Hyperbaric oxygen therapy aggravates liver reperfusion injury in rats[1]

Oxigenoterapia hiperbárica agrava lesão de reperfusão hepática em ratos

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ABSTRACT

Purpose: To evaluate the effects of hyperbaric oxygen (HO) therapy in the protection against liver ischemia/reperfusion injury. **Methods:** Thirty-two male Wistar rats were divided into four groups of eight animals each: group A – laparotomy and liver manipulation, group B – liver ischemia and reperfusion, group C – HO pretreatment for 60 min followed by liver ischemia and reperfusion, and group D – pretreatment with ambient air at 2.5 absolute atmospheres for 60 min followed by liver ischemia and reperfusion. Plasma was assayed for aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH). Intra-arterial blood pressure was monitored continuously. Myeloperoxidase activity in the liver and lung was assessed 30 min after reperfusion. **Results:** Plasma AST, ALT and LDH increased after reperfusion in all animals. Plasma ALT values and myeloperoxidase activity in the liver parenchyma were higher in HO-pretreated animals than in groups A, B and D. HO had a negative hemodynamic effect during liver reperfusion. **Conclusion:** Liver preconditioning with hyperbaric oxygen therapy aggravated liver ischemia/reperfusion injury in rats as demonstrated by plasma ALT and liver myeloperoxidase activity.
Key words: Reperfusion Injury. Liver. Hyperbaric Oxygenation. Rats.

RESUMO

Objetivo: Avaliar os efeitos da oxigenoterapia hiperbárica (OH) como método preventivo da lesão de isquemia e reperfusão (LIR) do fígado. **Métodos:** Trinta e dois ratos machos Wistar foram distribuídos em quatro grupos de oito animais cada: A – laparotomia e manipulação hepática, B – isquemia e reperfusão hepática, C – pré-tratamento com OH por 60 minutos seguido de isquemia e reperfusão hepática e D – pré-tratamento com ar ambiente a 2,5 atmosferas absolutas por 60 minuto e isquemia e reperfusão hepática. Dosagens seriadas de AST, ALT e DHL foram realizadas. A pressão intra arterial foi monitorizada continuamente. O grau de infiltração leucocitária no fígado e pulmões foi inferido pela dosagem de mieloperoxidade tecidual. **Resultados:** O nível sérico de AST, ALT e DHL aumentou em todos animais. Os animais expostos a OH apresentaram níveis de ALT e infiltração leucocitária hepática maior que os demais. A OH apresentou efeitos hemodinâmicos negativos durante a reperfusão hepática. **Conclusão:** O pré-condicionamento hepático por oxigenoteraia hiperbárica agrava a lesão de isquemia e reperfusão hepática em ratos.
Descritores: Traumatismo por Reperfusão. Fígado. Oxigenação Hiperbárica. Ratos

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Introduction

Liver ischemia-reperfusion injury (IRI) occurs in the case of temporary deprivation of blood flow to the liver (hepatectomy, liver transplant, hemorrhagic shock), and can cause from a mild increase in the serum level of liver enzymes to severe acute liver failure. The intensity of liver damage is directly related to the duration of ischemia and is the consequence of interactions between the depletion of adenosine triphosphate and the adhesion and activation of leukocytes, Kupffer cells and platelets in the liver sinusoids. Proteases, phospholipases, complement and reactive oxygen species also play a role[1].

The beneficial effects of HO on the treatment of diseases associated with tissue ischemia have been well established[2]. However, its clinical application to the liver is recent and is restricted to isolated cases of diseases such as chronic viral hepatitis[3], postoperative liver failure in cirrhotic patients[4], post-liver transplant artery ischemia[5], and acute fulminant hepatitis[6]. Despite promising results in these situations, the small number of reported cases and the lack of controlled clinical studies do not permit conclusions so far. An experimental study has demonstrated the beneficial effect of postoperative HO in rats submitted to hepatic vein ligation, with the observation of a reduction in postoperative mortality and attenuation of histological alterations in the liver[7].

The objective of the present study was to evaluate the effects of HO preconditioning on liver IRI in rats.

