Pathophysiological Changes During Ischemia-reperfusion Injury in Rodent Hepatic Steatosis

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Abstract. Background/Aim: Ischemia and reperfusion injuries may produce deleterious effects on hepatic tissue after liver surgery and transplantation. The impact of ischemia-reperfusion injury (IRI) on the liver depends on its substrate, the percentage of liver ischemic tissue subjected to IRI and the ischemia time. The consequences of IRI are more evident in pathologic liver substrates, such as steatotic livers. This review is the result of an extended bibliographic PubMed search focused on the last 20 years. It highlights basic differences encountered during IRI in lean and steatotic livers based on studies using rodent experimental models. Conclusion: The main difference in cell death between lean and steatotic livers is the prevalence of apoptosis in the former and necrosis in the latter. There are also major changes in the effect of intracellular mediators, such as TNFα and IL-1β. Further experimental studies are needed in order to increase current knowledge of IRI effects and relevant mechanisms in both lean and steatotic livers, so that new preventive and therapeutic strategies maybe developed.

Fatty liver disease represents a very common disorder with a global prevalence of 25%, and a rate of 20-30% in developed countries and up to 95% among the obese population. The existence of hepatic steatosis is a critical factor for liver surgery and transplantation and has aggravating effects when associated with ischemia-reperfusion injury (IRI) (1-7). Hepatic steatosis is associated with an operative mortality higher than 14% after extended liver resection, in contrast to 2% in patients with lean livers (8-11).

IRI refers to the enhanced cellular damage inflicted on a hypoxic liver following blood flow restoration observed in major liver resections and transplantation. Ischemia-reperfusion (IR) maneuver, which is applied to minimize blood loss during surgery, has detrimental effects on the liver due to ischemia (12-15). IR phenomena are present after restoration of reduced blood flow as a result of shock, hypotension, hypoxemia and secondary low blood flow due, for instance, to congestive heart failure (16-18). The liver substrate, the percentage of liver tissue undergoing ischemia and the duration of ischemia are critical for the viability of the hepatic tissue.

Pathophysiological Changes

The different reaction of the fatty liver to IRI is linked to its decreased ability to restore adenosine triphosphate (ATP) levels after IR stress, and its increased sensitivity to proinflammatory factors (19). Liver becomes steatotic via chronic overfeeding, triglycerides’ excess, gradual increase in the deposition of adipose tissue and adipocyte hypertrophy, as well as endoplasmic reticulum stress. The activation of apoptotic and inflammatory pathways results in increased concentration of hepatic stellate cells (HSCs) and Kupffer...
cells (KCs), which differentiate to myofibroblasts and lead to fibrosis (20). Selzner et al. have claimed that the augmented sensitivity of fatty liver is due to changes in the onset of apoptotic cell death and the types of cell death. Specifically, the main type of cell death in lean ischemic liver is rapid apoptosis, while its onset is delayed in fatty ischemic liver (10). Apoptosis requires adenosine triphosphate (ATP) and when ATP is depleted, apoptosis switches to necrosis (21). Apoptosis remains the main type of cell death in lean liver where necrosis is minimal (18%). On the other hand, fatty liver is characterized by moderate apoptosis and massive necrosis (73%). The difference between these livers has also been confirmed in experimental rat studies by evaluation of intracellular mediators of apoptosis; when the livers were subjected to 60 minutes of total hepatic ischemia, the rats with fatty livers died within 3 days, whereas those with normal livers survived 30 days (8, 10, 22).

Tiriveedhi et al. have demonstrated that even the proteome profiles of livers with steatosis subjected to IRI, are significantly different compared to lean livers (23).

During the ischemia phase, oxygen, glycogen and ATP are depleted, resulting in intracellular metabolic changes and the so-called “pH paradox”. In the early phase, due to the initiation of necrosis, intracellular pH drops so that hepatocytes are protected. Normalization of intracellular pH upon reperfusion, however, accelerates hepatocytes’ death. The supremacy of pro-oxidants characterizes the intermediate phase, while inflammatory and adhesion molecules the late phase (24, 25).

