



Cytoprotective effect of prostacyclin on hepatic ischemia-reperfusion injury

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Abstract

Hepatic ischemia-reperfusion injury is an important mechanism of liver failure that occurs in many clinical conditions, including massive hemorrhage, major hepatectomy and liver transplantation, and leads to poor outcomes. The underlying cellular and molecular reactions are extremely complex and not completely understood. Anaerobic metabolism, ATP depletion, intracellular acidosis, calcium overload, mitochondrial dysfunction, oxidative stress, activation of Kupffer cells and neutrophils, platelet aggregation, nitric oxide production, activation of the complement system and overexpression of cytokines and chemokines constitute the main pathophysiological actions and pathways for possible therapeutic strategies. Prostaglandins (PGs) are a group of biologically active lipid compounds called eicosanoids with many physiological activities. Prostacyclin (PGI₂) is a member of the PGs family with an unstable chemical structure and a very short half-life. PGI₂ has potent vasodilating activity, inhibits platelet activation and exerts anti-inflammatory effects. PGI₂ has been evaluated in chronic liver

disease as a mediator of hepatic stellate cell function, an antiproliferative and antifibrotic agent and a regulator of the hepatic microcirculation. In recent decades, the cytoprotective effects of PGI₂ analogs on hepatic ischemia-reperfusion injury have been experimentally and clinically studied. Moreover, the administration of synthetic PGI₂ analogs to patients who underwent liver transplantation produced very encouraging results. The downregulation of PGE₂ production, reduction of neutrophil aggregation in liver lobules, regulation of local microcirculatory homeostasis, improvement in mitochondrial function, alleviation of hepatic oxidative stress, suppression of the c-Jun N-terminal kinase and p38 cascades and downregulation of tumor necrosis factor- α and interleukin-1 β production constitute some of the underlying physiological mechanisms of the beneficial effects of PGI₂ on hepatic ischemia-reperfusion injury. Thus, PGI₂ analogs appear to hold great promise for the management of hepatic ischemia-reperfusion injury, but further research is needed.

Key Words: Hepatic ischemia-reperfusion injury; Oxidative stress; Prostacyclin analogs; Prostaglandins; Liver transplantation; Liver graft dysfunction

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Core Tip: Hepatic ischemia-reperfusion injury is a critical event that affects the outcomes of liver surgery, transplantation and many other major clinical conditions. The reoxygenation of ischemic hepatocytes activates complex inflammatory processes, which lead to oxidative stress that has deleterious local and global consequences. Prostacyclin (PGI₂) is a well-known member of the prostaglandin family with potent vasodilative, platelet-inhibiting and anti-inflammatory effects. Several reports have detailed the cytoprotective effects of PGI₂ analogs on hepatic ischemia-reperfusion injury. In this review, we discuss the underlying mechanisms of hepatic ischemia-reperfusion injury and the potential hepatoprotective effects of PGI₂ analogs.

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INTRODUCTION

The liver is a critical organ for the homeostasis of the human body because it regulates many physiological processes, such as glycogen storage and energy metabolism, protein production, lipid and cholesterol metabolism, and bile excretion. Moreover, the functions of the liver include blood volume regulation and immune system support *via* the production of most immune factors, including cytokines, chemokines, growth factors and other signaling proteins. Additionally, several drugs are metabolized in the liver by a specific group of cytochrome P-450 enzymes. Finally, hepatic enzymes play key roles in the xenobiotic detoxification process because these enzymes convert toxic compounds into forms suitable for elimination[1,2]. Worldwide, liver failure is a common cause of high morbidity and mortality. The list of factors and conditions that cause liver failure is growing, and liver transplantation remains the only effective therapeutic option for these patients[3-5].

Ischemia-reperfusion injury is an important mechanism of liver failure after several clinical events, such as extended hepatic resection, massive hemorrhage, Budd-Chiari syndrome and liver transplantation[6]. The processes involved in hepatic ischemia-reperfusion injury are extremely complex and involve different types of liver cells, including numerous factors and mediators [cytokines, adhesion molecules, vasoactive agents and reactive oxygen species (ROS)][7-9]. The essential functions of the liver can be affected during hepatic ischemia-reperfusion injury in multiple ways, as shown in Figure 1.

Prostaglandins (PGs) are a group of biologically active lipid compounds that, in combination with leukotrienes (LTs), thromboxanes (TXs), lipoxins (LXs) and epoxyeicosatrienoic acids (EETs), are called eicosanoids. The chemoenzymatic synthetic pathway of PGs includes oxidized derivatives of 20-carbon polyunsaturated fatty acids, primarily arachidonic acid and cyclooxygenase (COX). PGs are widely distributed in nearly all human cells and tissues, but they are well known for having many biological actions[10-13].

PG has favorable effects on liver tissue, but the underlying mechanisms have not been completely defined[14]. Many studies have shown the cytoprotective activity of PG through direct or indirect signaling pathways[15]. The regulation of liver microcirculation, mainly *via* vasodilation, antioxidant effects and the modulation of the immune response, is considered critical for hepatocyte homeostasis[16,17].

Several studies have evaluated the effectiveness of PG analogs in adult and pediatric liver transplant patients. PGE₁ administration has been shown to improve the hepatic microcirculation status, prevent primary allograft nonfunction and reduce hepatic ischemia-reperfusion injury in general. Additionally, PGE₁ pretreatment downregulates the expression of adhesion and inflammatory mediators, resulting in the inhibition of platelet and leukocyte aggregation and a reduction in

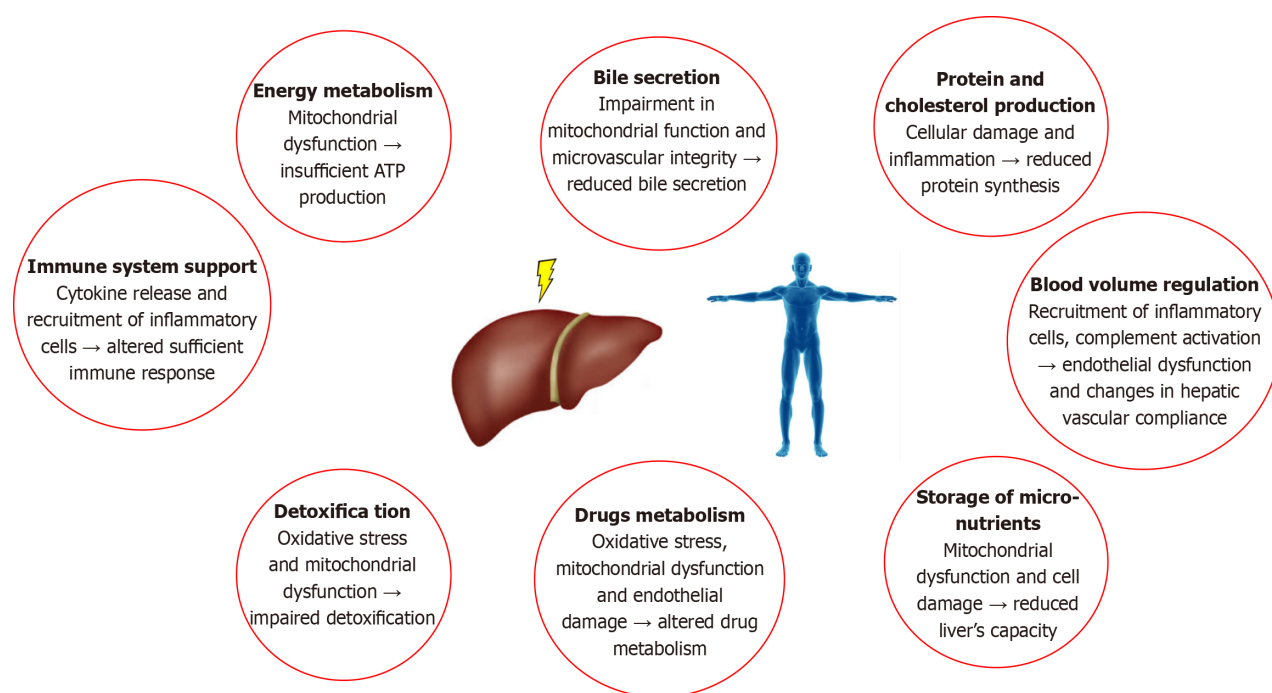


Figure 1 Main functions of the liver and how they are affected by ischemia-reperfusion injury.