Methods

Thirty-two male Wistar rats (*Rattus norvegicus albinos*), weighing between 210 and 270 g, from the animal house of Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, were used. The animals were kept at the Central Animal House of Faculdade de Medicina, Universidade Federal de Minas Gerais, and received balanced chow appropriate for rats (Purina, Campinas, SP) and drinking water *ad libitum*. The project was approved by the Ethics Committee on Animal Experimentation of Universidade Federal de Minas Gerais.

The 32 animals were divided into four groups of eight animals and each group was submitted to the following procedures:

• group A (n=8, control): laparotomy and manipulation of the hepatic pedicle;
• group B (n=8): laparotomy and occlusion of the vascular pedicle of the middle and left lateral lobe of the liver during 30 min, followed by reperfusion during 30 min;
• group C (n=8): HO therapy at 2.5 absolute atmospheres (ATA) for 60 min, laparotomy, and occlusion of the vascular pedicle of the middle and left lateral lobe of the liver during 30 min, followed by reperfusion during 30 min;
• group D (n=8): exposure to ambient air at 2.5 ATA for 60 min, laparotomy, and occlusion of the vascular pedicle of the middle and left lateral lobe of the liver during 30 min, followed by reperfusion during 30 min.

Hyperbaric treatment

The hyperbaric treatment sessions were performed in an A 240 multiplace hyperbaric chamber (Seaway Diver Ind Met e Mont Ltda, Santa Rosa, RS, Brazil). Oxygen (100%) (group C) or ambient air (group D) was used and the pressure of the chamber was maintained at 2.5 absolute ATA for 60 min. Compression and decompression were performed gradually at 0.1 ATA/min. The temperature inside the chamber was kept between 22ºC and 26°C.

Surgical procedure

The animals were anesthetized by intraperitoneal application of both 2% xylazine hydrochloride (15 mg/kg) and 5% ketamine hydrochloride (90 mg/kg). Submitted to orotracheal intubation and placed under ventilation (Harvard Ventilator Rodents, Cambridge, MA, USA) at a respiratory frequency of 60 breaths per minute and a tidal volume of 1.5 mL/100 g body weight. Heating pads under the animals were used to maintain the rectal temperature between 36-37 °C.

The left carotid artery was dissected and cannulated with a PE 10 polypropylene catheter (Clay Adams, Becton Dickinson, Sparks, MD, USA) for the measurement of blood pressure and collection of blood samples during the surgical procedure. The right jugular vein was dissected and catheterized with a PE10 polypropylene catheter (Clay Adams) for infusion of 0.9% NaCl solution.

The middle and left lateral lobes of the liver were then submitted to ischemia by occlusion of their pedicles with a vascular microclamp (Yasargil FE-751, Aesculap, Melsungen, Germany) for 30 min, followed by reperfusion for 30 min. At the end of the experiment, the middle and left lateral lobes of the liver and lower lobe of the right lung were excised and stored frozen at -80°C for further mieloperoxidase (MPO) activity measurement.

Blood samples (600 μL) were collected before the surgical procedure, after 30 min of ischemia and after 30 min of liver reperfusion for the measurement of plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH).

Pressure monitoring

The catheter introduced into the left carotid artery was connected to a pressure transducer (Transducer Amplifier, Model PM 1000, DATAQ Instruments, Inc., Akron, OH, USA) coupled to a computer equipped with the WinDaq Pro Acquisition program, version 2.09 (DATAQ Instruments, Inc.), and intra-arterial pressure was monitored during the intraoperative period.

Blood biochemical analysis

Changes in blood parameters resulting from liver IR injury were evaluated by the measurement of serum AST, ALT and LDH using an optimized ultraviolet kinetic method.

Quantification of neutrophil tissue infiltration by myeloperoxidase activity measurement

Tissue samples of the liver and lung weighing 100 mg each were suspended in 2.0 mL (4°C) phosphate buffer (0.1 M NaCl, 0.02 M $NaPO_4$, 0.015 M Na-EDTA, pH 4.7), vortex homogenized, and centrifuged at 4°C for 15 min at 10,000 g. Pellets were then resuspended in 2 mL phosphate buffer (0.05 M Na_3PO_4, 0.5% HETAB, pH 5.4) at room temperature. The suspension was frozen and thawed three times and centrifuged at 4°C for 15 min at 10,000 g. Supernatants were stored at -20°C for the MPO assay.