In the first two hours of reperfusion, oxidative stress is dominant. Activated endothelial cells of microvessels generate additional reactive oxygen species (ROS) and less nitric oxide (NO), causing immediate cellular injury (24-26). The subsequent imbalance between superoxide and NO in endothelial cells leads to an increase in pro-inflammatory factors (25). During the following 6-48 hours of reperfusion, activated neutrophils injure hepatocytes via inflammatory mechanisms mediating the release of ROS, elastase, cathepsin G, heparinase, collagenase and hydrolytic enzymes (24, 26).

Frequently encountered pathophysiological changes and differences between lean and steatotic livers regarding mainly IRI, are described below. The main parameters that increase are listed in Table I.

Mitochondral injury generally leads to cell necrosis and apoptosis in IRI. i. Mitochondria uncoupling protein-2 (UCP2) expression is normally cytoprotective when augmented by mitochondrial superoxide production. Nevertheless, during IR, UCP2 expression promotes hepatocyte injury. This is more evident in steatotic hepatocytes that contain higher levels of superoxide and H$_2$O$_2$. UCP2 higher levels in steatotic hepatocytes are also related to ATP depletion and to IRI (26-31). Evans ZP and his coworkers have concluded that UCP2 renders steatotic livers more sensitive to IRI through the regulation of hepatic ATP levels (31-36). ii. Mitochondrial permeability transition (MPT) is promoted by IR’s oxidative stress, increased mitochondrial calcium and inorganic phosphate in lean livers. When a certain amount of calcium accumulates, mitochondria start to swell (36). The permeability of the inner mitochondrial membrane increases, the mitochondrial membrane potential collapses, oxidative phosphorylation is inhibited, ATP is depleted, and apoptosis-induced factors are released. In fatty livers, MPT induction is increased due to the decreased mitochondrial membrane potential (38, 39).

ROS. ROS are of great importance both in hepatoprotective mechanisms and during IRI. Recently, endoplasmic reticulum stress has been associated with the production and accumulation of intracellular ROS, which are important mediators of inflammation (40). In the liver, the production of ROS is greater when excessive fat is present, as hepatocytes seem more susceptible to lipid peroxidation and mitochondrial function is disrupted (22, 41-44). According to Prieto I. and Monsalve M., the inability of the steatotic liver to react to ROS is linked to decreased levels of antioxidants, mitochondrial injury, hepatocyte cell death, and the stimulation of mediators of the immune system and profibrosis (45).

Nitric oxide (NO). NO is a diffusible mediator that originates from oxygen and L-arginine through the activity of NO synthase (NOS); it has vasodilating properties that prevent microcirculatory changes imposed by reperfusion, which are more profound in a steatotic liver (46-48). Generally, NO’s impact on IRI depends on its concentration, duration and site of production/isoform of NOS that generates it (46, 49, 50). A small quantity of NO is considered to decrease tumor cell growth and prostaglandin E2 and F2 alpha (proinflammatory products) levels, while it increases protein synthesis and
DNA-repair enzymes (51). Specifically, endothelial nitric oxide synthase (eNOS), which functions in the control of vascular tone, increases blood perfusion and therefore protects hepatocytes from IRI (46, 52). In contrast, limited quantities of inducible nitric oxide synthase (iNOS) may increase ROS thereby injuring hepatocytes (46, 53-56). Koeppl et al. have shown increased iNOS gene expression after IRI in steatotic liver which was more evident in hepatocytes with fatty degeneration (57). Due to the different actions of iNOS, its expression is regulated by the cooperation of cytokine-inducible transcription factors. Taylor et al. have shown that three cytokines, tumor necrosis factor alpha (TNFα), interleukin-1beta (IL-1β), and interferon-gamma (INFγ), are needed to attain a significant augmentation of iNOS in human hepatocytes (58). Transcription nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kb) also relates to iNOS production, in both rodent macrophages and human liver, along with signal transducer and activator of transcription factor 1α (STAT1) (41, 59-62). Interestingly, Koeppl et al. have noted that CCl4-mediated liver injury led to the activation of transcription factors (NF-kb, STAT1), resulting in further aggravation upon reperfusion (57).