hepatocytic degeneration[18-22]. Another eicosanoid, TXA₂, is a potent stimulator of platelet activation and aggregation; thus, its suppression leads to an attenuation of the inflammatory response and a reduction in the sinusoidal cell apoptosis rate. Moreover, recent studies have shown that the TX signaling pathway is involved in liver repair through the recruitment of macrophages to the injured hepatic tissue and increased transcription of growth factors[23,24].

Historically, PGs PGI₂ has been known to play a role in cardioprotection as an inhibitor of platelet activation and a vasodilator. Furthermore, it protects the heart from ischemia-reperfusion injury[25,26]. In addition, PGI₂ undoubtedly remains the most effective treatment for patients with pulmonary arterial hypertension[27]. However, increasing attention has been given to the cytoprotective and anti-inflammatory effects of PGI₂ analogs in the context of hepatic ischemia-reperfusion injury. Beraprost sodium is a PGI₂ analog with potential vasodilative, antiplatelet, anti-inflammatory and antioxidant activities. Inhibition of the P38 and c-Jun N-terminal kinase (JNK) signaling cascades with beraprost sodium preconditioning minimized the inflammatory response, apoptosis and autophagy processes[28]. Treprostinil is another PGI₂ analog with a stable structure, longer half-life and improved potency. Experimental and clinical data demonstrated the inhibition of platelet aggregation and proinflammatory cytokine production. Furthermore, hepatic oxidative stress and lipid peroxidation are attenuated after treprostinil administration, which reduces ischemia-induced hepatocyte injury[29-31].

Innovations in the field of liver surgery and the widespread use of vascular blockade for intraoperative bleeding control have made the liver particularly vulnerable to ischemia-reperfusion injury. The protective strategies mainly include specific intraoperative techniques and an adequate number of pharmacological agents. Here, we discuss the current knowledge of the mechanisms of hepatic ischemia-reperfusion injury and the potential cytoprotective effects of prostacyclin analogs.

HEPATIC ISCHEMIA-REPERFUSION INJURY

Despite progress in liver surgery, postoperative liver dysfunction continues to be an important and potentially fatal complication that is observed mainly after extensive hepatic resection and procedures in patients with reduced liver function or after liver transplantation. Hepatic ischemia-reperfusion injury remains one of the main causes of this complication[9,32-34]. This condition is characterized by complex cellular damage in a state of interruption of blood flow. Notably, the reperfusion of the ischemic tissue and the restoration of the oxygen supply exacerbate the degree of cellular injury. This injury has been described in various organs and systems because it is associated with several conditions, such as acute coronary syndrome, organ transplantation, limb injuries and sepsis[35,36].

Toledo-Petrey recognized this form of hepatocyte damage as clinically significant in 1975 during an experimental liver transplantation[37]. However, the term "hepatic ischemia-reperfusion injury" started being used much later, in the mid-1980s[38].

The complex blood supply of the liver in combination with its increased metabolic activity makes this organ extremely sensitive to circulatory disorders. The degree of cellular damage depends on the duration of ischemia-reperfusion. Additionally, several predisposing factors, such as diabetes mellitus, hyperlipidemia and arterial hypertension, contribute to atherosclerosis progression and affect the microcirculation. Disturbances in micronutrient homeostasis and energy

storage, as well as dysregulated detoxification and immune processes, lead to complex reactions that affect other organs and tissues and lead to multiorgan dysfunction syndrome. Hepatic ischemia-reperfusion injury remains a major cause of postoperative complications and worsened outcomes[38-42].

Hepatic ischemia-reperfusion injury can be categorized into warm and cold ischemia. Warm ischemia occurs during liver surgery or trauma, whereas cold ischemia is associated with organ storage before transplantation. The responsible mechanisms are extremely complex and involve multiple inflammatory mediators, cytokines, adhesion molecules, vasoactive factors and ROS, as shown in [Figure 2](#). The significance of the overproduced molecules is summarized in [Table 1](#). Because the liver circulation is disrupted, many reactions occur at the organelle level and stimulate cellular damage. The exposure of hepatocytes to low-oxygen conditions results in changes in the intracellular pH and a decrease in ATP production, causing a reduction in the intracellular energy level[6,9]. Excessive ROS and reactive nitrogen species production in mitochondria and intracellular calcium overload promote organelle destruction and cell death. The innate immune response includes the activation of Kupffer cells; the accumulation of circulating lymphocytes, neutrophils, platelets and monocytes; and hepatic macrophage differentiation[43-46]. A disruption of hepatic metabolism triggers an endogenous inflammatory cascade, which includes excessive cytokine and chemokine production, adhesion molecule expression and caspase-1 activation. The re-exposure of ischemic cells to high oxygen levels followed by blood flow restoration contribute to further hepatocyte injury through continued ROS generation[47-49].

Anaerobic metabolism, ATP depletion and acidosis

Impaired oxidative phosphorylation during ischemia results in the activation of anaerobic metabolism. Decreased ATP production and the intracellular accumulation of lactic acid and ketones almost always result in high anion gap metabolic acidosis[43,50]. As a response to the increased intracellular hydrogen ion concentration, the increase in Na⁺/H⁺ antiporter activity leads to the exchange of ions and an increase in the intracellular sodium concentration. The decreased activity of the ATP-dependent sodium-potassium pump further increases the intracellular sodium concentration, resulting in cell edema and death[51,52]. Moreover, diffuse cell edema affects microcirculatory structures and exacerbates ischemic damage.

However, acidic environments may also act to limit cell damage. Metabolic acidosis suppresses proteolytic enzyme and phospholipase activity and limits mitochondrial permeability transition pore (MPTP) function. Thus, during the reperfusion phase, a restoration of the intracellular pH leads to the activation of these enzymes, resulting in hepatocyte apoptosis and necrosis[53].

Intracellular calcium overload

Changes in intracellular calcium concentrations have emerged as important mechanisms of cellular damage because they lead to the activation of calcium-dependent enzymes. Under normal conditions, intracellular calcium homeostasis is based on ATP-dependent processes and reactions. When ischemia occurs, an increase in the intracellular sodium concentration induces sodium-calcium exchange, resulting in increased transfer of calcium ions inside the cells[54-56]. Cytoplasmic calcium overload subsequently stimulates calcium exchangers in the mitochondrial membrane. In combination with MPTP dysfunction, this action leads to the migration of calcium ions into the mitochondria[57]. Overall, calcium overload results in the activation of numerous enzymes, such as calpains, protein kinase C, phospholipase C, xanthine dehydrogenase and calcium-dependent proteases, which further affect the stability of the cell membrane and intracellular structures[53,58]. Eventually, the release of proapoptotic factors in the cytoplasm due to ischemia results in the acceleration of cell death processes[59]. The experimental administration of calcium channel blockers in animal models of hepatic ischemia-reperfusion injury assisted in the recovery of mitochondrial damage and hepatocyte functions, which indicates the importance of the calcium overload theory[60].