For the assay, 25 µL of 3,3'-5,5'-tetramethylbenzidine (TMB; Sigma, St. Louis, MO, USA) dissolved in dimethyl sulfoxide (Merck, Darmstadt, Germany) at a final concentration of 1.6 mM, 100 µL H_2O_2 dissolved in phosphate buffer (0.05 M Na_3PO_4, 0.5% HETAB, pH 5.4) at a final concentration of 0.003% v/v, and 25 µL of the tissue sample supernatant were used. The reaction was started at 37°C for 5 min in a 96-well microplate by adding the supernatant and TMB solution. Next, 100 µL H_2O_2 was added and the mixture was again incubated at 37°C for 5 min. The reaction was stopped by the addition of 100 µL 4 M H_2SO_4 and quantified at 450 nm in a spectrophotometer (E max, Molecular Devices Corporation, Chicago, IL, USA). Neutrophil content was calculated from a standard curve based on MPO activity and is expressed as the relative number of neutrophils per mg wet tissue.

Statistical analysis

The following variables were analyzed: mean arterial pressure (MAP), AST, ALT, LDH and hepatic and pulmonary MPO activity. The GraphPad Prism program for Windows, version 3.00 (GraphPad Software, San Diego, CA, USA), was used for construction of the graphs and statistical analysis. A level of significance of $p = 0.05$ was adopted.

Results

Intra-arterial pressure

Partial occlusion of the hepatic pedicle did not cause significant changes in mean intra-arterial pressure (MAP). A decline in MAP was observed during the first 5 min after liver reperfusion (Table 1). The decline in the MAP was prolonged by pretreatment with HO or hyperbaric ambient air throughout the time of reperfusion.

TABLE 1 – Mean arterial pressure (mmHg) in animals during the surgical procedure

GROUPS	Mean arterial pressure								
	1	2	3	4	5	6	7	8	9
A	96.6 ± 11.4	93.1 ± 5.0	93.0 ± 14.6	99.6 ± 22.2	92.7 ± 14.0	89.5 ± 13.0	92.6 ± 11.2	94.8 ± 9.3	94.6 ± 11.4
B	106.8 ± 15.4	82.3 ± 23.6	90.9 ± 26.5	91.9 ± 19.1	85.1 ± 19.7	73.9 ± 16.2 *	77.7 ± 20.1	79.9 ± 21.9	78.0 ± 28.3
C	106.7 ± 9.0	100.8 ± 11.1	99.1 ± 12.0	97.3 ± 18.3	88.1 ± 9.7	73.8 ± 6.1 *	71.1 ± 17.9 *	71.1 ± 5.9 *	68.7 ± 3.6 *
D	109.4 ± 17.9	94.6 ± 19.5	93.1 ± 16.5	104.1 ± 25.6	87.4 ± 13.2	73.1 ± 9.8 *	70.1 ± 9.2 *	75.8 ± 17.2 *	70.9 ± 7.2 *

Times: 1–before ischemia, 2–ischemia (5min), 3–ischemia (10min), 4–ischemia (20min), 5-ischemia (30min), 6–reperfusion (5min), 7–reperfusion (10min), 8–reperfusion (20min), 9–reperfusion (30min).
group A (n=8, control): laparotomy and manipulation of the liver pedicle;
group B (n=8): laparotomy and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group C (n=8): HO therapy at 2.5 ATA for 60 min, laparotomy, 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group D (n=8): exposure to ambient air at 2.5 ATA for 60 min, laparotomy, and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min.

Values are the mean ± standard deviation.
*($p < 0.05$) compared to mean arterial pressure at time 1.