**Glutathione (GSH).** Endogenous GSH concentrates intracellularly and is oxidized during reperfusion, forming glutathione disulfide (GSSG) (63, 64). In lean organs, GSH administration following 60, 90, or 120 minutes of ischemia or liver transplantation, attenuates rodent IRI (65, 66). Pratchke et al. have shown that intravenous administration of GSH, in order to achieve supraphysiological levels in hepatocytes, ameliorated IRI in both lean and steatotic livers. They postulated that most of the GSH reacted with ROS, therefore, GSSG was also found to be increased after GSH administration (44, 67). This is related to improved sinusoidal perfusion, decreased leukocyte adhesion and reduction of sinus endothelial cell injury in lean organs (66, 68, 69). Glycine, a product of GSH metabolism, has also hepatoprotective properties (70).

**Endoplasmic reticulum (ER).** ER function consists mainly in protein synthesis, oxidative folding and transportation, calcium storage and cellular stress detection. The accurate folding of proteins requires energy. The use of molecular oxygen produces ROS and oxidized glutathione, resulting in oxidative stress. In general, a disturbance in the redox homeostasis of the ER produces ER stress and ROS (70, 71). ROS are also increased through ER-released calcium which concentrates in the matrix of the mitochondria, depolarizes the inner mitochondrial membrane and disrupts electron transport (73). Mitochondrial ROS may further sensitize ER calcium-releasing channels. Aside from ROS and the release of calcium, the ER relates to inflammation through the unfolded-protein response (UPR) and other signaling pathways, involving the activation of NF-kB, JUN N-terminal kinase (JNK) and the initiation of an acute-phase response to inflammation. Conditions such as obesity, contribute to alterations in liver architecture, increased protein synthesis and different cellular energy pathways, which increase the demands on the ER (74, 75). Therefore, ER stress is related to the emergence of hepatic steatosis, hepatocellular injury and fibrosis. Nonetheless, when Henkel et al. used chemical chaperons to reduce ER stress in methionine- and choline-deficient (MCD) diet, they found that ER stress does not have a primary role in the pathogenesis of steatohepatitis (76).

**Chaperonins.** They are small molecules, belonging to the large class of chaperones, which contribute to protein folding and structure and therefore stabilize the unfolded proteins (75, 77). IRI disrupts cellular homeostasis and, as a result, unfolded proteins accumulate. A proteomic study performed by Tiriveedhi et al. has shown significant down-regulation of multiple chaperones upon IRI in steatotic liver, which may contribute to the augmented levels of ER stress and, subsequently, in apoptosis and necrosis observed in livers with steatosis, in contrast to lean ones (78). However, Henkel et al., have shown that chemical chaperons inhibit the ER stress response without reducing hepatic steatosis in MCD diet-fed mice (76).

**Selectins.** They are a family of lectin-like glycoproteins and adhesion molecules that initiate the rolling and attachment of leukocytes to the vascular intima. During early IRI, P- and E-selectins are produced by activated endothelial cells, while L-selectin is expressed by all classes of leukocytes. On this basis, Amersi et al. introduced the application of soluble recombinant selectin glycoprotein ligands to fatty livers as a new method against IRI (79, 79). In lean livers, application of a soluble recombinant form of P-selectin glycoprotein ligand-1 (PSGL-1) impedes the interaction of P-selectin with membrane-associated PSGL-1, leading to reduced polymorphonuclear leukocytes (PMN) penetration, improved liver survival and hepatocyte injury.

