003; Frank et al., 2000
		Reduction of TNF-α release	I/R	Duenschede et al., 2006; Yamanouchi et al., 2007
	Atrial natriuretic peptide	cGMP-dependent reduction of caspase-3 activity	I/R	Gerwig et al., 2003
		Activation of p38 MAPK	I/R	Kiemer et al., 2002b; Kobayashi et al., 2007
		Antiapoptotic signaling by Akt and bad phosphorylation	I/R	Grutzner et al., 2006
		Restriction of cytosolic hepatocellular Ca^{2+} increase	I/R	von Ruecker et al., 1989
	Melatonin	Improvement of hepatic redox state and hepatic perfusion index	Shock/resuscitation	Mathes et al., 2008a Mathes et al., 2008b
		Inhibition of lipid peroxidation	I/R	Sewerynek et al., 1996
			Steatosis	Pan et al., 2006
		Antinitrosative activity	Acetaminophen	Matsura et al., 2006
		Increase of NO bioavailability	I/R	Zhang et al., 2006b

The cytoprotection may result from the elimination of heme and the function of HO-1 downstream mediators that are biliverdin, CO, and free iron (511, 841). The HO system is thought to be protective by four major mechanisms, including *1*) the antioxidant action, *2*) the anti-inflammatory action, *3*) the vasodilation-induced preservation of the microcirculation, and *4*) the modulatory function upon the cell cycle. In line with this, HO-1 induction, using heat shock, PDTC, cobalt protoporphyrin, adenoviral-mediated gene transfer, or L-arginine, improves hepatic microcirculation and reduces tissue injury upon I/R (283, 450, 804, 920). It further protects against hepatic parenchymal injury and microvascular dysfunction during experimental rhabdomyolysis (156) and during the systemic inflammatory response syndrome (SIRS) (537). Vice versa, HO inhibition, which is achieved with the use of chromium mesoporphyrin (CrMP), significantly reduces sinusoidal diameters and volumetric flow and causes significantly increased numbers of stationary leukocytes and microvascular perfusion deficits. This results in increased hepatocellular injury and hepatocyte death in models of remote hepatic injury and systemic SIRS (538, 912).

In endotoxemic and septic livers, where iNOS and HO-1 overproduce NO and CO (691, 854), the role of HO-1 is rather ambiguous. A protective role of HO activation has been shown, possibly as a result of an interaction with the LPS-induced increase in NO formation (584). At the same time, CO, produced by excessively induced HO-1 after cecal ligation and puncture, promotes an immoderate dilation of the sinusoidal space through the upregulation of cGMP, resulting in liver dysfunction. In this case, the administration of HO inhibitors is beneficial for the attenuation of sepsis-induced liver dysfunction (331). In contrast, in perfused livers of endotoxemic rats, HbO_2, which captures NO and CO, causes marked vasoconstriction and cholestasis (438). Of importance, the reduction of increased cGMP by HO-1 inhibition is associated with an increased mortality (157).

HO-1 is regulated in a tissue-specific manner (774) with an AP-1-dependent induction in liver tissue under oxidative stress conditions, such as hemorrhagic shock and resuscitation. These are assumed to function as a stress-inducible vasodilator system, as does NF-κB-dependent iNOS expression in liver inflammation (665). The particular localization of HO-1 in liver mitochondria has important implications for the protection against stress conditions such as hypoxia or sepsis, in which substantially increased mitochondrial NO and oxidant production occurs (122). In accordance with the tissue-confined regulation of HO-1, CO protection against endotoxic shock involves reciprocal effects on iNOS in the lung and the liver (698). In detail, the HO-1 metabolite CO protects hepatocytes from apoptosis while augmenting iNOS expression and inhibits LPS-

induced cytokine production in lung macrophages, while reducing LPS-induced iNOS expression and nitrite accumulation (698). Taken together, CO, when endogenously synthesized or exogenously applied at low concentrations, can exert anti-inflammatory and antiapoptotic effects in a variety of cellular and rodent models of sepsis and, furthermore, reduces morbidity and mortality in vivo (300) (Table 2).

An intriguing fact is the preconditioning efficacy of volatile anesthetics, which have been demonstrated to increase mRNA HO-1 expression, thereby preventing liver tissue from manifestation of postischemic reperfusion injury (710). In contrast to that, isoflurane fails to show hepatoprotective effects against LPS-induced liver injury. On the other hand, ketamine is capable of attenuating LPS-induced liver injury by upregulation of HO-1 and downregulation of iNOS. This implies that ketamine may be the anesthetic agent of choice for septic patients requiring anesthesia (768).

Current research highlights the complex association between inflammation and coagulation. The molecular links between the two are unquestioned (181). Inflammatory mechanisms upregulate procoagulant factors, in particular intravascular tissue factor expression, elicit the expression of leukocyte adhesion molecules, downregulate natural anticoagulants, and inhibit fibrinolytic activity (181, 739). Of the natural anticoagulants, the protein C pathway appears to be the most negatively influenced by inflammation (180). Activated protein C is a potent anticoagulant serine protease and known to have cell-protective properties by virtue of its anti-inflammatory and antiapoptotic activities. For instance, activated protein C exerts cytoprotective effects after postischemic reperfusion of rat livers. This is evidenced by decreased tissue injury, reduced intrahepatic leukocyte accumulation, probably due to reduced expression of P-selectin, ICAM-1, and CINC, reduced cytokine release, and improved hepatic microcirculation (432, 922). By inhibition of intrasinusoidal fibrin deposition and attenuation of hepatocellular necrosis, activated protein C significantly improves survival of rats in a lethal posthepatectomy acute liver failure model (942). Also, pretreatment with antithrombin III significantly improves the energy status and microcirculation, as well as histological damage in postischemic (607) and cirrhotic livers (515). Potential mechanisms for the action of antithrombin are considered to be the release of PGI_2 and, comparably to activated protein C, the reduction of leukocyte-endothelium interaction by attenuation of CINC (297, 514, 607, 921). Comparably to antithrombin, other anticoagulants, like heparin, aprotinin, and hirudin, are reported to exert hepatoprotection in hepatic injury models (297, 426, 514) (Table 2).

B. Antiapoptotic Strategies

During inflammatory liver diseases, toxic free radicals and oxidants are produced, causing DNA damage, such as DNA single-strand breaks, which result in the activation of the nuclear enzyme poly(ADP-ribose)-polymerase (PARP). PARP assists in combination with the enzymes of the base-excision and -repair complex of the cell in energy-consuming reparative processes. The consequences of the activation of PARP1, which is the main isoform of the PARP family, are particularly important for the manifestation and propagation of tissue injury: *1*) its role in DNA repair; *2*) its consumption of oxidized NAD and capacity to deplete cellular energetic pools, which culminates in cell dysfunction and necrosis; and *3*) its capacity to promote the transcription of proinflammatory genes (346). ATP depletion by PARP directs cells towards necrotic cell death (267). This is confirmed by in vivo studies in postischemic reperfused livers, where PARP promoted hepatocellular necrosis and PARP inhibition or PARP gene deficiency were capable of reducing transaminase levels (378, 381, 777). In line with this, overactivation of PARP with hepatoprotective effects by PARP inhibitors is also observed in systemic I/R, such as hemorrhagic shock and resuscitation (683, 776, 893) (Table 2).

Intrahepatic apoptotic cell death is a common feature of tissue injury upon various injurious stimuli. Pathways of apoptosis execution include cascadelike proteolytic cleavage and, thus, activation of cysteinelike proteases, such as caspase-2, -3, -6, -7, -8, -9, and -10 (695). In cold I/R, therapeutic strategies with various caspase inhibitors have been shown to exert beneficial effects by counteracting sinusoidal endothelial cell apoptosis (588, 589). Small interfering RNA targeted to caspase-8 and -3 also provide significant protection against I/R injury of the liver (121). Moreover, Fas ligation-induced sinusoidal endothelial cell apoptosis and hepatic microvascular perfusion failure can be positively influenced by pancaspase inhibition using zVAD-fmk (887).

Noteworthy, prevention of P-selectin-mediated platelet adhesion in postischemic livers using sLe(x) oligosaccharides or P-selectin gene-deficient mice (379, 741) decreases SEC and hepatocellular apoptosis, caspase-3 activities, sinusoidal perfusion failure, and liver enzyme release. Comparably, blockade of P-selectin using a P-selectin antibody ameliorates leukocyte recruitment, hepatocellular injury, and apoptosis in endotoxemic mice (396). In line with this, induction of leukocytopenia and thrombocytopenia in endotoxemic rats abrogates hepatocyte apoptosis, similarly as observed when the pancaspase inhibitor zVAD-fmk is applied (168). This indicates that both microvascular leukocyte and platelet adhesion contribute to hepatocellular apoptosis (Table 2).

Therapeutic strategies counteracting hepatocellular apoptosis also include the transfer of genes with anti-

apoptotic effects or the ablation/silencing of proapoptotic genes. For instance, expression of the Bcl-2 gene protects against I/R injury, as shown by a significant decrease in transaminases, necrosis, and apoptosis, and by permanent survival compared with animals treated with the control AdCMVLacZ vector (48). Vice versa, ablation of the proapoptotic bax in postischemic livers reduces postischemic apoptotic liver injury, as indicated by a significantly weaker activation of caspase-3 and reduced numbers of TUNEL-positive cells (43).

It has been demonstrated that the release of cathepsin B, a cysteine protease, from the cytosol in liver injury induces mitochondrial release of cytochrome *c* and the activation of caspase-3 and -9, thereby leading to apoptosis. Thus therapeutic approaches to block cathepsin B prove to be effective, again given by the significantly fewer apoptotic hepatocytes detected immunohistochemically, by a weaker activation of caspase-3, and by less TUNEL positive cells (42). In line, cathepsin B knockout mice are resistant to TNF-α-mediated hepatocyte apoptosis and liver injury (250) and reveal reduced hepatic inflammation and neutrophil infiltration in cholestatic liver injury (84).

In addition, evidence is emerging that the endoplasmic reticulum participates in the initiation of apoptosis induced by the unfolded protein response and by aberrant Ca^{2+} signaling during cellular stress such as I/R injury, nonalcoholic steatohepatitis, and alcoholic liver disease (366, 559). Endoplasmic reticulum-induced apoptosis involves the activation of caspase-12 and C/EBP homologous protein (CHOP), and the shutdown of translation initiated by phosphorylation of eukaryotic translation initiation factor-2α (eIF2α) (366). Physiologically, liver cells cope with endoplasmic reticulum stress by an adaptive protective response termed "unfolded protein response," which includes enhanced protein folding and degradation in the endoplasmic reticulum and downregulated overall protein synthesis (354). The endoplasmic reticulum transmembrane eIF2α kinase PERK phosphorylates eIF2α to attenuate protein synthesis, including NF-κB-dependent antiapoptotic proteins. However, insufficient adaptation to endoplasmic reticulum stress, as observed for instance in endotoxin-challenged cirrhotic livers (799), unleashes pathological consequences, like inflammation and cell death, either leading to liver disease or worsening underlying causes of liver injury. There are various agents interfering with the endoplasmic reticulum-induced apoptosis, like the chemical chaperone sodium 4-phenylbutyrate, which reduces the load of mutant or unfolded proteins retained in the endoplasmic reticulum and exerts anti-inflammatory activity (630). In line with this, animals given sodium 4-phenylbutyrate survive with 50% in a lethal model of total liver I/R and reveal a decreased endoplasmic reticulum-mediated apoptosis, characterized by a significant reduction in caspase-12 activation and reduced levels of both phosphorylated eIF2α and CHOP (852). Also, temporary hypothermic machine preservation of cold-stored livers results in reduced endoplasmic stress and cleavage of caspase-12, with subsequent preservation of ultrastructural morphology (559). In cholestatic liver injury, which is associated with enhanced CHOP and bax expression, deficiency of mice for CHOP attenuates hepatocellular apoptosis and necrosis as well as subsequent liver fibrosis (788).

C. Vasoactive Drugs

Oxidative stress and inflammatory reactions may promote hepatic microcirculatory dysfunction, which is known to be a determinant for subsequent hepatic injury. Because an altered liver microcirculation often results from an imbalance in the expression of stress-induced vasoactive mediators, numerous studies have been conducted, confirming the distinct pattern of up- and downregulation of vasoregulatory enzyme systems (753). The most important candidates are NO, CO, and H_2S as vasodilative gaseous molecules and ET as vasoconstrictive peptide mediator (725). In addition, derivatives of the arachidonic acid cascade with release of vasoactive prostaglandins (690) and leukotrienes (89) play a role in hepatic microcirculatory deteriorations (Table 1). There are innumerous results from both experimental and clinical studies, supporting the idea of the concept of a critical balance to improve hepatic perfusion and function. Both endogenous and exogenous NO protect hepatocytes and endothelial cells against hepatic I/R injury (97, 114) and endotoxemic liver damage (566). However, also selective iNOS inhibition prevents live bacteria from causing key features of metabolic derangements in porcine hyperdynamic sepsis, most probably due to reduced oxidative stress with improved microcirculatory perfusion and restoration of cellular respiration (527).

Further strategies to improve the hepatic microcirculation comprise the application of ET receptor antagonists in I/R (795, 834), in endotoxemia and endotoxic shock (179, 375) as well as in endotoxin-challenged cirrhotic livers (840). Finally, the direct application of PGs (i.e., PGE_2) in hypoperfused livers (773) and gaseous molecules, like CO, may protect the nutritive perfusion of the hepatic microvasculature in endotoxemia and endotoxin shock (698).

D. Immunomodulatory and Pleiotropic Agents

Injurious stimuli evoke tissue damage through a complex pathophysiologic network, involving distinct cell populations and humoral mediators, molecular pathways, and signal transduction cascades. These can barely be counteracted by monocausal therapies. Instead, approaches implementing pleiotropic substances are increasingly considered most appropriate to restore dis-

turbed homeostasis. Among others, promising candidates are statins, erythropoietin (EPO), HO-1, L-glycine, melatonin, atrial natriuretic peptide (ANP), and G-CSF (Table 2).

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, namely, statins, exert pleiotropic actions beyond lipid-lowering effects, such as antioxidative, anti-inflammatory, and immunomodulatory effects in ex vivo and in vitro studies. Statins ameliorate hepatic inflammation, lipid peroxidation, and tissue injury in rats subjected to common bile duct ligation (145). In addition, statins induce HO-1 expression, which protects livers from apoptotic injury in the setting of I/R (439). The pleiotropic action of statins is also able to protect from unspecific inflammation such as sepsis (423), which might be due to inhibitory actions of statins on leukocyte rolling, adherence, and transmigration, as described for the intestinal microcirculation during exotoxemia (645).

EPO has well been characterized as a renal glycoprotein hormone regulating red blood cell production by inhibiting apoptosis of erythrocytic progenitors in hemopoietic tissues. Recently, EPO has also been recognized as antiapoptotic and tissue-protective pleiotropic viability and growth factor in various nonhemopoietic tissues (20, 230, 350, 351). These salutary effects seem to be independent from the hematopoietic properties, as nonerythropoietic derivatives of EPO have shown an almost comparable action profile (67, 200). EPO reduces serum levels of ALT, TNF-α, and IL-2, indicators of oxidative stress, caspase-3 activation, and the histopathological score, promoting the subsequent reduction of apoptosis in I/R-induced liver injury (299, 721, 935). Comparably, EPO abolishes liver injury in hemorrhagic shock (2). Furthermore, mice with acute septic liver failure show diminished systemic cytokine concentrations, intrahepatic leukocyte accumulation, and hepatic perfusion failure as well as a significantly reduced hepatocellular apoptosis upon prebut also posttreatment with the long-lasting EPO derivative darbepoetin-α (472).

L-Glycine is a simple, nonessential amino acid, acting as an inhibitory neurotransmitter in the central nervous system and long believed to be biologically neutral. However, recent experimental studies have demonstrated also anti-inflammatory, immunomodulatory, and cytoprotective actions (965). As a consequence, dietary glycine significantly improves the survival rate of endotoxemic mice. This is most probably due to an interference with the endotoxin signaling pathway, downregulating TLR4, NF-κB, and TNF-α and modulating KC response (590, 916). In fact, glycine has been shown to attenuate I/R injury by inhibition of oxidative stress-induced lipid peroxidation, reduction of inflammatory cell activation, and decrease of apoptosis-related cell death (149, 162, 929). In particular, SEC, which are most vulnerable upon cold storage and reperfusion, seem to be protected against apoptosis by glycine-associated maintenance of bcl-2 expression (959). In addition, cellular protection seems to involve the inhibition of ligand-gated chloride channels, thereby secondarily inhibiting sodium influx, as this has been considered the protective mechanism of glycine for hypoxic hepatocytes (207). In contrast to these positive reports, the nutritional effects of a glycine-rich amino acid solution are found similar to those of a standard amino acid solution for parenteral nutrition in endotoxemic rats (502).

Another potential candidate for hepatoprotection due to its pleiotropic action is atrial natriuretic peptide (ANP). Interestingly, reperfusion injury by activated KC can be attenuated by the hormone ANP (50, 53, 228). The hepatoprotection conveyed by ANP in settings of liver I/R seems to involve the activation of p38 MAPK (385, 402), the restriction of cytosolic calcium increase in hepatocytes (877), the limited release of TNF-α by KC (386), as well as the cGMP-dependent reduction of caspase-3 activity (229) and the antiapoptotic signaling by phosphorylation of Akt and bad (254).

The pineal hormone melatonin has been demonstrated to possess distinct protective potential in models of oxidative stress, i.e., local (486, 726) and systemic (528, 529) I/R injury of the liver as well as liver exposure to acetaminophen (535) and cyclosporine (668). The proposed mechanisms of protection are said to involve direct inactivation of ROS and nitrogen species (791) and indirect effects by inducing antioxidative enzymes (617) and by improving the balance between NO and ET (958). Improved liver mitochondrial function (210) and enhanced bile flow and ATP stores (842) in cold stored livers support the idea of using melatonin as pleiotropic agent for patients, e.g., during liver transplantation.

Thus the use of pleiotropic substances represents an interesting novel approach to attenuate hepatic injury by protecting microvascular and cellular dysfunction. Accordingly, the efficacy of these substances is now required to be proven in controlled clinical trials.

E. Preconditioning Maneuvers

The idea of preconditioning of tissues to enhance their robustness against subsequent insults originates from experiments in the canine myocardium performed by Murry et al. in 1986 (575). They demonstrated that multiple brief ischemic episodes protect the heart from a subsequent sustained ischemic insult (575). Ischemic preconditioning has been shown to exert protection by an immediate phase and a later phase. The immediate phase involves direct modulation of energy supplies, pH regulation, Na^+ and Ca^{2+} homeostasis, and caspase activation. The later phase includes the synthesis of multiple stress response proteins (86). The maneuver is considered a promising approach to effectively minimize hepatic I/R injury (88, 343, 418). In experimental studies it has been

shown that ischemic preconditioning reduces neutrophil-specific oxidant stress in hepatocytes (277), ameliorates hepatic microcirculation (232), attenuates hepatic tissue apoptosis and necrosis (111, 652, 800, 918, 943), and improves overall survival (918). Of interest, ischemic preconditioning also increases the tolerance of fatty (198, 692, 720, 722) and cirrhotic livers (102, 348) to hepatic I/R injury. This is shown by an improved preservation and restoration of tissue ATP contents (720), an inhibition of apoptotic cell death (481), and an attenuation of hepatic perfusion failure, neutrophil accumulation (102, 419, 722), neutrophil-dependent oxidant stress, and lipid peroxidation (277).

With the increasing knowledge on the mechanisms of ischemic preconditioning (88), like the release of adenosine with activation of ATP-sensitive potassium channels, the augmentation of NO production and the upregulation of heat shock proteins and antioxidant enzymes (86), many different approaches, which mimic ischemic preconditioning, were successfully applied to reduce I/R injury. These include the application of adenosine (724), adenosine A(1) and A(2) receptor agonists (9, 19, 451), as well as nitrite (NO^{2-}) as an intrinsic signaling molecule that is reduced to NO (738) and bilirubin as metabolite of the HO-1 metabolism (372). However, protection can also be achieved by induction of heat shock (558, 733), infusion of gluthatione (706), or exposure to ozone (10, 478) and hyperbaric oxygen (945).

Experimental studies have demonstrated that ischemic preconditioning protects ischemic livers from microcirculatory failure and leukocytic inflammation during reperfusion (232, 419, 843). Analogous to ischemic preconditioning, pharmacological strategies, like administration of phosphodiesterase inhibitor-3 (430, 779), *N*-acetylcysteine (NAC) (233), and pyrrolidine dithiocarbamate (PDTC) (279) or whole body hyperthermia for HO-1 induction (805, 920) are capable of specifically protecting the postischemic hepatic microcirculation. This protection includes an improvement of microvascular perfusion and tissue oxygenation, a reduction of leukocyte adherence, and the maintenance of KC phagocytic activity.

It was further shown that the hepatoprotective effects of preconditioning can be simulated by TNF-α. TNF-α initiates the priming phase of liver regeneration via NF-κB DNA binding and IL-6 production and exerts identical downstream effects on cell cycle entry, such as STAT3, cyclin D1, and cyclin-dependent kinase 4 (cdk4) expression (802). Hereby, IL-6, rather than TNF-α itself, seems to be the mediator of the hepatoprotective and proproliferative effects of ischemic preconditioning (801). Moreover, not only TNF-α as death ligand, but also FasL is reported to mimic ischemic preconditioning (349).

Many human trials have confirmed the beneficial effects of ischemic preconditioning on the postoperative course and liver regeneration after hepatectomy (106, 108, 110, 111, 284, 481). These studies reported about improved intraoperative hemodynamic stability (108), reduced blood loss (284), increased formation of adenosine (107), downregulation of potentially cytotoxic functions of leukocytes (106), and decreased liver injury, as assessed by aspartate aminotransferase (AST) and ALT release (110). However, there are also reports, either disproving efficacy of ischemic preconditioning for hepatectomy in humans (26), or demonstrating less advantage over or comparability with intermittent vascular clamping during liver resection (632, 750). Also, preconditioning of liver grafts from brain dead donors did not improve graft injury (409) and clinical outcome (94), or even increased reperfusion injury, termed as ischemic preconditioning paradox (410). In summary, most recent meta-analyses, systematic reviews, and Cochrane reports provide no evidence to support or refute the use of ischemic preconditioning in donor liver retrievals (265) and to recommend it as a standard procedure for hepatic resection (653).

F. Surgical Procedures

Several surgical approaches have been proposed to reduce portal blood inflow and portal pressure in the situation of portal hyperperfusion after extended hepatectomy and segmental liver transplantation. These approaches are applied to prevent the small-for-size syndrome, which is known to predominate graft dysfunction and poor survival in case of extreme size mismatch. The safety limit is thought to be 40% of the ideal liver weight (393) or 1% of the recipient body weight (500). As portal flow linearly correlates with spleen size, the parameter liver graft-to-recipient spleen size ratio has been suggested as a novel predictor of portal hyperperfusion syndrome in living donor liver transplantation (103). With the aim to counteract the small-for-size syndrome, splenic artery ligation or embolization, splenectomy as well as portocaval and hemiportocaval shunts are favored to relieve the remnant tissue from the deleterious effect of portal overflow (253, 818–820, 780, 919). Experimental studies applying these approaches could prove the efficacy of these techniques, i.e., the reduction of portal hyperperfusion (58, 231, 881).

To overcome the high risk of parenchymal dysfunction and liver failure in case of extended hepatectomy and insufficient remnant liver mass (574), portal vein occlusion has been introduced (516). Several weeks before hepatectomy, either ligation (69) or embolization (1, 509) of portal vein branches induce atrophy of the deprived lobe, while the anticipated lobe undergoes compensatory hypertrophy (1). This should guarantee an adequate mass of the liver remnant after the later hepatectomy. However, recent reports demonstrate that the loss of portal blood flow after portal vein ligation is compensated by the

HABR, which allows normalization of overall blood flow and oxygenation also in the ligated lobe (405, 676, 839). This arterialization even enhances cell proliferation in the ligated lobe, which may potentially bear the risk of tumor progression (405).

To minimize the anhepatic period and the period of partial rewarming of the ischemic graft in liver transplantation, it is generally accepted to reperfuse the liver with portal blood before arterial reconstruction, although this practice is discussed controversially (363). Detailed analysis of the hepatic microcirculation in a rat liver transplantation model has convincingly proven the superiority of simultaneous compared with delayed arterialization (638). In line with this, noninvasive OPS imaging performed in human living-donor liver transplantation confirmed the importance of timing of arterialization to the reperfusion of the liver. In this study, microvascular impairment has been shown significantly enhanced by the interval between portal venous and hepatic arterial reperfusion (646). This supports the view that simultaneous portal venous and hepatic arterial reperfusion should be achieved to prevent microvascular I/R injury in liver transplantation.

G. Clinical Application of Measures Targeting Hepatic Microvascular Disorders

Although there is a large body of experimental studies demonstrating that microcirculatory disorders are determinants for liver injury and that injury can be attenuated by preventing or reducing microvascular dysfunction, little of this knowledge has been successfully transferred to clinical practice. There is in fact great need of appropriate tools for diagnosis of hepatic microcirculatory disorders in patients with shock and sepsis and those undergoing extended hepatic resection or liver transplantation. While noninvasive techniques in conditions of shock and sepsis are difficult to apply, NIRS and OPS imaging have been successfully introduced to analyze the hepatic microcirculation as well as hemoglobin and cytochrome oxidase content as parameters of hepatic perfusion and oxygenation in hepatic resection and liver transplantation (604, 648). These techniques allowed the detection of microcirculatory dysfunctions (647, 709) and enabled the monitoring and control of microcirculatory improvement after surgical procedures such as hepatic or controlled portal venous arterialization (646, 709). Nonetheless, microcirculatory diagnostic tools such as NIRS and OPS imaging are still not used routinely in clinical practice.

The fact that experimental studies have demonstrated that portal hyperperfusion and hepatic arterial buffer response-mediated hepatic arterial constriction induce hepatic microcirculatory dysfunctions, and that downregulation of portal flow is capable of improving the microcirculation, has resulted in translation of this knowledge into clinical practice. Single cases or small series of patients have been successfully treated by splenic artery ligation of transient portocaval shunt to attenuate portal hyperperfusion and to improve hepatic arterial flow (57, 325, 796, 819). These surgical procedures, however, will always represent exceptions with major hepatic injury after extended hepatectomy and small-for-size transplantation.

The application of vasoactive substances, aiming at improving the hepatic microcirculation after cold I/R, has also been successfully transferred into the clinical setting. Therapeutic applications of prostacyclin (361) or prostacyclin donor preconditioning (394), but also PGE_1 (225, 416), have been shown to decrease arterial vascular resistance, improve arterial blood perfusion, increase oxygen supply, and ameliorate postischemic reperfusion injury.

Because many experimental studies have shown that oxygen radicals markedly contribute to ischemic and toxic liver injury, the use of antioxidants is long discussed to be used in critically endangered patients with liver ischemia, sepsis, and shock. In patients with hepatic dysfunction who were mechanically ventilated, either after liver transplantation or during an acute or decompensated chronic liver disorder, the antioxidant *N*-acetylcysteine has been shown to improve both indocyanine green extraction and oxygen transport (150). In addition, the University of Wisconsin (UW) and HTK preservation solutions have been, in addition to other ingredients, enriched with antioxidative agents. These solutions have been proven superior to others not containing antioxidative agents, although the distinct contribution of the individual antioxidants has not been clarified yet. In the clinical setting, both UW and HTK have become the gold standard for liver preservation worldwide (195).

Finally, a considerable number of clinical trials have shown a beneficial effect of ischemic preconditioning on the postoperative course after liver resection (106, 108, 110, 111, 284, 481). However, because there are also some studies in patients which disprove an efficacy after hepatectomy (26) or which could not show an improvement of graft injury in transplantation (94, 409, 410), it has not yet become a routine procedure in major liver surgery.

IX. SUMMARY AND CONCLUSIONS

The circulation of the liver has to be considered unique in that it consists of a dual blood supply. By this, the overall inflow of blood into the liver is regulated through the adenosine-mediated HABR, increasing hepatic arterial blood flow in the case of reduced portal vein perfusion and decreasing hepatic arterial flow in the case

of portal hyperperfusion. In contrast, intrahepatic blood flow is controlled by the balance between the vasoconstrictive ET and the vasodilative gaseous molecules NO, CO, and H_2S, which act on smooth muscle cells in feeding hepatic arteriolar and portal venular segments, but also through pericytes in hepatic sinusoids.

A considerable body of experimental work has now demonstrated that malperfusion of nutritive sinusoids in hepatic I/R, transplantation, and endotoxemia is due to a deterioration of the ET-NO balance with a shift towards the ET system, resulting in tissue hypoxia and apoptotic or necrotic cell death. According to this pathway, therapeutic interventions by inhibiting vasoconstrictive ET with appropriate receptor blockers or stimulating vasodilative NO or CO production are effective to attenuate microcirculatory deteriorations and to improve hepatocellular function and survival. These results confirm others achieved in cardiopulmonary research. Of interest, in cardiopulmonary medicine, this knowledge was introduced into clinical practice some years ago, and, today, critical patients with acute respiratory distress syndrome or pulmonary hypertension are treated successfully with NO and ET receptor antagonists (116, 360, 392). Thus future concepts in hepatology should also include the introduction of these treatment modalities for critical patients with liver failure, which is caused by microcirculatory disorders in sepsis, reperfusion injury, and hyperperfusion syndrome.

In addition to the dysfunction of the vasomotor control, the initiation of an inflammatory response contributes to the hepatic microcirculatory deteriorations in I/R, transplantation, and endotoxemia. The early mediators of inflammation are ROS and TNF-α, which induce a massive recruitment of leukocytes and platelets within the hepatic microvasculature. After activation of these cells, their adhesion to the microvascular endothelium is controlled by a sequence of adhesion molecules, expressed on the surface of leukocytes, platelets, and endothelial cells. The function of these adhesion molecules represents a prerequisite for successful transendothelial migration. According to mechanistic analyses with scavengers, antibodies, and gene-targeted animals, experimental studies have demonstrated that the inhibition of oxygen radicals and TNF-α is effective to reduce hepatic microcirculatory dysfunctions, microvascular injury, and organ failure. Nonetheless, these results could not be successfully translated into clinical practice. In septic patients, controlled randomized trials could not demonstrate substantial organ protection and improvement of survival after inhibition of TNF-α (203, 209, 586), while antioxidative selenium may improve clinical outcome, infections, and organ failure (46). Future therapeutic approaches to inhibit inflammation in I/R and sepsis may give more focus on those molecules that also maintain the vasomotor control. This view is based on the fact that ET may act proinflammatory, while NO and CO have been shown to exert anti-inflammatory actions (293, 697). Thus the use of ET receptor antagonists or NO and CO donors may not only attenuate microcirculatory disorders by inducing vasodilation, but may also reduce the deleterious leukocyte- and platelet-mediated inflammation in these critically ill patients. The efficacy of this treatment strategy, however, still needs careful evaluation, because, for example, NO may reduce cytokine-induced leukocyte-endothelial cell interaction by inhibiting endothelial adhesion molecule expression (320); however, it may aggravate oxygen radical-induced hepatic injury by formation of peroxynitrite (13). In addition, future studies should further clarify whether the sum of effects of H_2S on leukocytic inflammation is indeed anti-inflammatory (948), because recent reports have demonstrated also distinct proinflammatory H_2S actions (962).

The nature of cell death induced by microcirculatory disorders after hepatic I/R and endotoxemia may involve both apoptosis and necrosis. While endotoxemia induces primarily apoptotic cell death, there is still a major controversy of whether I/R primarily induces apoptosis (404) or necrosis (257). However, recent studies brought evidence that apoptosis and necrosis share common pathways and that individual cells undergoing death after I/R show characteristics of both apoptosis and necrosis (176). Accordingly, caspase inhibitors or p53 inhibitors, which are thought to interfere specifically with apoptotic cell death, do not only attenuate apoptosis but also necrosis, as indicated by reduced levels of liver enzymes (176, 705). A major drawback of these inhibitors, which have been proven in experimental studies successful to attenuate organ injury and survival, is that they exert considerable side effects. Thus they cannot be tested for patient treatment in clinical trials.

Taken together, the dysfunction of the hepatic microcirculation is a determinant for organ failure in ischemic and inflammatory disease and contributes significantly to the high mortality in these patients. This knowledge, however, is still not considered for diagnostics and treatment in daily clinical practice. With the introduction of techniques for hepatic microcirculatory analyses in patients, such as LDF, OPS imaging, and NIRS, this drawback may be overcome, allowing an estimate of the quality of nutritive perfusion. The techniques may be applied most easily during open surgery, which gives direct access to the liver. In these cases, they may help to predict deleterious microcirculatory dysfunctions after prolonged cold preservation and transplantation-associated reperfusion or after extended hepatectomy and split liver transplantation, which develop a small-for-size syndrome. This diagnostic information achieved during surgery should be of great importance, because it would allow the early initiation of treatment to prevent manifestation of liver injury and failure. In line with this, the knowledge deduced from the

experimental work on the mechanisms and treatment of hepatic microcirculatory dysfunctions should also be translated into clinical practice. Including diagnostics and monitoring with OPS or NIRS, the novel therapeutic strategies have to be proven in randomized clinical trials. This may improve future outcome of patients with liver failure caused by microcirculatory dysfunctions.

ACKNOWLEDGMENTS

Address for reprint requests and other correspondence: B. Vollmar, Institute for Experimental Surgery, Schillingallee 69a, 18057 Rostock, Germany (e-mail: brigitte.vollmar@med.uni-rostock.de).

GRANTS

Work in the institutes of B. Vollmar and M. D. Menger is supported by the German Research Foundation (DFG, Bonn-Bad Godesberg, Germany), the Wilhelm Sander Foundation (Munich, Germany), the Federal Ministry of Education and Research, and the University of Rostock (to B. Vollmar), and the University of Saarland (to M. D. Menger).