Transaminases

Preconditioning with HO or hyperbaric ambient air alone did not cause significant differences in serum AST, ALT or LDH levels. The same was observed after 30 min of partial liver ischemia. After 30 min of liver reperfusion, a significant increase ($p < 0.05$) in AST, ALT and LDH levels was observed in all groups submitted to liver I/R compared to group A (control). In comparison to the control group, the increase in serum ALT levels was significantly higher in animals submitted to preconditioning with HO than in the other groups ($p<0.05$) (Figures 1 to 3).

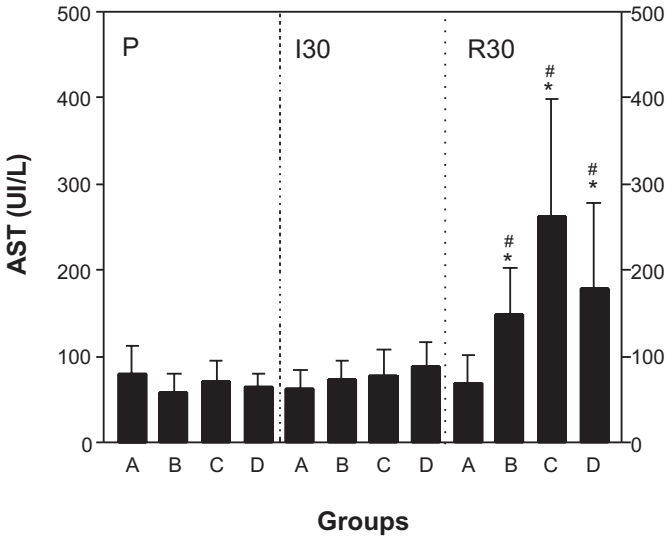

FIGURE 1 – Serum aspartate transferase (AST) level in animals during the surgical procedure

The columns represent the mean and the vertical bars indicate the standard deviation.
P – Before ischemia, I30 – 30 minutes of ischemia, R30 – 30 minutes of reperfusion
group A (n=8, control): laparotomy and manipulation of the liver pedicle;
group B (n=8): laparotomy and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group C (n=8): HO therapy at 2.5 ATA for 60 min, laparotomy, 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group D (n=8): exposure to ambient air at 2.5 ATA for 60 min, laparotomy, and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min.

* ($p < 0.05$) AST R30 compared to AST P and AST I30.
# ($p < 0.05$) AST R30 compared to AST R30 of group A .

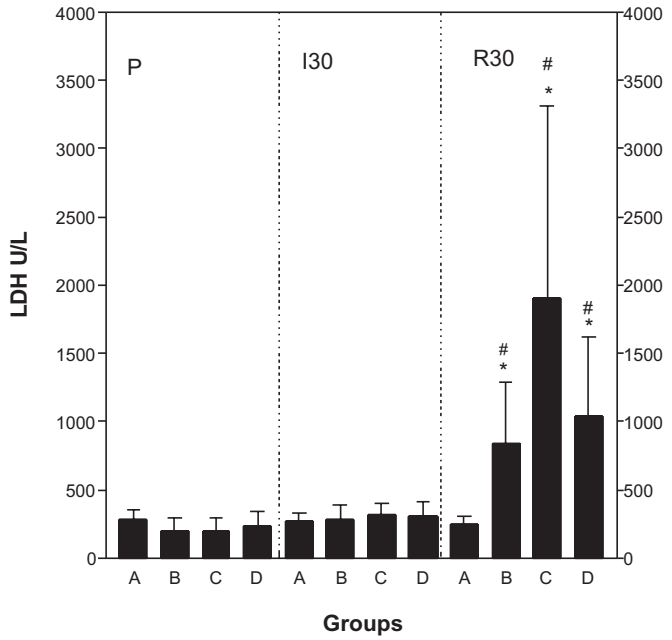

FIGURE 3 – Serum lactate dehydrogenase (LDH) level in animals during the surgical procedure