The role of mitochondria

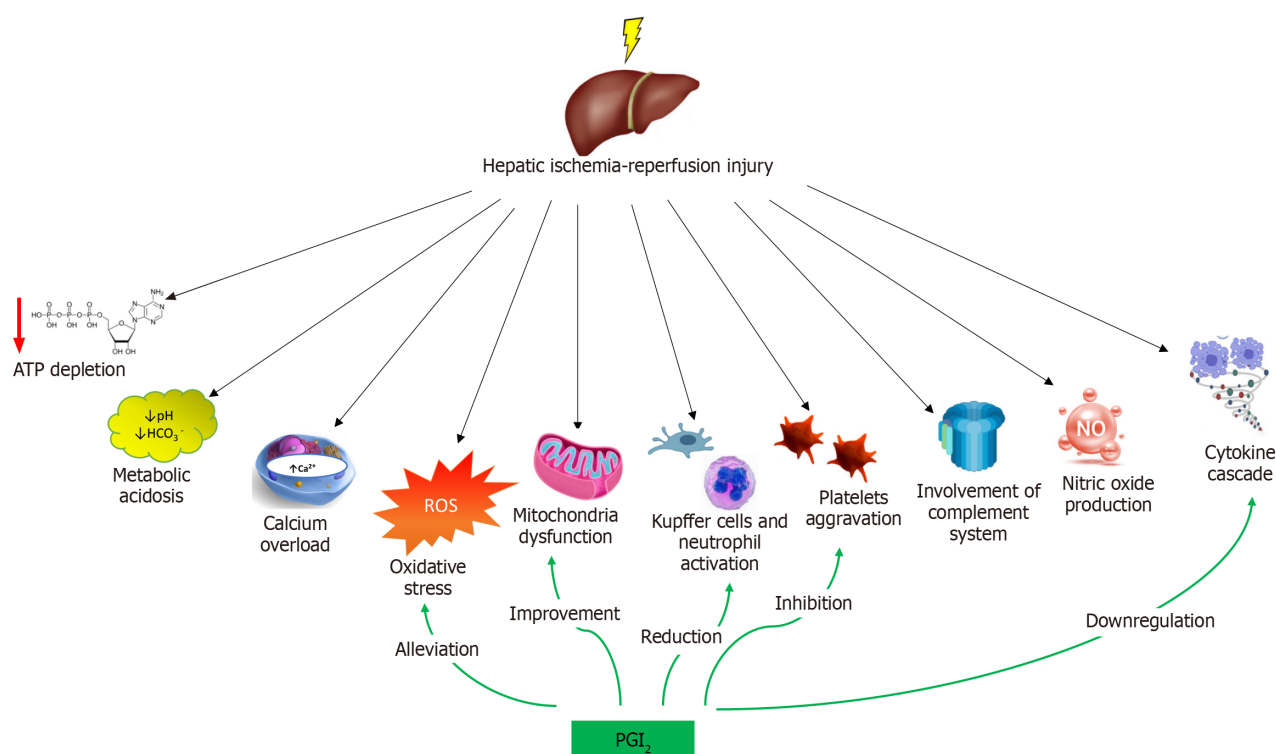
Mitochondria are the center of cellular energy metabolism and redox homeostasis. Nonetheless, mitochondrial function deteriorates in the hypoxic environment. During hepatic ischemia-reperfusion injury, increased intracellular concentrations of sodium, hydrogen, and calcium ions contribute to mitochondrial dysfunction and lead to MPTP formation[58]. The removal of damaged mitochondria through mitophagy is very important for the maintenance of intracellular homeostasis because mitochondria are responsible for both increased ATP consumption and increased ROS production [61,62]. Disruptions in mitophagy during ischemia-reperfusion injury are associated with mitochondrial dysfunction and the disruption of the oxidative phosphorylation pathway. In connection with increased mitochondrial membrane permeability, these processes are responsible for ATP depletion, resulting in cell death[63,64].

Oxidative stress and the roles of Kupffer cells and neutrophils

ROS are produced by normal physiological processes, including anaerobic metabolism, oxidative phosphorylation, lipid degradation and the inflammatory response. Accordingly, cells have evolved endogenous antioxidant systems, such as catalase, glutathione peroxidase and superoxide dismutase[65,66]. Increased production of ROS [hydroxyl radicals (·OH), superoxide anions (·O₂⁻), and hydrogen peroxide (H₂O₂)] has a toxic effect on hepatocytes. In the reperfusion phase, the excess ROS levels exceed the antioxidant capacity of hepatocytes, resulting in oxidative stress. In the liver, the main sources of these molecules are the mitochondrial membranes of Kupffer cells, neutrophils and monocytes. However, the metabolic reactions involve nicotinamide dinucleotide phosphate adenine oxidase (NADPH) and xanthine oxidase[67-69]. A low oxygen supply induces the activation of transcriptional regulators, such as hypoxia inducible factor-1, nuclear factor kappa B (NF-κB), activator protein 1 and stress-activated protein kinase, triggering further ROS production and cellular damage, including changes in enzyme activity, membrane lipid peroxidation and DNA damage[70]. The

Table 1 Overproduced molecules and its consequences in hepatic ischemia-reperfusion injury

Number	Molecule	Effect
1	Tumor necrosis factor α	Central mediator with multifactorial effect
2	Interleukin-1 α	Mediator of neutrophil infiltration
3	Interleukin-1 β	Induction of prostaglandin synthesis, enhancement of T-cell and neutrophil activation and cytokine production
4	Interleukin-12	Induction and development of hepatic ischemia-reperfusion injury
5	Interferon- γ	Increases or reduces neutrophil accumulation in a dose-depend manner
6	Damage-associated molecular patterns	Pro- and anti-inflammatory mediators that promote tissue damage
7	Intercellular adhesion molecule 1	Promotes neutrophil accumulation
8	Vascular cell adhesion molecule 1	Mediates inflammation and promotes neutrophil migration
9	P-selectin	Promotes neutrophil and platelets adhesion
10	Transforming growth factor- β	Promotes vessel wall inflammation and increase vascular permeability
11	Vascular endothelial growth factor	Promotes T lymphocyte, macrophage and neutrophil accumulation
12	Plasminogen activator inhibitor 1	Promotes neutrophil accumulation and suppresses fibrinolysis
13	Nitric oxide	Prevents or promotes cell damage depending on NO synthesis processes
14	Endothelin-1	Vasoconstriction
15	Combination of released factors	Heart-kidney damage, systematic inflammatory response syndrome SIRS, multiple organ dysfunction, death

**Figure 2** Mechanisms of hepatic ischemia-reperfusion injury and prostacyclin effect. PGI₂: Prostacyclin; ROS: Reactive oxygen species.

abovementioned mechanisms, combined with endothelial cell damage and subsequent microcirculation disturbances, induce hepatocyte death[71,72].