REFERENCES

1. **Abdalla EK, Hicks ME, Vauthey JN.** Portal vein embolization: rationale, technique and future prospects. *Br J Surg* 88: 165–175, 2001.
2. **Abdelrahman M, Mazzon E, Bauer M, Bauer I, Delbosc S, Cristol JP, Patel NS, Cuzzocrea S, Thiemermann C.** Inhibitors of NADPH oxidase reduce the organ injury in hemorrhagic shock. *Shock* 23: 107–114, 2005.
3. **Abdelrahman M, Sharples EJ, McDonald MC, Collin M, Patel NS, Yaqoob MM, Thiemermann C.** Erythropoietin attenuates the tissue injury associated with hemorrhagic shock and myocardial ischemia. *Shock* 22: 63–69, 2004.
4. **Abrahám S, Szabó A, Kaszaki J, Varga R, Eder K, Duda E, Lázár G, Tiszlavicz L, Boros M, Lázár G Jr.** Kupffer cell blockade improves the endotoxin-induced microcirculatory inflammatory response in obstructive jaundice. *Shock* 30: 69–74, 2008.
5. **Abshagen K, Eipel C, Kalff JC, Menger MD, Vollmar B.** Kupffer cells are mandatory for adequate liver regeneration by mediating hyperperfusion via modulation of vasoactive proteins. *Microcirculation* 15: 37–47, 2008.
6. **Abshagen K, Eipel C, Menger MD, Vollmar B.** Comprehensive analysis of the regenerating mouse liver: an in vivo fluorescence microscopic and immunohistological study. *J Surg Res* 134: 354–362, 2006.
7. **Aharinejad S, Nourani F, Egerbacher M, Larson EK, Miksovsky A, Böck P, Firbas W, McCuskey RS, Marks SC Jr.** Sphincters of canine hepatic sublobular veins respond to endothelin-1 and 3. *Anat Embryol* 196: 299–309, 1997.
8. **Aiba M, Takeyoshi I, Ohwada S, Kawashima Y, Iwanami K, Sunose Y, Yamada T, Tsutsumi H, Matsumoto K, Morishita Y.** Novel nitric oxide donor (FK409) ameliorates liver damage during extended liver resection with warm ischemia in dogs. *J Am Coll Surg* 193: 264–271, 2001.
9. **Ajamieh HH, Candelario-Jalil E, Fernández OS, Gerbes AL.** Ischaemic and pharmacological preconditionings protect liver via adenosine and redox status following hepatic ischaemia/reperfusion in rats. *Clin Sci* 115: 69–77, 2008.
10. **Ajamieh HH, Menéndez S, Martínez-Sánchez G, Candelario-Jalil E, Re L, Giuliani A, Fernández OS.** Effects of ozone oxidative preconditioning on nitric oxide generation and cellular redox balance in a rat model of hepatic ischaemia-reperfusion. *Liver Int* 24: 55–62, 2004.
11. **Akamatsu Y, Ohkohchi N, Doi H, Satomi S.** Effect of elimination of donor Kupffer cells and/or recipient macrophages on acute rejection in liver transplantation. *Hepatogastroenterology* 50: 1105–1110, 2003.
12. **Alexander B, Blumgart LH, Mathie RT.** The effect of propranolol on the hyperaemic response of the hepatic artery to portal venous occlusion in the dog. *Br J Pharmacol* 96: 356–362, 1989.
13. **Alexander B.** The role of nitric oxide in hepatic metabolism. *Nutrition* 14: 376–390, 1998.
14. **Almond NE, Wheatley AM.** Measurement of hepatic perfusion in rats by laser Doppler flowmetry. *Am J Physiol Gastrointest Liver Physiol* 262: G203–G209, 1992.
15. **Anderson JA, Lentsch AB, Hadjiminas DJ, Miller FN, Martin AW, Nakagawa K, Edwards MJ.** The role of cytokines, adhesion molecules, and chemokines in interleukin-2-induced lymphocytic infiltration in C57BL/6 mice. *J Clin Invest* 97: 1952–1959, 1996.
16. **Andonegui G, Trevani AS, López DH, Raiden S, Giordano M, Geffner JR.** Inhibition of human neutrophil apoptosis by platelets. *J Immunol* 158: 3372–3377, 1997.
17. **Andrés D, Sánchez-Reus I, Bautista M, Cascales M.** Depletion of Kupffer cell function by gadolinium chloride attenuates thioacetamide-induced hepatotoxicity. Expression of metallothionein and HSP70. *Biochem Pharmacol* 66: 917–926, 2003.
18. **Aoki T, Imamura H, Kaneko J, Sakamoto Y, Matsuyama Y, Kokudo N, Sugawara Y, Makuuchi M.** Intraoperative direct measurement of hepatic arterial buffer response in patients with or without cirrhosis. *Liver Transpl* 11: 684–691, 2005.
19. **Arai M, Thurman RG, Lemasters JJ.** Contribution of adenosine A(2) receptors and cyclic adenosine monophosphate to protective ischemic preconditioning of sinusoidal endothelial cells against storage/reperfusion injury in rat livers. *Hepatology* 32: 297–302, 2000.
20. **Arcasoy MO.** The non-haematopoietic biological effects of erythropoietin. *Br J Haematol* 141: 14–31, 2008.
21. **Arii S, Imamura M.** Physiological role of sinusoidal endothelial cells and Kupffer cells and their implication in the pathogenesis of liver injury. *J Hepatobiliary Pancreat Surg* 7: 40–48, 2000.
22. **Arteel GE, Guo L, Schlierf T, Beier JI, Kaiser JP, Chen TS, Liu M, Conklin DJ, Miller HL, von Montfort C, States JC.** Subhepatotoxic exposure to arsenic enhances lipopolysaccharide-induced liver injury in mice. *Toxicol Appl Pharmacol* 226: 128–139, 2008.
23. **Arvidsson D, Svensson H, Haglund U.** Laser-Doppler flowmetry for estimating liver blood flow. *Am J Physiol Gastrointest Liver Physiol* 254: G471–G476, 1988.
24. **Asfar P, Hauser B, Iványi Z, Ehrmann U, Kick J, Albicini M, Vogt J, Wachter U, Brückner UB, Radermacher P, Bracht H.** Low-dose terlipressin during long-term hyperdynamic porcine endotoxemia: effects on hepatosplanchnic perfusion, oxygen exchange, and metabolism. *Crit Care Med* 33: 373–380, 2005.
25. **Ayuse T, Brienza N, Revelly JP, O'Donnell CP, Boitnott JK, Robotham JL.** Alternations in liver hemodynamics in an intact porcine model of endotoxin shock. *Am J Physiol Heart Circ Physiol* 268: H1106–H1114, 1995.
26. **Azoulay D, Lucidi V, Andreani P, Maggi U, Sebagh M, Ichai P, Lemoine A, Adam R, Castaing D.** Ischemic preconditioning for major liver resection under vascular exclusion of the liver preserving the caval flow: a randomized prospective study. *J Am Coll Surg* 202: 203–211, 2006.
27. **Bajt ML, Farhood A, Jaeschke H.** Effects of CXC chemokines on neutrophil activation and sequestration in hepatic vasculature. *Am J Physiol Gastrointest Liver Physiol* 281: G1188–G1195, 2001.
28. **Bajt ML, Lawson JA, Vonderfecht SL, Gujral JS, Jaeschke H.** Protection against Fas receptor-mediated apoptosis in hepatocytes and nonparenchymal cells by a caspase-8 inhibitor in vivo: evidence for a postmitochondrial processing of caspase-8. *Toxicol Sci* 58: 109–117, 2000.
29. **Balasubramanian S, Paulose CS.** Induction of DNA synthesis in primary cultures of rat hepatocytes by serotonin: possible involvement of serotonin S2 receptor. *Hepatology* 27: 62–66, 1998.
30. **Balasubramaniyan V, Shukla R, Murugaiyan G, Bhonde RR, Nalini N.** Mouse recombinant leptin protects human hepatoma HepG2 against apoptosis, TNF-α response and oxidative stress

induced by the hepatotoxin-ethanol. *Biochim Biophys Acta* 1770: 1136–1144, 2007.
31. **Bashirova AA, Geijtenbeek TB, van Duijnhoven GC, van Vliet SJ, Eilering JB, Martin MP, Wu L, Martin TD, Viebig N, Knolle PA, KewalRamani VN, van Kooyk Y, Carrington M.** A dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN)-related protein is highly expressed on human liver sinusoidal endothelial cells and promotes HIV-1 infection. *J Exp Med* 193: 671–678, 2001.
32. **Bataller R, Ginès P, Nicolás JM, Görbig MN, Garcia-Ramallo E, Gasull X, Bosch J, Arroyo V, Rodés J.** Angiotensin II induces contraction and proliferation of human hepatic stellate cells. *Gastroenterology* 118: 1149–1156, 2000.
33. **Bauer C, Walcher F, Holanda M, Mertzlufft F, Larsen R, Marzi I.** Antioxidative resuscitation solution prevents leukocyte adhesion in the liver after hemorrhagic shock. *J Trauma* 46: 886–893, 1999.
34. **Bauer I, Vollmar B, Jaeschke H, Rensing H, Kraemer T, Larsen R, Bauer M.** Transcriptional activation of heme oxygenase-1 and its functional significance in acetaminophen-induced hepatitis and hepatocellular injury in the rat. *J Hepatol* 33: 395–406, 2000.
35. **Bauer M, Bauer I, Sonin NV, Kresge N, Baveja R, Yokoyama Y, Harding D, Zhang JX, Clemens MG.** Functional significance of endothelin B receptors in mediating sinusoidal and extrasinusoidal effects of endothelins in the intact rat liver. *Hepatology* 31: 937–947, 2000.
36. **Bauer M, Bauer I.** Heme oxygenase-1: redox regulation and role in the hepatic response to oxidative stress. *Antioxid Redox Signal* 4: 749–758, 2002.
37. **Bauer M, Marzi I, Thuma B, Bach F, Bühren V, Larsen R.** Dose-related pattern of sinusoidal leukocyte adhesion in sublobular regions of the liver after systemic endotoxin challenge in the rat. *Shock* 1: 135–140, 1994.
38. **Bauer M, Zhang JX, Bauer I, Clemens MG.** ET-1 induced alterations of hepatic microcirculation: sinusoidal and extrasinusoidal sites of action. *Am J Physiol Gastrointest Liver Physiol* 267: G143–G149, 1994.
39. **Bauer R, Walter B, Würker E, Kluge H, Zwiener U.** Colored microsphere technique as a new method for quantitative-multiple estimation of regional hepatic and portal blood flow. *Exp Toxicol Pathol* 48: 415–420, 1996.
40. **Baveja R, Kresge N, Ashburn JH, Keller S, Yokoyama Y, Sonin N, Zhang JX, Huynh T, Clemens MG.** Potentiated hepatic microcirculatory response to endothelin-1 during polymicrobial sepsis. *Shock* 18: 415–422, 2002.
41. **Beldi G, Enjyoji K, Wu Y, Miller L, Banz Y, Sun X, Robson SC.** The role of purinergic signaling in the liver and in transplantation: effects of extracellular nucleotides on hepatic graft vascular injury, rejection and metabolism. *Front Biosci* 13: 2588–2603, 2008.
42. **Ben-Ari Z, Mor E, Azarov D, Sulkes J, Tor R, Cheporko Y, Hochhauser E, Pappo O.** Cathepsin B inactivation attenuates the apoptotic injury induced by ischemia/reperfusion of mouse liver. *Apoptosis* 10: 1261–1269, 2005.
43. **Ben-Ari Z, Pappo O, Cheporko Y, Yasovich N, Offen D, Shainberg A, Leshem D, Sulkes J, Vidne BA, Hochhauser E.** Bax ablation protects against hepatic ischemia/reperfusion injury in transgenic mice. *Liver Transpl* 13: 1181–1188, 2007.
44. **Benaron DA, Cheong WF, Stevenson DK.** Tissue optics. *Science* 276: 2002–2003, 1997.
45. **Berczi I.** Neurohormonal host defense in endotoxin shock. *Ann NY Acad Sci* 840: 787–802, 1998.
46. **Berger MM, Chioléro RL.** Antioxidant supplementation in sepsis and systemic inflammatory response syndrome. *Crit Care Med* 35, *Suppl*: S584–S590, 2007.
47. **Biernat J, Pawlik WW, Sendur R, Dembiński A, Brzozowski T, Konturek SJ.** Role of afferent nerves and sensory peptides in the mediation of hepatic artery buffer response. *J Physiol Pharmacol* 56: 133–145, 2005.
48. **Bilbao G, Contreras JL, Eckhoff DE, Mikheeva G, Krasnykh V, Douglas JT, Thomas FT, Thomas JM, Curiel DT.** Reduction of ischemia-reperfusion injury of the liver by in vivo adenovirus-mediated gene transfer of the antiapoptotic Bcl-2 gene. *Ann Surg* 230: 185–193, 1999.
49. **Bilzer M, Baron A, Schauer R, Steib C, Ebensberger S, Gerbes AL.** Glutathione treatment protects the rat liver against injury after warm ischemia and Kupffer cell activation. *Digestion* 66: 49–57, 2002.
50. **Bilzer M, Jaeschke H, Vollmar AM, Paumgartner G, Gerbes AL.** Prevention of Kupffer cell-induced oxidant injury in rat liver by atrial natriuretic peptide. *Am J Physiol Gastrointest Liver Physiol* 276: G1137–G1144, 1999a.
51. **Bilzer M, Paumgartner G, Gerbes AL.** Glutathione protects the rat liver against reperfusion injury after hypothermic preservation. *Gastroenterology* 117: 200–210, 1999b.
52. **Bilzer M, Roggel F, Gerbes AL.** Role of Kupffer cells in host defense and liver disease. *Liver Int* 26: 1175–1186, 2006.
53. **Bilzer M, Witthaut R, Paumgartner G, Gerbes AL.** Prevention of ischemia/reperfusion injury in the rat liver by atrial natriuretic peptide. *Gastroenterology* 106: 143–151, 1994.
54. **Bloch EH, McCuskey RS.** Biodynamics of phagocytosis: an analysis of the dynamics of phagocytosis in the liver by in vivo micrsocopy. In: *Kupffer Cells and Other Liver Sinusoidal Cells*, edited by Wisse E and Knook DL. Amsterdam: Elsevier, 1977, p. 21–32.
55. **Bloch EH.** The in vivo microscopic vascular anatomy and physiology of the liver as determined with the quartz rod method of transillumination. *Angiology* 6: 340–349, 1955.
56. **Blomhoff R, Wake K.** Perisinusoidal stellate cells of the liver: important roles in retinol metabolism and fibrosis. *FASEB J* 5: 271–277, 1991.
57. **Boillot O, Delafosse B, Méchet I, Boucaud C, Pouyet M.** Small-for-size partial liver graft in an adult recipient: a new transplant technique. *Lancet* 359: 406–407, 2002.
58. **Boillot O, Mechet I, Le Derf Y, Bernard P, Figueiredo P, Berger F, Paquet C, Pouyet M.** Portomesenteric disconnection for small-for-size grafts in liver transplantation: preclinical studies in pigs. *Liver Transpl* 9: S42–S46, 2003.
59. **Bouwens L, Baekeland M, De Zanger R, Wisse E.** Quantitation, tissue distribution and proliferation kinetics of Kupffer cells in normal rat liver. *Hepatology* 6: 718–722, 1986.
60. **Bouwens L, De Bleser P, Vanderkerken K, Geerts B, Wisse E.** Liver cell heterogeneity: functions of non-parenchymal cells. *Enzyme* 46: 155–168, 1992.
61. **Braet F, Shleper M, Paizi M, Brodsky S, Kopeiko N, Resnick N, Spira G.** Liver sinusoidal endothelial cell modulation upon resection and shear stress in vitro. *Comp Hepatol* 3: 7, 2004.
62. **Braet F, Soon LL.** Diaphragmed fenestrae in the glomerular endothelium versus nondiaphragmed fenestrae in the hepatic endothelium. *Kidney Int* 68: 1902–1903, 2005.
63. **Braet F, Wisse E, Bomans P, Frederik P, Geerts W, Koster A, Soon L, Ringer S.** Contribution of high-resolution correlative imaging techniques in the study of the liver sieve in three-dimensions. *Microsc Res Tech* 70: 230–242, 2007.
64. **Braet F, Wisse E.** Structural and functional aspects of liver sinusoidal endothelial cell fenestrae: a review. *Comp Hepatol* 1: 1, 2002.
65. **Braide M, Amundson B, Chien S, Bagge U.** Quantitative studies on the influence of leukocytes on the vascular resistance in a skeletal muscle preparation. *Microvasc Res* 27: 331–352, 1984.
66. **Bredfeldt JE, Riley EM, Groszmann RJ.** Compensatory mechanisms in response to an elevated hepatic oxygen consumption in chronically ethanol-fed rats. *Am J Physiol Gastrointest Liver Physiol* 248: G507–G511, 1985.
67. **Brines M, Grasso G, Fiordaliso F, Sfacteria A, Ghezzi P, Fratelli M, Latini R, Xie QW, Smart J, Su-Rick CJ, Pobre E, Diaz D, Gomez D, Hand C, Coleman T, Cerami A.** Erythropoietin mediates tissue protection through an erythropoietin and common beta-subunit heteroreceptor. *Proc Natl Acad Sci USA* 101: 14907–14912, 2004.
68. **Brock RW, Carson MW, Harris KA, Potter RF.** Microcirculatory perfusion deficits are not essential for remote parenchymal injury within the liver. *Am J Physiol Gastrointest Liver Physiol* 277: G55–G60, 1999.
69. **Broering DC, Hillert C, Krupski G, Fischer L, Mueller L, Achilles EG, Schulte am Esch J, Rogiers X.** Portal vein embolization vs portal vein ligation for induction of hypertrophy of the future liver remnant. *J Gastrointest Surg* 6: 905–913, 2002.

70. **Browse DJ, Mathie RT, Benjamin IS, Alexander B.** The role of ATP and adenosine in the control of hepatic blood flow in the rabbit liver in vivo. *Comp Hepatol* 2: 9, 2003.
71. **Brunner F, Stessel H, Kukovetz WR.** Novel guanylyl cyclase inhibitor, ODQ reveals role of nitric oxide, but not of cyclic GMP in endothelin-1 secretion. *FEBS Lett* 376: 262–266, 1995.
72. **Burkel WE.** The fine structure of the terminal branches of the hepatic arterial system of the rat. *Anat Rec* 167: 329–349, 1970.
73. **Burkhardt M, Slotta JE, Garcia P, Seekamp A, Menger MD, Pohlemann T.** The effect of estrogen on hepatic microcirculation after ischemia/reperfusion. *Int J Colorectal Dis* 23: 113–119, 2008.
74. **Burkhardt M, Vollmar B, Menger MD.** In vivo analysis of hepatic NADH fluorescence. Methodological approach to exclude Ito-cell vitamin A-derived autofluorescence. *Adv Exp Med Biol* 454: 83–89, 1998.
75. **Burra P, Masier A.** Dynamic tests to study liver function. *Eur Rev Med Pharmacol Sci* 8: 19–21, 2004.
76. **Burton-Opitz R.** The vascularity of the liver: the influence of the portal blood flow upon the flow in the hepatic artery. *Q J Exp Physiol* 4: 93–102, 1911.
77. **Busse R, Fleming I.** Pulsatile stretch and shear stress: physical stimuli determining the production of endothelium-derived relaxing factors. *J Vasc Res* 35: 73–84, 1998.
78. **Bzeizi KI, Jalan R, MacGregor I, Drummond O, Lee A, Hayes PC.** Neutrophil elastase: a determinant of endothelial damage and reperfusion injury after liver transplantation? *Transplantation* 62: 916–920, 1996.
79. **Caldwell-Kenkel JC, Currin RT, Tanaka Y, Thurman RG, Lemasters JJ.** Reperfusion injury to endothelial cells following cold ischemic storage of rat livers. *Hepatology* 10: 292–299, 1989.
80. **Calkins CM, Bensard DD, Shames BD, Pulido EJ, Abraham E, Fernandez N, Meng X, Dinarello CA, McIntyre RC Jr.** IL-1 regulates in vivo C-X-C chemokine induction and neutrophil sequestration following endotoxemia. *J Endotoxin Res* 8: 59–67, 2002.
81. **Callery MP, Mangino MJ, Flye MW.** A biologic basis for limited Kupffer cell reactivity to portal-derived endotoxin. *Surgery* 110: 221–230, 1991.
82. **Campion SN, Johnson R, Aleksunes LM, Goedken MJ, van Rooijen N, Scheffer GL, Cherrington NJ, Manautou JE.** Hepatic Mrp4 induction following acetaminophen exposure is dependent on Kupffer cell function. *Am J Physiol Gastrointest Liver Physiol* 295: G294–G304, 2008.
83. **Canbay A, Feldstein AE, Higuchi H, Werneburg N, Grambihler A, Bronk SF, Gores GJ.** Kupffer cell engulfment of apoptotic bodies stimulates death ligand and cytokine expression. *Hepatology* 38: 1188–1198, 2003.
84. **Canbay A, Guicciardi ME, Higuchi H, Feldstein A, Bronk SF, Rydzewski R, Taniai M, Gores GJ.** Cathepsin B inactivation attenuates hepatic injury and fibrosis during cholestasis. *J Clin Invest* 112: 152–159, 2003.
85. **Cantré D, Schuett H, Hildebrandt A, Dold S, Menger MD, Vollmar B, Eipel C.** Nitric oxide reduces organ injury and enhances regeneration of reduced-size livers by increasing hepatic arterial flow. *Br J Surg* 95: 785–792, 2008.
86. **Carden DL, Granger DN.** Pathophysiology of ischaemia-reperfusion injury. *J Pathol* 190: 255–266, 2000.
87. **Cardoso JE, Giroux L, Kassissia I, Houssin D, Habib N, Huet PM.** Liver function improvement following increased portal blood flow in cirrhotic rats. *Gastroenterology* 107: 460–467, 1994.
88. **Carini R, Albano E.** Recent insights on the mechanisms of liver preconditioning. *Gastroenterology* 125: 1480–1491, 2003.
89. **Carvalho-Tavares J, Fox-Robichaud A, Kubes P.** Assessment of the mechanism of juxtacrine activation and adhesion of leukocytes in liver microcirculation. *Am J Physiol Gastrointest Liver Physiol* 276: G828–G834, 1999.
90. **Catal T, Bolkent S.** Combination of selenium and three naturally occurring antioxidants administration protects D-galactosamine-induced liver injury in rats. *Biol Trace Elem Res* 122: 127–136, 2008.
91. **Cavaillon JM, Annane D.** Compartmentalization of the inflammatory response in sepsis and SIRS. *J Endotoxin Res* 12: 151–170, 2006.
92. **Cazanave S, Vadrot N, Tinel M, Berson A, Lettéron P, Larosche I, Descatoire V, Feldmann G, Robin MA, Pessayre D.** Ibuprofen administration attenuates serum TNF-α levels, hepatic glutathione depletion, hepatic apoptosis and mouse mortality after Fas stimulation. *Toxicol Appl Pharmacol* 231: 336–343, 2008.
93. **Cerný V, Turek Z, Pařízková R.** In situ assessment of the liver microcirculation in mechanically ventilated rats using Sidestream dark-field (SDF) imaging. *Physiol Res* 58: 49–55, 2009.
94. **Cescon M, Grazi GL, Grassi A, Ravaioli M, Vetrone G, Ercolani G, Varotti G, D'Errico A, Ballardini G, Pinna AD.** Effect of ischemic preconditioning in whole liver transplantation from deceased donors. A pilot study. *Liver Transpl* 12: 628–635, 2006.
95. **Chance B, Cohen P, Jobis F, Schoener B.** Intracellular oxidation-reduction states in vivo. *Science* 137: 499–508, 1962.
96. **Chance B.** Pyridine nucleotide as an indicator of the oxygen requirements for energy-linked functions of mitochondria. *Circ Res* 38, *Suppl* 1: I31–I38, 1976.
97. **Chattopadhyay P, Verma N, Verma A, Kamboj T, Khan NA, Wahi AK.** L-Arginine protects from pringle manoeuvere of ischemia-reperfusion induced liver injury. *Biol Pharm Bull* 31: 890–892, 2008.
98. **Chaudry IH, Clemens MG, Baue AE.** Alterations in cell function with ischemia and shock and their correction. *Arch Surg* 116: 1309–1317, 1981.
99. **Chen LC, Gordon RE, Laskin JD, Laskin DL.** Role of TLR-4 in liver macrophage and endothelial cell responsiveness during acute endotoxemia. *Exp Mol Pathol* 83: 311–326, 2007.
100. **Chen T, Zamora R, Zuckerbraun B, Billiar TR.** Role of nitric oxide in liver injury. *Curr Mol Med* 3: 519–526, 2003.
101. **Cheng WH, Quimby FW, Lei XG.** Impacts of glutathione peroxidase-1 knockout on the protection by injected selenium against the pro-oxidant-induced liver aponecrosis and signaling in selenium-deficient mice. *Free Radic Biol Med* 34: 918–927, 2003.
102. **Cheng XD, Jiang XC, Liu YB, Peng CH, Xu B, Peng SY.** Effect of ischemic preconditioning on P-selectin expression in hepatocytes of rats with cirrhotic ischemia-reperfusion injury. *World J Gastroenterol* 9: 2289–2292, 2003.
103. **Cheng YF, Huang TL, Chen TY, Concejero A, Tsang LL, Wang CC, Wang SH, Sun CK, Lin CC, Liu YW, Yang CH, Yong CC, Ou SY, Yu CY, Chiu KW, Jawan B, Eng HL, Chen CL.** Liver graft-to-recipient spleen size ratio as a novel predictor of portal hyperperfusion syndrome in living donor liver transplantation. *Am J Transplant* 6: 2994–2999, 2006.
104. **Chien S.** The Microcirculatory Society Eugene M. Landis Award lecture. Role of blood cells in microcirculatory regulation. *Microvasc Res* 29: 129–151, 1985.
105. **Chosay JG, Essani NA, Dunn CJ, Jaeschke H.** Neutrophil margination and extravasation in sinusoids and venules of liver during endotoxin-induced injury. *Am J Physiol Gastrointest Liver Physiol* 272: G1195–G1200, 1997.
106. **Choukèr A, Martignoni A, Schauer R, Dugas M, Rau HG, Jauch KW, Peter K, Thiel M.** Beneficial effects of ischemic preconditioning in patients undergoing hepatectomy: the role of neutrophils. *Arch Surg* 140: 129–136, 2005.
107. **Choukèr A, Martignoni A, Schauer RJ, Rau HG, Volk A, Heizmann O, Dugas M, Messmer K, Peter K, Thiel M.** Ischemic preconditioning attenuates portal venous plasma concentrations of purines following warm liver ischemia in man. *Eur Surg Res* 37: 144–152, 2005.
108. **Choukèr A, Schachtner T, Schauer R, Dugas M, Löhe F, Martignoni A, Pollwein B, Niklas M, Rau HG, Jauch KW, Peter K, Thiel M.** Effects of Pringle manoeuvre and ischaemic preconditioning on haemodynamic stability in patients undergoing elective hepatectomy: a randomized trial. *Br J Anaesth* 93: 204–211, 2004.
109. **Chun K, Zhang J, Biewer J, Ferguson D, Clemens MG.** Microcirculatory failure determines lethal hepatocyte injury in ischemic/reperfused rat livers. *Shock* 1: 3–9, 1994.
110. **Clavien PA, Selzner M, Rüdiger HA, Graf R, Kadry Z, Rousson V, Jochum W.** A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. *Ann Sur* 238: 843–850, 2003.

111. **Clavien PA, Yadav S, Sindram D, Bentley RC.** Protective effects of ischemic preconditioning for liver resection performed under inflow occlusion in humans. *Ann Surg* 232: 155–162, 2000.
112. **Clemens MG, McDonagh PF, Chaudry IH, Baue AE.** Hepatic microcirculatory failure after ischemia and reperfusion: improvement with ATP-$MgCl_2$ treatment. *Am J Physiol Heart Circ Physiol* 248: H804–H811, 1985.
113. **Clemens MG, Zhang JX.** Regulation of sinusoidal perfusion: in vivo methodology and control by endothelins. *Semin Liver Dis* 19: 383–396, 1999.
114. **Clemens MG.** Nitric oxide in liver injury. *Hepatology* 30: 1–5, 1999.
115. **Cogger VC, Muller M, Fraser R, McLean AJ, Khan J, Le Couteur DG.** The effects of oxidative stress on the liver sieve. *J Hepatol* 41: 370–376, 2004.
116. **Coggins MP, Bloch KD.** Nitric oxide in the pulmonary vasculature. *Arterioscler Thromb Vasc Biol* 27: 1877–1885, 2007.
117. **Colletti LM, Cortis A, Lukacs N, Kunkel SL, Green M, Strieter RM.** Tumor necrosis factor up-regulates intercellular adhesion molecule 1, which is important in the neutrophil-dependent lung and liver injury associated with hepatic ischemia and reperfusion in the rat. *Shock* 10: 182–191, 1998.
118. **Colletti LM, Kunkel SL, Walz A, Burdick MD, Kunkel RG, Wilke CA, Strieter RM.** The role of cytokine networks in the local liver injury following hepatic ischemia/reperfusion in the rat. *Hepatology* 23: 506–514, 1996.
119. **Collin M, Anuar FB, Murch O, Bhatia M, Moore PK, Thiemermann C.** Inhibition of endogenous hydrogen sulfide formation reduces the organ injury caused by endotoxemia. *Br J Pharmacol* 146: 498–505, 2005.
120. **Conlan JW.** Critical roles of neutrophils in host defense against experimental systemic infections of mice by *Listeria monocytogenes*, *Salmonella typhimurium*, and *Yersinia enterocolitica*. *Infect Immun* 65: 630–635, 1997.
121. **Contreras JL, Vilatoba M, Eckstein C, Bilbao G, Anthony Thompson J, Eckhoff DE.** Caspase-8 and caspase-3 small interfering RNA decreases ischemia/reperfusion injury to the liver in mice. *Surgery* 136: 390–400, 2004.
122. **Converso DP, Taillé C, Carreras MC, Jaitovich A, Poderoso JJ, Boczkowski J.** HO-1 is located in liver mitochondria and modulates mitochondrial heme content and metabolism. *FASEB J* 20: 1236–1238, 2006.
123. **Conway JG, Popp JA, Thurman RG.** Microcirculation in periportal and pericentral regions of lobule in perfused rat liver. *Am J Physiol Gastrointest Liver Physiol* 249: G449–G456, 1985.
124. **Conway JG, Popp JA, Thurman RG.** Microcirculation of hepatic nodules from diethylnitrosamine-treated rats. *Cancer Res* 45: 3620–3625, 1985.
125. **Conzen PF, Hobbhahn J, Goetz AE, Habazettl H, Granetzny T, Peter K, Brendel W.** Splanchnic oxygen consumption and hepatic surface oxygen tensions during isoflurane anesthesia. *Anesthesiology* 69: 643–651, 1988.
126. **Conzen PF, Vollmar B, Habazettl H, Frink EJ, Peter K, Messmer K.** Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. *Anesth Analg* 74: 79–88, 1992.
127. **Corso CO, Gundersen Y, Dörger M, Lilleaasen P, Aasen AO, Messmer K.** Effects of the nitric oxide synthase inhibitors *N*(G)-nitro-L-arginine methyl ester and aminoethyl-isothiourea on the liver microcirculation in rat endotoxemia. *J Hepatol* 28: 61–69, 1998.
128. **Corso CO, Okamoto S, Rüttinger D, Messmer K.** Hypertonic saline dextran attenuates leukocyte accumulation in the liver after hemorrhagic shock and resuscitation. *J Trauma* 46: 417–423, 1999.
129. **Cover C, Liu J, Farhood A, Malle E, Waalkes MP, Bajt ML, Jaeschke H.** Pathophysiological role of the acute inflammatory response during acetaminophen hepatotoxicity. *Toxicol Appl Pharmacol* 216: 98–107, 2006.
130. **Croner RS, Hoerer E, Kulu Y, Hackert T, Gebhard MM, Herfarth C, Klar E.** Hepatic platelet and leukocyte adherence during endotoxemia. *Crit Care* 10: R15, 2006.
131. **Cursio R, Gugenheim J, Ricci JE, Crenesse D, Rostagno P, Maulon L, Saint-Paul MC, Ferrua B, Auberger AP.** A caspase inhibitor fully protects rats against lethal normothermic liver ischemia by inhibition of liver apoptosis. *FASEB J* 13: 253–261, 1999.
132. **Cursio R, Gugenheim J, Ricci JE, Crenesse D, Rostagno P, Maulon L, Saint-Paul MC, Ferrua B, Mouiel J, Auberger P.** Caspase inhibition protects from liver injury following ischemia and reperfusion in rats. *Transpl Int* 13, *Suppl* 1: S568–S572, 2000.
133. **Cuzzocrea S, Chatterjee PK, Mazzon E, Serraino I, Dugo L, Centorrino T, Barbera A, Ciccolo A, Fulia F, McDonald MC, Caputi AP, Thiemermann C.** Effects of calpain inhibitor I on multiple organ failure induced by zymosan in the rat. *Crit Care Med* 30: 2284–2294, 2002.
134. **Cuzzocrea S, de Sarro G, Costantino G, Mazzon E, Laurà R, Ciriaco E, de Sarro A, Caputi AP.** Role of interleukin-6 in a non-septic shock model induced by zymosan. *Eur Cytokine Netw* 10: 191–203, 1999.
135. **Cuzzocrea S, Mazzon E, Di Paola R, Esposito E, Macarthur H, Matuschak GM, Salvemini D.** A role for nitric oxide-mediated peroxynitrite formation in a model of endotoxin-induced shock. *J Pharmacol Exp Ther* 319: 73–81, 2006.
136. **Cywes R, Packham MA, Tietze L, Sanabria JR, Harvey PR, Phillips MJ, Strasberg SM.** Role of platelets in hepatic allograft preservation injury in the rat. *Hepatology* 18: 635–647, 1993.
137. **Czaja MJ.** Cell signaling in oxidative stress-induced liver injury. *Semin Liver Dis* 27: 378–389, 2007.
138. **Daemen MJ, Thijssen HH, van Essen H, Vervoort-Peters HT, Prinzen FW, Struyker Boudier HA, Smits JF.** Liver blood flow measurement in the rat. The electromagnetic versus the microsphere and the clearance methods. *J Pharmacol Methods* 21: 287–297, 1989.
139. **Daugas E, Susin SA, Zamzami N, Ferri KF, Irinopoulou T, Larochette N, Prévost MC, Leber B, Andrews D, Penninger J, Kroemer G.** Mitochondrio-nuclear translocation of AIF in apoptosis and necrosis. *FASEB J* 14: 729–739, 2000.
140. **Deaciuc IV, Bagby GJ, Niesman MR, Skrepnik N, Spitzer JJ.** Modulation of hepatic sinusoidal endothelial cell function by Kupffer cells: an example of intercellular communication in the liver. *Hepatology* 19: 464–470, 1994.
141. **Del Zoppo GJ, Schmid-Schönbein GW, Mori E, Copeland BR, Chang CM.** Polymorphonuclear leukocytes occlude capillaries following middle cerebral artery occlusion and reperfusion in baboons. *Stroke* 22: 1276–1283, 1991.
142. **Delaney JP.** Arteriovenous anastomotic blood flow in the mesenteric organs. *Am J Physiol* 216: 1556–1561, 1969.
143. **DeLeve LD.** Glutathione defense in non-parenchymal cells. *Semin Liver Dis* 18: 403–413, 1998.
144. **Demetris AJ, Kelly DM, Eghtesad B, Fontes P, Wallis Marsh J, Tom K, Tan HP, Shaw-Stiffel T, Boig L, Novelli P, Planinsic R, Fung JJ, Marcos A.** Pathophysiologic observations and histopathologic recognition of the portal hyperperfusion or small-for-size syndrome. *Am J Surg Pathol* 30: 986–993, 2006.
145. **Demirbilek S, Tas E, Gurunluoglu K, Akin M, Aksoy RT, Emre MH, Aydin NE, Ay S, Ozatay N.** Fluvastatin reduced liver injury in rat model of extrahepatic cholestasis. *Pediatr Surg Int* 23: 155–162, 2007.
146. **Deneme MA, Ok E, Akcan A, Akyildiz H, Soyuer I, Muhtaroglu S.** Single dose of anti-transforming growth factor-beta1 monoclonal antibody enhances liver regeneration after partial hepatectomy in biliary-obstructed rats. *J Surg Res* 136: 280–287, 2006.
147. **Deng X, Luyendyk JP, Zou W, Lu J, Malle E, Ganey PE, Roth RA.** Neutrophil interaction with the hemostatic system contributes to liver injury in rats cotreated with lipopolysaccharide and ranitidine. *J Pharmacol Exp Ther* 322: 852–861, 2007.
148. **Derbocio AM, Kelmer-Bracht AM, Bracht L, Bracht A, Ishii-Iwamoto EL.** The hemodynamic effects of zymosan in the perfused rat liver. *Vasc Pharmacol* 43: 75–85, 2005.
149. **Deters M, Strubelt O, Younes M.** Protection by glycine against hypoxia-reoxygenation induced hepatic injury. *Res Commun Mol Pathol Pharmacol* 97: 199–213, 1997.
150. **Devlin J, Ellis AE, McPeake J, Heaton N, Wendon JA, Williams R.** *N*-acetylcysteine improves indocyanine green extraction and oxygen transport during hepatic dysfunction. *Crit Care Med* 25: 236–242, 1997.
151. **Devoisselle JM, Soulié S, Mordon S, Maillols H.** Fluorescent characteristics and pharmacokinetic profiles of the fluorescent