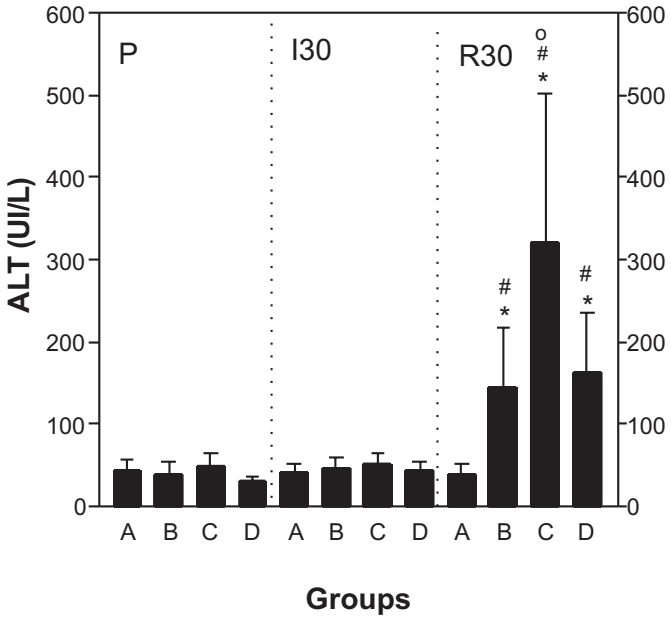

FIGURE 2 – Serum alanine transferase (ALT) level in animals during the surgical procedure

The columns represent the mean and the vertical bars indicate the standard deviation.
P – Before ischemia, I30 – 30 minutes of ischemia, R30 – 30 minutes of reperfusion
group A (n=8, control): laparotomy and manipulation of the liver pedicle;
group B (n=8): laparotomy and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group C (n=8): HO therapy at 2.5 ATA for 60 min, laparotomy, 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group D (n=8): exposure to ambient air at 2.5 ATA for 60 min, laparotomy, and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min.

* ($p < 0.05$) ALT R30 compared to ALT P and ALT I30.
# ($p < 0.05$) ALT R30 compared to ALT R30 of group A.
o ($p < 0.05$) ALT R30 of group C compared to ALT R30 of groups B and D

The columns represent the mean and the vertical bars indicate the standard deviation.
P – Before ischemia, I30 – 30 minutes of ischemia, R30 – 30 minutes of reperfusion
group A (n=8, control): laparotomy and manipulation of the liver pedicle;
group B (n=8): laparotomy and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group C (n=8): HO therapy at 2.5 ATA for 60 min, laparotomy, 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group D (n=8): exposure to ambient air at 2.5 ATA for 60 min, laparotomy, and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min.

* ($p < 0.05$) LDH R30 compared to LDH P and LDH I30.
# ($p < 0.05$) LDH R30 compared to LDH R30 of group A .

Tissue MPO activity

Liver MPO activity was significantly higher in group C (animals submitted to HO pretreATAent, followed by liver I/R) when compared to the other groups (Figure 4). An increase in pulmonary MPO was observed in all animals submitted to liver I/R compared to the control group. This effect was significantly more marked in animals exposed to 100% oxygen (group C) or hyperbaric ambient air (group D). However, no significant differences were observed between groups C and D (Figure 5).

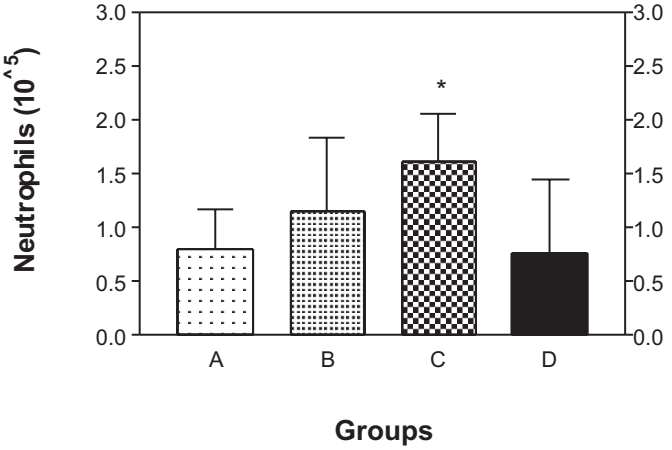

FIGURE 4 – Relative number of neutrophils/mg liver tissue after 30 min of segmental liver ischemia and 30 min of reperfusion

group A (n=8, control): laparotomy and manipulation of the liver pedicle;
group B (n=8): laparotomy and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group C (n=8): HO therapy at 2.5 ATA for 60 min, laparotomy, 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group D (n=8): exposure to ambient air at 2.5 ATA for 60 min, laparotomy, and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min.

