


Hexafluoroisopropanol decreases liver ischemia–reperfusion injury by downregulation of high mobility group box-1 protein

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Abstract

Liver ischemia–reperfusion (IR) injury is associated with poor outcome after liver transplantation and liver resections. Hexafluoroisopropanol (HFIP) is a tri-fluorinated metabolites of volatile anesthetics and has modulatory effects on inflammation that have been observed mainly in cell culture experiments. In this survey, we investigated the effects of HFIP in a rat model of normothermic hepatic ischemia–reperfusion injury. Twenty-four male Wistar rats were randomized into three groups: (1) control in which animals were submitted to 30min of partial liver ischemia with resection of non-ischemic liver lobes immediate after reperfusion, (2) pre-ischemia (PI) group in which animals received intravenous HFIP (67 mg/kg) 5 min before liver ischemia, and (3) pre-reperfusion (PR) group in which animals received intravenous HFIP (67 mg/kg) 5 min before reperfusion. Four hours after reperfusion, all animals were euthanized for sample collection. Aspartate and alanine transaminases, glucose, and high mobility group box-1 (HMGB-1) protein concentrations showed a significant decreased, and malondialdehyde was increased in the PR group compared with control and PI groups. Interleukin 6 (IL-6) was increased in the PI group compared with control and PR groups. IL-10 and -12 were increased in the PR and PI groups, respectively, when compared with the control group. Glucose decreased in the PR when compared with the control group. Post-conditioning with HFIP led to a decrease in hepatocellular injury and was associated with a downregulation of HMGB-1. The HFIP resulted in a better control of inflammatory response to ischemia–reperfusion even without causing a reduction in oxidative stress.

KEYWORDS

hexafluoroisopropanol, ischemia, ischemic postconditioning, ischemic preconditioning, liver, reperfusion injury

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1 | INTRODUCTION

Ischemia-reperfusion (IR) injury occurs frequently during liver resections and transplantations.¹⁻⁴ The tissue injury is characterized by a temporary interruption of blood flow followed by subsequent reperfusion and reoxygenation, which further exacerbates tissue damage and inflammation.⁵⁻⁷

For decades, different surgical and pharmacological strategies have been studied in the attempt to decrease organ damage secondary to IR injury.⁸⁻¹² More recently, growing evidence that volatile anesthetics provide protective effects in experimental and clinical settings of liver IR injury has been reported.^{1,2,13-15} The volatile anesthetic sevoflurane has been shown to mediate such effects in liver IR injury with better control of inflammatory and hemodynamic profiles,^{13,15} which has been associated with reduced expression of high mobility group box-1 protein.¹⁶ Sevoflurane is metabolized by cytochrome P450 2E1 (CYP2E1) enzyme to hexafluoroisopropanol (HFIP), a water-soluble trifluorinated compound, (CF₃)₂CHOH. HFIP and sevoflurane showed promising immunomodulatory effects in the treatment of sepsis using *in vitro* and *in vivo* experimental models¹⁷⁻¹⁹; however, it is currently unknown if HFIP modulates a positive response after liver IR injury. In the present study, we investigated the effects of HFIP in a standardized model of liver IR injury.

2 | METHODS

2.1 | Animals and experimental design

This study was approved by the Ethics Committee on the Use of Animals of University of Sao Paulo School of Medicine (no. 007/17). Twenty-four male adult Wistar rats weighing between 250 and 350g were randomized into three groups of eight animals¹: control group in which animals were submitted to 30min of partial liver ischemia followed by 4 h of reperfusion with resection of non-ischemic liver lobes immediately after reperfusion,² pre-ischemia (PI) group in which animals received intravenous HFIP (67 mg/kg) through the penile vein 5 min before liver ischemia, and³ pre-reperfusion (PR) group in which animals received intravenous HFIP, 67 mg/kg, 5 min before reperfusion. HFIP dosage and administration were based on a study by Urner et al.¹⁸