probe BCECF in various tissues: the role of blood content. *Photochem Photobiol* 64: 906–910, 1996.
152. **Dhar DK, Yamanoi A, Ohmori H, Nakashima Y, Yamamoto A, Osama NE, Kubota H, Kohno H, Nagasue N.** Modulation of endothelin and nitric oxide: a rational approach to improve canine hepatic microcirculation. *Hepatology* 28: 782–788, 1998.
153. **Ding WX, Shen HM, Ong CN.** Critical role of reactive oxygen species and mitochondrial permeability transition in microcystin-induced rapid apoptosis in rat hepatocytes. *Hepatology* 32: 547–555, 2000.
154. **Distrutti E, Mencarelli A, Santucci L, Renga B, Orlandi S, Donini A, Shah V, Fiorucci S.** The methionine connection: homocysteine and hydrogen sulfide exert opposite effects on hepatic microcirculation in rats. *Hepatology* 47: 659–667, 2008.
155. **Dorman RB, Gujral JS, Bajt ML, Farhood A, Jaeschke H.** Generation and functional significance of CXC chemokines for neutrophil-induced liver injury during endotoxemia. *Am J Physiol Gastrointest Liver Physiol* 288: G880–G886, 2005.
156. **Dorman RB, Wunder C, Brock RW.** Cobalt protoporphyrin protects against hepatic parenchymal injury and microvascular dysfunction during experimental rhabdomyolysis. *Shock* 23: 275–280, 2005.
157. **Downard PJ, Wilson MA, Spain DA, Matheson PJ, Siow Y, Garrison RN.** Heme oxygenase-dependent carbon monoxide production is a hepatic adaptive response to sepsis. *J Surg Res* 71: 7–12, 1997.
158. **Downey GP, Elson EL, Schwab B 3rd, Erzurum SC, Young SK, Worthen GS.** Biophysical properties and microfilament assembly in neutrophils: modulation by cyclic AMP. *J Cell Biol* 114: 1179–1190, 1991.
159. **Dranoff JA, Kruglov EA, Robson SC, Braun N, Zimmermann H, Sévigny J.** The ecto-nucleoside triphosphate diphosphohydrolase NTPDase2/CD39L1 is expressed in a novel functional compartment within the liver. *Hepatology* 36: 1135–1144, 2002.
160. **Drugas GT, Chun KE, Miescher EA, Clemens MG.** Maturational differences in hepatic microhemodynamics in rats. *J Surg Res* 54: 246–253, 1993.
161. **Dudenhoefer AA, Loureiro-Silva MR, Cadelina GW, Gupta T, Groszmann RJ.** Bioactivation of nitroglycerin and vasomotor response to nitric oxide are impaired in cirrhotic rat livers. *Hepatology* 36: 381–385, 2002.
162. **Duenschede F, Westermann S, Riegler N, Miesner I, Erbes K, Ewald P, Kircher A, Schaefer H, Schneider J, Schad A, Dutkowski P, Kiemer AK, Junginger T.** Different protection mechanisms after pretreatment with glycine or α-lipoic acid in a rat model of warm hepatic ischemia. *Eur Surg Res* 38: 503–512, 2006.
163. **Dulkanchainun TS, Goss JA, Imagawa DK, Shaw GD, Anselmo DM, Kaldas F, Wang T, Zhao D, Busuttil AA, Kato H, Murray NG, Kupiec-Weglinski JW, Busuttil RW.** Reduction of hepatic ischemia/reperfusion injury by a soluble P-selectin glycoprotein ligand-1. *Ann Surg* 227: 832–840, 1998.
164. **Dupuis J, Schwab AJ, Simard A, Cernacek P, Stewart DJ, Goresky CA.** Kinetics of endothelin-1 binding in the dog liver microcirculation in vivo. *Am J Physiol Gastrointest Liver Physiol* 277: G905–G914, 1999.
165. **Duryee MJ, Klassen LW, Freeman TL, Willis MS, Tuma DJ, Thiele GM.** Lipopolysaccharide is a cofactor for malondialdehyde-acetaldehyde adduct-mediated cytokine/chemokine release by rat sinusoidal liver endothelial and Kupffer cells. *Alcohol Clin Exp Res* 28: 1931–1938, 2004.
166. **Ebbing C, Rasmussen S, Godfrey KM, Hanson MA, Kiserud T.** Hepatic artery hemodynamics suggest operation of a buffer response in the human fetus. *Reprod Sci* 15: 166–178, 2008.
167. **Eguchi H, McCuskey PA, McCuskey RS.** Kupffer cell activity and hepatic microvascular events after acute ethanol ingestion in mice. *Hepatology* 13: 751–757, 1991.
168. **Eipel C, Bordel R, Nickels RM, Menger MD, Vollmar B.** Impact of leukocytes and platelets in mediating hepatocyte apoptosis in a rat model of systemic endotoxemia. *Am J Physiol Gastrointest Liver Physiol* 286: G769–G776, 2004.
169. **Eipel C, Glanemann M, Nuessler AK, Menger MD, Neuhaus P, Vollmar B.** Ischemic preconditioning impairs liver regeneration in extended reduced-size livers. *Ann Surg* 241: 477–484, 2005.
170. **Eipel C, Kidess E, Abshagen K, Leminh K, Menger MD, Burkhardt H, Vollmar B.** Antileukoproteinase protects against hepatic inflammation, but not apoptosis in the response of D-galactosamine-sensitized mice to lipopolysaccharide. *Br J Pharmacol* 151: 406–413, 2007.
171. **Ekataksin W, Kaneda K.** Liver microvascular architecture: an insight into the pathophysiology of portal hypertension. *Semin Liver Dis* 19: 359–382, 1999.
172. **El-Desoky A, Seifalian AM, Cope M, Delpy DT, Davidson BR.** Experimental study of liver dysfunction evaluated by direct indocyanine green clearance using near infrared spectroscopy. *Br J Surg* 86: 1005–1011, 1999.
173. **El-Desoky AE, Delpy DT, Davidson BR, Seifalian AM.** Assessment of hepatic ischaemia reperfusion injury by measuring intracellular tissue oxygenation using near infrared spectroscopy. *Liver* 21: 37–44, 2001.
174. **El-Desoky AE, Seifalian A, Cope M, Delpy D, Davidson B.** Changes in tissue oxygenation of the porcine liver measured by near-infrared spectroscopy. *Liver Transpl Surg* 5: 219–226, 1999.
175. **El-Desoky AE, Seifalian AM, Davidson BR.** Effect of graded hypoxia on hepatic tissue oxygenation measured by near infrared spectroscopy. *J Hepatol* 31: 71–76, 1999.
176. **El-Gibaly AM, Scheuer C, Menger MD, Vollmar B.** Improvement of rat liver graft quality by pifithrin-α-mediated inhibition of hepatocyte necrapoptosis. *Hepatology* 39: 1553–1562, 2004.
177. **El-Khawaga OA.** Role of selenium on antioxidant capacity in methomyl-treated mice. *J Physiol Biochem* 61: 501–506, 2005.
178. **Engler RL, Dahlgren MD, Morris DD, Peterson MA, Schmid-Schönbein GW.** Role of leukocytes in response to acute myocardial ischemia and reflow in dogs. *Am J Physiol Heart Circ Physiol* 251: H314–H323, 1986.
179. **Erdem A, Meltem Sevgili A, Akbiyik F, Atilla P, Cakar N, Balkanci ZD, Iskit AB, Guc MO.** Tezosentan attenuates organ injury and mesenteric blood flow decrease in endotoxemia and cecal ligation and puncture. *J Surg Res* 141: 211–219, 2007.
180. **Esmon CT.** Inflammation and thrombosis. *J Thromb Haemost* 1: 1343–1348, 2003.
181. **Esmon CT.** The interactions between inflammation and coagulation. *Br J Haematol* 131: 417–430, 2005.
182. **Essani NA, Fisher MA, Farhood A, Manning AM, Smith CW, Jaeschke H.** Cytokine-induced upregulation of hepatic intercellular adhesion molecule-1 messenger RNA expression and its role in the pathophysiology of murine endotoxin shock and acute liver failure. *Hepatology* 21: 1632–1639, 1995.
183. **Essani NA, McGuire GM, Manning AM, Jaeschke H.** Endotoxin-induced activation of the nuclear transcription factor kappa B and expression of E-selectin messenger RNA in hepatocytes, Kupffer cells, and endothelial cells in vivo. *J Immunol* 156: 2956–2963, 1996.
184. **Eum HA, Park SW, Lee SM.** Role of nitric oxide in the expression of hepatic vascular stress genes in response to sepsis. *Nitric Oxide* 17: 126–133, 2007.
185. **Fadok VA, Bratton DL, Konowal A, Freed PW, Westcott JY, Henson PM.** Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE_2, and PAF. *J Clin Invest* 101: 890–898, 1998.
186. **Fadok VA, Bratton DL, Rose DM, Pearson A, Ezekewitz RA, Henson PM.** A receptor for phosphatidylserine-specific clearance of apoptotic cells. *Nature* 405: 85–90, 2000.
187. **Fadok VA, Warner ML, Bratton DL, Henson PM.** CD36 is required for phagocytosis of apoptotic cells by human macrophages that use either a phosphatidylserine receptor or the vitronectin receptor (α v beta 3). *J Immunol* 161: 6250–6257, 1998.
188. **Fan MH, Klein RD, Steinstraesser L, Merry AC, Nemzek JA, Remick DG, Wang SC, Su GL.** An essential role for lipopolysaccharide-binding protein in pulmonary innate immune responses. *Shock* 18: 248–254, 2002.
189. **Fanburg BL, Lee SL.** A new role for an old molecule: serotonin as a mitogen. *Am J Physiol Lung Cell Mol Physiol* 272: L795–L806, 1997.
190. **Faouzi S, Burckhardt BE, Hanson JC, Campe CB, Schrum LW, Rippe RA, Maher JJ.** Anti-Fas induces hepatic chemokines and

promotes inflammation by an NF-kappa B-independent, caspase-3-dependent pathway. *J Biol Chem* 276: 49077–49082, 2001.
191. **Farrell GC, Teoh NC, McCuskey RS.** Hepatic microcirculation in fatty liver disease. *Anat Rec* 291: 684–692, 2008.
192. **Faurschou M, Borregaard N.** Neutrophil granules and secretory vesicles in inflammation. *Microbes Infect* 5: 1317–1327, 2003.
193. **Feder LS, Todaro JA, Laskin DL.** Characterization of interleukin-1 and interleukin-6 production by hepatic endothelial cells and macrophages. *J Leukoc Biol* 53: 126–132, 1993.
194. **Feldstein AE, Canbay A, Angulo P, Taniai M, Burgart LJ, Lindor KD, Gores GJ.** Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. *Gastroenterology* 125: 437–443, 2003.
195. **Feng L, Zhao N, Yao X, Sun X, Du L, Diao X, Li S, Li Y.** Histidine-tryptophan-ketoglutarate solution vs. University of Wisconsin solution for liver transplantation: a systematic review. *Liver Transpl* 13: 1125–1136, 2007.
196. **Fennekohl A, Schieferdecker HL, Jungermann K, Püschel GP.** Differential expression of prostanoid receptors in hepatocytes, Kupffer cells, sinusoidal endothelial cells and stellate cells of rat liver. *J Hepatol* 30: 38–47, 1999.
197. **Ferguson D, McDonagh PF, Biewer J, Paidas CN, Clemens MG.** Spatial relationship between leukocyte accumulation and microvascular injury during reperfusion following hepatic ischemia. *Int J Microcirc Clin Exp* 12: 45–60, 1993.
198. **Fernández L, Carrasco-Chaumel E, Serafín A, Xaus C, Grande L, Rimola A, Roselló-Catafau J, Peralta C.** Is ischemic preconditioning a useful strategy in steatotic liver transplantation? *Am J Transplant* 4: 888–899, 2004.
199. **Ferrari M, Binzoni T, Quaresima V.** Oxidative metabolism in muscle. *Philos Trans R Soc Lond B Biol Sci* 352: 677–683, 1997.
200. **Fiordaliso F, Chimenti S, Staszewsky L, Bai A, Carlo E, Cuccovillo I, Doni M, Mengozzi M, Tonelli R, Ghezzi P, Coleman T, Brines M, Cerami A, Latini R.** A nonerythropoietic derivative of erythropoietin protects the myocardium from ischemia-reperfusion injury. *Proc Natl Acad Sci USA* 102: 2046–2051, 2005.
201. **Fiorucci S, Antonelli E, Mencarelli A, Orlandi S, Renga B, Rizzo G, Distrutti E, Shah V, Morelli A.** The third gas: H_2S regulates perfusion pressure in both the isolated and perfused normal rat liver and in cirrhosis. *Hepatology* 42: 539–548, 2005.
202. **Fiorucci S, Distrutti E, Cirino G, Wallace JL.** The emerging roles of hydrogen sulfide in the gastrointestinal tract and liver. *Gastroenterology* 131: 259–271, 2006.
203. **Fisher CJ Jr, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, Abraham E, Schein RM, Benjamin E.** Treatment of septic shock with the tumor necrosis factor receptor: Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. *N Engl J Med* 334: 1697–1702, 1996.
204. **Fleming I, Busse R.** NO: the primary EDRF. *J Mol Cell Cardiol* 31: 5–14, 1999.
205. **Formigli L, Papucci L, Tani A, Schiavone N, Tempestini A, Orlandini GE, Capaccioli S, Orlandini SZ.** Aponecrosis: morphological and biochemical exploration of a syncretic process of cell death sharing apoptosis and necrosis. *J Cell Physiol* 182: 41–49, 2000.
206. **Forni M, Mazzola S, Ribeiro LA, Pirrone F, Zannoni A, Bernardini C, Bacci ML, Albertini M.** Expression of endothelin-1 system in a pig model of endotoxic shock. *Regul Pept* 131: 89–96, 2005.
207. **Frank A, Rauen U, de Groot H.** Protection by glycine against hypoxic injury of rat hepatocytes: inhibition of ion fluxes through nonspecific leaks. *J Hepatol* 32: 58–66, 2000.
208. **Frank RS.** Time-dependent alterations in the deformability of human neutrophils in response to chemotactic activation. *Blood* 76: 2606–2612, 1990.
209. **Freeman BD, Natanson C.** Anti-inflammatory therapies in sepsis and septic shock. *Exp Opin Invest Drugs* 9: 1651–1663, 2000.
210. **Freitas I, Bertone V, Guarnaschelli C, Ferrigno A, Boncompagni E, Rizzo V, Reiter RJ, Barni S, Vairetti M.** In situ demonstration of improvement of liver mitochondria function by melatonin after cold ischemia. *In Vivo* 20: 229–237, 2006.
211. **Friedman SL.** Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. *Physiol Rev* 88: 125–172, 2008.
212. **Fujii H, Seki S, Kobayashi S, Kitada T, Kawakita N, Adachi K, Tsutsui H, Nakanishi K, Fujiwara H, Ikarashi Y, Taniguchi M, Kronenberg M, Ikemoto M, Nakajima Y, Arakawa T, Kaneda K.** A murine model of NKT cell-mediated liver injury induced by α-galactosylceramide/D-galactosamine. *Virchows Arch* 446: 663–673, 2005.
213. **Fukui H.** Relation of endotoxin, endotoxin binding proteins and macrophages to severe alcoholic liver injury and multiple organ failure. *Alcohol Clin Exp Res* 29: 172S–179S, 2005.
214. **Fukuzawa K, Emre S, Senyuz O, Acarli K, Schwartz ME, Miller CM.** *N*-acetylcysteine ameliorates reperfusion injury after warm hepatic ischemia. *Transplantation* 59: 6–9, 1995.
215. **Furchgott RF, Jothianandan D.** Endothelium-dependent and -independent vasodilation involving cyclic GMP: relaxation induced by nitric oxide, carbon monoxide and light. *Blood Vessels* 28: 52–61, 1991.
216. **Furchgott RF, Zawadzki JV.** The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 288: 373–376, 1980.
217. **Fusai G, Glantzounis GK, Hafez T, Yang W, Quaglia A, Sheth H, Kanoria S, Parkes H, Seifalian A, Davidson BR.** *N*-acetylcysteine ameliorates the late phase of liver ischaemia/reperfusion injury in the rabbit with hepatic steatosis. *Clin Sci* 109: 465–473, 2005.
218. **Gandhi CR, Kuddus RH, Nemoto EM, Murase N.** Endotoxin treatment causes an upregulation of the endothelin system in the liver: amelioration of increased portal resistance by endothelin receptor antagonism. *J Gastroenterol Hepatol* 16: 61–69, 2001.
219. **Gao B, Jeong WI, Tian Z.** Liver: an organ with predominant innate immunity. *Hepatology* 47: 729–736, 2008.
220. **Gao B.** Therapeutic potential of interleukin-6 in preventing obesity- and alcohol-associated fatty liver transplant failure. *Alcohol* 34: 59–65, 2004.
221. **Gao W, Bentley RC, Madden JF, Clavien PA.** Apoptosis of sinusoidal endothelial cells is a critical mechanism of preservation injury in rat liver transplantation. *Hepatology* 27: 1652–1660, 1998.
222. **Gardner CR, Laskin JD, Dambach DM, Chiu H, Durham SK, Zhou P, Bruno M, Gerecke DR, Gordon MK, Laskin DL.** Exaggerated hepatotoxicity of acetaminophen in mice lacking tumor necrosis factor receptor-1. Potential role of inflammatory mediators. *Toxicol Appl Pharmacol* 192: 119–130, 2003.
223. **Gardner CR, Laskin JD, Dambach DM, Sacco M, Durham SK, Bruno MK, Cohen SD, Gordon MK, Gerecke DR, Zhou P, Laskin DL.** Reduced hepatotoxicity of acetaminophen in mice lacking inducible nitric oxide synthase: potential role of tumor necrosis factor-α and interleukin-10. *Toxicol Appl Pharmacol* 184: 27–36, 2002.
224. **Gasull X, Bataller R, Ginès P, Sancho-Bru P, Nicolás JM, Görbig MN, Ferrer E, Badía E, Gual A, Arroyo V, Rodés J.** Human myofibroblastic hepatic stellate cells express Ca^{2+}-activated K^+ channels that modulate the effects of endothelin-1 and nitric oxide. *J Hepatol* 35: 739–748, 2001.
225. **Gatta A, Dante A, Del Gaudio M, Pinna AD, Ravaioli M, Riganello I, Volta G, Faenza S.** The use of prostaglandins in the immediate postsurgical liver transplant period. *Transplant Proc* 38: 1092–1095, 2006.
226. **Gehring S, Dickson EM, San Martin ME, van Rooijen N, Papa EF, Harty MW, Tracy TF Jr, Gregory SH.** Kupffer cells abrogate cholestatic liver injury in mice. *Gastroenterology* 130: 810–822, 2006.
227. **George J, Rao KR, Stern R, Chandrakasan G.** Dimethylnitrosamine-induced liver injury in rats: the early deposition of collagen. *Toxicology* 156: 129–138, 2001.
228. **Gerbes AL, Vollmar AM, Kiemer AK, Bilzer M.** The guanylate cyclase-coupled natriuretic peptide receptor: a new target for prevention of cold ischemia-reperfusion damage of the rat liver. *Hepatology* 28: 1309–1317, 1998.
229. **Gerwig T, Meissner H, Bilzer M, Kiemer AK, Arnholdt H, Vollmar AM, Gerbes AL.** Atrial natriuretic peptide preconditioning protects against hepatic preservation injury by attenuating necrotic and apoptotic cell death. *J Hepatol* 39: 341–348, 2003.
230. **Ghezzi P, Brines M.** Erythropoietin as an antiapoptotic, tissue-protective cytokine. *Cell Death Differ* 11: S37–44, 2004.

231. **Glanemann M, Eipel C, Nussler AK, Vollmar B, Neuhaus P.** Hyperperfusion syndrome in small-for-size livers. *Eur Surg Res* 37: 335–341, 2005.
232. **Glanemann M, Vollmar B, Nussler AK, Schaefer T, Neuhaus P, Menger MD.** Ischemic preconditioning protects from hepatic ischemia/reperfusion-injury by preservation of microcirculation and mitochondrial redox-state. *J Hepatol* 38: 59–66, 2003.
233. **Glantzounis GK, Yang W, Koti RS, Mikhailidis DP, Seifalian AM, Davidson BR.** Continuous infusion of *N*-acetylcysteine reduces liver warm ischaemia-reperfusion injury. *Br J Surg* 91: 1330–1339, 2004.
234. **Goda N, Suzuki K, Naito M, Takeoka S, Tsuchida E, Ishimura Y, Tamatani T, Suematsu M.** Distribution of heme oxygenase isoforms in rat liver. Topographic basis for carbon monoxide-mediated microvascular relaxation. *J Clin Invest* 101: 604–612, 1998.
235. **Goligorsky MS, Tsukahara H, Magazine H, Andersen TT, Malik AB, Bahou WF.** Termination of endothelin signaling: role of nitric oxide. *J Cell Physiol* 158: 485–494, 1994.
236. **Golling M, Jahnke C, Fonouni H, Ahmadi R, Urbaschek R, Breitkreutz R, Schemmer P, Kraus TW, Gebhard MM, Büchler MW, Mehrabi A.** Distinct effects of surgical denervation on hepatic perfusion, bowel ischemia, and oxidative stress in brain dead and living donor porcine models. *Liver Transpl* 13: 607–617, 2007.
237. **Gores GJ, Herman B, Lemasters JJ.** Plasma membrane bleb formation and rupture: a common feature of hepatocellular injury. *Hepatology* 11: 690–698, 1990.
238. **Goresky CA, Ziegler WH, Bach GG.** Capillary exchange modeling. Barrier-limited and flow-limited distribution. *Circ Res* 27: 739–764, 1970.
239. **Goresky CA.** A linear method for determining liver sinusoidal and extravascular volumes. *Am J Physiol* 204: 626–640, 1963.
240. **Goresky CA.** Uptake in the liver: the nature of the process. *Int Rev Physiol* 21: 65–101, 1980.
241. **Goto M, Kawano S, Yoshihara H, Takei Y, Hijioka T, Fukui H, Matsunaga T, Oshita M, Kashiwagi T, Fusamoto H, Kamada T, Sato N.** Hepatic tissue oxygenation as a predictive indicator of ischemia-reperfusion liver injury. *Hepatology* 15: 432–437, 1992.
242. **Gottlieb GJ, Kubo SH, Alonso DR.** Ultrastructural characterization of the border zone surrounding early experimental myocardial infarcts in dogs. *Am J Pathol* 103: 292–303, 1981.
243. **Gouma DJ, Coelho JC, Schlegel J, Fisher JD, Li YF, Moody FG.** Estimation of hepatic blood flow by hydrogen gas clearance. *Surgery* 99: 439–445, 1986.
244. **Granger DN, Kubes P.** The microcirculation and inflammation: modulation of leukocyte-endothelial cell adhesion. *J Leukoc Biol* 55: 662–675, 1994.
245. **Graupera M, García-Pagán JC, Titos E, Claria J, Massaguer A, Bosch J, Rodés J.** 5-Lipoxygenase inhibition reduces intrahepatic vascular resistance of cirrhotic rat livers: a possible role of cysteinyl-leukotrienes. *Gastroenterology* 122: 387–393, 2002.
246. **Graupera M, March S, Engel P, Rodés J, Bosch J, García-Pagán JC.** Sinusoidal endothelial COX-1-derived prostanoids modulate the hepatic vascular tone of cirrhotic rat livers. *Am J Physiol Gastrointest Liver Physiol* 288: G763–G770, 2005.
247. **Greene AK, Wiener S, Puder M, Yoshida A, Shi B, Perez-Atayde AR, Efstathiou JA, Holmgren L, Adamis AP, Rupnick M, Folkman J, O'Reilly MS.** Endothelial-directed hepatic regeneration after partial hepatectomy. *Ann Surg* 237: 530–535, 2003.
248. **Gregory SH, Barczynski LK, Wing EJ.** Effector function of hepatocytes and Kupffer cells in the resolution of systemic bacterial infections. *J Leukoc Biol* 51: 421–424, 1992.
249. **Gregory SH, Cousens LP, van Rooijen N, Döpp EA, Carlos TM, Wing EJ.** Complementary adhesion molecules promote neutrophil-Kupffer cell interaction and the elimination of bacteria taken up by the liver. *J Immunol* 168: 308–315, 2002.
250. **Gregory SH, Wing EJ.** Neutrophil-Kupffer cell interaction: a critical component of host defenses to systemic bacterial infections. *J Leukoc Biol* 72: 239–248, 2002.
251. **Grewe M, Gausling R, Gyufko K, Hoffmann R, Decker K.** Regulation of the mRNA expression for tumor necrosis factor-α in rat liver macrophages. *J Hepatol* 20: 811–818, 1994.
252. **Groner W, Winkelman JW, Harris AG, Ince C, Bouma GJ, Messmer K, Nadeau RG.** Orthogonal polarization spectral imaging: a new method for study of the microcirculation. *Nat Med* 5: 1209–1212, 1999.
253. **Gruttadauria S, Mandala' L, Miraglia R, Caruso S, Minervini MI, Biondo D, Volpes R, Vizzini G, Marsh JW, Luca A, Marcos A, Gridelli B.** Successful treatment of small-for-size syndrome in adult-to-adult living-related liver transplantation: single center series. *Clin Transplant* 21: 761–766, 2007.
254. **Grutzner U, Keller M, Bach M, Kiemer AK, Meissner H, Bilzer M, Zahler S, Gerbes AL, Vollmar AM.** PI 3-kinase pathway is responsible for antiapoptotic effects of atrial natriuretic peptide in rat liver transplantation. *World J Gastroenterol* 12: 1049–1055, 2006.
255. **Gugenheim J, Crafa F, Dammerota G, Evangelista A, Saint-Paul MC, Cavanel C, Lapalus F, Mouiel J.** Role of non-parenchymal liver cells in ischaemia-reperfusion liver injury: protective effects of muramyl dipeptide. *Transpl Int* 7, *Suppl* 1: S139–S143, 1994.
256. **Guicciardi ME, Miyoshi H, Bronk SF, Gores GJ.** Cathepsin B knockout mice are resistant to tumor necrosis factor-α-mediated hepatocyte apoptosis and liver injury: implications for therapeutic applications. *Am J Pathol* 159: 2045–2054, 2001.
257. **Gujral JS, Bucci TJ, Farhood A, Jaeschke H.** Mechanism of cell death during warm hepatic ischemia-reperfusion in rats: apoptosis or necrosis? *Hepatology* 33: 397–405, 2001.
258. **Gujral JS, Hinson JA, Farhood A, Jaeschke H.** NADPH oxidase-derived oxidant stress is critical for neutrophil cytotoxicity during endotoxemia. *Am J Physiol Gastrointest Liver Physiol* 287: G243–G252, 2004.
259. **Gujral JS, Liu J, Farhood A, Jaeschke H.** Reduced oncotic necrosis in Fas receptor-deficient C57BL/6J-lpr mice after bile duct ligation. *Hepatology* 40: 998–1007, 2004.
260. **Gupta TK, Toruner M, Chung MK, Groszmann RJ.** Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. *Hepatology* 28: 926–931, 1998.
261. **Gupta TK, Toruner M, Groszmann RJ.** Intrahepatic modulation of portal pressure and its role in portal hypertension. Role of nitric oxide. *Digestion* 59: 413–415, 1998.
262. **Gundersen Y, Saetre T, Scholz T, Carlsen H, Kjekshus H, Smiseth OA, Lilleaasen P, Aasen AO.** NO donor sodium nitroprusside reverses the negative effects on hepatic arterial flow induced by endotoxin and the NO synthase inhibitor L-NAME. *Eur Surg Res* 28: 323–332, 1996.
263. **Gur D, Good WF, Herbert DL, Yonas H, Wozney P, Van Thiel DH, Wolfson SK Jr.** Blood flow mapping in the human liver by the xenon/CT method. *J Comput Assist Tomogr* 9: 447–450, 1985.
264. **Gur D, Yonas H, Wolfson SK Jr, Wozney P, Colsher JG, Good WF, Good BC, Herbert DL, Cook EE.** Xenon/CT blood flow mapping of the kidney and liver. *J Comput Assist Tomogr* 8: 1124–1127, 1984.
265. **Gurusamy KS, Kumar Y, Sharma D, Davidson BR.** Ischaemic preconditioning for liver transplantation. *Cochrane Database Syst Rev* 1: CD006315, 2008.
266. **Gutmann FD, Murthy VS, Wojciechowski MT, Wurm RM, Edzards RA.** Transient pulmonary platelet sequestration during endotoxemia in dogs. *Circ Shock* 21: 185–195, 1987.
267. **Ha HC, Snyder SH.** Poly(ADP-ribose) polymerase is a mediator of necrotic cell death by ATP depletion. *Proc Natl Acad Sci USA* 96: 13978–13982, 1999.
268. **Habazettl H, Vollmar B, Christ M, Baier H, Conzen PF, Peter K.** Heterogeneous microvascular coronary vasodilation by adenosine and nitroglycerin in dogs. *J Appl Physiol* 76: 1951–1960, 1994.
269. **Hamada T, Fondevila C, Busuttil RW, Coito AJ.** Metalloproteinase-9 deficiency protects against hepatic ischemia/reperfusion injury. *Hepatology* 47: 186–198, 2008.
270. **Hanawa N, Shinohara M, Saberi B, Gaarde WA, Han D, Kaplowitz N.** Role of JNK translocation to mitochondria leading to inhibition of mitochondria bioenergetics in acetaminophen-induced liver injury. *J Biol Chem* 283: 13565–13577, 2008.
271. **Harada N, Okajima K, Kushimoto S.** Gabexate mesilate, a synthetic protease inhibitor, reduces ischemia/reperfusion injury of rat