The columns represent the mean ± standard deviation.
*($p < 0.05$) compared to groups A, B and D.

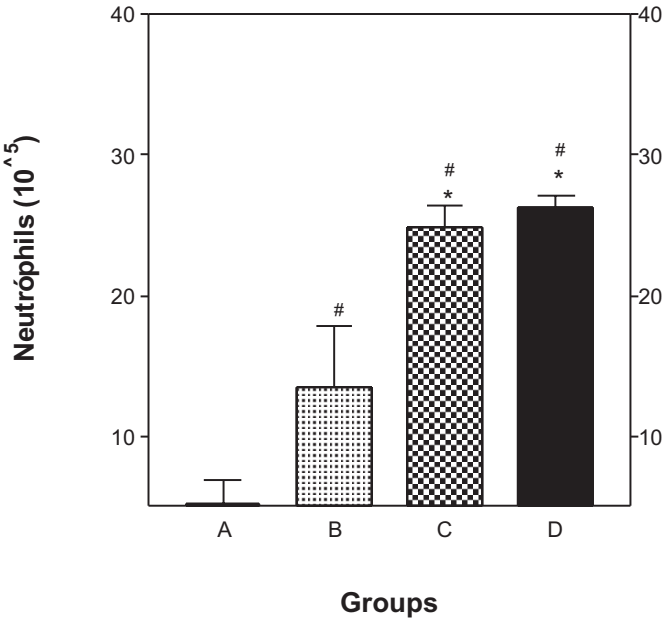

FIGURE 5 – Relative number of neutrophils/mg lung tissue after 30 min of segmental liver ischemia and 30 min of reperfusion

group A (n=8, control): laparotomy and manipulation of the liver pedicle;
group B (n=8): laparotomy and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group C (n=8): HO therapy at 2.5 ATA for 60 min, laparotomy, 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min;
group D (n=8): exposure to ambient air at 2.5 ATA for 60 min, laparotomy, and 30 min occlusion of the vascular liver pedicle, followed by reperfusion for 30 min.

The columns represent the mean ± standard deviation.
* ($p < 0.05$) compared to groups A and B.
# ($p < 0.05$) compared to group A.

Discussion

During hepatectomy, the techniques used for the prevention and control of transoperative bleeding expose the liver to periods of ischemia. Alterations observed during the reperfusion period, which are mainly related to the duration of ischemia, include hepatic microcirculatory disorders, arterial hypotension, elevated serum aminotransferase and LDH concentrations, mitochondrial dysfunction, and lipoperoxidation. These alterations are the result of the complex interactions between adenosine triphosphate depletion, adhesion and activation of leukocytes, Kupffer cells and platelets in hepatic sinusoids, release of proteases and phospholipases, complement activation, and formation of reactive oxygen species[1]. Surgical and pharmacological methods for the prevention and treatment of liver IRI have been described[2]. The myocardium becomes resistant to the deleterious effects of I/R when previously exposed to short periods of vascular occlusion led to the successful application of this technique, known as ischemic preconditioning, to liver resections and transplantation[8].

The biochemical and cellular effects of HO on IRI are still not completely understood. First, it was believed that HO may exacerbate injuries by increasing the oxygen supply to the organism, producing an increased number of free radicals. However, experimental studies in rats submitted to skin I/R have demonstrated the beneficial effects of HO during reperfusion[9]. HO decreases endothelial adhesion of neutrophils by reducing the expression of intercellular adhesion molecules on the surface of endothelial cells and may increase the tissue concentration of antioxidant enzymes such as myocardial catalase[10].

The experimental application of HO to liver IRI has been described in two situations: as a preventive method before liver ischemia or reperfusion[11,12], or as a postoperative therapeutic measure[13]. These studies indicate that the use of HO for short periods of time, causing cell oxidative stress, protects the liver against injuries associated with tissue reperfusion by a biochemical mechanism that is still unknown.