Kupffer cells and neutrophils contribute to hepatic ischemia-reperfusion injury at different stages. Hepatic ischemia-reperfusion injury can be divided into two phases: The initial phase (< 2 hour after reperfusion) and the late phase (6-48 hour after reperfusion). The early phase is characterized by the rapid activation of Kupffer cells, whereas the late phase processes are mediated by accumulated neutrophils[35,73]. Activated Kupffer cells release proinflammatory factors, such

as ROS, tumor necrosis factor- α (TNF- α), interleukin (IL) 1 β and damage-associated molecular patterns (DAMPs). In addition, the activation of sinusoidal endothelial cells and increased expression of intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) promote the migration and adhesion of neutrophils and CD4⁺ T cells[74-76]. Accumulated and activated neutrophils express oxidants, elastases and proteases, resulting in drastic increases in vascular permeability, edema and microvascular thrombosis. Furthermore, DAMPs are released during the reperfusion phase; they act as a complex cascade of pro- and anti-inflammatory mediators and promote tissue damage [44].

Activated neutrophils generate superoxide anions and subsequently produce hydrogen peroxide and myeloperoxidase [77]. Hydrogen peroxide is a strong agent with direct oxidative properties. However, myeloperoxidase converts hydrogen peroxide to hypochlorous acid, which also causes cell damage.

PGI₂ is an important PGs with powerful vasodilative activity and is a potent inhibitor of neutrophil activation. Therefore, endothelial PGI₂ might have a protective effect on hepatic ischemia-reperfusion injury by maintaining proper microcirculation and preventing neutrophil-induced endothelial cell damage. Neutrophil elastase, a protease released from activated neutrophils, reduces PGI₂ production by inhibiting nitric oxide (NO) synthase (NOS), thereby contributing to cell damage in the context of hepatic ischemia-reperfusion injury[78,79].

Platelets

Platelets play a very important role in hepatic ischemia-reperfusion injury because they produce a variety of factors, such as cytokines, growth factors [transforming growth factor- β ; vascular endothelial growth factor (VEGF) A], serotonin, TXA₂, and plasminogen activator inhibitor (PAI-1)[80]. When endothelial damage occurs, the release of these factors results in a microcirculatory obstruction due to their strong vasoconstrictive effect. In addition, PAI-1 suppresses fibrinolysis and downregulates the liver regeneration process by inhibiting urokinase-like plasminogen activator[81]. Finally, platelets release NO, which reacts with superoxide anion and forms peroxynitrite anion (ONOO⁻), an oxidative agent. Peroxynitrite interacts with lipids, DNS and proteins with direct or indirect pathways, committing cells to apoptosis or necrosis[82,83].

Role of the complement system

Studies of the hepatic ischemia-reperfusion process have increased our understanding of the role of the complement system, which appears to interfere with most of the pathophysiological mechanisms of the syndrome. The complement cascade mediates both ischemia-reperfusion injury pathways and liver regeneration[84]. The activation of the complement system results in the formation of biologically active, potent inflammatory mediators, such as C3a and C5a and the membrane attack complex (MAC)[85]. C3a and C5a promote cytokine production, neutrophil accumulation and degranulation. Additionally, they induce smooth muscle contraction, activate Kupffer cells, stimulate histamine release and increase vascular permeability[86,87]. The complement factor iC3b, which is formed by the cleavage of C3b by Factor I, mediates the binding of neutrophils to endothelial cells through CD11b/CD18, a member of the β 2 integrin family.

C5b-9 (MAC) activates the transcription factor NF- κ B, accelerating the expression of genes encoding various proinflammatory molecules, including adhesion molecules (ICAM-1 and VCAM-1), P-selectin and E-selectin. Moreover, C5b-9 increases the secretion of the chemotactic cytokines IL-8 and MCP-1 by human endothelial cells. The vascular microcirculation appears to be disturbed in the presence of C5b-9, resulting in a decrease in the tissue blood supply[88,89]. Finally, the MAC leads directly to cell lysis and death by disrupting the cell membrane, which has a variety of lipid compositions [84,90,91].

Roles of NO and endothelin

NO is a signaling molecule involved in many physiological biochemical reactions. It is synthesized from L-arginine and oxygen by NOS[90]. Three different NOS isoforms are known: Neuronal nNOS, endothelial eNOS and inducible iNOS. During hepatic ischemia-reperfusion injury, NO can either prevent or promote cell damage. A recent study revealed that NO can have either a positive or a negative effect during the early phase of ischemia-reperfusion injury and a protective effect in late stages[92,93]. NO derived from eNOS exerts a hepatoprotective effect by promoting vasodilation and improving the hepatic microcirculation, neutralizing ROS, preventing leukocyte adhesion, reducing the inflammatory response and inhibiting thrombus formation. NO derived from iNOS in the reperfusion phase leads to excessive cytokine and ROS production, which results in endothelial dysfunction and exacerbates hepatocellular injury[94,95]. Moreover, the continuous activation of iNOS leads to the maintenance of inflammatory reactions and further local and global damage. In general, NO participates in a variety of reactions, such as platelet and macrophage aggregation, the regulation of vasodilation and microcirculation, modification of the ATP level, caspase inhibition, a reduction in oxidative stress through respiratory chain inhibition, and the maintenance of appropriate glutathione levels. As a major mediator of the immune response, NO inhibits the secretion of many proinflammatory cytokines (TNF- α , IL-1 β , IL-1 α , and IL-12) and regulates the innate and adaptive immune systems[93,96,97]. In addition, NO downregulates LTsC4 synthase production by inhibiting the NF- κ B pathway and limits the secretion of apoptosis-related genes such as Bax and Bcl-2[93,98]. Under certain circumstances, NO may delay or promote neutrophil apoptosis, depending on the context. iNOS-derived NO prolongs neutrophil survival by activating the PI3K/Akt signaling pathway, inhibiting caspase-3 and caspase-9 and contributing to inflammatory reactions. Conversely, the promotion of neutrophil apoptosis is often associated with a lower proportion of eNOS-derived NO, which induces mitochondrial dysfunction, leading to the activation of caspase-dependent apoptosis and the suppression of NF- κ B activity[94]. Finally, NO can be converted to ONOO⁻, which causes cellular damage through lipid peroxidation, inhibition of the mitochondrial respiratory chain and modification of the levels of nitrotyrosine, an indirect marker of oxidative stress[99,100]. However, NO expression should be balanced to minimize the negative effect and to contribute to the attenuation of hepatic ischemia-reperfusion injury.

Endothelin-1 is a potent vasoconstrictive agent produced by endothelial and hepatic stellate cells to prevent liver injury [101]. The balance between endothelin and NO levels plays a pivotal role in regulating the hepatic microcirculation. Ischemia is an important stimulus for endothelin production, resulting in a disturbance in the balance of vasoregulatory factors. An increase in endothelin levels promotes vasoconstriction, hepatic sinusoidal dilatation, increased intrahepatic vascular resistance, enhanced endothelial interactions and portal hypertension [102,103].

Cytokines and chemokines

Reperfusion of the ischemic hepatic tissue triggers excessive cytokine release, which accelerates the inflammatory response. TNF- α represents a major mediator of both the local and global consequences of hepatic ischemia-reperfusion injury [40,104]. TNF- α , which is produced by numerous cell types in response to inflammatory stimuli, has been shown to modulate multiple signaling pathways with wide-ranging downstream effects [105-107]. Specifically, TNF- α binds to receptors on the surface of hepatocytes, causing the production of epithelial neutrophil-activating protein 78 and ROS. It also activates the nuclear factors NF- κ B, mitogen-activated protein kinase (MAPK) and JNK. The abovementioned mediators directly cause hepatocyte dysfunction. In addition, TNF- α upregulates the expression of the chemokines ICAM-1, VCAM-1 and P-selectin. Several studies have shown that TNF- α inhibitors protect the liver from ischemia-reperfusion injury by neutralizing the inflammatory response [48,108].