liver by inhibiting leukocyte activation. *Crit Care Med* 27: 1958–1964, 1999.
272. **Haratake J, Hisaoka M, Furuta A, Horie A, Yamamoto O.** A scanning electron microscopic study of postnatal development of rat peribiliary plexus. *Hepatology* 14: 1196–1200, 1991.
273. **Hardonk MJ, Dijkhuis FW, Hulstaert CE, Koudstaal J.** Heterogeneity of rat liver and spleen macrophages in gadolinium chloride-induced elimination and repopulation. *J Leukoc Biol* 52: 296–302, 1992.
274. **Harris EN, Kyosseva SV, Weigel JA, Weigel PH.** Expression, processing, and glycosaminoglycan binding activity of the recombinant human 315-kDa hyaluronic acid receptor for endocytosis (HARE). *J Biol Chem* 282: 2785–2797, 2007.
275. **Harty MW, Huddleston HM, Papa EF, Puthawala T, Tracy AP, Ramm GA, Gehring S, Gregory SH, Tracy TF Jr.** Repair after cholestatic liver injury correlates with neutrophil infiltration and matrix metalloproteinase 8 activity. *Surgery* 138: 313–320, 2005.
276. **Harty MW, Papa EF, Huddleston HM, Young E, Nazareth S, Riley CA, Ramm GA, Gregory SH, Tracy TF Jr.** Hepatic macrophages promote the neutrophil-dependent resolution of fibrosis in repairing cholestatic rat livers. *Surgery* 143: 667–678, 2008.
277. **Hasegawa T, Malle E, Farhood A, Jaeschke H.** Generation of hypochlorite-modified proteins by neutrophils during ischemia-reperfusion injury in rat liver: attenuation by ischemic preconditioning. *Am J Physiol Gastrointest Liver Physiol* 289: G760–G767, 2005.
278. **Hashimoto T, Miki K, Imamura H, Sano K, Satou S, Sugawara Y, Kokudo N, Makuuchi M.** Sinusoidal perfusion in the venoocclusive region of living liver donors evaluated by indocyanine green and near-infrared spectroscopy. *Liver Transpl* 14: 872–880, 2008.
279. **Hata K, Yamamoto Y, Nakajima A, Taura K, Yonezawa K, Uchinami H, Ikeda F, Yamaoka Y.** Induction of heme oxygenase-1 and dilatation of hepatic sinusoids by an administration of pyrrolidine dithiocarbamate in rat livers. *J Surg Res* 115: 310–317, 2003.
280. **Haworth R, Platt N, Keshav S, Hughes D, Darley E, Suzuki H, Kurihara Y, Kodama T, Gordon S.** The macrophage scavenger receptor type A is expressed by activated macrophages and protects the host against lethal endotoxic shock. *J Exp Med* 186: 1431–1439, 1997.
281. **Hayashi T, Kishiwada M, Fujii K, Yuasa H, Nishioka J, Ido M, Gabazza EC, Suzuki K.** Lipopolysaccharide-induced decreased protein S expression in liver cells is mediated by MEK/ERK signaling and NFkappaB activation: involvement of membrane-bound CD14 and toll-like receptor-4. *J Thromb Haemost* 4: 1763–1773, 2006.
282. **He SQ, Zhang YH, Venugopal SK, Dicus CW, Perez RV, Ramsamooj R, Nantz MH, Zern MA, Wu J.** Delivery of antioxidative enzyme genes protects against ischemia/reperfusion-induced liver injury in mice. *Liver Transpl* 12: 1869–1879, 2006.
283. **Heiman J, Wallin M, Gustafsson BI, Friman S, Delbro D.** Pharmacological preconditioning of rat liver by up-regulation of heme oxygenase 1. *Transplant Proc* 38: 2705–2707, 2006.
284. **Heizmann O, Loehe F, Volk A, Schauer RJ.** Ischemic preconditioning improves postoperative outcome after liver resections: a randomized controlled study. *Eur J Med Res* 13: 79–86, 2008.
285. **Hellerbrand Wang SC, Tsukamoto H, Brenner DA, Rippe RA.** Expression of intracellular adhesion molecule 1 by activated hepatic stellate cells. *Hepatology* 24: 670–676, 1996.
286. **Henderson JM, Gilmore GT, Mackay GJ, Galloway JR, Dodson TF, Kutner MH.** Hemodynamics during liver transplantation: the interactions between cardiac output and portal venous and hepatic arterial flows. *Hepatology* 16: 715–718, 1992.
287. **Henderson NC, Pollock KJ, Frew J, Mackinnon AC, Flavell RA, Davis RJ, Sethi T, Simpson KJ.** Critical role of c-jun (NH_2) terminal kinase in paracetamol-induced acute liver failure. *Gut* 56: 982–990, 2007.
288. **Henrich 1 D, Lehnert 1 M, Herzog C, Niederlaender S, Relja B, Conzelmann L, Marzi I.** Differential effects of GdCl(3)- or MDP treatment on rat liver microcirculation and gene expression in the hepatic non-parenchymal cell fraction in LPS shock. *Microcirculation* 15: 427–439, 2008.
289. **Henrion J, Schapira M, Luwaert R, Colin L, Delannoy A, Heller FR.** Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. *Medicine* 82: 392–406, 2003.
290. **Henriquez M, Armisén R, Stutzin A, Quest AF.** Cell death by necrosis, a regulated way to go. *Curr Mol Med* 8: 187–206, 2008.
291. **Heymann MA, Payne BD, Hoffman JI, Rudolph AM.** Blood flow measurements with radionuclide-labeled particles. *Prog Cardiovasc Dis* 20: 55–79, 1977.
292. **Hickey KA, Rubanyi G, Paul RJ, Highsmith RF.** Characterization of a coronary vasoconstrictor produced by cultured endothelial cells. *Am J Physiol Cell Physiol* 248: C550–C556, 1985.
293. **Hickey MJ, Granger DN, Kubes P.** Inducible nitric oxide synthase (iNOS) and regulation of leucocyte/endothelial cell interactions: studies in iNOS-deficient mice. *Acta Physiol Scand* 173: 119–126, 2001.
294. **Hill DA, Roth RA.** α-naphthylisothiocyanate causes neutrophils to release factors that are cytotoxic to hepatocytes. *Toxicol Appl Pharmacol* 148: 169–175, 1998.
295. **Hines IN, Harada H, Flores S, Gao B, McCord JM, Grisham MB.** Endothelial nitric oxide synthase protects the post-ischemic liver: potential interactions with superoxide. *Biomed Pharmacother* 59: 183–189, 2005.
296. **Hirata K, Kaneko A, Ogawa K, Hayasaka H, Onoé T.** Effect of endotoxin on rat liver. Analysis of acid phosphatase isozymes in the liver of normal and endotoxin-treated rats. *Lab Invest* 43: 165–171, 1980.
297. **Hisama N, Yamaguchi Y, Okajima K, Uchiba M, Murakami K, Mori K, Yamada S, Ogawa M.** Anticoagulant pretreatment attenuates production of cytokine-induced neutrophil chemoattractant following ischemia-reperfusion of rat liver. *Dig Dis Sci* 41: 1481–1486, 1996.
298. **Ho JS, Buchweitz JP, Roth RA, Ganey PE.** Identification of factors from rat neutrophils responsible for cytotoxicity to isolated hepatocytes. *J Leukoc Biol* 59: 716–724, 1996.
299. **Hochhauser E, Pappo O, Ribakovsky E, Ravid A, Kurtzwald E, Cheporko Y, Lelchuk S, Ben-Ari Z.** Recombinant human erythropoietin attenuates hepatic injury induced by ischemia/reperfusion in an isolated mouse liver model. *Apoptosis* 13: 77–86, 2008.
300. **Hoetzel A, Dolinay T, Schmidt R, Choi AM, Ryter SW.** Carbon monoxide in sepsis. *Antioxid Redox Signal* 9: 2013–2026, 2007.
301. **Hoetzel A, Vagts DA, Loop T, Humar M, Bauer M, Pahl HL, Geiger KK, Pannen BH.** Effect of nitric oxide on shock-induced hepatic heme oxygenase-1 expression in the rat. *Hepatology* 33: 925–937, 2001.
302. **Hoetzel A, Welle A, Schmidt R, Loop T, Humar M, Ryter SW, Geiger KK, Choi AM, Pannen BH.** Nitric oxide-deficiency regulates hepatic heme oxygenase-1. *Nitric Oxide* 18: 61–69, 2008.
303. **Hoffmann PR, deCathelineau AM, Ogden CA, Leverrier Y, Bratton DL, Daleke DL, Ridley AJ, Fadok VA, Henson PM.** Phosphatidylserine (PS) induces PS receptor-mediated macropinocytosis and promotes clearance of apoptotic cells. *J Cell Biol* 155: 649–659, 2001.
304. **Hori K, Saito S, Kubota K.** A novel combretastatin A-4 derivative, AC7700, strongly stanches tumour blood flow and inhibits growth of tumours developing in various tissues and organs. *Br J Cancer* 86: 1604–1614, 2002.
305. **Hoshi R, Murata S, Matsuo R, Myronovych A, Hashimoto I, Ikeda H, Ohkohchi N.** Freeze-dried platelets promote hepatocyte proliferation in mice. *Cryobiology* 55: 255–260, 2007.
306. **Hosoki R, Matsuki N, Kimura H.** The possible role of hydrogen sulfide as an endogenous smooth muscle relaxant in synergy with nitric oxide. *Biochem Biophys Res Commun* 237: 527–531, 1997.
307. **Housset C, Rockey DC, Bissell DM.** Endothelin receptors in rat liver: lipocytes as a contractile target for endothelin 1. *Proc Natl Acad Sci USA* 90: 9266–9270, 1993.
308. **Huet PM, Giroux L, Laurens M, Crenesse D.** Effect of cold ischemia-warm reperfusion on the cirrhotic rat liver. *Liver Transpl* 14: 486–493, 2008.
309. **Huet PM, Nagaoka MR, Desbiens G, Tarrab E, Brault A, Bralet MP, Bilodeau M.** Sinusoidal endothelial cell and hepatocyte death following cold ischemia-warm reperfusion of the rat liver. *Hepatology* 39: 1110–1119, 2004.

310. **Hui Y, Du J, Tang C, Bin G, Jiang H.** Changes in arterial hydrogen sulfide (H_2S) content during septic shock and endotoxin shock in rats. *J Infect* 47: 155–160, 2003.
311. **Hung DY, Siebert GA, Chang P, Whitehouse MW, Fletcher L, Crawford DH, Roberts MS.** Hepatic pharmacokinetics of propranolol in rats with adjuvant-induced systemic inflammation. *Am J Physiol Gastrointest Liver Physiol* 290: G343–G351, 2006.
312. **Hunter DR, Haworth RA, Southard JH.** Relationship between configuration, function, and permeability in calcium-treated mitochondria. *J Biol Chem* 251: 5069–5077, 1976.
313. **Husztik E, Lázár G, Párducz A.** Electron microscopic study of Kupffer-cell phagocytosis blockade induced by gadolinium chloride. *Br J Exp Pathol* 61: 624–630, 1980.
314. **Iannacone M, Sitia G, Isogawa M, Marchese P, Castro MG, Lowenstein PR, Chisari FV, Ruggeri ZM, Guidotti LG.** Platelets mediate cytotoxic T lymphocyte-induced liver damage. *Nat Med* 11: 1167–1169, 2005.
315. **Ikeda T, Yanaga K, Kishikawa K, Kakizoe S, Shimada M, Sugimachi K.** Ischemic injury in liver transplantation: difference in injury sites between warm and cold ischemia in rats. *Hepatology* 16: 454–461, 1992.
316. **Ilonen I, Koivusalo AM, Repo H, Höckerstedt K, Isoniemi H.** Cytokine profiles in acute liver failure treated with albumin dialysis. *Artif Organs* 32: 52–60, 2008.
317. **Ince C, Ashruf JF, Sanderse EA, Pierik EG, Coremans JM, Bruining HA.** in vivo NADH and Pd-porphyrin video fluori-phosphorimetry. *Adv Exp Med Biol* 317: 267–275, 1992.
318. **Ince C.** The microcirculation is the motor of sepsis. *Crit Care* 9, *Suppl* 4: S13–S19, 2005.
319. **Ingalls RR, Monks BG, Savedra R Jr, Christ WJ, Delude RL, Medvedev AE, Espevik T, Golenbock DT.** CD11/CD18 and CD14 share a common lipid A signaling pathway. *J Immunol* 161: 5413–5420, 1998.
320. **Inglott FS, Mathie RT.** Nitric oxide and hepatic ischemia-reperfusion injury. *Hepatogastroenterology* 47: 1722–1725, 2000.
321. **Inohara N, Nuñez G.** The NOD: a signaling module that regulates apoptosis and host defense against pathogens. *Oncogene* 20: 6473–6481, 2001.
322. **Iredale JP.** Models of liver fibrosis: exploring the dynamic nature of inflammation and repair in a solid organ. *J Clin Invest* 117: 539–548, 2007.
323. **Irwin JW, MacDonald J 3rd.** Microscopic observations of the intrahepatic circulation of living guinea pigs. *Anat Rec* 117: 1–15, 1953.
324. **Ishimaru S, Shichiri M, Mineshita S, Hirata Y.** Role of endothelin-1/endothelin receptor system in endotoxic shock rats. *Hypertens Res* 24: 119–126, 2001.
325. **Ito T, Kiuchi T, Yamamoto H, Oike F, Ogura Y, Fujimoto Y, Hirohashi K, Tanaka AK.** Changes in portal venous pressure in the early phase after living donor liver transplantation: pathogenesis and clinical implications. *Transplantation* 75: 1313–1317, 2003.
326. **Ito Y, Abril ER, Bethea NW, McCuskey MK, Cover C, Jaeschke H, McCuskey RS.** Mechanisms and pathophysiological implications of sinusoidal endothelial cell gap formation following treatment with galactosamine/endotoxin in mice. *Am J Physiol Gastrointest Liver Physiol* 291: G211–G218, 2006.
327. **Ito Y, Sørensen KK, Bethea NW, Svistounov D, McCuskey MK, Smedsrød BH, McCuskey RS.** Age-related changes in the hepatic microcirculation in mice. *Exp Gerontol* 42: 789–797, 2007.
328. **Itoh Y, Okanoue T, Morimoto M, Nagao Y, Mori T, Hori N, Kagawa K, Kashima K.** Functional heterogeneity of rat liver macrophages: interleukin-1 secretion and Ia antigen expression in contrast with phagocytic activity. *Liver* 12: 26–33, 1992.
329. **Iwakiri Y, Groszmann RJ.** The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology* 43, *Suppl* 1: S121–S131, 2006.
330. **Iwakiri Y, Groszmann RJ.** Vascular endothelial dysfunction in cirrhosis. *J Hepatol* 46: 927–934, 2007.
331. **Iwasashi H, Suzuki M, Unno M, Utiyama T, Oikawa M, Kondo N, Matsuno S.** Inhibition of heme oxygenase ameliorates sepsis-induced liver dysfunction in rats. *Surg Today* 33: 30–38, 2003.
332. **Jaeschke H, Essani NA, Fisher MA, Vonderfecht SL, Farhood A, Smith CW.** Release of soluble intercellular adhesion molecule 1 into bile and serum in murine endotoxin shock. *Hepatology* 23: 530–536, 1996.
333. **Jaeschke H, Farhood A, Bautista AP, Spolarics Z, Spitzer JJ.** Complement activates Kupffer cells and neutrophils during reperfusion after hepatic ischemia. *Am J Physiol Gastrointest Liver Physiol* 264: G801–G809, 1993.
334. **Jaeschke H, Farhood A, Fisher MA, Smith CW.** Sequestration of neutrophils in the hepatic vasculature during endotoxemia is independent of beta 2 integrins and intercellular adhesion molecule-1. *Shock* 6: 351–356, 1996.
335. **Jaeschke H, Farhood A.** Kupffer cell activation after no-flow ischemia versus hemorrhagic shock. *Free Radic Biol Med* 33: 210–219, 2002.
336. **Jaeschke H, Farhood A.** Neutrophil and Kupffer cell-induced oxidant stress and ischemia-reperfusion injury in rat liver. *Am J Physiol Gastrointest Liver Physiol* 260: G355–G362, 1991.
337. **Jaeschke H, Hasegawa T.** Role of neutrophils in acute inflammatory liver injury. *Liver Int* 26: 912–919, 2006.
338. **Jaeschke H, Ho YS, Fisher MA, Lawson JA, Farhood A.** Glutathione peroxidase-deficient mice are more susceptible to neutrophil-mediated hepatic parenchymal cell injury during endotoxemia: importance of an intracellular oxidant stress. *Hepatology* 29: 443–450, 1999.
339. **Jaeschke H, Kleinwaechter C, Wendel A.** The role of acrolein in allyl alcohol-induced lipid peroxidation and liver cell damage in mice. *Biochem Pharmacol* 36: 51–57, 1987.
340. **Jaeschke H, Lemasters JJ.** Apoptosis versus oncotic necrosis in hepatic ischemia/reperfusion injury. *Gastroenterology* 125: 1246–1257, 2003.
341. **Jaeschke H.** Cellular adhesion molecules: regulation and functional significance in the pathogenesis of liver diseases. *Am J Physiol Gastrointest Liver Physiol* 273: G602–G611, 1997.
342. **Jaeschke H.** Enhanced sinusoidal glutathione efflux during endotoxin-induced oxidant stress in vivo. *Am J Physiol Gastrointest Liver Physiol* 263: G60–G68, 1992.
343. **Jaeschke H.** Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. *Am J Physiol Gastrointest Liver Physiol* 284: G15–G26, 2003.
344. **Jaeschke H.** Reactive oxygen and mechanisms of inflammatory liver injury. *J Gastroenterol Hepatol* 15: 718–724, 2000.
345. **Jaeschke H.** Role of inflammation in the mechanism of acetaminophen-induced hepatotoxicity. *Expert Opin Drug Metab Toxicol* 1: 389–397, 2005.
346. **Jagtap P, Szabó C.** Poly(ADP-ribose) polymerase and the therapeutic effects of its inhibitors. *Nat Rev Drug Discov* 4: 421–440, 2005.
347. **Jahanmehr SA, Hyde K, Geary CG, Cinkotai KI, Maciver JE.** Simple technique for fluorescence staining of blood cells with acridine orange. *J Clin Pathol* 40: 926–929, 1987.
348. **Jang JH, Kang KJ, Kang Y, Lee IS, Graf R, Clavien PA.** Ischemic preconditioning and intermittent clamping confer protection against ischemic injury in the cirrhotic mouse liver. *Liver Transpl* 14: 980–988, 2008.
349. **Jang JH, Moritz W, Graf R, Clavien PA.** Preconditioning with death ligands FasL and TNF-α protects the cirrhotic mouse liver against ischaemic injury. *Gut* 57: 492–499, 2008.
350. **Jelkmann W, Wagner K.** Beneficial and ominous aspects of the pleiotropic action of erythropoietin. *Ann Hematol* 83: 673–686, 2004.
351. **Jelkmann W.** Molecular biology of erythropoietin. *Intern Med* 43: 649–659, 2004.
352. **Jenkins SA, Taylor A, Shimirty SK, Johnson J, Baxter JN, Taylor I, Shields R.** The clearance of xenon-133 following its parenchymal injection: a rapid method for estimating functional liver blood-flow. *Clin Physiol* 5: 433–442, 1985.
353. **Jerome SN, Smith CW, Korthuis RJ.** CD18-dependent adherence reactions play an important role in the development of the no-reflow phenomenon. *Am J Physiol Heart Circ Physiol* 264: H479–H483, 1993.
354. **Ji C, Kaplowitz N.** ER stress: can the liver cope? *J Hepatol* 45: 321–333, 2006.

355. **Jia CJ, Dai CL, Zhang X, Cui K, Xu F, Xu YQ.** Alanyl-glutamine dipeptide inhibits hepatic ischemia-reperfusion injury in rats. *World J Gastroenterol* 12: 1373–1378, 2006.
356. **Jiao LR, El-Desoky AA, Seifalian AM, Habib N, Davidson BR.** Effect of liver blood flow and function on hepatic indocyanine green clearance measured directly in a cirrhotic animal model. *Br J Surg* 87: 568–574, 2000.
357. **Ju C, Reilly TP, Bourdi M, Radonovich MF, Brady JN, George JW, Pohl LR.** Protective role of Kupffer cells in acetaminophen-induced hepatic injury in mice. *Chem Res Toxicol* 15: 1504–1513, 2002.
358. **Jung MY, Park SY, Kim IS.** Stabilin-2 is involved in lymphocyte adhesion to the hepatic sinusoidal endothelium via the interaction with αMbeta2 integrin. *J Leukoc Biol* 82: 1156–1165, 2007.
359. **Kaido T, Yoshikawa A, Seto S, Yamaoka S, Furuyama H, Arii S, Takahashi Y, Imamura M.** Pretreatment with soluble thrombomodulin prevents intrasinusoidal coagulation and liver dysfunction following extensive hepatectomy in cirrhotic rats. *Thromb Haemost* 82: 1302–1306, 1999.
360. **Kaisers U, Busch T, Deja M, Donaubauer B, Falke KJ.** Selective pulmonary vasodilation in acute respiratory distress syndrome. *Crit Care Med* 31: S337–342, 2003.
361. **Kaisers U, Neumann U, Kuhlen R, Sprenger M, Neuhaus P, Rossaint R.** Nitroglycerin versus epoprostenol: effects on hemodynamics, oxygen delivery, and hepatic venous oxygenation after liver transplantation. *Liver Transpl Surg* 2: 455–460, 1996.
362. **Kakimi K, Lane TE, Wieland S, Asensio VC, Campbell IL, Chisari FV, Guidotti LG.** Blocking chemokine responsive to gamma-2/interferon (IFN)-gamma inducible protein and monokine induced by IFN-gamma activity in vivo reduces the pathogenetic but not the antiviral potential of hepatitis B virus-specific cytotoxic T lymphocytes. *J Exp Med* 194: 1755–1766, 2001.
363. **Kakizoe S, Yanaga K, Starzl TE, Demetris AJ.** Evaluation of protocol before transplantation and after reperfusion biopsies from human orthotopic liver allografts: considerations of preservation and early immunological injury. *Hepatology* 11: 932–941, 1990.
364. **Kanduc D, Mittelman A, Serpico R, Sinigaglia E, Sinha AA, Natale C, Santacroce R, Di Corcia MG, Lucchese A, Dini L, Pani P, Santacroce S, Simone S, Bucci R, Farber E.** Cell death: apoptosis versus necrosis (review). *Int J Oncol* 21: 165–170, 2002.
365. **Kaneda K, Ekataksin W, Sogawa M, Matsumura A, Cho A, Kawada N.** Endothelin-1-induced vasoconstriction causes a significant increase in portal pressure of rat liver: localized constrictive effect on the distal segment of preterminal portal venules as revealed by light and electron microscopy and serial reconstruction. *Hepatology* 27: 735–747, 1998.
366. **Kaplowitz N, Than TA, Shinohara M, Ji C.** Endoplasmic reticulum stress and liver injury. *Semin Liver Dis* 27: 367–377, 2007.
367. **Kardon RH, Kessel RG.** Three-dimensional organization of the hepatic microcirculation in the rodent as observed by scanning electron microscopy of corrosion casts. *Gastroenterology* 79: 72–81, 1980.
368. **Kashiwagi T, Kimura K, Suematsu T, Schichiri M, Kamada T, Abe H.** Heterogeneous intrahepatic distribution of blood flow in humans. *Eur J Nucl Med* 6: 545–549, 1981.
369. **Kataoka M, Shimizu H, Mitsuhashi N, Ohtsuka M, Wakabayashi Y, Ito H, Kimura F, Nakagawa K, Yoshidome H, Shimizu Y, Miyazaki M.** Effect of cold-ischemia time on C-X-C chemokine expression and neutrophil accumulation in the graft liver after orthotopic liver transplantation in rats. *Transplantation* 73: 1730–1735, 2002.
370. **Kato A, Gabay C, Okaya T, Lentsch AB.** Specific role of interleukin-1 in hepatic neutrophil recruitment after ischemia/reperfusion. *Am J Pathol* 161: 1797–1803, 2002.
371. **Kato A, Yoshidome H, Edwards MJ, Lentsch AB.** Reduced hepatic ischemia/reperfusion injury by IL-4: potential anti-inflammatory role of STAT6. *Inflamm Res* 49: 275–279, 2000.
372. **Kato Y, Shimazu M, Kondo M, Uchida K, Kumamoto Y, Wakabayashi G, Kitajima M, Suematsu M.** Bilirubin rinse: a simple protectant against the rat liver graft injury mimicking heme oxygenase-1 preconditioning. *Hepatology* 38: 364–373, 2003.
373. **Kato Y, Tanaka J, Koyama K.** Intralobular heterogeneity of oxidative stress and cell death in ischemia-reperfused rat liver. *J Surg Res* 95: 99–106, 2001.
374. **Kawachi S, Hines IN, Laroux FS, Hoffman J, Bharwani S, Gray L, Leffer D, Grisham MB.** Nitric oxide synthase and post-ischemic liver injury. *Biochem Biophys Res Commun* 276: 851–854, 2000.
375. **Keller S, Karaa A, Paxian M, Clemens MG, Zhang JX.** Inhibition of endothelin-1-mediated up-regulation of iNOS by bosentan ameliorates endotoxin-induced liver injury in cirrhosis. *Shock* 25: 306–313, 2006.
376. **Kennedy JA, Lewis H, Clements WD, Kirk SJ, Campbell G, Halliday MI, Rowlands BJ.** Kupffer cell blockade, tumour necrosis factor secretion and survival following endotoxin challenge in experimental biliary obstruction. *Br J Surg* 86: 1410–1414, 1999.
377. **Kerr JF, Wyllie AH, Currie AR.** Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer* 26: 239–257, 1972.
378. **Khandoga A, Biberthaler P, Enders G, Krombach F.** 5-Aminoisoquinolinone, a novel inhibitor of poly(adenosine disphosphate-ribose) polymerase, reduces microvascular liver injury but not mortality rate after hepatic ischemia-reperfusion. *Crit Care Med* 32: 472–477, 2004.
379. **Khandoga A, Biberthaler P, Enders G, Teupser D, Axmann S, Luchting B, Hutter J, Messmer K, Krombach F.** P-selectin mediates platelet-endothelial cell interactions and reperfusion injury in the mouse liver in vivo. *Shock* 18: 529–535, 2002a.
380. **Khandoga A, Biberthaler P, Messmer K, Krombach F.** Platelet-endothelial cell interactions during hepatic ischemia-reperfusion in vivo: a systematic analysis. *Microvasc Res* 65: 71–77, 2003.
381. **Khandoga A, Enders G, Biberthaler P, Krombach F.** Poly-(ADP-ribose) polymerase triggers the microvascular mechanisms of hepatic ischemia-reperfusion injury. *Am J Physiol Gastrointest Liver Physiol* 283: G553–G560, 2002b.
382. **Khandoga A, Hanschen M, Kessler JS, Krombach F.** CD4+ T cells contribute to postischemic liver injury in mice by interacting with sinusoidal endothelium and platelets. *Hepatology* 43: 306–315, 2006.
383. **Khandoga A, Kessler JS, Hanschen M, Khandoga AG, Burggraf D, Reichel C, Hamann GF, Enders G, Krombach F.** Matrix metalloproteinase-9 promotes neutrophil and T cell recruitment and migration in the postischemic liver. *J Leukoc Biol* 79: 1295–1305, 2006.
384. **Khandoga A, Kessler JS, Meissner H, Hanschen M, Corada M, Motoike T, Enders G, Dejana E, Krombach F.** Junctional adhesion molecule-A deficiency increases hepatic ischemia-reperfusion injury despite reduction of neutrophil transendothelial migration. *Blood* 106: 725–733, 2005.
385. **Kiemer AK, Baron A, Gerbes AL, Bilzer M, Vollmar AM.** The atrial natriuretic peptide as a regulator of Kupffer cell functions. *Shock* 17: 365–371, 2002a.
386. **Kiemer AK, Kulhanek-Heinze S, Gerwig T, Gerbes AL, Vollmar AM.** Stimulation of p38 MAPK by hormonal preconditioning with atrial natriuretic peptide. *World J Gastroenterol* 8: 707–711, 2002b.
387. **Kim JS, He L, Qian T, Lemasters JJ.** Role of the mitochondrial permeability transition in apoptotic and necrotic death after ischemia/reperfusion injury to hepatocytes. *Curr Mol Med* 3: 527–535, 2003.
388. **Kim JS, Qian T, Lemasters JJ.** Mitochondrial permeability transition in the switch from necrotic to apoptotic cell death in ischemic rat hepatocytes. *Gastroenterology* 124: 494–503, 2003.
389. **Kim SH, Lee SM.** Expression of hepatic vascular stress genes following ischemia/reperfusion and subsequent endotoxemia. *Arch Pharm Res* 27: 769–775, 2004.
390. **Kim YH, Lee SM.** Role of Kupffer cells in the vasoregulatory gene expression during hepatic ischemia/reperfusion. *Arch Pharm Res* 27: 111–117, 2004.
391. **Kimura K, Nagaki M, Kakimi K, Saio M, Saeki T, Okuda Y, Kuwata K, Moriwaki H.** Critical role of CD44 in hepatotoxin-mediated liver injury. *J Hepatol* 48: 952–961, 2008.

392. **Kirkby NS, Hadoke PW, Bagnall AJ, Webb DJ.** The endothelin system as a therapeutic target in cardiovascular disease: great expectations or bleak house? *Br J Pharmacol* 153: 1105–1119, 2008.
393. **Kiuchi T, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K, Egawa H, Fujita S, Hayashi M, Tanaka K.** Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation* 67: 321–327, 1999.
394. **Klein M, Geoghegan J, Wangemann R, Böckler D, Schmidt K, Scheele J.** Preconditioning of donor livers with prostaglandin I_2 before retrieval decreases hepatocellular ischemia-reperfusion injury. *Transplantation* 67: 1128–1132, 1999.
395. **Klintman D, Hedlund G, Thorlacius H.** Protective effect of Linomide on TNF-α-induced hepatic injury. *J Hepatol* 36: 226–232, 2002.
396. **Klintman D, Li X, Thorlacius H.** Important role of P-selectin for leukocyte recruitment, hepatocellular injury, and apoptosis in endotoxemic mice. *Clin Diagn Lab Immunol* 11: 56–62, 2004.
397. **Knisely MH, Bloch EH, Warner L.** Selective phagocytosis. I. Microscopic observations concerning the regulation of the blood flow through the liver and other organs and the mechanism and rate of phygocytic removal of particles from the blood. *Kgl Danske Videnskab Selskab Biol Skrifter* 4: 1–93, 1948.
398. **Knisely MH, Harding F, DeBacker H.** Hepatic sphincters: brief summary of present-day knowledge. *Science* 125: 1023–1026, 1957.
399. **Knisely MH.** A method of illuminating living structure for microscopic study. *Anat Rec* 64: 499–524, 1936.
400. **Knisely MH.** Microscopic observations of the circulatory conditions in living frog liver lobules. *Anat Rec* 73: 269–270, 1939.
401. **Kobayashi A, Imamura H, Isobe M, Matsuyama Y, Soeda J, Matsunaga K, Kawasaki S.** Mac-1 (CD11b/CD18) and intercellular adhesion molecule-1 in ischemia-reperfusion injury of rat liver. *Am J Physiol Gastrointest Liver Physiol* 281: G577–G585, 2001.
402. **Kobayashi K, Oshima K, Muraoka M, Akao T, Totsuka O, Shimizu H, Sato H, Tanaka K, Konno K, Matsumoto K, Takeyoshi I.** Effect of atrial natriuretic peptide on ischemia-reperfusion injury in a porcine total hepatic vascular exclusion model. *World J Gastroenterol* 13: 3487–3492, 2007.
403. **Koeppel TA, Lehmann TG, Thies JC, Gehrcke R, Gebhard MM, Herfarth C, Otto G, Post S.** Impact of *N*-acetylcysteine on the hepatic microcirculation after orthotopic liver transplantation. *Transplantation* 61: 1397–1402, 1996.
404. **Kohli V, Selzner M, Madden JF, Bentley RC, Clavien PA.** Endothelial cell and hepatocyte deaths occur by apoptosis after ischemia-reperfusion injury in the rat liver. *Transplantation* 67: 1099–1105, 1999.
405. **Kollmar O, Corsten M, Scheuer C, Vollmar B, Schilling MK, Menger MD.** Portal branch ligation induces a hepatic arterial buffer response, microvascular remodeling, normoxygenation, and cell proliferation in portal blood-deprived liver tissue. *Am J Physiol Gastrointest Liver Physiol* 292: G1534–G1542, 2007.
406. **Komatsu H, Koo A, Guth PH.** Leukocyte flow dynamics in the rat liver microcirculation. *Microvasc Res* 40: 1–13, 1990.
407. **Kon K, Kim JS, Jaeschke H, Lemasters JJ.** Mitochondrial permeability transition in acetaminophen-induced necrosis and apoptosis of cultured mouse hepatocytes. *Hepatology* 40: 1170–1179, 2004.
408. **Kondo T, Terajima H, Todoroki T, Hirano T, Ito Y, Usia T, Messmer K.** Prevention of hepatic ischemia-reperfusion injury by SOD-DIVEMA conjugate. *J Surg Res* 85: 26–36, 1999.
409. **Koneru B, Fisher A, He Y, Klein KM, Skurnick J, Wilson DJ, de la Torre AN, Merchant A, Arora R, Samanta AK.** Ischemic preconditioning in deceased donor liver transplantation: a prospective randomized clinical trial of safety and efficacy. *Liver Transpl* 11: 196–202, 2005.
410. **Koneru B, Shareef A, Dikdan G, Desai K, Klein KM, Peng B, Wachsberg RH, de la Torre AN, Debroy M, Fisher A, Wilson DJ, Samanta AK.** The ischemic preconditioning paradox in deceased donor liver transplantation—evidence from a prospective randomized single blind clinical trial. *Am J Transplant* 7: 2788–2796, 2007.
411. **Kono H, Rusyn I, Uesugi T, Yamashina S, Connor HD, Dikalova A, Mason RP, Thurman RG.** Diphenyleneiodonium sulfate, an NADPH oxidase inhibitor, prevents early alcohol-induced liver injury in the rat. *Am J Physiol Gastrointest Liver Physiol* 280: G1005–G1012, 2001a.
412. **Kono H, Uesugi T, Froh M, Rusyn I, Bradford BU, Thurman RG.** ICAM-1 is involved in the mechanism of alcohol-induced liver injury: studies with knockout mice. *Am J Physiol Gastrointest Liver Physiol* 280: G1289–G1295, 2001.
413. **Koo A, Breit G, Intaglietta M.** Leukocyte adherence in hepatic microcirculation in ischemia reperfusion. In: *Microcirculation in Circulatory Disorders*, edited by Manabe H, Zweifach BW, Messmer K. Tokyo: Springer, 1988, p. 205–213.
414. **Koo A, Komatsu H, Tao G, Inoue M, Guth PH, Kaplowitz N.** Contribution of no-reflow phenomenon to hepatic injury after ischemia-reperfusion: evidence for a role for superoxide anion. *Hepatology* 15: 507–514, 1992.
415. **Koo A, Liang IY.** Microvascular filling pattern in rat liver sinusoids during vagal stimulation. *J Physiol* 295: 191–199, 1979.
416. **Kornberg A, Schotte U, Kupper B, Hommann M, Scheele J.** Impact of selective prostaglandin E1 treatment on graft perfusion and function after liver transplantation. *Hepatogastroenterology* 51: 526–531, 2004.
417. **Kotake Y, Yamamoto M, Matsumoto M, Morisaki H, Takeda J.** Sivelestat, a neutrophil elastase inhibitor, attenuates neutrophil priming after hepatoenteric ischemia in rabbits. *Shock* 23: 156–160, 2005.
418. **Koti RS, Seifalian AM, Davidson BR.** Protection of the liver by ischemic preconditioning: a review of mechanisms and clinical applications. *Dig Surg* 20: 383–396, 2003.
419. **Koti RS, Yang W, Glantzounis G, Quaglia A, Davidson BR, Seifalian AM.** Effect of ischaemic preconditioning on hepatic oxygenation, microcirculation and function in a rat model of moderate hepatic steatosis. *Clin Sci* 108: 55–63, 2005.
420. **Koyama S, Sato Y, Hatakeyama K.** The subcutaneous splenic transposition prevents liver injury induced by excessive portal pressure after massive hepatectomy. *Hepatogastroenterology* 50: 37–42, 2003.
421. **Kresse M, Latta M, Künstle G, Riehle HM, van Rooijen N, Hentze H, Tiegs G, Biburger M, Lucas R, Wendel A.** Kupffer cell-expressed membrane-bound TNF mediates melphalan hepatotoxicity via activation of both TNF receptors. *J Immunol* 175: 4076–4083, 2005.
422. **Kristiansen M, Graversen JH, Jacobsen C, Sonne O, Hoffman HJ, Law SK, Moestrup SK.** Identification of the haemoglobin scavenger receptor. *Nature* 409: 198–201, 2001.
423. **Kruger PS.** Statins: the next anti-endotoxin. *Crit Care Resusc* 8: 223–226, 2006.
424. **Krumschnabel G, Manzl C, Berger C, Hofer B.** Oxidative stress, mitochondrial permeability transition, and cell death in Cu-exposed trout hepatocytes. *Toxicol Appl Pharmacol* 209: 62–73, 2005.
425. **Kubes P, Kerfoot SM.** Leukocyte recruitment in the microcirculation: the rolling paradigm revisited. *News Physiol Sci* 16: 76–80, 2001.
426. **Kubes P, Payne D, Woodman RC.** Molecular mechanisms of leukocyte recruitment in postischemic liver microcirculation. *Am J Physiol Gastrointest Liver Physiol* 283: G139–G147, 2002.
427. **Kubo H, Graham L, Doyle NA, Quinlan WM, Hogg JC, Doerschuk CM.** Complement fragment-induced release of neutrophils from bone marrow and sequestration within pulmonary capillaries in rabbits. *Blood* 92: 283–290, 1998.
428. **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* 29: 583–590, 2008.
429. **Kukan M, Vajdová K, Horecký J, Nagyová A, Mehendale HM, Trnovec T.** Effects of blockade of Kupffer cells by gadolinium chloride on hepatobiliary function in cold ischemia-reperfusion injury of rat liver. *Hepatology* 26: 1250–1257, 1997.
430. **Kume M, Banafsche R, Yamamoto Y, Yamaoka Y, Nobiling R, Gebhard MM, Klar E.** Dynamic changes of post-ischemic hepatic microcirculation improved by a pre-treatment of phosphodiesterase-3 inhibitor, milrinone. *J Surg Res* 136: 209–218, 2006.
431. **Kume M, Hayashi T, Yuasa H, Tanaka H, Nishioka J, Ido M, Gabazza EC, Kawarada Y, Suzuki K.** Bacterial lipopolysaccha-

ride decreases thrombomodulin expression in the sinusoidal endothelial cells of rats—a possible mechanism of intrasinusoidal microthrombus formation and liver dysfunction. *J Hepatol* 38: 9–17, 2003.