**Interleukins.** i. IL-1 promotes the inflammatory processes by up-regulating ROS production (22, 81, 82). Impediment of IL-1 has been found to reduce IRI in non-steatotic livers (22, 81, 83-85). Specifically, Serafin et al. have found that IL-1α probably does not contribute to hepatic IRI, because IL-1α levels were similar in lean and steatotic livers, at 6 hours of reperfusion when 70% of the liver had subjected to 60 min of ischemia. Conversely, IL-1β’s values were two-fold higher in the fatty livers compared to lean livers. ii. IL-6 is a multifunctional cytokine which is increased in the plasma and peripheral blood monocytes in cases of obesity. It is
correlated both with the development and the severity of hepatic diseases, as increasing evidence indicates IL-6’s importance in promoting liver regeneration and therefore protecting against injury in lean liver (86-101). Liver regeneration depends upon IL-6 activity; reduction of this cytokine may result in graft failure, in both lean and steatotic livers (79, 102). Hong et al. have found that long term treatment with IL-6 alleviates steatosis, and IRI and normalizes serum aminotransferase activity. They concluded that the in vivo effect of IL-6 on hepatic triglycerides is mediated by indirect mechanisms, such as down-regulation of hepatic TNFα expression, reduction in serum TNFα levels or upregulation of hepatic peroxisome proliferator-activated receptor. Taccine et al. have suggested that the study of transcription factors that trigger the production of IL-6, could lead to the identification of possible molecular events that may impair its protective effect on IRI in fatty livers (102). Similarly, Jimenez-Castro et al. have considered the use of adipocytokines (IL-6, leptin etc.) as indicators of steatosis’ grading and liver injury; they proposed i.e. that adipocytokines could help recognize marginal steatotic livers and assess postoperative liver injury (104). iii. IL-10 is hepatoprotective and augments allograft survival following liver transplantation (22, 105-107). This quality has been confirmed for endogenous IL-10 in lean livers, but the effects of exogenous IL-10 depend on its dosage. Serafin et al. have related hepatoprotection seen by high doses of exogenous IL-10 to the decreased release of IL-1β (22). Also, they have found that exogenous IL-10 was not accumulated in fatty livers, concluding that the observed imbalance of pro- and anti-inflammatory ILs in IRI of steatotic livers could be involved in their decreased tolerance. The above IL changes are listed in Table II.

**Kupffer cells (KCs).** KCs are activated liver macrophages found in liver’s sinusoids, and the major source of ROS and pro-inflammatory mediators (109, 110). To better understand their function, Mustafa SB and Olson MS treated rat KCs with lipopolysaccharide. They showed that rat KCs produced great quantities of nitrite and nitrate, synthesized and released several cytokines, which stimulated neighboring hepatocytes to produce NO resulting in degenerative changes (111-112). In total IR, KCs reduced hepatic IRI and inflammation. In lean livers, KCs may maintain a homeostatic level of inflammation through the production of IL-10 (114). Dysregulated inflammatory responses are even more important for IRI in steatotic livers. Phagocytically active KCs seem to be hepatoprotective in livers with steatosis. Sutter et al. pretreated lean and genetically obese mice with IL-10 or the liposomally-encapsulated bisphosphonate clodronate, which depletes KCs, before total IR. They found that KCs’ depletion sensitizes steatotic livers to IRI through non-IL-10-dependent mechanisms.

| Interleukins | Liver | References |
|-------------|-------|-----------|
| IL-1α       | Same levels | 81-83     |
| IL-1β       | Increased | Doubled 22, 81-85 |
| IL-6        | Normal   | Decreased 86-104 |
| IL-10       | Increased | Non-significant Increase 22, 105-108 |