T cells and natural killer T cells produce interferon- γ (IFN- γ), which affects the inflammatory response in various ways by increasing or reducing neutrophil accumulation in a dose-dependent manner [109]. In addition to TNF- α and IFN- γ , numerous other cytokines have been found to be involved in hepatic ischemia-reperfusion injury. Several ILs (IL-1 β , IL-6, IL-10, IL-12, IL-13, and IL-23), VEGF and hepatocyte growth factor (HGF) are notable factors.

IL-1 β mediates NO synthesis *via* protein kinase (Akt) and iNOS, whereas the activation of the nuclear factor NF- κ B increases neutrophil migration and adhesion. Moreover, the IL-12 and IL-23 increase TNF- α production. Furthermore, IL-10 and IL-13 produced by Kupffer cells and T cells play important roles in reducing hepatocellular damage and promoting liver regeneration. The protective effects of IL-10 and IL-13 are mediated by the upregulation of transmembrane molecules (Bcl-2/bcl-x and heme oxygenase and the downregulation of NF- κ B, IL-2, IL-1b, MIP-2, IFN- γ , and E selectin [110,111]. VEGF, which is produced by Kupffer cells, T lymphocytes, sinusoidal cells and hepatocytes, plays dual roles in hepatic ischemia-reperfusion injury. An increase in the VEGF concentration during hypoxia increases TNF- α , INF- γ , MCP-1 and E-selectin secretion, resulting in T lymphocyte, macrophage and neutrophil accumulation. In contrast, exogenous VEGF administration has a favorable effect on hypoxia resolution *via* iNOS production. HGF is produced primarily by Kupffer cells and increases hepatocyte DNA synthesis, cell proliferation, and glutathione expression (which is decreased in the ischemic phase), decreases ICAM-1 secretion and inhibits neutrophil accumulation. HGF plays a vital role in the initial stage of liver repair [112,113].

Chemokines are low-molecular-weight proteins that stimulate neutrophil recruitment. During hepatic reperfusion, high levels of the ELR+ CXC subclass (based on the presence of the amino acid sequence Glu-Leu-Arg) are produced and contribute to neutrophil activation. This robust chemokine release leads to the recruitment of large numbers of immune cells into injured tissue and inflammation-mediated cytotoxicity [113]. The neutralization of ELR+ CXC chemokines significantly reduces inflammatory cell accumulation and alleviates hepatocellular damage [73,114-117].

Notably, studies investigating hepatic ischemia-reperfusion injury face several methodological limitations, which can affect the interpretation of their findings. Key points include the variability in experimental models, a focus on an isolated type of ischemia (warm or cold), modifications in the duration and design of surgical procedures, and a lack of approved criteria to evaluate liver damage. Moreover, *in vivo* models may more thoroughly demonstrate systemic reactions and hemodynamic changes, which are absent in isolated hepatocyte lines (*in vitro* studies). The reliance on animal models introduces several limitations due to species-specific differences in immune system reactions, drug pharmacokinetics and pharmacodynamics, metabolism and the expression of various molecules, such as complement proteins or PGI₂ receptors. In addition, the translation of experimental study findings to human pathophysiology may be challenging, as many patients with liver disease have comorbidities, which are not always represented in animal models. The abovementioned methodological limitations in standardized protocols, improved experimental models and comprehensive outcome evaluations must be addressed to make progress in identifying effective therapeutic strategies and to advance the interpretation of research data related to hepatic ischemia-reperfusion injury.

PGs

PGs are 20-carbon hydroxyl fatty acids that regulate many physiological processes, including immune cell activation, platelet aggregation, neurotransmitter release and kidney function. PGs are synthesized from arachidonic acid and cleaved from cell membrane lipids. The enzymatic oxidation of arachidonic acid is catalyzed by COX and 5-lipoxygenase, resulting in the synthesis of PGs and LTs, respectively. Specifically, the two isoforms of COX (COX-1 and COX-2) activate a two-step synthetic process, first generating PGG₂ from arachidonic acid and then reducing the 15-hydroperoxy group to form PGH₂. Subsequently, cell-specific PG synthases catalyze the conversion of PGH₂ to biologically active metabolites [118-121]. First, PGs were discovered independently in human semen in 1935 by the Swedish physiologist Ulf von Euler and the British physiologist M. W. Goldblatt. PGs are a biologically important group of fatty acids called eicosanoids. Other classes include LTs, TXs, LXs and EETs (as shown in Figure 3) [122,123].

The major classes of PG are known as PGA, PGB, PGD₂, PGE₂, PGF₂, and PGI₂ (prostacyclin). The differences among the classes are based on the chemical structure, particularly the nature of the 5-membered ring functionalities, as well as the number and location of side-chain double bonds [10,124,125]. PGs have been detected in nearly all human cells and tissues. They are well known for possessing a wide variety of biological actions, including homeostasis, activation/inhibition of platelet aggregation, thrombosis, glomerular filtration, ovulation, maintenance of pregnancy and initiation of labor, inflammatory mechanisms, vascular tone regulation, hormone level regulation, modulation of the immune