2.2 | Anesthesia and surgical procedures

After receiving standard intraperitoneal anesthesia with 100mg/kg of 5% ketamine hydrochloride (Ketalar®, Cristália), and 10 mg/kg of 2% xylazine hydrochloride (Rompum®, Bayer), rats underwent standardized orotracheal intubation with Jelco® 18G and mechanical ventilation (Small Animal Ventilator model 683; Harvard Apparatus) with a tidal volume of 0.08mL/g of body weight, respiratory rate of 60/min, and fraction of inspired oxygen/ (FiO₂) of 21%.²⁰ The right common carotid artery was catheterized with a polyethylene catheter (PE50) to record reperfusion hemodynamics and to conduct an arterial blood

analysis. A median laparotomy extending for about 4 cm from the xiphoid appendix was performed. The common pedicle of the median and left anterolateral lobes was occluded with an atraumatic microvascular clamp that allowed specific liver ischemia without splanchnic vasculature obstruction. After 30min the clamp was removed, reperfusion was initiated, and the non-ischemic right and caudate lobes (upper and lower portions) were immediately resected. The abdominal incision was closed with continuous sutures to allow the rat to recover. After 4 h, the animals were re-anesthetized for autopsies, blood and tissue sample collection, and euthanization by exsanguination.

2.3 | Serum biochemical analysis

The optimized ultraviolet (UV) method using COBAS MIRA (Roche Diagnostics, Rotkreuz, Switzerland) quantified aspartate and alanine aminotransferase (AST and ALT, UI/L, respectively) and alanine aminotransferases. The ABL800 Flex gas analyzer (Radiometer Medical ApS) was used to quantify glucose (mg/dL), lactate (mg/dL), ionic calcium (iCa²⁺, mg/dL), and potassium (K⁺, mEq/L).

2.4 | Analysis of inflammatory mediators

Multiple Analyte-Profilin (xMAP) technology (Luminex Corporation) was used to quantify tumor necrosis alpha and interleukins 1 beta, 6, 10, and 12 (TNF α and IL-1 β , -6, -10, and 12 in pg/mL, respectively), and an enzyme-linked immunosorbent assay (ELISA, Bio-Rad) was performed to quantify the high mobility group box-1 protein (pg/mL) in the serum.

2.5 | Lipid peroxidation

Malondialdehyde (MDA) content in the serum was determined by measuring thiobarbituric acid reactive substances (TBARS) as previously described.²¹ Briefly, liver samples were homogenized in potassium chloride (KCL) and the supernatant containing thiobarbituric acid, sodium dodecyl sulfate, glacial acetic acid were diluted by distilled water addition and heated to 90°C for 45 min. After cooling to room temperature, the samples were centrifuged at 15000rpm for 10 min. Lipid peroxidation product concentrations were expressed by TBARS quantification (Gen5 Software, Bio Tek Instruments). Results were expressed in nmol of MDA/mg of protein.

2.6 | Hemodynamic evaluation

The MP150 Starter System (Biopac Systems Inc.) was used to record the mean blood pressure (mmHg) through the carotid artery catheter. The flowmeter (TS420 Animal Research Flowmeter, Transonic Systems Inc.) connected to the perivascular probe was used to measure portal venous flow (mL/min). Portal venous flow was recorded at

three timepoints¹: after induction of anesthesia,² 5 min after induction of ischemia, and³ 4 h after reperfusion.

2.7 | Statistical analysis

The 8 Prism Software (GraphPad Software) was used to perform statistical analyses. Unpaired Student's *t*- or the Mann-Whitney test were performed when indicated. $p \leq .05$ was considered significant. Results were expressed as mean \pm standard deviation.

3 | RESULTS

3.1 | Biochemical results

Four hours after reperfusion, AST (Figure 1A) and ALT (Figure 1B) mean serum concentrations were significantly lower in PR (1672 \pm 879 and 1596 \pm 924 UI/L, respectively) compared with the

control (3876 \pm 2034 and 3891 \pm 2122 UI/L) and PI (3723 \pm 2352 and 3437 \pm 1561 UI/L) groups. However, no significant differences between control and PI groups were found.