**Caspases.** They are a family of proteases essential for inflammation and programmed cell death. In the extrinsic signaling pathway of apoptosis, TNFα and Fas ligand promote the binding of procaspase 8, and activate caspase 8 and procaspase 3 leading to apoptosis (115, 116). In the intrinsic pathway, MPT causes cytochrome c release, activation of caspase 9 and subsequently of caspase 3 (116-118). Suzuki et al. have found that caspase 8 did not differ between lean and fatty livers. On the contrary, caspases 9 and 3 were further increased in fatty livers after IRI, indicating the importance of MPT. Furthermore, it is known that the intrinsic pathway occurs in hepatocytes and induces apoptosis faster than the extrinsic pathway. When the caspase cascade is inhibited, lean liver is significantly protected and IRI is reduced, while apoptosis in fatty liver is also reduced, with no change in the degree of necrosis (10). In a study by Jiang et al., significant differences were observed in malondialdehyde (MDA), superoxide dismutase (SOD) and myeloperoxidase (MPO) concentrations between lean and fatty rat liver groups (119). MDA is known to result from free radical lipid peroxidation and thus is a marker of ROS (120). SOD participates in the balance between oxidants and antioxidants, so it represents tissues’ ability to discharge free radicals (121). Instead, MPO is mainly expressed in neutrophil granulocytes, so its activity indicates the quantity of neutrophils (122). The increase of MDA and MPO levels and the decrease in SOD in the fatty liver group, concur with a more severe IRI in the steatotic liver, and its hepatocytes are more sensitive to lipid peroxidation and ROS (119).

Following IRI in lean and fatty livers, higher serum alanine transaminase (ALT) levels are observed in fatty livers, representing more severe liver IRI, even when different methods of implementing fatty livers are chosen (39, 86, 123). According to Kostakis et al. there is a steady augmentation of ALT and aspartate transaminase (AST) serum levels after hepatic ischemia in both lean and steatotic livers during the first 24 postoperative hours. Transaminases’ levels remain significantly higher at 24 hours in steatotic livers (124).
Microcirculatory Disorders

Microcirculatory blood flow disorders after IR significantly affect the extent of liver injury and the prognosis of its function (57, 125). In normal livers, control of local sinusoidal blood flow is moderated by sinusoidal constriction in reply to inflammatory mediators, e.g., endothelin (ET-1), NO and carbon monoxide, which are generated within the sinusoids (126, 127). Alterations in the regulation and synthesis of these vasoactive mediators may result in intracellular deposits of fatty droplets in pericentral hepatocytes, which contribute to significant iNOS protein expression. The swollen hepatocytes in steatotic livers can induce chronic hypoxia, ATP depletion and increased leukocyte adhesion, resulting in decreased sinusoidal blood flow (43, 44, 128-132).

During reperfusion, regional L-arginine depletion causes reduced local NO synthesis which counteracts the effect of endothelins on liver microcirculation, resulting in hepatic sinusoidal reperfusion failure (133, 134). ET-1 is a peptide whose levels increase in both sinusoidal endothelial and hepatic stellate cells upon reperfusion, when TNF-α and other inflammatory cytokines are released by KCs and attach to hepatic endothelial cells (57, 135). The resulting extreme sinusoidal vasoconstriction may cause microcirculatory damage to the hepatic parenchyma, heterogeneous perfusion and local hypoxia that results in hepatic failure (136-140).

In a study by Koeppel et al., IR induced an additional augmentation in ET-1 gene expression in most reperfused steatotic livers. As a result, it was considered that the disturbance in the sinusoidal perfusion caused by ET-1 is likely to contribute to steatotic liver IRI (57). Additionally, injection of an anti-intercellular adhesion molecule-1 monoclonal antibody, to prevent sinusoidal congestion, ameliorated only the survival rates of rodents with fatty livers (122, 141).