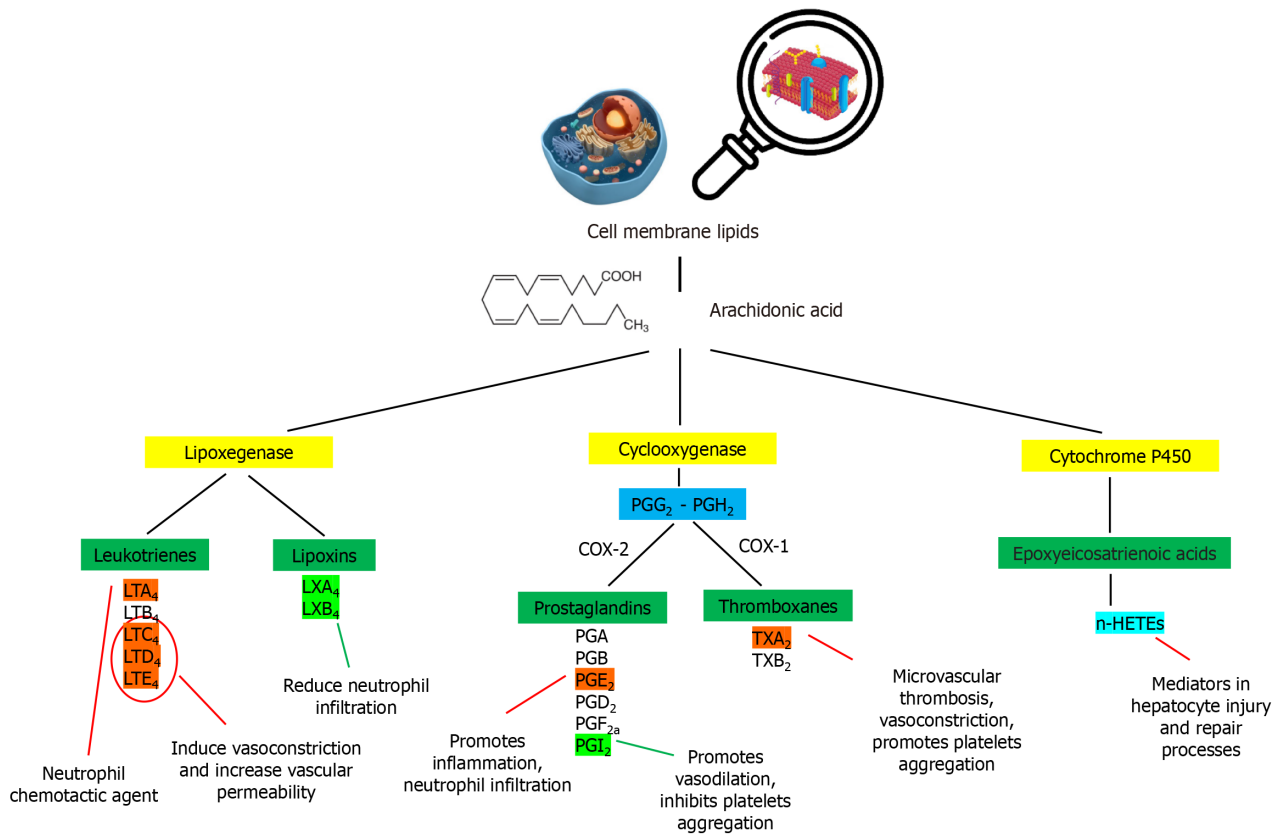


Figure 3 Simplified eicosanoids synthetic pathway and their role in hepatic ischemia-reperfusion injury.

response, and even more local reactions[126,127]. PGs bind to cell surface membrane molecules known as PG receptors to exert their biological actions. All PG receptors are rhodopsin-like G protein-coupled receptors that respond to all active PGH₂ metabolites, with some differences in action. Nine categories of PG receptors are currently known, and their classification is based on the PG and signaling pathways that they regulate (DP₁, DP₂, EP₁, EP₂, EP₃, EP₄, FP, IP, and TP)[119,128,129].

PROSTACYCLIN

PGI₂ is a member of the PG family with an unstable chemical structure at physiological pH. PGI₂ is a fragile molecule with a very short half-life (2-3 minutes) and rapidly forms the biologically inactive hydration product 6-keto-PG F1α[130]. In addition to other members of the PG family, PGI₂ is synthesized from cell membrane lipids derived from arachidonic acid, mainly through the COX-2 and prostacyclin synthase catalysis pathways[131]. PGI₂ is a potent inhibitor of platelet aggregation and activation and an effective vasodilator. Vascular smooth muscle cells and endothelial cells are the main sources of PGI₂ production in the human body, where it is activated by a paracrine signaling cascade that involves the prostacyclin receptor (IP). Specifically, a cell membrane receptor coupled with a GS-type protein binds PGI₂ resulting in the stimulation of cyclic adenosine monophosphate (cAMP) production[132-134]. By acting as a second messenger (an action that occurs within cells), cAMP modulates a variety of biological processes. In vascular smooth muscles, cAMP mediates relaxation and inhibits proliferation, whereas in platelets, it reduces activation and thrombosis *via* the downregulation of calcium-associated pathways[135]. In this context, PGI₂ interacts with a system consisting of eNOS-NO-guanylate cyclase-cyclic guanosine monophosphate[136,137]. Notably, TXA₂, another arachidonic metabolite, acts as a physiological antagonist of PGI₂ by stimulating platelet aggregation and vasoconstriction[138]. Several reports have shown that changes in the PGI₂/TXA₂ ratio contribute to the development of endothelial dysfunction and atherosclerosis, as well as the progression of diabetes, pulmonary and systemic hypertension and renal dysfunction[139].

As mentioned above, PGI₂ has a chemically unstable structure and degrades rapidly into stable but biologically inactive metabolites. The structures of PGI₂ synthetic analogs are more stable, have longer half-lives and have improved potency. These analogs are used intravenously, subcutaneously or by inhalation as potent vasodilators, mainly in patients with pulmonary hypertension, Raynaud's syndrome or limb ischemia[140,141]. Recent studies have described the cytoprotective effect of the PGI₂-cAMP pathway in endothelial cells[142,143]. Furthermore, PGI₂ enhances endothelial cell function and promotes angiogenesis in the ischemic environment by supporting the upregulation of NADPH oxidase 4 in cells[144]. The effects of PGI₂ are summarized in Table 2.

Table 2 Prostacyclin effects (IP receptors)

Number	Prostacyclin effects
1	Inhibition of platelets aggregation
2	Vasodilation
3	Inhibition of platelets adhesion
4	Angiogenesis
5	Reduction of myo-vascular remodelling
6	Inhibition of proliferation
7	Reduction of fibroblast migration
8	Reduction of cytokine release
9	Reduction of lipid peroxidation
10	Downregulation of adhesion molecules and growth factors
11	Inhibition of apoptosis
12	Reinforcement of endothelial cell function
13	Regulation of lipid metabolism

Protective role of prostacyclin in liver disease

PGI₂ appears to have important biological functions in chronic liver injury progression. It acts as a local mediator to regulate hepatic stellate cell function by binding to specific cellular receptors[144]. In addition to hemodynamic variations in portal hypertension, the *in vitro* administration of PGI₂ has been shown to have antiproliferative and antifibrotic effects on human hepatic stellate cells by inhibiting fibroblast migration and decreasing TNF- α production[145,146]. Furthermore, PGI₂ analogs have been shown to have hepatoprotective and antiapoptotic effects[147].

In fact, the management of the hepatic microcirculation by preventing liver sinusoidal vasoconstriction, in combination with the downregulation of inflammatory cell migration and hepatic stellate cell activation and proliferation, make PGI₂ an important factor in delaying liver fibrosis[148]. In light of the scientific evidence, PGI₂ analogs have been suggested as new therapeutic options for the management of patients with chronic liver disease, such as nonalcoholic fatty liver disease, nonalcoholic steatohepatitis and alcohol-related liver disease[144]. In agreement with previous findings, PGI₂ inhibition during acute liver injury exacerbated hepatic cell damage. Although the underlying mechanisms are not fully understood, the cytoprotective effect of PGI₂ may be related to vasodilation and the maintenance of hepatic perfusion, as well as a reduction in lipid peroxidation and the release of inflammatory mediators[149-151]. An analysis of gene expression revealed increased expression of hepatic SIRT1 protein and peroxisome proliferator-activated receptor- α after experimental beraprost sodium administration to mice. Specifically, the activation of the SIRT1 pathway leads to the attenuation of hepatic steatosis and the regulation of lipid metabolism[152]. These interesting findings concerning the hepatoprotective effect of PGI₂ require further research to verify its potential therapeutic use in the management of patients with progressive liver disease.

Prostacyclin in hepatic ischemia-reperfusion injury

The benefits of PGI₂ analogs for hepatic ischemia-reperfusion injury have been studied for nearly 40 years since the first study was published in 1982, where 24- and 48-hour canine liver preservation in solutions containing PGI₂ led to successful orthotopic liver transplantation[153]. Moreover, subsequent studies verified the previous findings, resulting in the clinical application of PGI₂ in optimizing cadaveric and living organ donation[154-156]. Other investigations focused on elucidating the underlying hepatoprotective mechanisms (Figure 2) along with attempting to integrate PGI₂ analogs into therapeutic options.