Glucose arterial blood concentrations were significantly lower in PR compared with control ($p = .0492$) and PI ($p = .0077$) groups. However, no differences in K^+ , iCa^{2+} , and lactate arterial blood concentrations between any groups were detected (Table 1).

3.2 | Inflammatory mediators

At 4 h of reperfusion, significantly higher IL-6 serum concentrations were measured in the PI groups when compared with the control group (P and $PR = .0011$ and $.0009$, respectively). IL-10 and -12 serum concentrations were higher in PR and PI groups ($p = .0465$ and $.0490$, respectively) when compared with the control group. However, no differences in $TNF\alpha$ and IL-1 serum levels between any groups were found (Table 2).

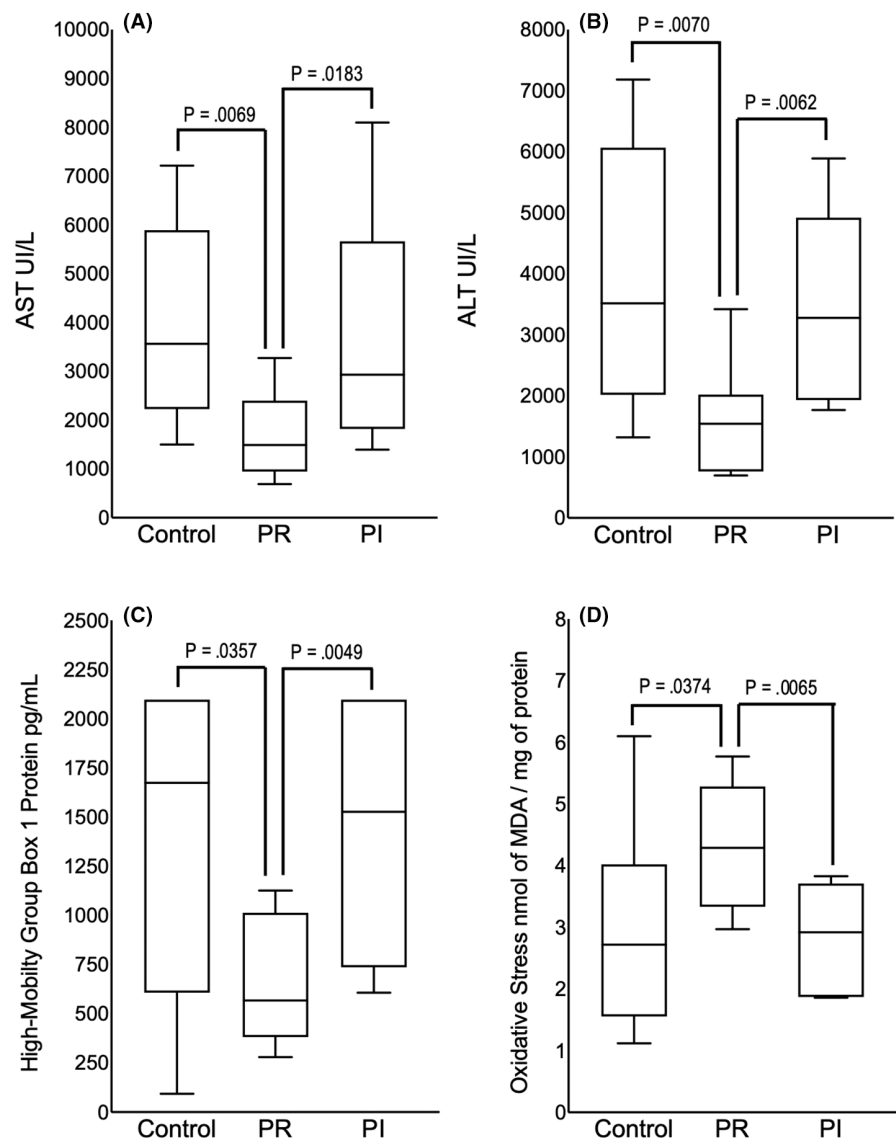


FIGURE 1 Aspartate transaminase, AST (A); alanine transferase, ALT (B); high mobility group box-1 protein, HMGB-1 (C); oxidative stress (D). Groups: control, administration of hexafluoroisopropanol pre-reperfusion (PR) and pre-ischemia (PI). Statistical analysis was performed using unpaired Student's *t* test, $n = 8$ in each group