Histopathological Findings

The liver is considered fatty when its cells are steatotic in a low magnification view (119, 142). Specifically, hepatic steatosis of less than 30% is considered mild, 30%- 60% moderate, and more than 60% severe (119, 143, 144). Hepatic inflammation and fibrosis differentiate steatohepatitis from...
plain steatosis. Following MCD, rats’ livers exhibit massive fatty infiltration, which is mainly macrovesicular. Fat accumulation in the cytoplasm of the hepatocytes increases cell volume, leading to various degrees of obstruction of liver sinusoids (4, 134, 145). Therefore, sinusoids appear narrow and irregularly shaped due to compression by the fat-loaded hepatocytes. Single-cell necrosis is not often, whereas there is no inflammation and/or fibrosis.

In normal livers, IRI presents moderate early hepatocyte necrosis, minor coagulative necrosis with neutrophil infiltration, haphazardly spread throughout the liver parenchyma (22). At the end of the ischemic period, some hepatocytes are spotted with vacuolization or ballooning, while at the same time in fatty livers there are small foci of hepatocyte necrosis. In a higher magnification view, normal livers after IRI exhibit modest inflammatory infiltration in the hepatic lobule and the portal area in comparison to fatty livers. Furthermore, fatty livers present increased infiltration of neutrophils and lymphocytes. Soon after reperfusion in normal livers, focal points of necrosis, regions of vacuolar abnormalities, separation of the endothelial lining, moderate sinusoidal congestion and maintenance of the lobular architecture are observed. At this moment, the degree of sinusoidal congestion is the main histopathological difference between lean and fatty livers.

Later in reperfusion, most normal livers resolve the sinusoidal congestion, maintain their sinusoidal lining and present tiny regions of necrosis. In contrast, hepatocytes with pyknotic or karyorrhectic nuclei are dispersed all over the lobule in fatty livers, and the sinusoids dilate significantly without preserving their lining. Red blood cells are located in fat globules and diffuse hemorrhagic necrosis is present. Subsequent to sinusoidal architecture failure, red cells extravasate within large areas of the parenchyma. The alterations noted are spotty hemorrhage, hepatocyte necrosis, decreased sinusoidal density and blood flow, which lead to decreased oxygen delivery and energy metabolism (57, 131, 146). After IRI, all livers show predominantly single cell necrosis/apoptosis, with numerous great, acute necrotic regions, mainly around the central veins, which are significantly increased in fatty livers.

Table III summarizes the main histopathological differences between lean and fatty livers before ischemia and during IRI.

**Fasting Effect**

Pre-ischemic fasting does not seem to have any significant effect on animal survival when the liver is normal. Even though the degree of the hepatic damage is more severe in lean livers of fasted animals, the histological findings are similar to the non-fasted ones (145).

On the contrary, pre-ischemic fasting reduces survival of rats with fatty liver tremendously. Fasting and fatty degeneration act synergistically to exacerbate hepatic IRI. Mitochondrial injury is the main characteristic of ultrastructural hepatocyte damage in fasted rodents with fatty livers. Clinically, rats with fatty liver that were fasted, took longer to recover from anesthesia, and their majority developed labored respiration and finally succumbed the following hours after reperfusion (123).

**Conclusion**

Ischemia-reperfusion injury consists a significant problem in liver surgery and transplantation which is aggravated by the increased prevalence of hepatic steatosis. Steatotic livers are more sensitive to IRI compared to lean livers, leading to increased postoperative graft failure, morbidity, and mortality. Moreover, the constant growth in the demand for liver donors has already led to accepting livers with moderate steatosis for transplantation, introducing potentially more postoperative complications. Therefore, additional research on IRI underlying mechanisms is needed, so that new preventive and therapeutic strategies will emerge through pharmaceutical agents, surgical interventions or gene therapy.

**Conflicts of Interest**

The Authors report no conflicts of interest regarding this study.

**Authors’ Contributions**

AAN: Conception of the study, acquisition, analysis and interpretation of references, critical revision; IAD: conception of the study, supervision, critical revision and final approval of the article; DCI: critical revision, final approval of the article; TK: conception of the study, supervision, critical revision and final approval of the article.

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