PGI₂ analog (OP 2507) administration in complete warm ischemia of the animal liver had a hepatoprotective effect by downregulating PGE₂ production in the reperfused liver and ameliorating serum transferase release[157]. These findings were supported by another animal model in which TXA₂ inhibition by the synthase inhibitor OKY-046 increased endogenous PGI₂ production, resulting in the prevention of liver damage[158]. Undoubtedly, the PGI₂/TXA₂ balance is very important for microcirculatory homeostasis because of its antagonistic effects. Endothelium-derived PGI₂ is well known for its potent vasodilating, vasoprotective and thromboresistive activities, along with its ability to inhibit platelet aggregation, whereas TXA₂ causes vasoconstriction and platelet activation and triggers vascular inflammatory processes [119,139,159-161]. Several reports have indicated that the dysregulation of the PGI₂/TXA₂ balance is responsible for the development of endothelial dysfunction, systemic and pulmonary hypertension, diabetes progression, a decrease in the glomerular filtration rate and tumor growth[162-166].

Liver transplantation is the only therapeutic option for patients with end-stage liver disease and has high 5- and 10-year survival rates. Despite the continuous improvement in surgical techniques, a significant number of patients still suffer from postoperative graft dysfunction[167,168]. Severe hepatic ischemia-reperfusion injury can be responsible for early graft dysfunction and may require retransplantation[169]. Therefore, operative and pharmacological approaches to

ameliorate graft postreperfusion injury are urgently needed. Experimental preconditioning with epoprostenol (a PGI₂ analog) in a rat liver transplantation model resulted in improved perfusion of the liver sinusoids, increased bile production and reduced leukocyte aggregation in liver lobules and postsinusoidal venules[170]. Moreover, a prospective randomized placebo-controlled study that investigated the effects of PGI₂ on postoperative graft function following clinical liver transplantation was published in 2000[171]. Patients who received continuous PGI₂ at a dose of 4 ng/min per kg until the 7th postoperative day presented improved hepatic-splanchnic oxygenation. Additionally, these findings are supported by previous reports that suggested the use of stable PGI₂ analogs for liver allograft preservation prior to transplantation along with the treatment of primary liver graft nonfunction[172,173]. Furthermore, Zardi *et al*[174] successfully improved hepatic perfusion with iloprost (another PGI₂ analog) in 15 patients with systemic sclerosis to prevent vascular complications. Specifically, a continuous infusion of iloprost for 5 days increased the portal flow velocity and portal flow volume, as confirmed by color Doppler ultrasonography, resulting in increased local microcirculatory homeostasis. However, PGI₂ appears to have dose- and phase-dependent effects on hepatic perfusion and microcirculation[175-177].

In the context of ischemia-reperfusion, neutrophils are known to promote hepatocyte injury because they are responsible for the initiation of a sterile inflammatory response[178]. Neutrophil apoptosis constitutes an essential mechanism to attenuate inflammatory reactions and minimize tissue damage. Altered neutrophil apoptosis has been proposed to play an important role in a variety of inflammatory diseases and may be a marker of disease severity[179]. Chen *et al*[180] examined an experimental liver ischemia-reperfusion model and observed that the PGI₂ analog OP-2507 inhibited neutrophil apoptosis compared with untreated animals. In addition, OP-2507 administration moderated leukocyte adhesion in postsinusoidal venules and improved flow velocity in those areas[180].

Activated neutrophils release various inflammatory mediators, resulting in the upregulation of adhesion molecules on the endothelium and the promotion of endothelial damage. Neutrophil elastase is a protease that is stored in azurophilic granules and released following the activation of neutrophils by inflammatory stimuli[181]. Neutrophil elastase has been shown to inhibit endogenous PGI₂ production by inhibiting eNOS activity, thereby contributing to the development of hepatic ischemia-reperfusion injury[182,183]. The administration of neutrophil elastase inhibitors significantly improved hepatic tissue blood flow, as confirmed by increased hepatic levels of 6-keto-PGF1 α , a stable metabolite of PGI₂[78,79].

Mitochondria play a vital role in cell homeostasis; thus, mitochondrial dysfunction is closely associated with many pathological conditions. PGI₂ analogs have been proposed to regulate the expression of several mitochondria-related proteins, such as mitochondrial cytochrome C oxidase II and IV, beclin1, LC3 II protein, and PINK1. A reduction in mitochondrial damage was observed in lung fibroblasts treated with treprostinil, another PGI₂ analog[184,185]. Indeed, a previous report indicated that the administration of a PGI₂ analog in combination with superoxide dismutase and catalase in an animal model of warm hepatic ischemia led to significant improvement in mitochondrial function and improved survival[186]. In support of these findings, Hou *et al*[30] described the beneficial role of treprostinil in liver injury during renal ischemia-reperfusion injury: It alleviated hepatic oxidative stress and lipid peroxidation, downregulated hepatic toll-like receptor 9 and inflammatory processes, and inhibited hepatocyte apoptosis. Moreover, in animals treated with treprostinil, hepatic ATP levels appeared to be restored due to the upregulation of ATP synthase. Finally, treprostinil preserved mitochondrial biogenesis, restored mRNA expression to baseline levels and improved hepatic mitochondrial dynamics[30].

As mentioned above, oxidative stress is one of the main mechanisms of hepatic ischemia-reperfusion injury. PGI₂ analogs, in addition to their potent vasodilative and inhibitory activities, have cytoprotective effects by decreasing oxidative stress[187]. Specifically, a recent study showed that treatment with the PGI₂ analog iloprost resulted in increased superoxide dismutase, catalase, and glutathione peroxidase activity, resulting in the inhibition of ROS generation and recovery of hepatic microcirculation after ischemia-reperfusion injury[188].

New data regarding the cytoprotective mechanisms of PGI₂ analogs have been published in the last decade. MAPK signaling pathways regulate several biological processes, including apoptosis, through various cellular mechanisms. Stress-activated JNK and p38 MAPK (p38) mRNA and protein expression are increased following hepatic ischemia-reperfusion injury as a reaction to ROS overproduction[189,190]. A recent study demonstrated that beraprost sodium preconditioning ameliorated hepatic ischemia-reperfusion injury by suppressing the JNK and p38 cascades in a dose-dependent manner[28]. Anti-inflammatory, antiapoptotic and autophagic effects have been suggested as underlying mechanisms, mainly *via* the downregulation of TNF- α and IL-1 β production and altered expression of the Bax, Bcl-2, Caspase-3, Caspase-8, Caspase-9, LC3, Beclin-1, and P62 genes. Similarly, the anti-inflammatory effects of PGI₂ analogs were observed in an experimental liver transplantation model. Specifically, animals treated with treprostinil before liver transplantation presented decreased hepatic tissue mRNA expression of ICAM-1, thereby reducing neutrophil accumulation. The mRNA levels of TNF- α , IL-6 and IFN- γ were decreased in the treprostinil group, whereas the mRNA expression of the anti-inflammatory cytokine IL-10 was increased[29]. Furthermore, the activity of cytochrome P450, an important indicator of allograft function, was significantly increased in animals treated with treprostinil in the early posttransplantation period[191].