	Control	Pre-reperfusion	Pre-ischemia
Potassium, mEq/L	5.88 ± 0.87	5.83 ± 0.61	6.14 ± 1.13
Ionized calcium, mg/dL	4.61 ± 0.47	4.61 ± 0.41	4.77 ± 0.25
Glucose, mg/dL	320 ± 131	217 ± 98 ^{a,b}	337 ± 60
Lactate, mg/dL	21 ± 5	23 ± 12	32 ± 19

^a*p* < .05 compared with control group.

^b*p* < .05 compared with pre-ischemia group.

TABLE 1 Biochemical results

	Control	Pre-reperfusion	Pre-ischemia
TNF-alfa, pg/mL	12.0 ± 6.38	13.53 ± 4.35	10.92 ± 3.66
IL-1, pg/mL	255 ± 264	443 ± 343	290 ± 248
IL-6, pg/mL	647 ± 767	816 ± 505 ^b	2418 ± 942 ^a
IL-10, pg/mL	395 ± 223	629 ± 272 ^a	553 ± 269
IL-12, pg/mL	17.52 ± 3.29	23.22 ± 7.06	27.61 ± 14.51 ^a

^a*p* < .05 compared to control group.

^b*p* < .05 compared to pre-ischemia group.

TABLE 2 Results of inflammatory mediators

HMGB-1 serum concentrations (Figure 1C) were significantly lower in PR (645 ± 313 pg/mL) when compared with the control and PI groups (1301 ± 820 and 1450 ± 637 pg/mL, respectively).

3.3 | Lipid peroxidation

At 4 h of reperfusion, MDA content was significantly elevated in PR (4.27 ± 1.01 mmol/mg of protein) compared to the control (2.96 ± 1.65 mmol/mg of protein) and PI (2.88 ± 0.32 mmol/mg of protein) groups (Figure 1D).

3.4 | Hemodynamics

Portal venous flow (Figure 2B) was significantly decreased in the control, PR, and PI groups at 5 min after initiation of ischemia (1.60 ± 1.34 mL/min [*p* = .0048]; 2.75 ± 1.67 mL/min [*p* = .0001]; and 2.0 ± 1.41 mL/min [*p* < .0001], respectively) and after 4 h of reperfusion (2.0 ± 1.29 mL/min [*p* = .0023]; 1.71 ± 1.38 mL/min [*p* = 0.0001], and 1.13 ± 0.35 [*p* < .0001], respectively) when compared with basal venous flow (7.83 ± 3.66 mL/min, 8.63 ± 1.60 mL/min, and 11.88 ± 3.98 mL/min, respectively). In the PR group, portal venous flow increased at 5 min after the start of ischemia compared with 4 h of reperfusion (*p* = .0465). However, no differences in mean blood pressure between any groups were detected.

4 | DISCUSSION

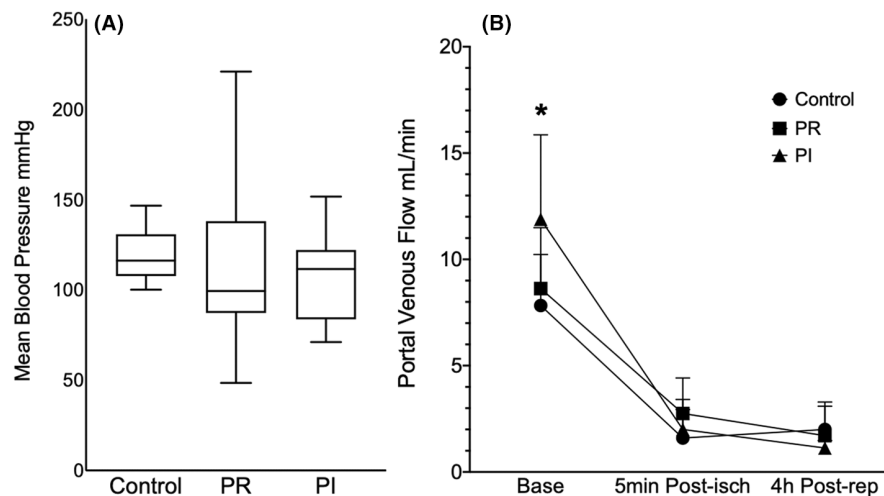
Our laboratory and others have used the present well-established model of liver IR to study specifically liver ischemia without splanchnic vasculature obstruction and concomitant congestive bowel