432. **Kuriyama N, Isaji S, Hamada T, Kishiwada M, Ohsawa I, Usui M, Sakurai H, Tabata M, Suzuki K, Uemoto S.** Activated protein C prevents hepatic ischaemia-reperfusion injury in rats. *Liver Int* 29: 299–307, 2009.
433. **Kurosaka K, Takahashi M, Watanabe N, Kobayashi Y.** Silent cleanup of very early apoptotic cells by macrophages. *J Immunol* 171: 4672–4679, 2003.
434. **Kurosaka K, Watanabe N, Kobayashi Y.** Potentiation by human serum of anti-inflammatory cytokine production by human macrophages in response to apoptotic cells. *J Leukoc Biol* 71: 950–956, 2002.
435. **Kurosaka K, Watanabe N, Kobayashi Y.** Production of proinflammatory cytokines by resident tissue macrophages after phagocytosis of apoptotic cells. *Cell Immunol* 211: 1–7, 2001.
436. **Kurosawa M, Unno T, Aikawa Y, Yoneda M.** Neural regulation of hepatic blood flow in rats: an in vivo study. *Neurosci Lett* 321: 145–148, 2002.
437. **Kwon AH, Qiu Z.** Neutrophil elastase inhibitor prevents endotoxin-induced liver injury following experimental partial hepatectomy. *Br J Surg* 94: 609–619, 2007.
438. **Kyokane T, Norimizu S, Taniai H, Yamaguchi T, Takeoka S, Tsuchida E, Naito M, Nimura Y, Ishimura Y, Suematsu M.** Carbon monoxide from heme catabolism protects against hepatobiliary dysfunction in endotoxin-treated rat liver. *Gastroenterology* 120: 1227–1240, 2001.
439. **Lai IR, Chang KJ, Tsai HW, Chen CF.** Pharmacological preconditioning with simvastatin protects liver from ischemia-reperfusion injury by heme oxygenase-1 induction. *Transplantation* 85: 732–738, 2008.
440. **Laleman W, Omasta A, Van de Casteele M, Zeegers M, Vander Elst I, Van Landeghem L, Severi T, van Pelt J, Roskams T, Fevery J, Nevens F.** A role for asymmetric dimethylarginine in the pathophysiology of portal hypertension in rats with biliary cirrhosis. *Hepatology* 42: 1382–1390, 2005.
441. **Laleman W, Van Landeghem L, Severi T, Vander Elst I, Zeegers M, Bisschops R, Van Pelt J, Roskams T, Cassiman D, Fevery J, Nevens F.** Both Ca^{2+}-dependent and -independent pathways are involved in rat hepatic stellate cell contraction and intrahepatic hyperresponsiveness to methoxamine. *Am J Physiol Gastrointest Liver Physiol* 292: G556–G564, 2007.
442. **Laleman W, Van Landeghem L, Van der Elst I, Zeegers M, Fevery J, Nevens F.** Nitroflurbiprofen, a nitric oxide-releasing cyclooxygenase inhibitor, improves cirrhotic portal hypertension in rats. *Gastroenterology* 132: 709–719, 2007.
443. **Lalor PF, Sun PJ, Weston CJ, Martin-Santos A, Wakelam MJ, Adams DH.** Activation of vascular adhesion protein-1 on liver endothelium results in an NF-kappaB-dependent increase in lymphocyte adhesion. *Hepatology* 45: 465–474, 2007.
444. **Lalor PF, Tuncer C, Weston C, Martin-Santos A, Smith DJ, Adams DH.** Vascular adhesion protein-1 as a potential therapeutic target in liver disease. *Ann NY Acad Sci* 1110: 485–496, 2007.
445. **Lam PH, Mathie RT, Harper AM, Blumgart LH.** A simple technique of measuring liver blood flow—intrasplenic injection of ^{133}Xenon. *Acta Chir Scand* 145: 95–100, 1979.
446. **Lang PA, Contaldo C, Georgiev P, El-Badry AM, Recher M, Kurrer M, Cervantes-Barragan L, Ludewig B, Calzascia T, Bolinger B, Merkler D, Odermatt B, Bader M, Graf R, Clavien PA, Hegazy AN, Löhning M, Harris NL, Ohashi PS, Hengartner H, Zinkernagel RM, Lang KS.** Aggravation of viral hepatitis by platelet-derived serotonin. *Nat Med* 14: 756–761, 2008.
447. **Langdale LA, Hoagland V, Benz W, Riehle KJ, Campbell JS, Liggitt DH, Fausto N.** Suppressor of cytokine signaling expression with increasing severity of murine hepatic ischemia-reperfusion injury. *J Hepatol* 49: 198–206, 2008.
448. **Langer HF, Gawaz M.** Platelets in regenerative medicine. *Basic Res Cardiol* 103: 299–307, 2008.
449. **Langer S, Harris AG, Biberthaler P, von Dobschuetz E, Messmer K.** Orthogonal polarization spectral imaging as a tool for the assessment of hepatic microcirculation: a validation study. *Transplantation* 71: 1249–1256, 2001.
450. **Lanteri R, Acquaviva R, Di Giacomo C, Caltabiano R, Li Destri G, Vanella L, Santangelo M, Lanzafame S, Di Cataldo A.** Heme oxygenase 1 expression in postischemic reperfusion liver damage: effect of L-arginine. *Microsurgery* 26: 25–32, 2006.
451. **Lappas CM, Day YJ, Marshall MA, Engelhard VH, Linden J.** Adenosine A_{2A} receptor activation reduces hepatic ischemia reperfusion injury by inhibiting CD1d-dependent NKT cell activation. *J Exp Med* 203: 2639–2648, 2006.
452. **Larsen E, Palabrica T, Sajer S, Gilbert GE, Wagner DD, Furie BC, Furie B.** PADGEM-dependent adhesion of platelets to monocytes and neutrophils is mediated by a lineage-specific carbohydrate, LNF III (CD15). *Cell* 63: 467–474, 1990.
453. **Laschke MW, Dold S, Menger MD, Jeppsson B, Thorlacius H.** Platelet-dependent accumulation of leukocytes in sinusoids mediates hepatocellular damage in bile duct ligation-induced cholestasis. *Br J Pharmacol* 153: 148–156, 2008.
454. **Laschke MW, Menger MD, Wang Y, Lindell G, Jeppsson B, Thorlacius H.** Sepsis-associated cholestasis is critically dependent on P-selectin-dependent leukocyte recruitment in mice. *Am J Physiol Gastrointest Liver Physiol* 292: G1396–G1402, 2007.
455. **Laskin DL, Gardner CR, Price VF, Jollow DJ.** Modulation of macrophage functioning abrogates the acute hepatotoxicity of acetaminophen. *Hepatology* 21: 1045–1050, 1995.
456. **Latchoumycandane C, Goh CW, Ong MM, Boelsterli UA.** Mitochondrial protection by the JNK inhibitor leflunomide rescues mice from acetaminophen-induced liver injury. *Hepatology* 45: 412–421, 2007.
457. **Laurens M, Scozzari G, Patrono D, St-Paul MC, Gugenheim J, Huet PM, Crenesse D.** Warm ischemia-reperfusion injury is decreased by tacrolimus in steatotic rat liver. *Liver Transpl* 12: 217–225, 2006.
458. **Lautt WW, Legare DJ, d'Almeida MS.** Adenosine as putative regulator of hepatic arterial flow (the buffer response). *Am J Physiol Heart Circ Physiol* 248: H331–H338, 1985.
459. **Lautt WW, Legare DJ, Ezzat WR.** Quantitation of the hepatic arterial buffer response to graded changes in portal blood flow. *Gastroenterology* 98: 1024–1028, 1990.
460. **Lautt WW, Legare DJ.** The use of 8-phenyltheophylline as a competitive antagonist of adenosine and inhibitor of the intrinsic regulatory mechanism of the hepatic artery. *Can J Physiol Pharmacol* 63: 717–722, 1985.
461. **Lautt WW.** Control of hepatic arterial blood flow: independence from liver metabolic activity. *Am J Physiol Heart Circ Physiol* 239: H559–H564, 1980.
462. **Lautt WW.** Minireview. The hepatic artery: subservient to hepatic metabolism or guardian of normal hepatic clearance rates of humoral substances. *Gen Pharmacol* 8: 73–78, 1977.
463. **Lautt WW.** Regulatory processes interacting to maintain hepatic blood flow constancy: vascular compliance, hepatic arterial buffer response, hepatorenal reflex, liver regeneration, and escape from vasoconstriction. *Hepatol Res* 37: 891–903, 2007.
464. **Lautt WW.** Relationship between hepatic blood flow and overall metabolism: the hepatic arterial buffer response. *Federation Proc* 42: 1662–1666, 1983.
465. **Lautt WW.** Role and control of the hepatic artery. In: *Hepatic Circulation in Health and Disease*, edited by Lautt WW. New York: Raven, 1981, p. 203–226.
466. **Lawlor DK, Brock RW, Harris KA, Potter RF.** Cytokines contribute to early hepatic parenchymal injury and microvascular dysfunction after bilateral hindlimb ischemia. *J Vasc Surg* 30: 533–541, 1999.
467. **Lawson JA, Fisher MA, Simmons CA, Farhood A, Jaeschke H.** Parenchymal cell apoptosis as a signal for sinusoidal sequestration and transendothelial migration of neutrophils in murine models of endotoxin and Fas-antibody-induced liver injury. *Hepatology* 28: 761–767, 1998.
468. **Lázár G Jr, Paszt A, Kaszaki J, Duda E, Szakács J, Tiszlavicz L, Boros M, Balogh A, Lázár G.** Kupffer cell phagocytosis blockade decreases morbidity in endotoxemic rats with obstructive jaundice. *Inflamm Res* 51: 511–518, 2002.

469. **Le Couteur DG, Cogger VC, McCuskey RS, Cabo R DE, Smedsrød B, Sorensen KK, Warren A, Fraser R.** Age-related changes in the liver sinusoidal endothelium: a mechanism for dyslipidemia. *Ann NY Acad Sci* 1114: 79–87, 2007.
470. **Le Couteur DG, Fraser R, Cogger VC, McLean AJ.** Hepatic pseudocapillarisation and atherosclerosis in ageing. *Lancet* 359: 1612–1615, 2002.
471. **Le Couteur DG, Warren A, Cogger VC, Smedsrød B, Sørensen KK, De Cabo R, Fraser R, McCuskey RS.** Old age and the hepatic sinusoid. *Anat Rec* 291: 672–683, 2008.
472. **Le Minh K, Klemm K, Abshagen K, Eipel C, Menger MD, Vollmar B.** Attenuation of inflammation and apoptosis by pre- and posttreatment of darbepoetin-α in acute liver failure of mice. *Am J Pathol* 170: 1954–1963, 2007.
473. **Legare DJ, Lautt WW.** Hepatic venous resistance site in the dog: localization and validation of intrahepatic pressure measurements. *Can J Physiol Pharmacol* 65: 352–359, 1987.
474. **Lehr HA, Vollmar B, Vajkoczy P, Menger MD.** Intravital fluorescence microscopy for the study of leukocyte interaction with platelets and endothelial cells. *Methods Enzymol* 300: 462–481, 1999.
475. **Lemasters JJ, Qian T, He L, Kim JS, Elmore SP, Cascio WE, Brenner DA.** Role of mitochondrial inner membrane permeabilization in necrotic cell death, apoptosis, and autophagy. *Antioxid Redox Signal* 4: 769–781, 2002.
476. **Lemasters JJV.** Necrapoptosis and the mitochondrial permeability transition: shared pathways to necrosis and apoptosis. *Am J Physiol Gastrointest Liver Physiol* 276: G1–G6, 1999.
477. **Lentsch AB, Yoshidome H, Cheadle WG, Miller FN, Edwards MJ.** Chemokine involvement in hepatic ischemia/reperfusion injury in mice: roles for macrophage inflammatory protein-2 and KC. *Hepatology* 27: 1172–1177, 1998.
478. **León Fernández OS, Ajamieh HH, Berlanga J, Menéndez S, Viebahn-Hánsler R, Re L, Carmona AM.** Ozone oxidative preconditioning is mediated by A1 adenosine receptors in a rat model of liver ischemia/reperfusion. *Transpl Int* 21: 39–48, 2008.
479. **Lesurtel M, Graf R, Aleil B, Walther DJ, Tian Y, Jochum W, Gachet C, Bader M, Clavien PA.** Platelet-derived serotonin mediates liver regeneration. *Science* 312: 104–107, 2006.
480. **Li L, Bhatia M, Zhu YZ, Zhu YC, Ramnath RD, Wang ZJ, Anuar FB, Whiteman M, Salto-Tellez M, Moore PK.** Hydrogen sulfide is a novel mediator of lipopolysaccharide-induced inflammation in the mouse. *FASEB J* 19: 1196–1198, 2005.
481. **Li SQ, Liang LJ, Huang JF, Li Z.** Ischemic preconditioning protects liver from hepatectomy under hepatic inflow occlusion for hepatocellular carcinoma patients with cirrhosis. *World J Gastroenterol* 10: 2580–2584, 2004.
482. **Li X, Klintman D, Liu Q, Sato T, Jeppsson B, Thorlacius H.** Critical role of CXC chemokines in endotoxemic liver injury in mice. *J Leukoc Biol* 75: 443–452, 2004.
483. **Li X, Klintman D, Sato T, Hedlund G, Schramm R, Jeppsson B, Thorlacius H.** Interleukin-10 mediates the protective effect of Linomide by reducing CXC chemokine production in endotoxin-induced liver injury. *Br J Pharmacol* 143: 865–871, 2004.
484. **Li XK, Matin AF, Suzuki H, Uno T, Yamaguchi T, Harada Y.** Effect of protease inhibitor on ischemia/reperfusion injury of the rat liver. *Transplantation* 56: 1331–1336, 1993.
485. **Li Y, Muruve DA, Collins RG, Lee SS, Kubes P.** The role of selectins and integrins in adenovirus vector-induced neutrophil recruitment to the liver. *Eur J Immunol* 32: 3443–3452, 2002.
486. **Liang R, Nickkholgh A, Hoffmann K, Kern M, Schneider H, Sobirey M, Zorn M, Büchler MW, Schemmer P.** Melatonin protects from hepatic reperfusion injury through inhibition of IKK and JNK pathways and modification of cell proliferation. *J Pineal Res* 46: 8–14, 2009.
487. **Liang TB, Man K, Kin-Wah Lee T, Hong-Teng Tsui S, Lo CM, Xu X, Zheng SS, Fan ST, Wong J.** Distinct intragraft response pattern in relation to graft size in liver transplantation. *Transplantation* 75: 673–678, 2003.
488. **Lima A, Bakker J.** Noninvasive monitoring of peripheral perfusion. *Intensive Care Med* 31: 1316–1326, 2005.
489. **Lin H, McGrath JJ.** Vasodilating effects of carbon monoxide. *Drug Chem Toxicol* 11: 371–385, 1988.
490. **Lin HI, Wang D, Leu FJ, Chen CF, Chen HI.** Ischemia and reperfusion of liver induces eNOS and iNOS expression: effects of a NO donor and NOS inhibitor. *Chin J Physiol* 47: 121–127, 2004.
491. **Lindnér P, Tölli J, Naredi P, Oman M, Hafström L.** Blood flow in liver tumors–effects of vasoactive drugs estimated with xenon (^{133}Xe) clearance. *Hepatogastroenterology* 51: 781–786, 2004.
492. **Linehan SA, Martínez-Pomares L, Gordon S.** Macrophage lectins in host defence. *Microbes Infect* 2: 279–288, 2000.
493. **Liu J, Li C, Waalkes MP, Clark J, Myers P, Saavedra JE, Keefer LK.** The nitric oxide donor, V-PYRRO/NO, protects against acetaminophen-induced hepatotoxicity in mice. *Hepatology* 37: 324–333, 2003.
494. **Liu J, Saavedra JE, Lu T, Song JG, Clark J, Waalkes MP, Keefer LK.** O_2-Vinyl 1-(pyrrolidin-1-yl)diazen-1-ium-1,2-diolate protection against D-galactosamine/endotoxin-induced hepatotoxicity in mice: genomic analysis using microarrays. *J Pharmacol Exp Ther* 300: 18–25, 2002.
495. **Liu L, Kubes P.** Molecular mechanisms of leukocyte recruitment: organ-specific mechanisms of action. *Thromb Haemost* 89: 213–220, 2003.
496. **Liu LM, Dubick MA.** Hemorrhagic shock-induced vascular hyporeactivity in the rat: relationship to gene expression of nitric oxide synthase, endothelin-1, and select cytokines in corresponding organs. *J Surg Res* 125: 128–136, 2005.
497. **Liu P, Vonderfecht SL, Fisher MA, McGuire GM, Jaeschke H.** Priming of phagocytes for reactive oxygen production during hepatic ischemia-reperfusion potentiates the susceptibility for endotoxin-induced liver injury. *Circ Shock* 43: 9–17, 1994.
498. **Liu S, Premont RT, Kontos CD, Zhu S, Rockey DC.** A crucial role for GRK2 in regulation of endothelial cell nitric oxide synthase function in portal hypertension. *Nat Med* 11: 952–958, 2005.
499. **Liu ZX, Han D, Gunawan B, Kaplowitz N.** Neutrophil depletion protects against murine acetaminophen hepatotoxicity. *Hepatology* 43: 1220–1230, 2006.
500. **Lo CM, Fan ST, Liu CL, Chan JK, Lam BK, Lau GK, Wei WI, Wong J.** Minimum graft size for successful living donor liver transplantation. *Transplantation* 68: 1112–1116, 1999.
501. **Lo CM, Liu CL, Fan ST.** Portal hyperperfusion injury as the cause of primary nonfunction in a small-for-size liver graft-successful treatment with splenic artery ligation. *Liver Transpl* 9: 626–628, 2003.
502. **Loï C, Kana G, Blanc MC, Genthon C, Cynober L.** Evaluation of a glycine-rich amino acid solution for parenteral nutrition in endotoxemic rats. *Crit Care Med* 33: 2344–2349, 2005.
503. **Louis H, Van Laethem JL, Wu W, Quertinmont E, Degraef C, Van den Berg K, Demols A, Goldman M, Le Moine O, Geerts A, Devière J.** Interleukin-10 controls neutrophilic infiltration, hepatocyte proliferation, and liver fibrosis induced by carbon tetrachloride in mice. *Hepatology* 28: 1607–1615, 1998.
504. **Loureiro-Silva MR, Cadelina GW, Groszmann RJ.** Deficit in nitric oxide production in cirrhotic rat livers is located in the sinusoidal and postsinusoidal areas. *Am J Physiol Gastrointest Liver Physiol* 284: G567–G574, 2003.
505. **Luster AD.** Chemokines—chemotactic cytokines that mediate inflammation. *N Engl J Med* 338: 436–445, 1998.
506. **Luster MI, Germolec DR, Yoshida T, Kayama F, Thompson M.** Endotoxin-induced cytokine gene expression and excretion in the liver. *Hepatology* 19: 480–488, 1994.
507. **Mackenzie RJ, Leiberman DP, Mathie RT, Rice GC, Harper AM, Blumgart LH.** Liver blood flow measurement the interpretation of xenon133 clearance curves. *Acta Chir Scand* 142: 519–525, 1976.
508. **MacPhee PJ, Schmidt EE, Groom AC.** Evidence for Kupffer cell migration along liver sinusoids, from high-resolution in vivo microscopy. *Am J Physiol Gastrointest Liver Physiol* 263: G17–G23, 1992.
509. **Madoff DC, Hicks ME, Abdalla EK, Morris JS, Vauthey JN.** Portal vein embolization with polyvinyl alcohol particles and coils in preparation for major liver resection for hepatobiliary malignancy: safety and effectiveness—study in 26 patients. *Radiology* 227: 251–260, 2003.
510. **Maher JJ, Scott MK, Saito JM, Burton MC.** Adenovirus-mediated expression of cytokine-induced neutrophil chemoattractant in

rat liver induces a neutrophilic hepatitis. *Hepatology* 25: 624–630, 1997.
511. **Maines MD.** The heme oxygenase system: update 2005. *Antioxid Redox Signal* 7: 1761–1766, 2005.
512. **Majno G, Joris I.** Apoptosis, oncosis and necrosis. An overview of cell death. *Am J Pathol* 146: 3–15, 1995.
513. **Makino H, Shimizu H, Ito H, Kimura F, Ambiru S, Togawa A, Ohtsuka M, Yoshidome H, Kato A, Yoshitomi H, Sawada S, Miyazaki M.** Changes in growth factor and cytokine expression in biliary obstructed rat liver and their relationship with delayed liver regeneration after partial hepatectomy. *World J Gastroenterol* 12: 2053–2059, 2006.
514. **Maksan SM, Maksan MO, Gebhard MM, Herfarth C, Klar E.** Reduction of hepatic reperfusion injury by antithrombin III and aprotinin. *Transpl Int* 13, *Suppl* 1: S562–S564, 2000.
515. **Maksan SM, Ulger Z, Gebhard MM, Schmidt J.** Impact of antithrombin III on hepatic and intestinal microcirculation in experimental liver cirrhosis and bowel inflammation: an in vivo analysis. *World J Gastroenterol* 11: 4997–5001, 2005.
516. **Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunvén P, Yamazaki S, Hasegawa H, Ozaki H.** Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 107: 521–527, 1990.
517. **Malarkey DE, Johnson K, Ryan L, Boorman G, Maronpot RR.** New insights into functional aspects of liver morphology. *Toxicol Pathol* 33: 27–34, 2005.
518. **Man K, Fan ST, Lo CM, Liu CL, Fung PC, Liang TB, Lee TK, Tsui SH, Ng IO, Zhang ZW, Wong J.** Graft injury in relation to graft size in right lobe live donor liver transplantation: a study of hepatic sinusoidal injury in correlation with portal hemodynamics and intragraft gene expression. *Ann Surg* 237: 256–264, 2003.
519. **March S, Garcia-Pagán JC, Massaguer A, Pizcueta P, Panés J, Engel P, Bosch J.** P-selectin mediates leukocyte rolling in concanavalin-A-induced hepatitis. *Liver Int* 25: 1053–1060, 2005.
520. **Mariggiò MA, Pettini F, Fumarulo R.** Sulfide influence on polymorphonuclear functions: a possible role for Ca^{2+} involvement. *Immunopharmacol Immunotoxicol* 19: 393–404, 1997.
521. **Martelius T, Salmi M, Wu H, Bruggeman C, Höckerstedt K, Jalkanen S, Lautenschlager I.** Induction of vascular adhesion protein-1 during liver allograft rejection and concomitant cytomegalovirus infection in rats. *Am J Pathol* 157: 1229–1237, 2000.
522. **Marubayashi S, Dohi K, Ochi K, Kawasaki T.** Role of free radicals in ischemic rat liver cell injury: prevention of damage by α-tocopherol administration. *Surgery* 99: 184–192, 1986.
523. **Marubayashi S, Takenaka M, Dohi K, Ezaki H, Kawasaki T.** Adenine nucleotide metabolism during hepatic ischemia and subsequent blood reflow periods and its relation to organ viability. *Transplantation* 30: 294–296, 1980.
524. **Marzi I, Knee J, Bühren V, Menger M, Trentz O.** Reduction by superoxide dismutase of leukocyte-endothelial adherence after liver transplantation. *Surgery* 111: 90–97, 1992.
525. **Marzi I, Zhong Z, Lemasters JJ, Thurman RG.** Evidence that graft survival is not related to parenchymal cell viability in rat liver transplantation. The importance of nonparenchymal cells. *Transplantation* 48: 463–468, 1989.
526. **Massberg S, Enders G, Leiderer R, Eisenmenger S, Vestweber D, Krombach F, Messmer K.** Platelet-endothelial cell interactions during ischemia/reperfusion: the role of P-selectin. *Blood* 92: 507–515, 1998.
527. **Matejovic M, Krouzecky A, Martinkova V, Rokyta R Jr, Kralova H, Treska V, Radermacher P, Novak I.** Selective inducible nitric oxide synthase inhibition during long-term hyperdynamic porcine bacteremia. *Shock* 21: 458–465, 2004.
528. **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* 29: 112–118, 2008a.
529. **Mathes AM, Kubulus D, Weiler J, Bentley A, Waibel L, Wolf B, Bauer I, Rensing H.** Melatonin receptors mediate improvements of liver function but not of hepatic perfusion and integrity after hemorrhagic shock in rats. *Crit Care Med* 36: 24–29, 2008b.
530. **Mathews WR, Guido DM, Fisher MA, Jaeschke H.** Lipid peroxidation as molecular mechanism of liver cell injury during reperfusion after ischemia. *Free Radic Biol Med* 16: 763–770, 1994.
531. **Mathie RT, Lam PHM, Harper AM, Blumgart LH.** The hepatic arterial blood flow response to portal vein occlusion in the dog. The effect of hepatic denervation. *Pflügers Arch* 386: 77–83, 1980.
532. **Mathie RT.** Hepatic blood flow measurement with inert gas clearance. *J Surg Res* 41: 92–110, 1986.
533. **Matsumoto T, Kawakami M.** The unit-concept of hepatic parenchyma—a re-examination based on angioarchitectural studies. *Acta Pathol Jpn* 32, *Suppl* 2: 285–314, 1982.
534. **Matsuo R, Ohkohchi N, Murata S, Ikeda O, Nakano Y, Watanabe M, Hisakura K, Myronovych A, Kubota T, Narimatsu H, Ozaki M.** Platelets strongly induce hepatocyte proliferation with IGF-1 and HGF in vitro. *J Surg Res* 145: 279–286, 2008.
535. **Matsura T, Nishida T, Togawa A, Horie S, Kusumoto C, Ohata S, Nakada J, Ishibe Y, Yamada K, Ohta Y.** Mechanisms of protection by melatonin against acetaminophen-induced liver injury in mice. *J Pineal Res* 41: 211–219, 2006.
536. **Matsuura K, Ishida T, Setoguchi M, Higuchi Y, Akizuki S, Yamamoto S.** Upregulation of mouse CD14 expression in Kupffer cells by lipopolysaccharide. *J Exp Med* 179: 1671–1676, 1994.
537. **McCarter SD, Akyea TG, Lu X, Bihari A, Scott JR, Badhwar A, Dungey AA, Harris KA, Feng Q, Potter RF.** Endogenous heme oxygenase induction is a critical mechanism attenuating apoptosis and restoring microvascular perfusion following limb ischemia/reperfusion. *Surgery* 136: 67–75, 2004a.
538. **McCarter SD, Badhwar A, Scott JR, Akyea TG, Bihari A, Dungey AA, Harris KA, Potter RF.** Remote liver injury is attenuated by adenovirus-mediated gene transfer of heme oxygenase-1 during the systemic inflammatory response syndrome. *Microcirculation* 11: 587–595, 2004b.
539. **McCuskey RS, Urbaschek R, McCuskey PA, Urbaschek B.** In vivo microscopic studies of the responses of the liver to endotoxin. *Klin Wochenschr* 60: 749–751, 1982.
540. **McCuskey RS.** Hepatic microvascular responses to endotoxemia and sepsis. *Prog Appl Microcirc* 19: 76–84, 1993.
541. **McCuskey RS.** Morphological mechanisms for regulating blood flow through hepatic sinusoids. *Liver* 20: 3–7, 2000.
542. **McDonald B, McAvoy EF, Lam F, Gill V, de la Motte C, Savani RC, Kubes P.** Interaction of CD44 and hyaluronan is the dominant mechanism for neutrophil sequestration in inflamed liver sinusoids. *J Exp Med* 205: 915–927, 2008.
543. **McKee Olds J, Stafford ES.** On the manner of anastomosis of the hepatic and portal circulations. *Bull Johns Hopkins Hosp* 47: 176–185, 1930.
544. **McKeown CM, Edwards V, Phillips MJ, Harvey PR, Petrunka CN, Strasberg SM.** Sinusoidal lining cell damage: the critical injury in cold preservation of liver allografts in the rat. *Transplantation* 46: 178–191, 1988.
545. **McNab G, Reeves JL, Salmi M, Hubscher S, Jalkanen S, Adams DH.** Vascular adhesion protein 1 mediates binding of T cells to human hepatic endothelium. *Gastroenterology* 110: 522–528, 1996.
546. **Meguro M, Katsuramaki T, Kimura H, Isobe M, Nagayama M, Kukita K, Nui A, Hirata K.** Apoptosis and necrosis after warm ischemia-reperfusion injury of the pig liver and their inhibition by ONO-1714. *Transplantation* 75: 703–710, 2003.
547. **Mehendale HM, Limaye PB.** Calpain: a death protein that mediates progression of liver injury. *Trends Pharmacol Sci* 26: 232–236, 2005.
548. **Mehrabi A, Golling M, Jahnke C, Zapletal CH, Busch CH, Schemmer P, Gebhard MM, Büchler MW, Klar E, Kraus T.** Characterization of hepatic parenchymous perfusion heterogeneity and regional flow kinetics after porcine liver transplantation. *Microvasc Res* 65: 78–87, 2003.
549. **Meier P, Zierler KL.** On the theory of the indicator-dilution method for measurement of blood flow and volume. *J Appl Physiol* 6: 731–744, 1954.
550. **Menger MD, Lehr HA.** Scope and perspectives of intravital microscopy–bridge over from in vitro to in vivo. *Immunol Today* 14: 519–522, 1993.