In the present study, HO was used as a preconditioning method in rats submitted to selective liver ischemia and reperfusion. The effects of HO on liver IRI were studied by measurement of serum AST, ALT and LDH, MAP, and the degree of leukocyte infiltration as demonstrated by hepatic and pulmonary MPO activity. Exposure of the animals to HO for 60 min did not cause any alteration in serum transaminase or LDH levels, changes commonly observed during surgical methods of ischemic preconditioning. One hypothesis for this finding is that, in contrast to other methods, the effect of liver preconditioning with HO is based on mild hepatocellular oxidative stress which ceases before the formation of AST and ALT[12]. However, there are no specific studies addressing this question.

This is the first study demonstrating the deleterious effects of HO preconditioning on liver IRI. Post-reperfusion serum ALT levels were significantly higher in animals submitted to HO therapy compared to the other groups. Previous studies in which HO was used as a preconditioning method reported no increase of serum AST or ALT concentration after I/R[11,12]. The present data also show no change in the serum level of these enzymes during the period of ischemia.

Changes in MAP after hepatic pedicle occlusion pedicle are expected since the interruption of hepatic blood flow causes splanchnic blood stasis and reduces venous return to the heart, with a consequent decrease in cardiac output. The return of blood flow to the ischemic portion of the liver induces the release of vasodilatory substances into the systemic circulation, reducing peripheral vascular resistance, with consequent arterial hypotension . In the present study, partial occlusion of the hepatic pedicle for 30 min was not associated with intraoperative death and did not result in any significant decline of MAP possibly because only part of liver flow was interrupted with no severe change in splanchnic venous drainage. A significant decrease in MAP was observed after liver reperfusion, which was rapidly reversed in animals without preconditioning but persistent in animals submitted to preconditioning with HO or hyperbaric ambient air

Kupffer cells play a central role in liver IRI because they produce inflammatory mediators such as TNF-α and IL-6, followed by transmigration of activated polymorphonuclear neutrophils into the liver interstitium. The important presence of polymorphonuclear neutrophils in the pulmonary circulation renders the lung highly vulnerable to the cytotoxic action of inflammatory mediators and this organ was therefore studied in the present model of liver IRI[14].

Hepatic MPO concentration after reperfusion was higher in the group of animals pretreated with HO. This change was probably associated with HO since hyperbaric exposure alone (group D) did not provoke any increase in hepatic MPO concentration. Pulmonary MPO concentration was significantly higher in animals pretreated with HO or hyperbaric ambient air compared to the control group and to animals submitted only to liver I/R (group B). The last group, however, presented significantly higher MPO levels than the control group. These findings suggest that IR by itself causes the increase of MPO activity in liver and lung and that this increase is accentuated by HO pretreatment of the animals. In a review of the literature, we did not find other studies evaluating the role of HO preconditioning and pulmonary alterations resulting from liver IRI, although an experimental study on rats using HO in a muscle I/R model has shown a reduction in the concentration of pulmonary leukocytes when HO was used[15].

The present results are divergent from those reported in two other studies, in which HO preconditioning exerted a protective effect on liver I/R[10,11]. However, these studies should be compared in view of the following observations. Differences in the duration of I/R between studies led to the evaluation of different periods of the inflammatory response. Other investigations have emphasized an increase in the tissue level of enzymatic systems that protect against lipoperoxidation, such as catalase and superoxide dismutase, in animals submitted to cardiac preconditioning with HO[10], which may also indicate a proinflammatory response.

Conclusion

The rats submitted to hyperbaric oxygen therapy before selective normothermic liver ischemia and reperfusion presented an increase in serum ALT concentration and hepatic and pulmonary myeloperoxidase concentration, as well as a decrease in mean arterial pressure, during the surgical procedure. These results suggest that liver preconditioning with hyperbaric oxygen therapy aggravates hepatocellular injury and leukocyte infiltration in the liver and lung immediately after ischemia and reperfusion of the liver.

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