ischemia.^{10,13,20,22} In this experiment, this model was tested after 4 h of reperfusion to which verify markers were involved in late immunological anti-inflammatory effects of liver IR after the effect markers involved in the normal acute inflammatory phase. Interestingly, we observed that post-conditioning with intravenous HFIP markedly attenuated late IR injury as measured by reduced serum transaminases, which represent the main markers indicating hepatocellular necrosis.²³ Furthermore, lower concentrations of HMGB-1 were related to a decrease in hepatocellular necrosis and an attenuation of inflammatory responses with higher concentrations of IL-10. Altogether, it can be suggested that HFIP-attenuated liver tissue damage by modulating anti-inflammation immunological reaction mediators, such IL-10, which is involved in later period of liver IR experiment.

Our results are well-aligned with findings from previous studies that investigated volatile anesthetics and high-mobility group box 1 (HMGB-1) and support the hypothesis that modulation of HMGB-1 by HFIP might play an important role as a mediator of protective effects in IR injury. HMGB-1, a damage-associated molecular pattern (DAMP) molecule, and is a potent “danger signal,” associated with the innate immune response, is passively secreted through necrosis.²⁴ Xu et al.¹⁶ previously suggested that sevoflurane post-conditioning protects against liver IR injury by reducing HMGB-1, which then that leads to inhibition of the high-mobility group box 1/Toll-like receptor 4/nuclear factor kappa beta/pro-inflammatory cytokine axis (HMGB-1/TLR-4/NF-kB/pro-inflammatory cytokine axis). Furthermore, Cavalcante et al.²⁵ showed conditioning with sevoflurane caused a reduction in hepatocellular necroses and lung permeability in liver IR.

Inflammatory mediators play a key role in IR injury. It was demonstrated that HFIP modulated the inflammatory response to liver IR injury. In a prior work, Urner et al.¹⁸ suggested immunomodulatory effects of HFIP in a model of endotoxemia in which

FIGURE 2 Mean blood pressure (A). Groups: control, PR (administration of hexafluoroisopropanol pre-reperfusion), and PI (pre-ischemia). Portal venous flow (B) evaluated before ischemia (base), 5 min after ischemia (5 min Post-isch), and 4 h after reperfusion (4 h Post-rep). * $p < .05$ compared with other groups. Statistical analysis was performed using unpaired Student's *t* test, $n = 8$ in each group



HFIP stimulated lipopolysaccharide (LPS)-triggered inflammation and caused an increase in interleukin 6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and cytokine-induced neutrophil chemoattractant protein-1 (CINC-1) plasma concentrations. At the same time, HFIP caused a decrease in inflammatory mediators possibly associated with inhibition of the NF- κ B pathway. Herrmann et al.,¹⁹ using a model of septic peritonitis, found that administration of HFIP caused a decrease in the injury via HMGB-1 downregulation and an improvement in survival without causing a decrease in IL-6 and MCP-1 plasma concentrations. These differences are probably related to the differences in animal species (mice and rats) and the timing of measurements.