551. **Menger MD, Marzi I, Messmer K.** In vivo fluorescence microscopy for quantitative analysis of the hepatic microcirculation in hamsters and rats. *Eur Surg Res* 23: 158–169, 1991.
552. **Menger MD, Richter S, Yamauchi J, Vollmar B.** Role of microcirculation in hepatic ischemia/reperfusion injury. *Hepatogastroenterology* 46, *Suppl* 2: 1452–1457, 1999.
553. **Menger MD, Richter S, Yamauchi JI, Vollmar B.** Intravital microscopy for the study of the microcirculation in various disease states. *Ann Acad Med Singapore* 28: 542–556, 1999.
554. **Menger MD, Vollmar B.** Adhesion molecules as determinants of disease: from molecular biology to surgical research. *Br J Surg* 83: 588–601, 1996.
555. **Menger MD, Vollmar B.** Pathomechanisms of ischemia-reperfusion injury as the basis for novel preventive strategies: is it time for the introduction of pleiotropic compounds? *Transplant Proc* 39: 485–488, 2007.
556. **Meren H, Varin F, Ruwart M, Thurman RG.** Effect of 16,16-dimethyl prostaglandin E_2 on oxygen uptake and microcirculation in the perfused rat liver. *Hepatology* 6: 917–921, 1986.
557. **Michael SL, Pumford NR, Mayeux PR, Niesman MR, Hinson JA.** Pretreatment of mice with macrophage inactivators decreases acetaminophen hepatotoxicity and the formation of reactive oxygen and nitrogen species. *Hepatology* 30: 186–195, 1999.
558. **Mikami K, Otaka M, Goto T, Miura K, Ohshima S, Yoneyama K, Lin JG, Watanabe D, Segawa D, Kataoka E, Odashima M, Watanabe S.** Induction of a 72-kDa heat shock protein and protection against lipopolysaccharide-induced liver injury in cirrhotic rats. *J Gastroenterol Hepatol* 19: 884–890, 2004.
559. **Minor T, Manekeller S, Sioutis M, Dombrowski F.** Endoplasmic and vascular surface activation during organ preservation: refining upon the benefits of machine perfusion. *Am J Transplant* 6: 1355–1366, 2006.
560. **Mitsuoka H, Suzuki S, Sakaguchi T, Baba S, Miwa M, Konno H, Nakamura S.** Contribution of endothelin-1 to microcirculatory impairment in total hepatic ischemia and reperfusion injury. *Transplantation* 67: 514–520, 1999.
561. **Mitsuta H, Ohdan H, Fudaba Y, Irei T, Tashiro H, Itamoto T, Asahara T.** Near-infrared spectroscopic analysis of hemodynamics and mitochondrial redox in right lobe grafts in living-donor liver transplantation. *Am J Transplant* 6: 797–805, 2006.
562. **Mitsutomi N, Akashi C, Odagiri J, Matsumura Y.** Effects of endogenous and exogenous nitric oxide on endothelin-1 production in cultured vascular endothelial cells. *Eur J Pharmacol* 364: 65–73, 1999.
563. **Mittal MK, Gupta TK, Lee FY, Sieber CC, Groszmann RJ.** Nitric oxide modulates hepatic vascular tone in normal rat liver. *Am J Physiol Gastrointest Liver Physiol* 267: G416–G422, 1994.
564. **Miyagawa Y, Imamura H, Soeda J, Matsunaga K, Mochida S, Fujiwara K, Matsuyama Y, Kawasaki S.** Fate of hepatocyte and sinusoidal lining cell function and kinetics after extended cold preservation and transplantation of the rat liver. *Liver Transpl* 8: 370–381, 2002.
565. **Mizuoka H, Shikata N, Yang J, Takasu M, Inoue K, Tsubura A.** Biphasic effect of colchicine on acute liver injury induced by carbon tetrachloride or by dimethylnitrosamine in mice. *J Hepatol* 31: 825–833, 1999.
566. **Mojena M, Hortelano S, Castrillo A, Diaz-Guerra MJ, Garcia-Barchino MJ, Saez GT, Bosca L.** Protection by nitric oxide against liver inflammatory injury in animals carrying a nitric oxide synthase-2 transgene. *FASEB J* 15: 583–585, 2001.
567. **Mookerjee RP, Malaki M, Davies NA, Hodges SJ, Dalton RN, Turner C, Sen S, Williams R, Leiper J, Vallance P, Jalan R.** Increasing dimethylarginine levels are associated with adverse clinical outcome in severe alcoholic hepatitis. *Hepatology* 45: 62–71, 2007.
568. **Morales-Ruiz M, Cejudo-Martín P, Fernández-Varo G, Tugues S, Ros J, Angeli P, Rivera F, Arroyo V, Rodés J, Sessa WC, Jiménez W.** Transduction of the liver with activated Akt normalizes portal pressure in cirrhotic rats. *Gastroenterology* 125: 522–531, 2003.
569. **Morita T, Kourembanas S.** Endothelial cell expression of vasoconstrictors and growth factors is regulated by smooth muscle cell-derived carbon monoxide. *J Clin Invest* 96: 2676–2682, 1995.
570. **Mortensen KE, Conley LN, Hedegaard J, Kalstad T, Sorensen P, Bendixen C, Revhaug A.** Regenerative response in the pig liver remnant varies with the degree of resection and rise in portal pressure. *Am J Physiol Gastrointest Liver Physiol* 294: G819–G830, 2008.
571. **Motterlini R, Hidalgo A, Sammut I, Shah KA, Mohammed S, Srai K, Green CJ.** A precursor of the nitric oxide donor SIN-1 modulates the stress protein heme oxygenase-1 in rat liver. *Biochem Biophys Res Commun* 225: 167–172, 1996.
572. **Mücke I, Richter S, Menger MD, Vollmar B.** Significance of hepatic arterial responsiveness for adequate tissue oxygenation upon portal vein occlusion in cirrhotic livers. *Int J Colorectal Dis* 15: 335–341, 2000.
573. **Müller MJ, Vollmar B, Friedl HP, Menger MD.** Xanthine oxidase and superoxide radicals in portal triad crossclamping-induced microvascular reperfusion injury of the liver. *Free Radic Biol Med* 21: 189–197, 1996.
574. **Mullin EJ, Metcalfe MS, Maddern GJ.** How much liver resection is too much? *Am J Surg* 190: 87–97, 2005.
575. **Murry CE, Jennings RB, Reimer KA.** Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 74: 1124–1136, 1986.
576. **Nagata K, Tsuji T, Todoroki N, Katagiri Y, Tanoue K, Yamazaki H, Hanai N, Irimura T.** Activated platelets induce superoxide anion release by monocytes and neutrophils through P-selectin (CD62). *J Immunol* 151: 3267–3273, 1993.
577. **Nahum E, Skippen PW, Gagnon RE, Macnab AJ, Skarsgard ED.** Correlation of near-infrared spectroscopy with perfusion parameters at the hepatic and systemic levels in an endotoxemic shock model. *Med Sci Monit* 12: BR313–317, 2006.
578. **Nahum E, Skippen PW, Gagnon RE, Macnab AJ, Skarsgard ED.** Correlation of transcutaneous hepatic near-infrared spectroscopy readings with liver surface readings and perfusion parameters in a piglet endotoxemic shock model. *Liver Int* 26: 1277–1282, 2006.
579. **Naito M, Hasegawa G, Ebe Y, Yamamoto T.** Differentiation and function of Kupffer cells. *Med Electron Microsc* 37: 16–28, 2004.
580. **Nakamura T, Ueno T, Sakamoto M, Sakata R, Torimura T, Hashimoto O, Ueno H, Sata M.** Suppression of transforming growth factor-beta results in upregulation of transcription of regeneration factors after chronic liver injury. *J Hepatol* 41: 974–982, 2004.
581. **Nakano H, Kuzume M, Namatame K, Yamaguchi M, Kumada K.** Efficacy of intraportal injection of anti-ICAM-1 monoclonal antibody against liver cell injury following warm ischemia in the rat. *Am J Surg* 170: 64–66, 1995.
582. **Nakano Y, Kondo T, Matsuo R, Hashimoto I, Kawasaki T, Kohno K, Myronovych A, Tadano S, Hisakura K, Ikeda O, Watanabe M, Murata S, Fukunaga K, Ohkohchi N.** Platelet dynamics in the early phase of postischemic liver in vivo. *J Surg Res* 149: 192–198, 2008.
583. **Nakata K, Leong GF, Brauer RW.** Direct measurement of blood pressures in minute vessels of the liver. *Am J Physiol* 199: 1181–1188, 1960.
584. **Nalos M, Vassilev D, Pittner A, Asfar P, Brückner UB, Schneider EM, Georgieff M, Radermacher P, Froeba G.** Tin-mesoporphyrin for inhibition of heme oxygenase during long-term hyperdynamic porcine endotoxemia. *Shock* 19: 526–532, 2003.
585. **Nanji AA, Griniuviene B, Yacoub LK, Fogt F, Tahan SR.** Intercellular adhesion molecule-1 expression in experimental alcoholic liver disease: relationship to endotoxemia and TNF α messenger RNA. *Exp Mol Pathol* 62: 42–51, 1995.
586. **Natanson C, Hoffman WD, Suffredini AF, Eichacker PQ, Danner RL.** Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. *Ann Intern Med* 120: 771–783, 1994.
587. **Natori S, Fujii Y, Kurosawa H, Nakano A, Shimada H.** Prostaglandin E_1 protects against ischemia-reperfusion injury of the liver by inhibition of neutrophil adherence to endothelial cells. *Transplantation* 64: 1514–1520, 1997.
588. **Natori S, Higuchi H, Contreras P, Gores GJ.** The caspase inhibitor IDN-6556 prevents caspase activation and apoptosis in sinusoidal endothelial cells during liver preservation injury. *Liver Transpl* 9: 278–284, 2003.

589. **Natori S, Selzner M, Valentino KL, Fritz LC, Srinivasan A, Clavien PA, Gores GJ.** Apoptosis of sinusoidal endothelial cells occurs during liver preservation injury by a caspase-dependent mechanism. *Transplantation* 68: 89–96, 1999.
590. **Neyrinck AM, Margagliotti S, Delzenne NM.** Insight into the involvement of Kupffer cell-derived mediators in the hepatoprotective effect of glycine upon inflammation: study on rat precision-cut liver slices. *Inflamm Res* 54: 106–112, 2005.
591. **Nieminen AL, Byrne AM, Herman B, Lemasters JJ.** Mitochondrial permeability transition in hepatocytes induced by *t*-BuOOH: NAD(P)H and reactive oxygen species. *Am J Physiol Cell Physiol* 272: C1286–C1294, 1997.
592. **Nieminen AL, Saylor AK, Herman B, Lemasters JJ.** ATP depletion rather than mitochondrial depolarization mediates hepatocyte killing after metabolic inhibition. *Am J Physiol Cell Physiol* 267: C67–C74, 1994.
593. **Niiya T, Murakami M, Aoki T, Murai N, Shimizu Y, Kusano M.** Immediate increase of portal pressure, reflecting sinusoidal shear stress, induced liver regeneration after partial hepatectomy. *J Hepatobiliary Pancreat Surg* 6: 275–280, 1999.
594. **Niwano M, Arii S, Monden K, Ishiguro S, Nakamura T, Mizumoto M, Takeda Y, Fujioka M, Imamura M.** Amelioration of sinusoidal endothelial cell damage by Kupffer cell blockade during cold preservation of rat liver. *J Surg Res* 72: 36–48, 1997.
595. **Nocito A, Dahm F, Jochum W, Jang JH, Georgiev P, Bader M, Renner EL, Clavien PA.** Serotonin mediates oxidative stress and mitochondrial toxicity in a murine model of nonalcoholic steatohepatitis. *Gastroenterology* 133: 608–618, 2007.
596. **Nocito A, Georgiev P, Dahm F, Jochum W, Bader M, Graf R, Clavien PA.** Platelets and platelet-derived serotonin promote tissue repair after normothermic hepatic ischemia in mice. *Hepatology* 45: 369–376, 2007.
597. **O'Brien T, Babcock G, Cornelius J, Dingeldein M, Talaska G, Warshawsky D, Mitchell K.** A comparison of apoptosis and necrosis induced by hepatotoxins in HepG2 cells. *Toxicol Appl Pharmacol* 164: 280–290, 2000.
598. **Oda M, Han JY, Nakamura M.** Endothelial cell dysfunction in microvasculature: relevance to disease processes. *Clin Hemorheol Microcirc* 23: 199–211, 2000.
599. **Oda M, Kaneko H, Suematsu M, Suzuki H, Kazemoto S, Honda K, Yonei Y, Tsuchiya M.** A new aspect of the hepatic microvasculature: electron-microscopic evidence for the presence of Ito cells around portal and hepatic venules as pericytes. *Prog Appl Microcirc* 19: 25–39, 1993.
600. **Oda M, Yokomori H, Han JY.** Regulatory mechanisms of hepatic microcirculation. *Clin Hemorheol Microcirc* 29: 167–182, 2003.
601. **Oda M, Yokomori H, Han JY.** Regulatory mechanisms of hepatic microcirculatory hemodynamics: hepatic arterial system. *Clin Hemorheol Microcirc* 34: 11–26, 2006.
602. **Ofek I, Sharon N.** Lectinophagocytosis: a molecular mechanism of recognition between cell surface sugars and lectins in the phagocytosis of bacteria. *Infect Immun* 56: 539–547, 1988.
603. **Oh GS, Pae HO, Lee BS, Kim BN, Kim JM, Kim HR, Jeon SB, Jeon WK, Chae HJ, Chung HT.** Hydrogen sulfide inhibits nitric oxide production and nuclear factor-kappaB via heme oxygenase-1 expression in RAW264.7 macrophages stimulated with lipopolysaccharide. *Free Radic Biol Med* 41: 106–119, 2006.
604. **Ohdan H, Mizunuma K, Tashiro H, Tokita D, Hara H, Onoe T, Ishiyama K, Shibata S, Mitsuta H, Ochi M, Nakahara H, Itamoto T, Asahara T.** Intraoperative near-infrared spectroscopy for evaluating hepatic venous outflow in living-donor right lobe liver. *Transplantation* 76: 791–797, 2003.
605. **Ohira H, Abe K, Yokokawa J, Takiguchi J, Rai T, Shishido S, Sato Y.** Adhesion molecules and CXC chemokines in endotoxin-induced liver injury. *Fukushima J Med Sci* 49: 1–13, 2003.
606. **Ohuchi T, Tada K, Akamatsu K.** Endogenous ET-1 contributes to liver injury induced by galactosamine and endotoxin in isolated perfused rat liver. *Am J Physiol Gastrointest Liver Physiol* 268: G997–G1003, 1995.
607. **Okano K, Kokudo Y, Okajima K, Hossain MA, Ishimura K, Yachida S, Tsubouchi T, Wakabayashi H, Maeba T, Maeta H.** Protective effects of antithrombin III supplementation on warm ischemia and reperfusion injury in rat liver. *World J Surg* 20: 1069–1075, 1996.
608. **Okaya T, Lentsch AB.** Cytokine cascades and the hepatic inflammatory response to ischemia and reperfusion. *J Invest Surg* 16: 141–147, 2003.
609. **Onori P, Morini S, Franchitto A, Sferra R, Alvaro D, Gaudio E.** Hepatic microvascular features in experimental cirrhosis: a structural and morphometrical study in CCl_4-treated rats. *J Hepatol* 33: 555–563, 2000.
610. **Oshita M, Takei Y, Kawano S, Fusamoto H, Kamada T.** Protective effect of ebselen on constrictive hepatic vasculature: prevention of alcohol-induced effects on portal pressure in perfused livers. *J Pharmacol Exp Ther* 271: 20–24, 1994.
611. **Ou J, Carlos TM, Watkins SC, Saavedra JE, Keefer LK, Kim YM, Harbrecht BG, Billiar TR.** Differential effects of nonselective nitric oxide synthase (NOS) and selective inducible NOS inhibition on hepatic necrosis, apoptosis, ICAM-1 expression, and neutrophil accumulation during endotoxemia. *Nitric Oxide* 1: 404–416, 1997.
612. **Oyama T, Sadamori H, Matsukawa H, Murata H, Umeda Y, Watanabe Y, Ozaki M, Iwagaki H, Tanaka N, Yagi T.** Small liver graft regenerates through immediate increase of HGF and IL-6—possible involvement of sinusoidal tensile/shear stress in small liver graft. *Hepatogastroenterology* 54: 2078–2083, 2007.
613. **Ozaki M, Deshpande SS, Angkeow P, Bellan J, Lowenstein CJ, Dinauer MC, Goldschmidt-Clermont PJ, Irani K.** Inhibition of the Rac1 GTPase protects against nonlethal ischemia/reperfusion-induced necrosis and apoptosis in vivo. *FASEB J* 14: 418–429, 2000.
614. **Palmer RM, Ferrige AG, Moncada S.** Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 327: 524–526, 1987.
615. **Palmes D, Minin E, Budny T, Uhlmann D, Armann B, Stratmann U, Herbst H, Spiegel HU.** The endothelin/nitric oxide balance determines small-for-size liver injury after reduced-size rat liver transplantation. *Virchows Arch* 447: 731–741, 2005.
616. **Palmes D, Skawran S, Stratmann U, Armann B, Minin E, Herbst H, Spiegel HU.** Amelioration of microcirculatory damage by an endothelin A receptor antagonist in a rat model of reversible acute liver failure. *J Hepatol* 42: 350–357, 2005.
617. **Pan M, Song YL, Xu JM, Gan HZ.** Melatonin ameliorates nonalcoholic fatty liver induced by high-fat diet in rats. *J Pineal Res* 41: 79–84, 2006.
618. **Pang KS, Schwab AJ, Goresky CA, Chiba M.** Transport, binding, and metabolism of sulfate conjugates in the liver. *Chem Biol Interact* 92: 179–207, 1994.
619. **Pannarale L, Onori P, Borghese F, Conte D, Gaudio E.** Three-dimensional organization of the hepatic artery terminal branches: a scanning electron microscopic study of vascular corrosion casts of rat liver. *Ital J Anat Embryol* 112: 1–12, 2007.
620. **Pannen BH, Al-Adili F, Bauer M, Clemens MG, Geiger KK.** Role of endothelins and nitric oxide in hepatic reperfusion injury in the rat. *Hepatology* 27: 755–764, 1998.
621. **Pannen BH, Bauer M, Zhang JX, Robotham JL, Clemens MG.** A time-dependent balance between endothelins and nitric oxide regulating portal resistance after endotoxin. *Am J Physiol Heart Circ Physiol* 271: H1953–H1961, 1996.
622. **Pannen BH, Bauer M, Zhang JX, Robotham JL, Clemens MG.** Endotoxin pretreatment enhances portal venous contractile response to endothelin-1. *Am J Physiol Heart Circ Physiol* 270: H7–H15, 1996.
623. **Pannen BH, Bauer M.** Differential regulation of hepatic arterial and portal venous vascular resistance by nitric oxide and carbon monoxide in rats. *Life Sci* 62: 2025–2033, 1998.
624. **Pannen BH, Schroll S, Loop T, Bauer M, Hoetzel A, Geiger KK.** Hemorrhagic shock primes the hepatic portal circulation for the vasoconstrictive effects of endothelin-1. *Am J Physiol Heart Circ Physiol* 281: H1075–H1084, 2001.
625. **Pannen BH.** New insights into the regulation of hepatic blood flow after ischemia and reperfusion. *Anesth Analg* 94: 1448–1457, 2002.
626. **Patrick AL, Rullo J, Beaudin S, Liaw P, Fox-Robichaud AE.** Hepatic leukocyte recruitment in response to time-limited expres-

sion of TNF-α and IL-1beta. *Am J Physiol Gastrointest Liver Physiol* 293: G663–G672, 2007.
627. **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* 17: 993–1002, 2003.
628. **Paxian M, Keller SA, Cross B, Huynh TT, Clemens MG.** High-resolution visualization of oxygen distribution in the liver in vivo. *Am J Physiol Gastrointest Liver Physiol* 286: G37–G44, 2004.
629. **Pereboom IT, Lisman T, Porte RJ.** Platelets in liver transplantation: friend or foe? *Liver Transpl* 14: 923–931, 2008.
630. **Perlmutter DH.** Chemical chaperones: a pharmacological strategy for disorders of protein folding and trafficking. *Pediatr Res* 52: 832–836, 2002.
631. **Perri RE, Langer DA, Chatterjee S, Gibbons SJ, Gadgil J, Cao S, Farrugia G, Shah VH.** Defects in cGMP-PKG pathway contribute to impaired NO-dependent responses in hepatic stellate cells upon activation. *Am J Physiol Gastrointest Liver Physiol* 290: G535–G542, 2006.
632. **Petrowsky H, McCormack L, Trujillo M, Selzner M, Jochum W, Clavien PA.** A prospective, randomized, controlled trial comparing intermittent portal triad clamping versus ischemic preconditioning with continuous clamping for major liver resection. *Ann Surg* 244: 921–928, 2006.
633. **Philpott DJ, Girardin SE.** The role of Toll-like receptors and Nod proteins in bacterial infection. *Mol Immunol* 41: 1099–1108, 2004.
634. **Pinzani M, Failli P, Ruocco C, Casini A, Milani S, Baldi E, Giotti A, Gentilini P.** Fat-storing cells as liver-specific pericytes. Spatial dynamics of agonist-stimulated intracellular calcium transients. *J Clin Invest* 90: 642–646, 1992.
635. **Polfliet MM, Fabriek BO, Daniëls WP, Dijkstra CD, van den Berg TK.** The rat macrophage scavenger receptor CD163: expression, regulation and role in inflammatory mediator production. *Immunobiology* 211: 419–425, 2006.
636. **Post S, Gonzalez AP, Palma P, Rentsch M, Stiehl A, Menger MD.** Assessment of hepatic phagocytic activity by in vivo microscopy after liver transplantation in the rat. *Hepatology* 16: 803–809, 1992.
637. **Post S, Menger MD, Rentsch M, Gonzalez AP, Herfarth C, Messmer K.** The impact of arterialization on hepatic microcirculation and leukocyte accumulation after liver transplantation in the rat. *Transplantation* 54: 789–794, 1992.
638. **Post S, Palma P, Gonzalez AP, Rentsch M, Menger MD.** Timing of arterialization in liver transplantation. *Ann Surg* 220: 691–698, 1994.
639. **Post S, Rentsch M, Gonzalez AP, Palma P, Otto G, Menger MD.** Effects of Carolina rinse and adenosine rinse on microvascular perfusion and intrahepatic leukocyte-endothelium interaction after liver transplantation in the rat. *Transplantation* 55: 972–977, 1993.
640. **Prins HA, Meijer C, Boelens PG, Diks J, Holtz R, Masson S, Daveau M, Meijer S, Scotté M, van Leeuwen PA.** Kupffer cell-depleted rats have a diminished acute-phase response following major liver resection. *Shock* 21: 561–565, 2004.
641. **Prinzen FW, Bassingthwaighte JB.** Blood flow distributions by microsphere deposition methods. *Cardiovasc Res* 45: 13–21, 2000.
642. **Prinzen FW, Glenny RW.** Developments in non-radioactive microsphere techniques for blood flow measurement. *Cardiovasc Res* 28: 1467–1475, 1994.
643. **Proskuryakov SY, Gabai VL, Konoplyannikov AG.** Necrosis is an active and controlled form of programmed cell death. *Biochemistry* 67: 387–408, 2002.
644. **Proskuryakov SY, Konoplyannikov AG, Gabai VL.** Necrosis: a specific form of programmed cell death? *Exp Cell Res* 283: 1–16, 2003.
645. **Pruefer D, Makowski J, Schnell M, Buerke U, Dahm M, Oelert H, Sibelius U, Grandel U, Grimminger F, Seeger W, Meyer J, Darius H, Buerke M.** Simvastatin inhibits inflammatory properties of *Staphylococcus aureus* α-toxin. *Circulation* 106: 2104–2110, 2002.
646. **Puhl G, Schaser KD, Pust D, Köhler K, Vollmar B, Menger MD, Neuhaus P, Settmacher U.** The delay of rearterialization after initial portal reperfusion in living donor liver transplantation significantly determines the development of microvascular graft dysfunction. *J Hepatol* 41: 299–306, 2004.
647. **Puhl G, Schaser KD, Pust D, Köhler K, Vollmar B, Menger MD, Neuhaus P, Settmacher U.** Initial hepatic microcirculation correlates with early graft function in human orthotopic liver transplantation. *Liver Transpl* 11: 555–563, 2005.
648. **Puhl G, Schaser KD, Vollmar B, Menger MD, Settmacher U.** Noninvasive in vivo analysis of the human hepatic microcirculation using orthogonal polorization spectral imaging. *Transplantation* 75: 756–761, 2003.
649. **Qian T, Herman B, Lemasters JJ.** The mitochondrial permeability transition mediates both necrotic and apoptotic death of hepatocytes exposed to Br-A23187. *Toxicol Appl Pharmacol* 154: 117–125, 1999.
650. **Qingyou Z, Junbao D, Weijin Z, Hui Y, Chaoshu T, Chunyu Z.** Impact of hydrogen sulfide on carbon monoxide/heme oxygenase pathway in the pathogenesis of hypoxic pulmonary hypertension. *Biochem Biophys Res Commun* 317: 30–37, 2004.
651. **Quintini C, Hirose K, Hashimoto K, Diago T, Aucejo F, Eghtesad B, Vogt D, Pierce G, Baker M, Kelly D, Miller CM.** "Splenic artery steal syndrome" is a misnomer: the cause is portal hyperperfusion, not arterial siphon. *Liver Transpl* 14: 374–379, 2008.
652. **Quireze C, Montero EF, Leitão RM, Juliano Y, Fagundes DJ, Poli-de-Figueiredo LF.** Ischemic preconditioning prevents apoptotic cell death and necrosis in early and intermediate phases of liver ischemia-reperfusion injury in rats. *J Invest Surg* 19: 229–236, 2006.
653. **Rahbari NN, Wente MN, Schemmer P, Diener MK, Hoffmann K, Motschall E, Schmidt J, Weitz J, Büchler MW.** Systematic review and meta-analysis of the effect of portal triad clamping on outcome after hepatic resection. *Br J Surg* 95: 424–432, 2008.
654. **Randle LE, Sathish JG, Kitteringham NR, Macdonald I, Williams DP, Park BK.** α(1)-Adrenoceptor antagonists prevent paracetamol-induced hepatotoxicity in mice. *Br J Pharmacol* 153: 820–830, 2008.
655. **Rao SB, Mehendale HM.** Protective role of fructose 1,6-bisphosphate during CCl_4 hepatotoxicity in rats. *Biochem J* 262: 721–725, 1989.
656. **Rappaport AM.** Hepatic blood flow: morphologic aspects and physiologic regulation. *Int Rev Physiol* 21: 1–63, 1980.
657. **Rappaport AM.** The microcirculatory hepatic unit. *Microvasc Res* 6: 212–228, 1973.
658. **Rappaport AM.** The structural and functional unit in the human liver (liver acinus). *Anat Rec* 130: 673–689, 1958.
659. **Reichen J, Gerbes AL, Steiner MJ, Sägesser H, Clozel M.** The effect of endothelin and its antagonist Bosentan on hemodynamics and microvascular exchange in cirrhotic rat liver. *J Hepatol* 28: 1020–1030, 1998.
660. **Reichen J.** Assessment of liver microcirculation with the multiple indicator dilution technique. In: *Progress in Applied Microcirculation. Liver Microciruclation and Hepatobiliary Function*, edited by Messmer K and Menger MD. Basel: Karger, 1993, p. 40–51.
661. **Reilly FD, Dimlich RV, Cilento EV, McCuskey RS.** Hepatic microvascular regulatory mechanisms. III. Aminergic mechanisms as related to mast cells. *Int J Microcirc Clin Exp* 2: 61–73, 1983.
662. **Reilly FD, McCuskey RS, Cilento EV.** Hepatic microvascular regulatory mechanisms. I. Adrenergic mechanisms. *Microvasc Res* 21: 103–116, 1981.
663. **Rensing H, Bauer I, Datene V, Pätau C, Pannen BH, Bauer M.** Differential expression pattern of heme oxygenase-1/heat shock protein 32 and nitric oxide synthase-II and their impact on liver injury in a rat model of hemorrhage and resuscitation. *Crit Care Med* 27: 2766–2775, 1999.
664. **Rensing H, Bauer I, Zhang JX, Paxian M, Pannen BH, Yokoyama Y, Clemens MG, Bauer M.** Endothelin-1 and heme oxygenase-1 as modulators of sinusoidal tone in the stress-exposed rat liver. *Hepatology* 36: 1453–1465, 2002.
665. **Rensing H, Jaeschke H, Bauer I, Pätau C, Datene V, Pannen BH, Bauer M.** Differential activation pattern of redox-sensitive transcription factors and stress-inducible dilator systems heme oxygenase-1 and inducible nitric oxide synthase in hemorrhagic and endotoxic shock. *Crit Care Med* 29: 1962–1971, 2001.

666. **Rentsch M, Post S, Palma P, Lang G, Menger MD, Messmer K.** Anti-ICAM-1 blockade reduces postsinusoidal WBC adherence following cold ischemia and reperfusion, but does not improve early graft function in rat liver transplantation. *J Hepatol* 32: 821–828, 2000.
667. **Rentsch M, Puellmann K, Sirek S, Iesalnieks I, Kienle K, Mueller T, Bolder U, Geissler E, Jauch KW, Beham A.** Benefit of Kupffer cell modulation with glycine versus Kupffer cell depletion after liver transplantation in the rat: effects on postischemic reperfusion injury, apoptotic cell death graft regeneration and survival. *Transpl Int* 18: 1079–1089, 2005.
668. **Rezzani R, Buffoli B, Rodella L, Stacchiotti A, Bianchi R.** Protective role of melatonin in cyclosporine A-induced oxidative stress in rat liver. *Int Immunopharmacol* 5: 1397–1405, 2005.
669. **Richards HC.** On the Doppler effect. *Science* 24: 466–467, 1906.
670. **Richter S, Mücke I, Menger MD, Vollmar B.** Impact of intrinsic blood flow regulation in cirrhosis: maintenance of hepatic arterial buffer response. *Am J Physiol Gastrointest Liver Physiol* 279: G454–G462, 2000.
671. **Richter S, Olinger A, Hildebrandt U, Menger MD, Vollmar B.** Loss of physiologic hepatic blood flow control ("hepatic arterial buffer response") during CO_2-pneumoperitoneum in the rat. *Anesth Analg* 93: 872–877, 2001.
672. **Richter S, Vollmar B, Mücke I, Post S, Menger MD.** Hepatic arteriolo-portal venular shunting guarantees maintenance of nutritional microvascular supply in hepatic arterial buffer response of rat livers. *J Physiol* 531: 193–201, 2001.
673. **Rinaldi L, Gobbi G, Pambianco M, Micheloni C, Mirandola P, Vitale M.** Hydrogen sulfide prevents apoptosis of human PMN via inhibition of p38 and caspase 3. *Lab Invest* 86: 391–397, 2006.
674. **Rivera CA, Adegboyega P, van Rooijen N, Tagalicud A, Allman M, Wallace M.** Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis. *J Hepatol* 47: 571–579, 2007.
675. **Roberts RA, Ganey PE, Ju C, Kamendulis LM, Rusyn I, Klaunig JE.** Role of the Kupffer cell in mediating hepatic toxicity and carcinogenesis. *Toxicol Sci* 96: 2–15, 2007.
676. **Rocheleau B, Ethier C, Houle R, Huet PM, Bilodeau M.** Hepatic artery buffer response following left portal vein ligation: its role in liver tissue homeostasis. *Am J Physiol Gastrointest Liver Physiol* 277: G1000–G1007, 1999.
677. **Rockey DC, Chung JJ.** Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial dysfunction in portal hypertension. *Gastroenterology* 114: 344–351, 1998.
678. **Rockey DC, Fouassier L, Chung JJ, Carayon A, Vallee P, Rey C, Housset C.** Cellular localization of endothelin-1 and increased production in liver injury in the rat: potential for autocrine and paracrine effects on stellate cells. *Hepatology* 27: 472–480, 1998.
679. **Rockey DC, Weisiger RA.** Endothelin induced contractility of stellate cells from normal and cirrhotic rat liver: implications for regulation of portal pressure and resistance. *Hepatology* 24: 233–240, 1996.
680. **Rockey DC.** Characterization of endothelin receptors mediating rat hepatic stellate cell contraction. *Biochem Biophys Res Commun* 207: 725–731, 1995.
681. **Rockey DC.** Hepatic blood flow regulation by stellate cells in normal and injured liver. *Semin Liver Dis* 21: 337–349, 2001.
682. **Rodeberg DA, Chaet MS, Bass RC, Arkovitz MS, Garcia VF.** Nitric oxide: an overview. *Am J Surg* 170: 292–303, 1995.
683. **Roesner JP, Vagts DA, Iber T, Eipel C, Vollmar B, Nöldge-Schomburg GF.** Protective effects of PARP inhibition on liver microcirculation and function after haemorrhagic shock and resuscitation in male rats. *Intensive Care Med* 32: 1649–1657, 2006.
684. **Rogers HW, Callery MP, Deck B, Unanue ER.** *Listeria monocytogenes* induces apoptosis of infected hepatocytes. *J Immunol* 156: 679–684, 1996.
685. **Roggin KK, Papa EF, Kurkchubasche AG, Tracy TF Jr.** Kupffer cell inactivation delays repair in a rat model of reversible biliary obstruction. *J Surg Res* 90: 166–173, 2000.
686. **Rothe CF, Maass-Moreno R.** Active and passive liver microvascular responses from angiotensin, endothelin, norepinephrine, and vasopressin. *Am J Physiol Heart Circ Physiol* 279: H1147–H1156, 2000.
687. **Rovai LE, Herschman HR, Smith JB.** The murine neutrophil-chemoattractant chemokines LIX, KC, and MIP-2 have distinct induction kinetics, tissue distributions, and tissue-specific sensitivities to glucocorticoid regulation in endotoxemia. *J Leukoc Biol* 64: 494–502, 1998.
688. **Rubanyi GM, Polokoff MA.** Endothelins: molecular biology, biochemistry, pharmacology, physiology and pathophysiology. *Pharmacol Rev* 46: 325–415, 1994.
689. **Ruf A, Patscheke H.** Platelet-induced neutrophil activation: platelet-expressed fibrinogen induces the oxidative burst in neutrophils by an interaction with CD11C/CD18. *Br J Haematol* 90: 791–796, 1995.
690. **Ruwart MJ, Henley KS.** Prostaglandins in liver disease and liver transplantation. *Gastroenterol Clin North Am* 25: 397–407, 1996.
691. **Ryter SW, Choi AM.** Cytoprotective and anti-inflammatory actions of carbon monoxide in organ injury and sepsis models. *Novartis Found Symp* 280: 165–181, 2007.
692. **Saidi RF, Chang J, Brooks S, Nalbantoglu I, Adsay V, Jacobs MJ.** Ischemic preconditioning and intermittent clamping increase the tolerance of fatty liver to hepatic ischemia-reperfusion injury in the rat. *Transplant Proc* 39: 3010–3014, 2007.
693. **Sakamoto S, Okanoue T, Itoh Y, Nakagawa Y, Nakamura H, Morita A, Daimon Y, Sakamoto K, Yoshida N, Yoshikawa T, Kashima K.** Involvement of Kupffer cells in the interaction between neutrophils and sinusoidal endothelial cells in rats. *Shock* 18: 152–157, 2002.
694. **Sakamoto S, Okanoue T, Itoh Y, Sakamoto K, Nishioji K, Nakagawa Y, Yoshida N, Yoshikawa T, Kashima K.** Intercellular adhesion molecule-1 and CD18 are involved in neutrophil adhesion and its cytotoxicity to cultured sinusoidal endothelial cells in rats. *Hepatology* 26: 658–663, 1997.
695. **Salvesen GS.** Caspases and apoptosis. *Essays Biochem* 38: 9–19, 2002.
696. **Sano K, Nagaki M, Sugiyama A, Hatakeyama H, Ohnishi H, Muto Y, Moriwaki H.** Effects of cytokines on the binding of leukocytes to cultured rat hepatocytes and on the expression of ICAM-1 by hepatocytes. *Dig Dis Sci* 44: 796–805, 1999.
697. **Sanz MJ, Johnston B, Issekutz A, Kubes P.** Endothelin-1 causes P-selectin-dependent leukocyte rolling and adhesion within rat mesenteric microvessels. *Am J Physiol Heart Circ Physiol* 277: H1823–H1830, 1999.
698. **Sarady JK, Zuckerbraun BS, Bilban M, Wagner O, Usheva A, Liu F, Ifedigbo E, Zamora R, Choi AM, Otterbein LE.** Carbon monoxide protection against endotoxic shock involves reciprocal effects on iNOS in the lung and liver. *FASEB J* 18: 854–856, 2004.
699. **Sarphie TG, Deaciuc IV, Spitzer JJ, D'Souza NB.** Liver sinusoid during chronic alcohol consumption in the rat: an electron microscopic study. *Alcohol Clin Exp Res* 19: 291–298, 1995.
700. **Sasse D, Staubesand J.** Electron microscopic evidence for a muscle layer in the wall of the terminal hepatic venule in the rat. *Cell Tissue Res* 165: 391–396, 1976.
701. **Sato Y, Koyama S, Tsukada K, Hatakeyama K.** Acute portal hypertension reflecting shear stress as a trigger of liver regeneration following partial hepatectomy. *Surg Today* 27: 518–526, 1997.
702. **Sato Y, Tsukada K, Hatakeyama K.** Role of shear stress and immune responses in liver regeneration after a partial hepatectomy. *Surg Today* 29: 1–9, 1999.
703. **Savill J, Hogg N, Ren Y, Haslett C.** Thrombospondin cooperates with CD36 and the vitronectin receptor in macrophage recognition of neutrophils undergoing apoptosis. *J Clin Invest* 90: 1513–1522, 1992.
704. **Scaffidi P, Misteli T, Bianchi ME.** Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature* 418: 191–195, 2002.
705. **Schäfer T, Scheuer C, Roemer K, Menger MD, Vollmar B.** Inhibition of p53 protects liver tissue against endotoxin-induced apoptotic and necrotic cell death. *FASEB J* 17: 660–667, 2003.
706. **Schauer RJ, Gerbes AL, Vonier D, Meissner H, Michl P, Leiderer R, Schildberg FW, Messmer K, Bilzer M.** Glutathione protects the rat liver against reperfusion injury after prolonged warm ischemia. *Ann Surg* 239: 220–231, 2004.
707. **Schemmer P, Liang R, Kincius M, Flechtenmacher C, Bunzendahl H, Gutt CN, Mehrabi A, Gebhard MM, Büchler MW,**