The safety and efficacy of PGI₂ analogs have already been evaluated in liver transplant patients in clinical trials. Iloprost was administered by continuous intravenous infusion for 7 days after liver transplantation, and graft function was evaluated[192]. Improvements in allograft function and synthetic activity were observed, particularly in the early postoperative period. The results of another prospective, pilot, single-center, open-label, nonrandomized, phase I/II study were published in 2020 and further supported the efficacy of intravenous treprostinil in liver transplant patients[193]. A small group of patients who underwent liver transplantation and received peri- and postoperative treprostinil showed improved graft function, reduced ICU and hospital stays, and restored hemodynamic stability. In addition, the use of epoprostenol in the preservation solution to improve flushing of the peribiliary vascular plexus and biliary mucosa minimizes postschemic injury to biliary ducts, improves liver function tests and protects biliary strictures[194,195]. The

Table 3 Summarizing the main characteristics of the studies before 2000 regarding effects of prostacyclin analogs on hepatic ischemia-reperfusion injury

Ref.	Prostacyclin analog	Dose	Intervention	Species	Study size	Outcome
Monden <i>et al</i> [152], 1982	PGI ₂	100 µg	Liver preservation for orthotopic liver transplantation	Mongrel dogs	6	100% 48 hours survival
Sikujara <i>et al</i> [155], 1983	PGI ₂	350 ng/kg/min <i>i.v</i>	75 min Hepatic ischemia	Wistar rats	31	67% one-week survival
Tanaka <i>et al</i> [186], 1990	aPGI ₂	350 ng/kg/min for 60 min <i>i.v</i>	90 min Hepatic ischemia	Rats		No effect alone
Sanchez-Urdazpal <i>et al</i> [172], 1991	Iloprost	200 µl/L storage solution. 3 µg/kg/min bolus administration through the aortic patch	Liver graft preservation	Lewis rats	12	91% survival
Goto <i>et al</i> [154], 1992	OP-41483	500 ng/kg/min <i>i.v</i>	Liver transplantation	Wistar rats	7	86% one-week survival
Abe <i>et al</i> [176], 1993	OP-41483	400 ng/kg/min	40 min normothermic liver ischemia	Wistar rats	8	Improved microcirculation and increased effective hepatic blood flow
Kim <i>et al</i> [156], 1994	OP-2507	2 pg/kg/min for 30 min, intraportal infusion 200 µg/l	Liver donor pretreatment, graft preservation. Dissolution in preservation solution	Mongrel pigs	6	Improved 5-day survival
Kim <i>et al</i> [157], 1994	OP-2507	2 pg/kg/min for 30 min <i>via</i> mesenteric vein administration	1 hour complete hepatic vascular exclusion	Mongrel pigs	7	86% 5-day survival
Anthuber <i>et al</i> [170], 1996	Epoprostenol	50 µg/ml solution	Liver donor bolus pretreatment	Lewis rats	8	Improved perfusion of liver sinusoids, reduced leukocyte adherence, increased bile production
Klein <i>et al</i> [195], 1999	Epoprostenol	500 µg	Orthotopic liver transplantation	Human	57	Reduced ischemia-reperfusion injury

PGI₂: Prostacyclin.

main characteristics of the studies regarding the effects of PGI₂ analogs on hepatic ischemia-reperfusion injury are summarized in Tables 3 and 4.

Although several experimental studies have investigated the effects of PGI₂ analogs on hepatic ischemia-reperfusion injury, clinical data remain limited. Practical challenges due to the short life of PGI₂ analogs and the need for continuous administration have improved with the development of stable analogs, but further optimization is needed. Furthermore, PGI₂ analogs may have limited accessibility to some populations because of the high cost of the treatment. In addition, the clinical application of PGI₂ analogs in high-risk populations, such as cirrhotic and immunocompromised patients, poses significant safety concerns, primarily because of the potent vasodilatory effects of these drugs, their impact on immune reactions, metabolic considerations and altered drug metabolism.

Given the abovementioned challenges associated with PGI₂ analogs, well-designed clinical trials are essential to determine their optimal role in the treatment of hepatic ischemia-reperfusion injury. Large randomized controlled trials could determine whether PGI₂ analogs offer a clinical benefit over existing therapies. Combination therapy trials may evaluate whether the coadministration of PGI₂ analogs with various vasoactive agents increases the therapeutic benefits while reducing adverse events. Safety studies may assess the long-term safety and tolerability of PGI₂ analogs and define safe dosing strategies in high-risk populations. Pharmacokinetic and delivery optimization studies will lead to the development of novel stable formulations of PGI₂ analogs to overcome practical difficulties in administration and improve cost-effectiveness.

CONCLUSION

Hepatic ischemia-reperfusion injury is an important complication of liver transplantation and other clinical conditions, such as hemorrhagic and septic shock, trauma surgery, Budd-Chiari syndrome and major hepatectomy. Depending on the duration and degree of tissue damage, hepatic ischemia-reperfusion injury may result in a wide range of clinical presentations, from mild liver dysfunction to multiple organ failure. Many factors and pathways are involved in the pathophysiology of liver damage, including anaerobic metabolism, ATP depletion, intracellular acidosis, intracellular

Table 4 Summarizing the main characteristics of the studies after 2000 regarding effects of prostacyclin analogs on hepatic ischemia-reperfusion injury

Ref.	Prostacyclin analog	Dose	Intervention	Species	Study size	Outcome
Neumann <i>et al</i> [171], 2000	Epoprostenol	4 ng/kg/min <i>i.v</i> for 7 days	Continuous infusion after liver transplantation	Human	15	Improvement of hepatic-splanchnic oxygenation
Chen <i>et al</i> [180], 2001	OP-2507	1 µg/kg/min, 0.1 µg/kg/min	Hepatic ischemia	Sprague-Dawley rats	24	Ameliorated ischemia-reperfusion of the liver
Zardi <i>et al</i> [174], 2006	Iloprost	2 ng/kg/min, 6 h/day for 5 days	Portal flow velocity evaluation	Human	15	Improved hepatic perfusion
Gedik <i>et al</i> [188], 2009	Iloprost	10 µg/kg	45 min hepatic ischemia followed by reperfusion	Sprague-Dawley rats	10	Hepatoprotective effects
Ghonem <i>et al</i> [191], 2012	Treprostinil	100 ng/kg/min	Donor and recipient treatment prior liver transplantation	Lewis rats	58	Ameliorated hepatic injury reduced cytokines expression and improved CYP450 activity
Deng <i>et al</i> [28], 2018	Beraprost sodium	50-100 µg/kg	Hepatic ischemia-reperfusion	Mice	36	Ameliorated hepatic IR injury by suppressing inflammation, apoptosis, and autophagy
Almazroo <i>et al</i> [193], 2022	Treprostinil	20 ng/mL of storage solution	Hepatic ischemia-reperfusion	Sprague-Dawley rats	8	Reduced liver injury

calcium overload, mitochondrial dysfunction, oxidative stress, the activation of Kupffer cells and neutrophils, platelet aggregation, NO production, and cytokine release. Overall, hepatic ischemia-reperfusion injury has adverse effects on morbidity and mortality rates; therefore, new options to reduce liver damage are needed. Prostacyclin analogs confer protective effects on ischemic livers, mainly by regulating hepatic microcirculation, inhibiting platelet aggregation and alleviating oxidative stress. Experimental and clinical applications of PGI₂ analogs have revealed their ability to manage hepatic ischemia-reperfusion injury. Nevertheless, controlled clinical trials are needed to determine the safety and effectiveness of PGI₂ analogs in routine clinical practice.

FOOTNOTES

Author contributions: Mouratidou C, Pavlidis ET, Katsanos G, Tsoulfas G designed research, performed research and analyzed data; Kotoulas SC, Mouloudi E, Galanis IN contributed new analytic tools, analyzed data and review the paper; Papaioannou M, Niti A contributed to data collection and analyzed data; Pavlidis TE analyzed data review and approved the paper.

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