Oxidative stress as a result of ischemia/reperfusion has been suggested as a major driver of inflammation and tissue injury.⁸ Figueira et al.¹³ showed a decrease in IL-6 and liver injury with sevoflurane conditioning without a reduction in oxidative stress at 4 hours of reperfusion. In this study, we used only MDA to evaluate oxidative stress, however, Hydroxynonenal, or 4-hydroxy-2-nonenal (4-HNE or HNE), is another cytotoxic aldehyde largely produced during lipid peroxidation that may be used for ischemia-reperfusion injury. 4-HNE could be another option to evaluate liver IR and will be considered using this marker in our further experiments assessing ischemia-reperfusion injury.²⁶ Conversely, our results showed increased levels of oxidative stress associated with increased proinflammatory interleukins (IL-1, I-6, and -12) and TNF- α , but not related to the beneficial effects of HFIP in attenuating liver IR injury. In this context, Xu et al.²⁷ suggested that sevoflurane produced downregulation of oxidative stress after 1 h of liver reperfusion. It is possible that the increase in oxidative stress during the late phase of liver IR is not suppressed with HFIP or sevoflurane administration. In contrast, Liao et al.²⁸ showed conditioning with sevoflurane in liver IR caused a decrease in IL-1 and -6 and TNF α at 2 h after reperfusion through the expression of microRNA-9-5p that downregulates the NF- κ B signaling pathway.

In experimental studies, liver IR injury was associated with a decrease in mean blood pressure and portal venous flow and

biochemical imbalance.^{10,13} We measured consistently decreased portal flow despite administration of HFIP, without significant impact on blood pressure, which maintained within the range of normal values found in other studies.^{10,13} Although conditioning with sevoflurane in liver IR did not lead to the recovery of portal venous flow 4 h after reperfusion,¹³ ischemic pre-conditioning caused restored of 78% of portal flow.¹⁰ Liver IR can induce increased serum concentrations of K⁺ and lactate and cause a reduction in iCa²⁺.^{10,20} Also, glucose levels can vary within a wide range depending on the severity of liver injury. Figueira et al.¹³ showed profound hypoglycemia in a model of liver IR after 45 min of hepatic ischemia. In our study, administration of HFIP did not alter K⁺, lactate, and iCa²⁺ serum concentrations. However, glucose levels were elevated, and post-conditioning with HFIP promoted partial normalization of glucose levels.

Sevoflurane is a volatile anesthetic widely used in the clinical setting, and its use is associated with beneficial effects during liver surgery. Beck-Schimmer et al.²⁹ showed a decrease in liver injury and post-operative complications with sevoflurane pre-conditioning in hepatic resection with clamping of the portal triad for 30 min. In liver transplantation, while Minou et al.³⁰ showed sevoflurane pre-conditioning produced a decrease in liver injury and post-operative liver dysfunction, Beck-Schimmer et al.² suggested a decrease in the grade of post-operative complications with sevoflurane post-conditioning. At present, reports of the application of HFIP have been limited to experimental research. However, sevoflurane is rapidly metabolized to HFIP and has been shown to remain in the bloodstream of patients for a long period of time after the anesthetic effects of sevoflurane have disappeared.³¹ Our findings that HFIP has such modulatory effects raise the question of whether a major part of the immunomodulatory effects provided by sevoflurane are mediated by the long-lasting metabolite, HFIP.

In conclusion, HFIP-attenuated tissue damage in a model of experimental liver ischemia-reperfusion injury. The beneficial effects were associated with the downregulation of HMGB-1 and reduced inflammation. Further experiments are needed to confirm our

findings in pre-clinical studies using larger animal samples following the premises of the translational research.

AUTHORS' CONTRIBUTIONS

Agustin Vintimilla Moscoso, Estela Regina Ramos Figueira, and Joel Avancini Rocha-Filho: conceptualization, methodology, manuscript writing, manuscript reviewing. Martin Urner, and Cinthia Lanchotte: data curation, manuscript draft preparation, research investigation. Jose Jukemura and Jorge Luiz Saraiva Ximenes: manuscript writing, manuscript reviewing. Sergio Carlos Nahas, Luiz Augusto Carneiro D'Albuquerque, Flavio Henrique Ferreira Galvao: supervision and writing-reviewing. All authors: final manuscript reviewing and approval before submission.

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CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT

The study was approved by Ethics Committee on the Use of Animals of University of Sao Paulo School of Medicine (no 007/17).

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