Kraus TW. Taurine improves graft survival after experimental liver transplantation. *Liver Transpl* 11: 950–959, 2005.
708. **Schiffer ER, Mentha G, Schwieger IM, Morel DR.** Sequential changes in the splanchnic circulation during continuous endotoxin infusion in sedated sheep: evidence for a selective increase of hepatic artery blood flow and loss of the hepatic arterial buffer response. *Acta Physiol Scand* 147: 251–261, 1993.
709. **Schleimer K, Stippel DL, Kasper HU, Suer C, Tawadros S, Hoelscher AH, Beckurts KT.** Improved microcirculation of a liver graft by controlled portal vein arterialization. *J Surg Res* 116: 202–210, 2004.
710. **Schmidt R, Tritschler E, Hoetzel A, Loop T, Humar M, Halverscheid L, Geiger KK, Pannen BH.** Heme oxygenase-1 induction by the clinically used anesthetic isoflurane protects rat livers from ischemia/reperfusion injury. *Ann Surg* 245: 931–942, 2007.
711. **Schoen JM, Wang HH, Minuk GY, Lautt WW.** Shear stress-induced nitric oxide release triggers the liver regeneration cascade. *Nitric Oxide* 5: 453–464, 2001.
712. **Schoen Smith JM, Lautt WW.** The role of prostaglandins in triggering the liver regeneration cascade. *Nitric Oxide* 13: 111–117, 2005.
713. **Schreiber R, Stoll B, Lang F, Häussinger D.** Effects of aniso-osmolarity and hydroperoxides on intracellular pH in isolated rat hepatocytes as assessed by (2′,7′)-bis(carboxyethyl)-5(6)-carboxyfluorescein and fluorescein isothiocyanate-dextran fluorescence. *Biochem J* 303: 113–120, 1994.
714. **Schuchmann M, Hermann F, Herkel J, van der Zee R, Galle PR, Lohse AW.** HSP60 and CpG-DNA-oligonucleotides differentially regulate LPS-tolerance of hepatic Kupffer cells. *Immunol Lett* 93: 199–204, 2004.
715. **Schwab AJ, Pang KS.** The multiple indicator-dilution method for the study of enzyme heterogeneity in liver: theoretical basis. *Drug Metab Dispos* 27: 746–755, 1999.
716. **Scoazec JY, Feldmann G.** The cell adhesion molecules of hepatic sinusoidal endothelial cells. *J Hepatol* 20: 296–300, 1994.
717. **Scommotau S, Uhlmann D, Löffler BM, Breu V, Spiegel HU.** Involvement of endothelin/nitric oxide balance in hepatic ischemia/reperfusion injury. *Langenbecks Arch Surg* 384: 65–70, 1999.
718. **Seifalian AM, El-Desoky H, Delpy DT, Davidson BR.** Effect of graded hypoxia on the rat hepatic tissue oxygenation and energy metabolism monitored by near-infrared and ^{31}P nuclear magnetic resonance spectroscopy. *FASEB J* 15: 2642–2648, 2001.
719. **Selzner M, Rüdiger HA, Sindram D, Madden J, Clavien PA.** Mechanisms of ischemic injury are different in the steatotic and normal rat liver. *Hepatology* 32: 1280–1288, 2000.
720. **Selzner N, Selzner M, Odermatt B, Tian Y, Van Rooijen N, Clavien PA.** ICAM-1 triggers liver regeneration through leukocyte recruitment and Kupffer cell-dependent release of TNF-α/IL-6 in mice. *Gastroenterology* 124: 692–700, 2003.
721. **Sepodes B, Maio R, Pinto R, Sharples E, Oliveira P, McDonald M, Yaqoob M, Thiemermann C, Mota-Filipe H.** Recombinant human erythropoietin protects the liver from hepatic ischemia-reperfusion injury in the rat. *Transpl Int* 19: 919–926, 2006.
722. **Serafín A, Roselló-Catafau J, Prats N, Xaus C, Gelpí E, Peralta C.** Ischemic preconditioning increases the tolerance of fatty liver to hepatic ischemia-reperfusion injury in the rat. *Am J Pathol* 161: 587–601, 2002.
723. **Serizawa A, Nakamura S, Suzuki Baba S, Nakano M.** Involvement of platelet-activating factor in cytokine production and neutrophil activation after hepatic ischemia-reperfusion. *Hepatology* 23: 1656–1663, 1996.
724. **Serracino-Inglott F, Virlos IT, Habib NA, Williamson RC, Mathie RT.** Adenosine preconditioning attenuates hepatic reperfusion injury in the rat by preventing the down-regulation of endothelial nitric oxide synthase. *BMC Gastroenterol* 2: 22, 2002.
725. **Serracino-Inglott F, Virlos IT, Habib NA, Williamson RC, Mathie RT.** Differential nitric oxide synthase expression during hepatic ischemia-reperfusion. *Am J Surg* 185: 589–595, 2003.
726. **Sewerynek E, Reiter RJ, Melchiorri D, Ortiz GG, Lewinski A.** Oxidative damage in the liver induced by ischemia-reperfusion: protection by melatonin. *Hepatogastroenterology* 43: 898–905, 1996.
727. **Shah V, Haddad FG, Garcia-Cardena G, Frangos JA, Mennone A, Groszmann RJ, Sessa WC.** Liver sinusoidal endothelial cells are responsible for nitric oxide modulation of resistance in the hepatic sinusoids. *J Clin Invest* 100: 2923–2930, 1997.
728. **Shah V, Toruner M, Haddad F, Cadelina G, Papapetropoulos A, Choo K, Sessa WC, Groszmann RJ.** Impaired endothelial nitric oxide synthase activity associated with enhanced caveolin binding in experimental cirrhosis in the rat. *Gastroenterology* 117: 1222–1228, 1999.
729. **Shah V.** Molecular mechanisms of increased intrahepatic resistance in portal hypertension. *J Clin Gastroenterol* 41 *Suppl* 3: S259–S261, 2007.
730. **Shen XD, Ke B, Zhai Y, Tsuchihashi SI, Gao F, Duarte S, Coito A, Busuttil RW, Allison AC, Kupiec-Weglinski JW.** Diannexin, a novel annexin V homodimer, protects rat liver transplants against cold ischemia-reperfusion injury. *Am J Transplant* 7: 2463–2471, 2007.
731. **Sherman IA, Fisher MM.** Hepatic transport of fluorescent molecules: in vivo studies using intravital TV microscopy. *Hepatology* 6: 444–449, 1986.
732. **Shi J, Gilbert GE, Kokubo Y, Ohashi T.** Role of the liver in regulating numbers of circulating neutrophils. *Blood* 98: 1226–1230, 2001.
733. **Shimabukuro T, Yamamoto Y, Kume M, Kimoto S, Okamoto R, Morimoto T, Yamaoka Y.** Induction of heat shock response: effect on the rat liver with carbon tetrachloride-induced fibrosis from ischemia-reperfusion injury. *World J Surg* 22: 464–468, 1998.
734. **Shimamura T, Zhu Y, Zhang S, Jin MB, Ishizaki N, Urakami A, Totsuka E, Kishida A, Lee R, Subbotin V, Furukawa H, Starzl TE, Todo S.** Protective role of nitric oxide in ischemia and reperfusion injury of the liver. *J Am Coll Surg* 188: 43–52, 1999.
735. **Shimizu J, Oka H, Dono K, Sakon M, Takamura M, Murakami T, Hayashi S, Nagano H, Nakamori S, Umeshita K, Sase S, Gotoh M, Wakasa K, Nakamura H, Monden M.** Noninvasive quantitative measurement of tissue blood flow in hepatocellular carcinoma using xenon-enhanced computed tomography. *Dig Dis Sci* 48: 1510–1516, 2003.
736. **Shindo T, Kurihara H, Kurihara Y, Morita H, Yazaki Y.** Up-regulation of endothelin-1 and adrenomedullin gene expression in the mouse endotoxin shock model. *J Cardiovasc Pharmacol* 31, *Suppl* 1: S541–S544, 1998.
737. **Shiratori Y, Takada H, Hikiba Y, Okano K, Niwa Y, Matsumura M, Komatsu Y, Omata M.** Increased release of KC/gro protein, intercrine cytokine family, from hepatocytes of the chronically ethanol fed rats. *Biochem Biophys Res Commun* 197: 319–325, 1993.
738. **Shiva S, Sack MN, Greer JJ, Duranski M, Ringwood LA, Burwell L, Wang X, MacArthur PH, Shoja A, Raghavachari N, Calvert JW, Brookes PS, Lefer DJ, Gladwin MT.** Nitrite augments tolerance to ischemia/reperfusion injury via the modulation of mitochondrial electron transfer. *J Exp Med* 204: 2089–2102, 2007.
739. **Shrivastava S, McVey JH, Dorling A.** The interface between coagulation and immunity. *Am J Transplant* 7: 499–506, 2007.
740. **Simonet WS, Hughes TM, Nguyen HQ, Trebasky LD, Danilenko DM, Medlock ES.** Long-term impaired neutrophil migration in mice overexpressing human interleukin-8. *J Clin Invest* 94: 1310–1319, 1994.
741. **Sindram D, Porte RJ, Hoffman MR, Bentley RC, Clavien PA.** Platelets induce sinusoidal endothelial cell apoptosis upon reperfusion of the cold ischemic rat liver. *Gastroenterology* 118: 183–191, 2000.
742. **Sindram D, Porte RJ, Hoffman MR, Bentley RC, Clavien PA.** Synergism between platelets and leukocytes in inducing endothelial cell apoptosis in the cold ischemic rat liver: a Kupffer cell-mediated injury. *FASEB J* 15: 1230–1232, 2001.
743. **Singer G, Urakami H, Specian RD, Stokes KY, Granger DN.** Platelet recruitment in the murine hepatic microvasculature during experimental sepsis: role of neutrophils. *Microcirculation* 13: 89–97, 2006.
744. **Sitia G, Iannacone M, Müller S, Bianchi ME, Guidotti LG.** Treatment with HMGB1 inhibitors diminishes CTL-induced liver disease in HBV transgenic mice. *J Leukoc Biol* 81: 100–107, 2007.

745. **Sitia G, Isogawa M, Kakimi K, Wieland SF, Chisari FV, Guidotti LG.** Depletion of neutrophils blocks the recruitment of antigen-nonspecific cells into the liver without affecting the antiviral activity of hepatitis B virus-specific cytotoxic T lymphocytes. *Proc Natl Acad Sci USA* 99: 13717–13722, 2002.
746. **Sleyster EC, Knook DL.** Relation between localization and function of rat liver Kupffer cells. *Lab Invest* 47: 484–490, 1982.
747. **Slotta JE, Scheuer C, Menger MD, Vollmar B.** Immunostimulatory CpG-oligodeoxynucleotides (CpG-ODN) induce early hepatic injury, but provide a late window for protection against endotoxin-mediated liver damage. *J Hepatol* 44: 576–585, 2006.
748. **Smedsrød B, De Bleser PJ, Braet F, Lovisetti P, Vanderkerken K, Wisse E, Geerts A.** Cell biology of liver endothelial and Kupffer cells. *Gut* 35: 1509–1516, 1994.
749. **Smyrniotis V, Kostopanagiotou G, Kondi A, Gamaletsos E, Theodoraki K, Kehagias D, Mystakidou K, Contis J.** Hemodynamic interaction between portal vein and hepatic artery flow in small-for-size split liver transplantation. *Transpl Int* 15: 355–360, 2002.
750. **Smyrniotis V, Theodoraki K, Arkadopoulos N, Fragulidis G, Condi-Pafiti A, Plemenou-Fragou M, Voros D, Vassiliou J, Dimakakos P.** Ischemic preconditioning versus intermittent vascular occlusion in liver resections performed under selective vascular exclusion: a prospective randomized study. *Am J Surg* 192: 669–674, 2006.
751. **Soejima Y, Yanaga K, Nishizaki T, Yoshizumi T, Uchiyama H, Sugimachi K.** Effect of specific neutrophil elastase inhibitor on ischemia/reperfusion injury in rat liver transplantation. *J Surg Res* 86: 150–154, 1999.
752. **Sohail MA, Hashmi AZ, Hakim W, Watanabe A, Zipprich A, Groszmann RJ, Dranoff JA, Torok NJ, Mehal WZ.** Adenosine induces loss of actin stress fibers and inhibits contraction in hepatic stellate cells via Rho inhibition. *Hepatology* 49: 185–194, 2009.
753. **Sonin NV, Garcia-Pagan JC, Nakanishi K, Zhang JX, Clemens MG.** Patterns of vasoregulatory gene expression in the liver response to ischemia/reperfusion and endotoxemia. *Shock* 11: 175–179, 1999.
754. **Sostman HD, Zoghbi SS, Smith GJ, Carbo P, Neumann RD, Gottschalk A, Greenspan RH.** Platelet kinetics and biodistribution in canine endotoxemia. *Invest Radiol* 18: 425–435, 1983.
755. **Spapen H.** Liver perfusion in sepsis, septic shock, and multiorgan failure. *Anat Rec* 291: 714–720, 2008.
756. **Spolarics Z, Spitzer JJ.** Augmented glucose use and pentose cycle activity in hepatic endothelial cells after in vivo endotoxemia. *Hepatology* 17: 615–620, 1993.
757. **Spolarics Z.** Endotoxemia, pentose cycle, and the oxidant/antioxidant balance in the hepatic sinusoid. *J Leukoc Biol* 63: 534–541, 1998.
758. **Spolarics Z.** Endotoxin stimulates gene expression of ROS-eliminating pathways in rat hepatic endothelial and Kupffer cells. *Am J Physiol Gastrointest Liver Physiol* 270: G660–G666, 1996.
759. **Steinhoff G, Behrend M, Schrader B, Duijvestijn AM, Wonigeit K.** Expression patterns of leukocyte adhesion ligand molecules on human liver endothelia. Lack of ELAM-1 and CD62 inducibility on sinusoidal endothelia and distinct distribution of VCAM-1, ICAM-1, ICAM-2, and LFA-3. *Am J Pathol* 142: 481–488, 1993.
760. **Stewart GN.** Researches on the circulation time in organs and on the influences which affect it. *J Physiol* 15: 1–89, 1894.
761. **Stock RJ, Cilento EV, McCuskey RS.** A quantitative study of fluorescein isothiocyanate-dextran transport in the microcirculation of the isolated perfused rat liver. *Hepatology* 9: 75–82, 1989.
762. **Sturm E, Havinga R, Baller JF, Wolters H, van Rooijen N, Kamps JA, Verkade HJ, Karpen SJ, Kuipers F.** Kupffer cell depletion with liposomal clodronate prevents suppression of Ntcp expression in endotoxin-treated rats. *J Hepatol* 42: 102–109, 2005.
763. **Su GL, Goyert SM, Fan MH, Aminlari A, Gong KQ, Klein RD, Myc A, Alarcon WH, Steinstraesser L, Remick DG, Wang SC.** Activation of human and mouse Kupffer cells by lipopolysaccharide is mediated by CD14. *Am J Physiol Gastrointest Liver Physiol* 283: G640–G645, 2002.
764. **Su GL.** Lipopolysaccharides in liver injury: molecular mechanisms of Kupffer cell activation. *Am J Physiol Gastrointest Liver Physiol* 283: G256–G265, 2002.
765. **Suematsu M, Goda N, Sano T, Kashiwagi S, Egawa T, Shinoda Y, Ishimura Y.** Carbon monoxide: an endogenous modulator of sinusoidal tone in the perfused rat liver. *J Clin Invest* 96: 2431–2437, 1995.
766. **Suematsu M, Oda M, Suzuki H, Kaneko H, Watanabe N, Furusho T, Masushige S, Tsuchiya M.** Intravital and electron microscopic observation of Ito cells in rat hepatic microcirculation. *Microvasc Res* 46: 28–42, 1993.
767. **Suematsu M, Wakabayashi Y, Ishimura Y.** Gaseous monoxides: a new class of microvascular regulator in the liver. *Cardiovasc Res* 32: 679–686, 1996.
768. **Suliburk JW, Gonzalez EA, Kennison SD, Helmer KS, Mercer DW.** Differential effects of anesthetics on endotoxin-induced liver injury. *J Trauma* 58: 711–716, 2005.
769. **Sumimoto K, Matsura T, Oku JI, Fukuda Y, Yamada K, Dohi K.** Protective effect of UW solution on postischemic injury in rat liver: suppression of reduction in hepatic antioxidants during reperfusion. *Transplantation* 62: 1391–1398, 1996.
770. **Sun CK, Zhang XY, Wheatley AM.** Increased NAD(P)H fluorescence with decreased blood flow in the steatotic liver of the obese Zucker rat. *Microvasc Res* 66: 15–21, 2003.
771. **Sun F, Hamagawa E, Tsutsui C, Ono Y, Ogiri Y, Kojo S.** Evaluation of oxidative stress during apoptosis and necrosis caused by carbon tetrachloride in rat liver. *Biochim Biophys Acta* 1535: 186–191, 2001.
772. **Sun F, Hamagawa E, Tsutsui C, Sakaguchi N, Kakuta Y, Tokumaru S, Kojo S.** Evaluation of oxidative stress during apoptosis and necrosis caused by D-galactosamine in rat liver. *Biochem Pharmacol* 65: 101–107, 2003.
773. **Suzuki H, Suematsu M, Ishii H, Kato S, Miki H, Mori M, Ishimura Y, Nishino T, Tsuchiya M.** Prostaglandin E_1 abrogates early reductive stress and zone-specific paradoxical oxidative injury in hypoperfused rat liver. *J Clin Invest* 93: 155–164, 1994.
774. **Suzuki T, Takahashi T, Yamasaki A, Fujiwara T, Hirakawa M, Akagi R.** Tissue-specific gene expression of heme oxygenase-1 (HO-1) and non-specific delta-aminolevulinate synthase (ALAS-N) in a rat model of septic multiple organ dysfunction syndrome. *Biochem Pharmacol* 60: 275–283, 2000.
775. **Syntichaki P, Tavernarakis N.** Death by necrosis. Uncontrollable catastrophe, or is there order behind the chaos? *EMBO Rep* 3: 604–609, 2002.
776. **Szabó C.** Potential role of the peroxynitrate-poly(ADP-ribose) synthetase pathway in a rat model of severe hemorrhagic shock. *Shock* 9: 341–344, 1998.
777. **Szijártó A, Batmunkh E, Hahn O, Mihály Z, Kreiss A, Kiss A, Lotz G, Schaff Z, Váli L, Blázovics A, Geró D, Szabó C, Kupcsulik P.** Effect of PJ-34 PARP-inhibitor on rat liver microcirculation and antioxidant status. *J Surg Res* 142: 72–80, 2007a.
778. **Szijártó A, Hahn O, Batmunkh E, Stangl R, Kiss A, Lotz G, Schaff Z, Váli L, Blázovics A, Gero D, Szabó C, Kupcsulik P, Harsányi L.** Short-term alanyl-glutamine dipeptide pretreatment in liver ischemia-reperfusion model: effects on microcirculation and antioxidant status in rats. *Clin Nutr* 26: 640–648, 2007b.
779. **Szijártó A, Hahn O, Lotz G, Schaff Z, Madarász E, Kupcsulik PK.** Effect of ischemic preconditioning on rat liver microcirculation monitored with laser Doppler flowmetry. *J Surg Res* 131: 150–157, 2006.
780. **Takada Y, Ueda M, Ishikawa Y, Fujimoto Y, Miyauchi H, Ogura Y, Ochiai T, Tanaka K.** End-to-side portocaval shunting for a small-for-size graft in living donor liver transplantation. *Liver Transpl* 10: 807–810, 2004.
781. **Takahashi-Iwanaga H, Fujita T, Takeda M.** Canine hepatic vein branches associated with subendothelial mast cells and an adventitial lymphatic plexus. *Arch Histol Cytol* 53 *Suppl*: 189–197, 1990.
782. **Takasaki S, Hano H.** Three-dimensional observations of the human hepatic artery (arterial system in the liver). *J Hepatol* 34: 455–466, 2001.
783. **Takeda S, Masuda R, Kanazawa T, Tomaru T.** Esmolol attenuates hepatic blood flow responses during sodium nitroprusside-induced hypotension in dogs. *Can J Anaesth* 51: 348–353, 2004.
784. **Takei Y, Marzi I, Gao WS, Gores GJ, Lemasters JJ, Thurman RG.** Leukocyte adhesion and cell death following orthotopic liver transplantation in the rat. *Transplantation* 51: 959–965, 1991.

785. **Takemura S, Minamiyama Y, Inoue M, Kubo S, Hirohashi K, Kinoshita H.** Nitric oxide synthase inhibitor increases hepatic injury with formation of oxidative DNA damage and microcirculatory disturbance in endotoxemic rats. *Hepatogastroenterology* 47: 1364–1370, 2000.
786. **Takeuchi D, Yoshidome H, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M, Morita Y, Miyazaki M.** Interleukin 18 causes hepatic ischemia/reperfusion injury by suppressing anti-inflammatory cytokine expression in mice. *Hepatology* 39: 699–710, 2004.
787. **Takeuchi M, Nakashima Y, Miura Y, Nakagawa K, Uragoh K, Iwanaga S, Hori Y, Sueishi K.** The localization of lipopolysaccharide in an endotoxemic rat liver and its relation to sinusoidal thrombogenesis: light and electron microscopic studies. *Pathol Res Pract* 190: 1123–1133, 1994.
788. **Tamaki N, Hatano E, Taura K, Tada M, Kodama Y, Nitta T, Iwaisako K, Seo S, Nakajima A, Ikai I, Uemoto S.** CHOP deficiency attenuates cholestasis-induced liver fibrosis by reduction of hepatocyte injury. *Am J Physiol Gastrointest Liver Physiol* 294: G498–G505, 2008.
789. **Tamandl D, Jørgensen P, Gundersen Y, Fuegger R, Sautner T, Aasen AO, Goetzinger P.** Nitric oxide administration restores the hepatic artery buffer response during porcine endotoxemia. *J Invest Surg* 21: 183–194, 2008.
790. **Tamori K, Yoneda M, Nakamura K, Makino I.** Effect of intracisternal thyrotropin-releasing hormone on hepatic blood flow in rats. *Am J Physiol Gastrointest Liver Physiol* 274: G277–G282, 1998.
791. **Tan DX, Manchester LC, Terron MP, Flores LJ, Reiter RJ.** One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? *J Pineal Res* 42: 28–42, 2007.
792. **Tanaka Y, Hayashi N, Kaneko A, Ito T, Horimoto M, Sasaki Y, Kasahara A, Fusamoto H, Kamada T.** Characterization of signaling pathways to Na^+/H^+ exchanger activation with epidermal growth factor in hepatocytes. *Hepatology* 20: 966–974, 1994.
793. **Taneja C, Prescott L, Koneru B.** Critical preservation injury in rat fatty liver is to hepatocytes, not sinusoidal lining cells. *Transplantation* 65: 167–172, 1998.
794. **Taniai H, Hines IN, Bharwani S, Maloney RE, Nimura Y, Gao B, Flores SC, McCord JM, Grisham MB, Aw TY.** Susceptibility of murine periportal hepatocytes to hypoxia-reoxygenation: role for NO and Kupffer cell-derived oxidants. *Hepatology* 39: 1544–1552, 2004.
795. **Taniai H, Suematsu M, Suzuki T, Norimizu S, Hori R, Ishimura Y, Nimura Y.** Endothelin B receptor-mediated protection against anoxia-reoxygenation injury in perfused rat liver: nitric oxide-dependent and -independent mechanisms. *Hepatology* 33: 894–901, 2001.
796. **Taniguchi M, Shimamura T, Suzuki T, Yamashita K, Oura T, Watanabe M, Kamiyama T, Matsushita M, Furukawa H, Todo S.** Transient portacaval shunt for a small-for-size graft in living donor liver transplantation. *Liver Transpl* 13: 932–934, 2007.
797. **Tawadrous MN, Zhang XY, Wheatley AM.** Microvascular origin of laser-Doppler flux signal from the surface of normal and injured liver of the rat. *Microvasc Res* 62: 355–365, 2001.
798. **Tawadrous MN, Zimmermann A, Zhang XY, Wheatley AM.** Persistence of impaired hepatic microcirculation after nonarterialized liver transplantation in the rat. *Microcirculation* 9: 363–375, 2002.
799. **Tazi KA, Bièche I, Paradis V, Guichard C, Laurendeau I, Dargère D, Legrand A, Fay M, Pedruzzi E, Robin MA, Cazals-Hatem D, Tellier Z, Bernuau D, Feldmann G, Vidaud M, Lebrec D, Ogier-Denis E, Moreau R.** in vivo altered unfolded protein response and apoptosis in livers from lipopolysaccharide-challenged cirrhotic rats. *J Hepatol* 46: 1075–1088, 2007.
800. **Teoh N, Dela Pena A, Farrell G.** Hepatic ischemic preconditioning in mice is associated with activation of NF-kappaB, p38 kinase, and cell cycle entry. *Hepatology* 36: 94–102, 2002.
801. **Teoh N, Field J, Farrell G.** Interleukin-6 is a key mediator of the hepatoprotective and pro-proliferative effects of ischaemic preconditioning in mice. *J Hepatol* 45: 20–27, 2006.
802. **Teoh N, Leclercq I, Pena AD, Farrell G.** Low-dose TNF-α protects against hepatic ischemia-reperfusion injury in mice: implications for preconditioning. *Hepatology* 37: 118–128, 2003.
803. **Teoh NC, Farrell GC.** Hepatic ischemia reperfusion injury: pathogenic mechanisms and basis for hepatoprotection. *J Gastroenterol Hepatol* 18: 891–902, 2003.
804. **Terajima H, Enders G, Thiaener A, Hammer C, Kondo T, Thiery J, Yamamoto Y, Yamaoka Y, Messmer K.** Impact of hyperthermic preconditioning on postischemic hepatic microcirculatory disturbances in an isolated perfusion model of the rat liver. *Hepatology* 31: 407–415, 2000.
805. **Terajima H, Kondo T, Enders G, Hammer C, Thiery J, Yamamoto Y, Yamaoka Y, Messmer K.** Reduction of hepatic microcirculatory failure caused by normothermic ischemia/reperfusion-induced injury by means of heat shock preconditioning. *Shock* 12: 329–334, 1999.
806. **Teutsch HF, Schuerfeld D, Groezinger E.** Three-dimensional reconstruction of parenchymal units in the liver of the rat. *Hepatology* 29: 494–505, 1999.
807. **Theruvath TP, Zhong Z, Currin RT, Ramshesh VK, Lemasters JJ.** Endothelial nitric oxide synthase protects transplanted mouse livers against storage/reperfusion injury: role of vasodilatory and innate immunity pathways. *Transplant Proc* 38: 3351–3357, 2006.
808. **Thiele GM, Duryee MJ, Freeman TL, Sorrell MF, Willis MS, Tuma DJ, Klassen LW.** Rat sinusoidal liver endothelial cells (SECs) produce pro-fibrotic factors in response to adducts formed from the metabolites of ethanol. *Biochem Pharmacol* 70: 1593–1600, 2005.
809. **Thies JC, Teklote J, Clauer U, Töx U, Klar E, Hofmann WJ, Herfarth C, Otto G.** The efficacy of *N*-acetylcysteine as a hepatoprotective agent in liver transplantation. *Transpl Int* 11, *Suppl* 1: S390–S392, 1998.
810. **Thomson RY, Clarke AM.** Role of portal blood supply in liver regeneration. *Nature* 208: 392–393, 1965.
811. **Thornton AJ, Strieter RM, Lindley I, Baggiolini M, Kunkel SL.** Cytokine-induced gene expression of a neutrophil chemotactic factor/IL-8 in human hepatocytes. *J Immunol* 144: 2609–2613, 1990.
812. **Tirona RG, Schwab AJ, Geng W, Pang KS.** Hepatic clearance models: comparison of the dispersion and Goresky models in outflow profiles from multiple indicator dilution rat liver studies. *Drug Metab Dispos* 26: 465–475, 1998.
813. **Totsuka E, Todo S, Zhu Y, Ishizaki N, Kawashima Y, Jin MB, Urakami A, Shimamura T, Starzl TE.** Attenuation of ischemic liver injury by prostaglandin E_1 analogue, misoprostol, and prostaglandin I_2 analogue, OP-41483. *J Am Coll Surg* 187: 276–286, 1998.
814. **Tracz MJ, Juncos JP, Grande JP, Croatt AJ, Ackerman AW, Rajagopalan G, Knutson KL, Badley AD, Griffin MD, Alam J, Nath KA.** Renal hemodynamic, inflammatory, and apoptotic responses to lipopolysaccharide in HO-1−/− mice. *Am J Pathol* 170: 1820–1830, 2007.
815. **Träger K, Matejovic M, Zülke C, Vlatten A, Vogt J, Wachter U, Altherr J, Brinkmann A, Jauch KW, Georgieff M, Radermacher P.** Hepatic O_2 exchange and liver energy metabolism in hyperdynamic porcine endotoxemia: effects of iloprost. *Intensive Care Med* 26: 1531–1539, 2000.
816. **Tran CT, Leiper JM, Vallance P.** The DDAH/ADMA/NOS pathway. *Atheroscler Suppl* 4: 33–40, 2003.
817. **Tran Duc AT, Schwab AJ, Simard A, Villeneuve L, Dupuis J.** Reduction in hepatic endothelin-1 clearance in cirrhosis. *Clin Sci* 105: 227–234, 2003.
818. **Troisi R, Cammu G, Militerno G, De Baerdemaeker L, Decruyenaere J, Hoste E, Smeets P, Colle I, Van Vlierberghe H, Petrovic M, Voet D, Mortier E, Hesse UJ, de Hemptinne B.** Modulation of portal graft inflow: a necessity in adult living-donor liver transplantation? *Ann Surg* 237: 429–436, 2003.
819. **Troisi R, de Hemptinne B.** Clinical relevance of adapting portal vein flow in living donor liver transplantation in adult patients. *Liver Transpl* 9: S36–S41, 2003.
820. **Troisi R, Ricciardi S, Smeets P, Petrovic M, Van Maele G, Colle I, Van Vlierberghe H, de Hemptinne B.** Effects of hemiportocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. *Am J Transplant* 5: 1397–1404, 2005.

821. **Tsuchihashi S, Fondevila C, Kupiec-Weglinski JW.** Heme oxygenase system in ischemia and reperfusion injury. *Ann Transplant* 9: 84–87, 2004.
822. **Tsuchihashi S, Fondevila C, Shaw GD, Lorenz M, Marquette K, Benard S, Shen XD, Ke B, Busuttil RW, Kupiec-Weglinski JW.** Molecular characterization of rat leukocyte P-selectin glycoprotein ligand-1 and effect of its blockade: protection from ischemia-reperfusion injury in liver transplantation. *J Immunol* 176: 616–624, 2006.
823. **Tsung A, Hoffman RA, Izuishi K, Critchlow ND, Nakao A, Chan MH, Lotze MT, Geller DA, Billiar TR.** Hepatic ischemia/reperfusion injury involves functional TLR4 signaling in nonparenchymal cells. *J Immunol* 175: 7661–7668, 2005.
824. **Tsung A, Klune JR, Zhang X, Jeyabalan G, Cao Z, Peng X, Stolz DB, Geller DA, Rosengart MR, Billiar TR.** HMGB1 release induced by liver ischemia involves Toll-like receptor 4 dependent reactive oxygen species production and calcium-mediated signaling. *J Exp Med* 204: 2913–2923, 2007.
825. **Tsung A, Sahai R, Tanaka H, Nakao A, Fink MP, Lotze MT, Yang H, Li J, Tracey KJ, Geller DA, Billiar TR.** The nuclear factor HMGB1 mediates hepatic injury after murine liver ischemia-reperfusion. *J Exp Med* 201: 1135–1143, 2005.
826. **Tsutsui H, Adachi K, Seki E, Nakanishi K.** Cytokine-induced inflammatory liver injuries. *Curr Mol Med* 3: 545–559, 2003.
827. **Tsutsui H, Matsui K, Okamura H, Nakanishi K.** Pathophysiological roles of interleukin-18 in inflammatory liver diseases. *Immunol Rev* 174: 192–209, 2000.
828. **Tukov FF, Luyendyk JP, Ganey PE, Roth RA.** The role of tumor necrosis factor α in lipopolysaccharide/ranitidine-induced inflammatory liver injury. *Toxicol Sci* 100: 267–280, 2007.
829. **Tweardy DJ, Khoshnevis MR, Yu B, Mastrangelo MA, Hardison EG, López JA.** Essential role for platelets in organ injury and inflammation in resuscitated hemorrhagic shock. *Shock* 26: 386–390, 2006.
830. **Uchida Y, Kaibori M, Hijikawa T, Ishizaki M, Ozaki T, Tanaka H, Matsui K, Tokuhara K, Kwon AH, Kamiyama Y, Okumura T.** Protective effect of neutrophil elastase inhibitor (FR136706) in lethal acute liver failure induced by D-galactosamine and lipopolysaccharide in rats. *J Surg Res* 145: 57–65, 2008.
831. **Uchimura E, Kodaira T, Kurosaka K, Yang D, Watanabe N, Kobayashi Y.** Interaction of phagocytes with apoptotic cells leads to production of pro-inflammatory cytokines. *Biochem Biophys Res Commun* 239: 799–803, 1997.
832. **Uehara T, Xi Peng X, Bennett B, Satoh Y, Friedman G, Currin R, Brenner DA, Lemasters J.** c-Jun N-terminal kinase mediates hepatic injury after rat liver transplantation. *Transplantation* 78: 324–332, 2004.
833. **Uesugi T, Froh M, Arteel GE, Bradford BU, Wheeler MD, Gäbele E, Isayama F, Thurman RG.** Role of lipopolysaccharide-binding protein in early alcohol-induced liver injury in mice. *J Immunol* 168: 2963–2969, 2002.
834. **Uhlmann D, Gaebel G, Armann B, Ludwig S, Hess J, Pietsch UC, Fiedler M, Tannapfel A, Hauss J, Witzigmann H.** Attenuation of proinflammatory gene expression and microcirculatory disturbances by endothelin A receptor blockade after orthotopic liver transplantation in pigs. *Surgery* 139: 61–72, 2006.
835. **Uhlmann D, Glasser S, Gaebel G, Armann B, Ludwig S, Tannapfel A, Hauss J, Witzigmann H.** Improvement of postischemic hepatic microcirculation after endothelinA receptor blockade–endothelin antagonism influences platelet-endothelium interactions. *J Gastrointest Surg* 9: 187–197, 2005.
836. **Uhlmann D, Glasser S, Lauer H, Ludwig S, Gaebel G, Serr F, Hauss J, Witzigmann H.** Endothelin—a receptor blockade improves postischemic hepatic microhemodynamics. *J Cardiovasc Pharmacol* 44, *Suppl* 1: S103–S104, 2004.
837. **Uhlmann D, Uhlmann S, Spiegel HU.** Endothelin/nitric oxide balance influences hepatic ischemia-reperfusion injury. *J Cardiovasc Pharmacol* 36, *Suppl* 1: S212–S214, 2000.
838. **Uhlmann D, Uhlmann S, Spiegel HU.** Important role for endothelins in acute hepatic ischemia/reperfusion injury. *J Invest Surg* 14: 31–45, 2001.
839. **Um SH, Nishida O, Tokubayashi M, Kimura F, Takimoto Y, Yoshioka H, Inque R, Kita T.** Hemodynamic changes after ligation of a major branch of the portal vein in rats: comparison with rats with portal vein constriction. *Hepatology* 19: 202–209, 1994.
840. **Urbanowicz W, Sogni P, Moreau R, Tazi KA, Barriere E, Poirel O, Martin A, Guimont MC, Cazals-Hatem D, Lebrec D.** Tezosentan, an endothelin receptor antagonist, limits liver injury in endotoxin challenged cirrhotic rats. *Gut* 53: 1844–1849, 2004.
841. **Vachharajani TJ, Work J, Issekutz AC, Granger DN.** Heme oxygenase modulates selectin expression in different regional vascular beds. *Am J Physiol Heart Circ Physiol* 278: H1613–H1617, 2000.
842. **Vairetti M, Ferrigno A, Bertone R, Rizzo V, Richelmi P, Bertè F, Reiter RJ, Freitas I.** Exogenous melatonin enhances bile flow and ATP levels after cold storage and reperfusion in rat liver: implications for liver transplantation. *J Pineal Res* 38: 223–230, 2005.
843. **Vajdová K, Heinrich S, Tian Y, Graf R, Clavien PA.** Ischemic preconditioning and intermittent clamping improve murine hepatic microcirculation and Kupffer cell function after ischemic injury. *Liver Transpl* 10: 520–528, 2004.
844. **Van Amersfoort ES, Van Berkel TJ, Kuiper J.** Receptors, mediators, and mechanisms involved in bacterial sepsis and septic shock. *Clin Microbiol Rev* 16: 379–414, 2003.
845. **Van Andel RA, Hook RR Jr, Franklin CL, Besch-Williford CL, van Rooijen N, Riley LK.** Effects of neutrophil, natural killer cell, and macrophage depletion on murine *Clostridium piliforme* infection. *Infect Immun* 65: 2725–2731, 1997.
846. **Van Beers BE, Materne R, Annet L, Hermoye L, Sempoux C, Peeters F, Smith AM, Jamart J, Horsmans Y.** Capillarization of the sinusoids in liver fibrosis: noninvasive assessment with contrast-enhanced MRI in the rabbit. *Magn Reson Med* 49: 692–699, 2003.
847. **Van Berkel TJ, Van Eck M, Herijgers N, Fluiter K, Nion S.** Scavenger receptor classes A and B. Their roles in atherogenesis and the metabolism of modified LDL and HDL. *Ann NY Acad Sci* 902: 113–126, 2000.
848. **Van Oosten M, van de Bilt E, de Vries HE, van Berkel TJ, Kuiper J.** Vascular adhesion molecule-1 and intercellular adhesion molecule-1 expression on rat liver cells after lipopolysaccharide administration in vivo. *Hepatology* 22: 1538–1546, 1995.
849. **Van Oosten M, van de Bilt E, van Berkel TJ, Kuiper J.** New scavenger receptor-like receptors for the binding of lipopolysaccharide to liver endothelial and Kupffer cells. *Infect Immun* 66: 5107–5112, 1998.
850. **Vardareli E, Saricam T, Koken T, Degirmenci I, Aral E, Erenoglu E.** The effect of α-tocopherol and pentoxyfilline on ischemia-reperfusion induced liver injury in rats. *Hepatogastroenterology* 45: 1505–1508, 1998.
851. **Verdrengh M, Tarkowski A.** Role of neutrophils in experimental septicemia and septic arthritis induced by *Staphylococcus aureus*. *Infect Immun* 65: 2517–2521, 1997.
852. **Vilatoba M, Eckstein C, Bilbao G, Smyth CA, Jenkins S, Thompson JA, Eckhoff DE, Contreras JL.** Sodium 4-phenylbutyrate protects against liver ischemia reperfusion injury by inhibition of endoplasmic reticulum-stress mediated apoptosis. *Surgery* 138: 342–351, 2005.
853. **Villeneuve JP, Dagenais M, Huet PM, Roy A, Lapointe R, Marleau D.** The hepatic microcirculation in the isolated perfused human liver. *Hepatology* 23: 24–31, 1996.
854. **Vodovotz Y, Kim PK, Bagci EZ, Ermentrout GB, Chow CC, Bahar I, Billiar TR.** Inflammatory modulation of hepatocyte apoptosis by nitric oxide: in vivo, in vitro, and in silico studies. *Curr Mol Med* 4: 753–762, 2004.
855. **Vogten JM, Smakman N, Voest EE, Borel Rinkes IH.** Intravital analysis of microcirculation in the regenerating mouse liver. *J Surg Res* 113: 264–269, 2003.
856. **Vollmar B, Burkhardt M, Minor T, Klauke H, Menger MD.** High-resolution microscopic determination of hepatic NADH fluorescence for in vivo monitoring of tissue oxygenation during hemorrhagic shock and resuscitation. *Microvasc Res* 54: 164–173, 1997.
857. **Vollmar B, Conzen P, Habazettl H, Adili F, Peter K.** Does nitrous oxide affect coronary microcirculation? An intravital microscopic study in the canine heart. *Anesth Analg* 80: 249–255, 1995a.

858. **Vollmar B, Conzen PF, Kerner T, Habazettl H, Vierl M, Waldner H, Peter K.** Blood flow and tissue oxygen pressures of liver and pancreas in rats: effects of volatile anesthetics and of hemorrhage. *Anesth Analg* 75: 421–430, 1992.
859. **Vollmar B, Glasz J, Leiderer R, Post S, Menger MD.** Hepatic microcirculatory perfusion failure is a determinant of liver dysfunction in warm ischemia-reperfusion. *Am J Pathol* 145: 1421–1431, 1994.
860. **Vollmar B, Glasz J, Menger MD, Messmer K.** Leukocytes contribute to hepatic ischemia/reperfusion injury via intercellular adhesion molecule-1-mediated venular adherence. *Surgery* 117: 195–200, 1995b.
861. **Vollmar B, Glasz J, Post S, Menger MD.** Depressed phagocytic activity of Kupffer cells after warm ischemia-reperfusion of the liver. *J Hepatol* 20: 301–304, 1994.
862. **Vollmar B, Glasz J, Post S, Menger MD.** Role of microcirculatory derangements in manifestation of portal triad cross-clamping-induced hepatic reperfusion injury. *J Surg Res* 60: 49–54, 1996.
863. **Vollmar B, Heckmann C, Richter S, Menger MD.** High, but not low, dietary retinoids aggravate manifestation of rat liver fibrosis. *J Gastroenterol Hepatol* 17: 791–799, 2002.
864. **Vollmar B, Lang G, Menger MD, Messmer K.** Hypertonic hydroxyethyl starch restores hepatic microvascular perfusion in hemorrhagic shock. *Am J Physiol Heart Circ Physiol* 266: H1927–H1934, 1994.
865. **Vollmar B, Menger MD, Glasz J, Leiderer R, Messmer K.** Impact of leukocyte-endothelial cell interaction in hepatic ischemia-reperfusion injury. *Am J Physiol Gastrointest Liver Physiol* 267: G786–G793, 1994.
866. **Vollmar B, Messner S, Wanner GA, Hartung T, Menger MD.** Immunomodulatory action of G-CSF in a rat model of endotoxin-induced liver injury: an intravital microscopic analysis of Kupffer cell and leukocyte response. *J Leukoc Biol* 62: 710–718, 1997.
867. **Vollmar B, Pradarutti S, Richter S, Menger MD.** In vivo quantification of ageing changes in the rat liver from early juvenile to senescent life. *Liver* 22: 330–341, 2002.
868. **Vollmar B, Richter S, Menger MD.** Leukocyte stasis in hepatic sinusoids. *Am J Physiol Gastrointest Liver Physiol* 270: G798–G803, 1996.
869. **Vollmar B, Richter S, Menger MD.** Liver ischemia/reperfusion induces an increase of microvascular leukocyte flux, but not heterogeneity of leukocyte trafficking. *Liver* 17: 93–98, 1997.
870. **Vollmar B, Rücker M, Menger MD.** A new method for the intravital microscopic quantification of hepatic sinusoidal perfusion failure using the dye bisbenzamide H33342. *Microvasc Res* 51: 250–259, 1996.
871. **Vollmar B, Rüttinger D, Wanner GA, Leiderer R, Menger MD.** Modulation of Kupffer cell activity by gadolinium chloride in endotoxemic rats. *Shock* 6: 434–441, 1996.
872. **Vollmar B, Senkel A, Menger MD.** In vivo evidence that intercellular adhesion molecule-1 does not mediate endotoxin-induced hepatic leukocyte-endothelial cell interaction. *J Hepatol* 23: 613–616, 1995.
873. **Vollmar B, Siegmund S, Menger MD.** An intravital fluorescence microscopic study of hepatic microvascular and cellular derangements in developing cirrhosis in rats. *Hepatology* 27: 1544–1553, 1998.
874. **Vollmar B, Slotta JE, Nickels RM, Wenzel E, Menger MD.** Comparative analysis of platelet isolation techniques for the in vivo study of the microcirculation. *Microcirculation* 10: 143–152, 2003.
875. **Vollmar B, Wolf B, Siegmund S, Katsen AD, Menger MD.** Lymph vessel expansion and function in the development of hepatic fibrosis and cirrhosis. *Am J Pathol* 151: 169–175, 1997.
876. **Volpes R, van den Oord JJ, Desmet VJ.** Immunohistochemical study of adhesion molecules in liver inflammation. *Hepatology* 12: 59–65, 1990.
877. **Von Ruecker AA, Wild M, Rao GS, Bidlingmaier F.** Atrial natriuretic peptide protects hepatocytes against damage induced by hypoxia and reactive oxygen. Possible role of intracellular free ionized calcium. *J Clin Chem Clin Biochem* 27: 531–537, 1989.
878. **Waller A.** Microscopic examination of some of the principal tissues of the animal frame, as observed in the tongue of the living frog and toad. *Philos Mag J Sci* 29: 397–405, 1846.
879. **Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, Frazier A, Yang H, Ivanova S, Borovikova L, Manogue KR, Faist E, Abraham E, Andersson J, Andersson U, Molina PE, Abumrad NN, Sama A, Tracey KJ.** HMG-1 as a late mediator of endotoxin lethality in mice. *Science* 285: 248–251, 1999.
880. **Wang HH, Lautt WW.** Evidence of nitric oxide, a flow-dependent factor, being a trigger of liver regeneration in rats. *Can J Physiol Pharmacol* 76: 1072–1079, 1998.
881. **Wang HS, Ohkohchi N, Enomoto Y, Usuda M, Miyagi S, Asakura T, Masuoka H, Aiso T, Fukushima K, Narita T, Yamaya H, Nakamura A, Sekiguchi S, Kawagishi N, Sato A, Satomi S.** Excessive portal flow causes graft failure in extremely small-for-size liver transplantation in pigs. *World J Gastroenterol* 11: 6954–6959, 2005.
882. **Wang JF, Komarov P, Sies H, de Groot H.** Inhibition of superoxide and nitric oxide release and protection from reoxygenation injury by Ebselen in rat Kupffer cells. *Hepatology* 15: 1112–1116, 1992.
883. **Wang P, Ayala A, Ba ZF, Zhou M, Perrin MM, Chaudry IH.** Tumor necrosis factor-α produces hepatocellular dysfunction despite normal cardiac output and hepatic microcirculation. *Am J Physiol Gastrointest Liver Physiol* 265: G126–G132, 1993.
884. **Wang P, Ba ZF, Burkhardt J, Chaudry IH.** Measurement of hepatic blood flow after severe hemorrhage: lack of restoration despite adequate resuscitation. *Am J Physiol Gastrointest Liver Physiol* 262: G92–G98, 1992.
885. **Wang P, Ba ZF, Galardy RE, Chaudry IH.** Administration of a matrix metalloproteinase inhibitor after hemorrhage improves cardiovascular and hepatocellular function. *Shock* 6: 377–382, 1996.
886. **Wang WW, Smith DL, Zucker SD.** Bilirubin inhibits iNOS expression and NO production in response to endotoxin in rats. *Hepatology* 40: 424–433, 2004.
887. **Wanner GA, Mica L, Wanner-Schmid E, Kolb SA, Hentze H, Trentz O, Ertel W.** Inhibition of caspase activity prevents CD95-mediated hepatic microvascular perfusion failure and restores Kupffer cell clearance capacity. *FASEB J* 13: 1239–1248, 1999.
888. **Warren A, Chaberek S, Ostrowski K, Cogger VC, Hilmer SN, McCuskey RS, Fraser R, Le Couteur DG.** Effects of old age on vascular complexity and dispersion of the hepatic sinusoidal network. *Microcirculation* 15: 191–202, 2008.
889. **Warren A, Le Couteur DG, Fraser R, Bowen DG, McCaughan GW, Bertolino P.** T lymphocytes interact with hepatocytes through fenestrations in murine liver sinusoidal endothelial cells. *Hepatology* 44: 1182–1190, 2006.
890. **Warren DJ, Ledingham JG.** Measurement of cardiac output distribution using microspheres. Some practical and theoretical considerations. *Cardiovasc Res* 8: 570–581, 1974.
891. **Watanabe R, Munemasa T, Matsumura M, Fujimaki M.** Fluorescent liposomes for intravital staining of Kupffer cells to aid in vivo microscopy in rats. *Methods Find Exp Clin Pharmacol* 29: 321–327, 2007.
892. **Watanabe T, Kubota S, Nagaya M, Ozaki S, Nagafuchi H, Akashi K, Taira Y, Tsukikawa S, Oowada S, Nakano S.** The role of HMGB-1 on the development of necrosis during hepatic ischemia and hepatic ischemia/reperfusion injury in mice. *J Surg Res* 124: 59–66, 2005.
893. **Watts JA, Grattan RM 2nd, Whitlow BS, Kline JA.** Activation of poly(ADP-ribose) polymerase in severe hemorrhagic shock and resuscitation. *Am J Physiol Gastrointest Liver Physiol Gastrointest Liver Physiol* 281: G498–G506, 2001.
894. **Wei Y, Weng D, Li F, Zou X, Young DO, Ji J, Shen P.** Involvement of JNK regulation in oxidative stress-mediated murine liver injury by microcystin-LR. *Apoptosis* 13: 1031–1042, 2008.
895. **Weiss M, Ballinger LN, Roberts MS.** Kinetic analysis of vascular marker distribution in perfused rat livers after regeneration following partial hepatectomy. *J Hepatol* 29: 476–481, 1998.
896. **Weng D, Lu Y, Wei Y, Liu Y, Shen P.** The role of ROS in microcystin-LR-induced hepatocyte apoptosis and liver injury in mice. *Toxicology* 232: 15–23, 2007.
897. **Wheatley AM, Almond NE, Stuart ET, Zhao D.** Interpretation of the laser Doppler flow signal from the liver of the rat. *Microvasc Res* 45: 290–301, 1993.

898. **Whiteman M, Li L, Kostetski I, Chu SH, Siau JL, Bhatia M, Moore PK.** Evidence for the formation of a novel nitrosothiol from the gaseous mediators nitric oxide and hydrogen sulphide. *Biochem Biophys Res Commun* 343: 303–310, 2006.
899. **Wiest R, Groszmann RJ.** The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. *Hepatology* 35: 478–491, 2002.
900. **Wilhelm A, Leister I, Sabandal P, Krause P, Becker H, Markus PM.** Acute impairment of hepatic microcirculation and recruitment of nonparenchymal cells by intrasplenic hepatocyte transplantation. *J Pediatr Surg* 39: 1214–1219, 2004.
901. **Wisse E, Braet F, Luo D, De Zanger R, Jans D, Crabbé E, Vermoesen A.** Structure and function of sinusoidal lining cells in the liver. *Toxicol Pathol* 24: 100–111, 1996.
902. **Wisse E, De Zanger RB, Charels K, Van Der Smissen P, McCuskey RS.** The liver sieve: considerations concerning the structure and function of endothelial fenestrae, the sinusoidal wall and the space of Disse. *Hepatology* 5: 683–692, 1985.
903. **Wisse E.** An electron microscopic study of fenestrated endothelium lining of rat liver sinusoids. *J Ultrastruct Res* 31: 125–150, 1970.
904. **Witthaut R, Farhood A, Smith CW, Jaeschke H.** Complement and tumor necrosis factor-α contribute to Mac-1 (CD11b/CD18) up-regulation and systemic neutrophil activation during endotoxemia in vivo. *J Leukoc Biol* 55: 105–111, 1994.
905. **Wong J, Johnston B, Lee SS, Bullard DC, Smith CW, Beaudet AL, Kubes P.** A minimal role for selectins in the recruitment of leukocytes into the inflamed liver microvasculature. *J Clin Invest* 99: 2782–2790, 1997.
906. **Worthen GS, Schwab B 3rd, Elson EL, Downey GP.** Mechanics of stimulated neutrophils: cell stiffening induces retention in capillaries. *Science* 245: 183–186, 1989.
907. **Wright SD, Jong MT.** Adhesion-promoting receptors on human macrophages recognize *Escherichia coli* by binding to lipopolysaccharide. *J Exp Med* 164: 1876–1888, 1986.
908. **Wu D, Zhai Q, Shi X.** Alcohol-induced oxidative stress and cell responses. *J Gastroenterol Hepatol* 21, *Suppl* 3: S26–S29, 2006.
909. **Wu J, Danielsson A, Zern MA.** Toxicity of hepatotoxins: new insights into mechanisms and therapy. *Expert Opin Investig Drugs* 8: 585–607, 1999.
910. **Wu J, Liu L, Yen RD, Catana A, Nantz MH, Zern MA.** Liposome-mediated extracellular superoxide dismutase gene delivery protects against acute liver injury in mice. *Hepatology* 40: 195–204, 2004.
911. **Wunder C, Brock RW, McCarter SD, Bihari A, Harris K, Eichelbrönner O, Potter RF.** Inhibition of haem oxygenase activity increases leukocyte accumulation in the liver following limb ischaemia-reperfusion in mice. *J Physiol* 540: 1013–1021, 2002.
912. **Wunder C, Scott JR, Lush CW, Brock RW, Bihari A, Harris K, Eichelbrönner O, Potter RF.** Heme oxygenase modulates hepatic leukocyte sequestration via changes in sinusoidal tone in systemic inflammation in mice. *Microvasc Res* 68: 20–29, 2004.
913. **Wurfel MM, Kunitake ST, Lichenstein H, Kane JP, Wright SD.** Lipopolysaccharide (LPS)-binding protein is carried on lipoproteins and acts as a cofactor in the neutralization of LPS. *J Exp Med* 180: 1025–1035, 1994.
914. **Xiang L, Klintman D, Thorlacius H.** Allopurinol inhibits CXC chemokine expression and leukocyte adhesion in endotoxemic liver injury. *Inflamm Res* 52: 353–358, 2003.
915. **Xie XQ, Shinozawa Y, Sasaki J, Takuma K, Akaishi S, Yamanouchi S, Endo T, Nomura R, Kobayashi M, Kudo D, Hojo N.** The effects of arginine and selective inducible nitric oxide synthase inhibitor on pathophysiology of sepsis in a CLP model. *J Surg Res* 146: 298–303, 2008.
916. **Xu FL, You HB, Li XH, Chen XF, Liu ZJ, Gong JP.** Glycine attenuates endotoxin-induced liver injury by downregulating TLR4 signaling in Kupffer cells. *Am J Surg* 196: 139–148, 2008.
917. **Yadav SS, Howell DN, Gao W, Steeber DA, Harland RC, Clavien PA.** L-selectin and ICAM-1 mediate reperfusion injury and neutrophil adhesion in the warm ischemic mouse liver. *Am J Physiol Gastrointest Liver Physiol* 275: G1341–G1352, 1998.
918. **Yadav SS, Sindram D, Perry DK, Clavien PA.** Ischemic preconditioning protects the mouse liver by inhibition of apoptosis through a caspase-dependent pathway. *Hepatology* 30: 1223–1231, 1999.
919. **Yamada T, Tanaka K, Uryuhara K, Ito K, Takada Y, Uemoto S.** Selective hemi-portocaval shunt based on portal vein pressure for small-for-size graft in adult living donor liver transplantation. *Am J Transplant* 8: 847–853, 2008.
920. **Yamagami K, Enders G, Schauer RJ, Leiderer R, Hutter J, Yamamoto Y, Yamaoka Y, Hammer C, Messmer K.** Heat-shock preconditioning protects fatty livers in genetically obese Zucker rats from microvascular perfusion failure after ischemia reperfusion. *Transpl Int* 16: 456–463, 2003.
921. **Yamaguchi Y, Akizuki E, Ichiguchi O, Matsumura F, Goto M, Miyanari N, Mori K, Yamada S, Ogawa M.** Neutrophil elastase inhibitor reduces neutrophil chemoattractant production after ischemia-reperfusion in rat liver. *Gastroenterology* 112: 551–560, 1997a.
922. **Yamaguchi Y, Hisama N, Okajima K, Uchiba M, Murakami K, Takahashi Y, Yamada S, Mori K, Ogawa M.** Pretreatment with activated protein C or active human urinary thrombomodulin attenuates the production of cytokine-induced neutrophil chemoattractant following ischemia/reperfusion in rat liver. *Hepatology* 25: 1136–1140, 1997b.
923. **Yamaguchi Y, Matsumura F, Liang J, Okabe K, Ohshiro H, Ishihara K, Matsuda T, Mori K, Ogawa M.** Neutrophil elastase and oxygen radicals enhance monocyte chemoattractant protein: expression after ischemia/reperfusion in rat liver. *Transplantation* 68: 1459–1468, 1999.
924. **Yamaguchi Y, Ohshiro H, Nagao Y, Odawara K, Okabe K, Hidaka H, Ishihara K, Uchino S, Furuhashi T, Yamada S, Mori K, Ogawa M.** Urinary trypsin inhibitor reduces C-X-C chemokine production in rat liver ischemia/reperfusion. *J Surg Res* 94: 107–115, 2000.
925. **Yamakawa Y, Takano M, Patel M, Tien N, Takada T, Bulkley GB.** Interaction of platelet activating factor, reactive oxygen species generated by xanthine oxidase, and leukocytes in the generation of hepatic injury after shock/resuscitation. *Ann Surg* 231: 387–398, 2000.
926. **Yamamoto K, Sherman I, Phillips MJ, Fisher MM.** Three-dimensional observations of the hepatic arterial terminations in rat, hamster and human liver by scanning electron microscopy of microvascular casts. *Hepatology* 5: 452–456, 1985.
927. **Yamamoto K.** Ultrastructural study on the venous sphincter in the sublobular vein of the canine liver. *Microvasc Res* 55: 215–222, 1998.
928. **Yamano T, Hirai R, Hato S, Uemura T, Shimizu N.** Delayed liver regeneration with negative regulation of hepatocyte growth factor and positive regulation of transforming growth factor-beta1 mRNA after portal branch ligation in biliary obstructed rats. *Surgery* 131: 163–171, 2002.
929. **Yamanouchi K, Eguchi S, Kamohara Y, Yanaga K, Okudaira S, Tajima Y, Kanematsu T.** Glycine reduces hepatic warm ischaemia-reperfusion injury by suppressing inflammatory reactions in rats. *Liver Int* 27: 1249–1254, 2007.
930. **Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Masaki T.** A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 332: 411–415, 1988.
931. **Yang BS, Ma YJ, Wang Y, Chen LY, Bi MR, Yan BZ, Bai L, Zhou H, Wang FX.** Protective effect and mechanism of stronger neominophagen C against fulminant hepatic failure. *World J Gastroenterol* 13: 462–466, 2007.
932. **Yang W, Hafez T, Thompson CS, Mikhailidis DP, Davidson BR, Winslet MC, Seifalian AM.** Direct measurement of hepatic tissue hypoxia by using a novel $tcpO_2/pCO_2$ monitoring system in comparison with near-infrared spectroscopy. *Liver Int* 23: 163–170, 2003.
933. **Yasumi Y, Takikawa Y, Endo R, Suzuki K.** Interleukin-17 as a new marker of severity of acute hepatic injury. *Hepatol Res* 37: 248–254, 2007.
934. **Yerushalmi B, Dahl R, Devereaux MW, Gumpricht E, Sokol RJ.** Bile acid-induced rat hepatocyte apoptosis is inhibited by antioxidants and blockers of the mitochondrial permeability transition. *Hepatology* 33: 616–626, 2001.

935. **Yilmaz S, Ates E, Tokyol C, Pehlivan T, Erkasap S, Koken T.** The protective effect of erythropoietin on ischaemia/reperfusion injury of liver. *HPB* 6: 169–173, 2004.
936. **Yokomori H, Oda M, Yoshimura K, Nomura M, Wakabayashi G, Kitajima M, Ishii H.** Elevated expression of caveolin-1 at protein and mRNA level in human cirrhotic liver: relation with nitric oxide. *J Gastroenterol* 38: 854–860, 2003.
937. **Yokoyama Y, Baveja R, Sonin N, Nakanishi K, Zhang JX, Clemens MG.** Altered endothelin receptor subtype expression in hepatic injury after ischemia/reperfusion. *Shock* 13: 72–78, 2000.
938. **Yokoyama Y, Nimura Y, Nagino M, Bland KI, Chaudry IH.** Role of thromboxane in producing hepatic injury during hepatic stress. *Arch Surg* 140: 801–807, 2005.
939. **Yokoyama Y, Wawrzyniak A, Baveja R, Sonin N, Clemens MG, Zhang JX.** Altered endothelin receptor expression in prehepatic portal hypertension predisposes the liver to microcirculatory dysfunction in rats. *J Hepatol* 35: 29–36, 2001.
940. **Yoshidome H, Kato A, Edwards MJ, Lentsch AB.** Interleukin-10 suppresses hepatic ischemia/reperfusion injury in mice: implications of a central role for nuclear factor kappaB. *Hepatology* 30: 203–208, 1999.
941. **Yoshidome H, Kato A, Miyazaki M, Edwards MJ, Lentsch AB.** IL-13 activates STAT6 and inhibits liver injury induced by ischemia/reperfusion. *Am J Pathol* 155: 1059–1064, 1999.
942. **Yoshikawa A, Kaido T, Seto S, Katsuura Y, Imamura M.** Activated protein C prevents multiple organ injury following extensive hepatectomy in cirrhotic rats. *J Hepatol* 33: 953–960, 2000.
943. **Yoshizumi T, Yanaga K, Soejima Y, Maeda T, Uchiyama H, Sugimachi K.** Amelioration of liver injury by ischaemic preconditioning. *Br J Surg* 85: 1636–1640, 1998.
944. **Yu Q, Shao R, Qian HS, George SE, Rockey DC.** Gene transfer of the neuronal NO synthase isoform to cirrhotic rat liver ameliorates portal hypertension. *J Clin Invest* 105: 741–748, 2000.
945. **Yu SY, Chiu JH, Yang SD, Yu HY, Hsieh CC, Chen PJ, Lui WY, Wu CW.** Preconditioned hyperbaric oxygenation protects the liver against ischemia-reperfusion injury in rats. *J Surg Res* 128: 28–36, 2005.
946. **Zaedi S, Jesmin S, Yamaguchi N, Shimojo N, Maeda S, Gando S, Yamaguchi I, Goto K, Miyauchi T.** Altered expression of endothelin, vascular endothelial growth factor, and its receptor in hepatic tissue in endotoxemic rat. *Exp Biol Med* 231: 1182–1186, 2006.
947. **Zamara E, Galastri S, Aleffi S, Petrai I, Aragno M, Mastrocola R, Novo E, Bertolani C, Milani S, Vizzutti F, Vercelli A, Pinzani M, Laffi G, LaVilla G, Parola M, Marra F.** Prevention of severe toxic liver injury and oxidative stress in MCP-1-deficient mice. *J Hepatol* 46: 230–238, 2007.
948. **Zanardo RC, Brancaleone V, Distrutti E, Fiorucci S, Cirino G, Wallace JL.** Hydrogen sulfide is an endogenous modulator of leukocyte-mediated inflammation. *FASEB J* 20: 2118–2120, 2006.
949. **Zapletal C, Heyne S, Breitkreutz R, Gebhard MM, Golling M.** The influence of selenium substitution on microcirculation and glutathione metabolism after warm liver ischemia/reperfusion in a rat model. *Microvasc Res* 76: 104–109, 2008.
950. **Zhai Y, Shen XD, Hancock WW, Gao F, Qiao B, Lassman C, Belperio JA, Strieter RM, Busuttil RW, Kupiec-Weglinski JW.** CXCR3+CD4+ T cells mediate innate immune function in the pathophysiology of liver ischemia/reperfusion injury. *J Immunol* 176: 6313–6322, 2006.
951. **Zhang B, Borderie D, Sogni P, Soubrane O, Houssin D, Calmus Y.** NO-mediated vasodilation in the rat liver. Role of hepatocytes and liver endothelial cells. *J Hepatol* 26: 1348–1355, 1997.
952. **Zhang H, Zhi L, Moochhala SM, Moore PK, Bhatia M.** Endogenous hydrogen sulfide regulates leukocyte trafficking in cecal ligation and puncture-induced sepsis. *J Leukoc Biol* 82: 894–905, 2007.
953. **Zhang H, Zhi L, Moore PK, Bhatia M.** Role of hydrogen sulfide in cecal ligation and puncture-induced sepsis in the mouse. *Am J Physiol Lung Cell Mol Physiol* 290: L1193–L1201, 2006a.
954. **Zhang JX, Bauer M, Clemens MG.** Vessel- and target cell-specific actions of endothelin-1 and endothelin-3 in rat liver. *Am J Physiol Gastrointest Liver Physiol* 269: G269–G277, 1995.
955. **Zhang JX, Jones DV, Clemens MG.** Effect of activation on neutrophil-induced hepatic microvascular injury in isolated rat liver. *Shock* 1: 273–278, 1994.
956. **Zhang JX, Wu HS, Wang H, Zhang JH, Wang Y, Zheng QC.** Protection against hepatic ischemia/reperfusion injury via downregulation of toll-like receptor 2 expression by inhibition of Kupffer cell function. *World J Gastroenterol* 11: 4423–4426, 2005.
957. **Zhang P, Xie M, Zagorski J, Spitzer JA.** Attenuation of hepatic neutrophil sequestration by anti-CINC antibody in endotoxic rats. *Shock* 4: 262–268, 1995.
958. **Zhang WH, Li JY, Zhou Y.** Melatonin abates liver ischemia/reperfusion injury by improving the balance between nitric oxide and endothelin. *Hepatobiliary Pancreat Dis Int* 5: 574–579, 2006b.
959. **Zhang Y, Ikejima K, Honda H, Kitamura T, Takei Y, Sato N.** Glycine prevents apoptosis of rat sinusoidal endothelial cells caused by deprivation of vascular endothelial growth factor. *Hepatology* 32: 542–546, 2000.
960. **Zhang Y, Qi X, Gong L, Li Y, Liu L, Xue X, Xiao Y, Wu X, Ren J.** Roles of reactive oxygen species and MAP kinases in the primary rat hepatocytes death induced by toosendanin. *Toxicology* 249: 62–68, 2008.
961. **Zhao W, Zhang J, Lu Y, Wang R.** The vasorelaxant effect of H_2S as a novel endogenous gaseous K(ATP) channel opener. *EMBO J* 20: 6008–6016, 2001.
962. **Zhi L, Ang AD, Zhang H, Moore PK, Bhatia M.** Hydrogen sulfide induces the synthesis of proinflammatory cytokines in human monocyte cell line U937 via the ERK-NF-kappaB pathway. *J Leukoc Biol* 81: 1322–1332, 2007.
963. **Zhong Z, Jones S, Thurman RG.** Glycine minimizes reperfusion injury in a low-flow, reflow liver perfusion model in the rat. *Am J Physiol Gastrointest Liver Physiol* 270: G332–G338, 1996.
964. **Zhong Z, Theruvath TP, Currin RT, Waldmeier PC, Lemasters JJ.** NIM811, a mitochondrial permeability transition inhibitor, prevents mitochondrial depolarization in small-for-size rat liver grafts. *Am J Transplant* 7: 1103–1111, 2007.
965. **Zhong Z, Wheeler MD, Li X, Froh M, Schemmer P, Yin M, Bunzendaul H, Bradford B, Lemasters JJ.** L-Glycine: a novel antiinflammatory, immunomodulatory, and cytoprotective agent. *Curr Opin Clin Nutr Metab Care* 6: 229–240, 2003.
966. **Zhou Q, Hennenberg M, Trebicka J, Jochem K, Leifeld L, Biecker E, Sauerbruch T, Heller J.** Intrahepatic upregulation of RhoA and Rho-kinase signalling contributes to increased hepatic vascular resistance in rats with secondary biliary cirrhosis. *Gut* 55: 1296–1305, 2006.
967. **Zhou W, Zhang Y, Hosch MS, Lang A, Zwacka RM, Engelhardt JF.** Subcellular site of superoxide dismutase expression differentially controls AP-1 activity and injury in mouse liver following ischemia/reperfusion. *Hepatology* 33: 902–914, 2001.
968. **Ziegler-Heitbrock HW, Ulevitch RJ.** CD14: cell surface receptor and differentiation marker. *Immunol Today* 14: 121–125, 1993.
969. **Zimmerhackl B, Parekh N, Brinkhus H, Steinhausen M.** The use of fluorescent labeled erythrocytes for intravital investigation of flow and local hematocrit in glomerular capillaries in the rat. *Int J Microcirc Clin Exp* 2: 119–129, 1983.
970. **Zinchuk VS, Okada T, Seguchi H.** Lipopolysaccharide alters ecto-ATP-diphosphohydrolase and causes relocation of its reaction product in experimental intrahepatic cholestasis. *Cell Tissue Res* 304: 103–109, 2001.
971. **Ziol M, Tepper M, Lohez M, Arcangeli G, Ganne N, Christidis C, Trinchet JC, Beaugrand M, Guillet JG, Guettier C.** Clinical and biological relevance of hepatocyte apoptosis in alcoholic hepatitis. *J Hepatol* 34: 254–260, 2001.
972. **Zipprich A, Steudel N, Behrmann C, Meiss F, Sziegoleit U, Fleig WE, Kleber G.** Functional significance of hepatic arterial flow reserve in patients with cirrhosis. *Hepatology* 37: 385–392, 2003.
973. **Zipprich A.** Hemodynamics in the isolated cirrhotic liver. *J Clin Gastroenterol* 41 *Suppl* 3: S254–S258, 2007.
974. **Zuo GQ, Gong JP, Liu CA, Li SW, Wu XC, Yang K, Li Y.** Expression of lipopolysaccharide binding protein and its receptor CD14 in experimental alcoholic liver disease. *World J Gastroenterol* 7: 836–840, 2001.
975. **Zweifach BW.** The microcirculation in the intestinal mesentery. *Microvasc Res* 5: 363–367, 1973.

The Hepatic Microcirculation: Mechanistic Contributions and Therapeutic Targets in Liver Injury and Repair

Brigitte Vollmar and Michael D. Menger

Physiol Rev 89:1269-1339, 2009. doi:10.1152/physrev.00027.2008