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Posthepatic Manipulative Blood Extraction with Blood Transfusion Alleviates Liver Transplant Ischemia/Reperfusion Injury and Its Induced Lung Injury

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1. Introduction

Liver ischemia-reperfusion (I/R) occurs in a number of clinical syndromes, including liver transplantation (Huguet et al., 1994). Liver I/R is a major obstacle to liver transplantation (Rosen et al., 1998; Banga et al., 2005). It causes liver graft primary nonfunction, up to 10% of early liver transplant failures and higher incidence of acute and chronic rejection (Banga et al., 2005; Henderson et al., 1999; Farmer et al., 2008). Despite many experimental improvements and efforts have been made to attenuate liver I/R injury heretofore, clinical liver I/R was not effectively prevented (Olthoff., 2001; Lehmann et al., 2000; Clarke et al., 2009). And apart from the liver injury, extrahepatic factors like pulmonary injury also play an important role in the outcome of liver transplantation recipients (Sykes et al., 2007; Pereboom et al., 2009; Shimizu et al., 2005; Liu et al., 1996). The incidence rate of acute lung injury is about 40% and greatly threatens the lives of recipients and their quality of life after transplantion (Aduen et al., 2003). So it is meaningful to take strategy to protect the lung against liver transplantation induced injury.

Multiple mechanisms are involved in the pathogenesis of liver transplant I/R in which reactive oxygen species (ROS) have been shown to play a central role in aggravating tissue injury of the transplant (Zhang et al., 2007).

In previous study, using rat warm I/R injury model, we demonstrated that posthepatic ROS concentration elevated gradually with time after reperfusion. And in the early period of reperfusion posthepatic ROS concentration is higher than that in infrahepatic vena cava (IH-VC). Furthermore, we provided that 2% of body weight SH-VC manipulative blood extraction with blood transfusion at 10 min after reperfusion significantly alleviated liver warm I/R injury (Jia et al., 2008). In this study we evaluated the potential effects of posthepatic manipulative blood extraction and blood transfusion on the liver transplant cold I/R injury and the lung injury induced by liver cold I/R in rat.

2. Materials and methods

2.1 Animals and reagents

Male Sprague-Dawley rats, weighing 200-250 g, were supplied by the Shanghai Experimental Animal Center. Rats were housed under standard environmental conditions with a 12:12-h light-dark cycle. Before use in experiments, rats were fasted overnight with free access to water. All animals received humane care in accordance with the Guidelines of the Animal Care Committee of Zhejiang Medical University.

Reagents：(1) MDA and myeloperoxidase (MPO) assay kit (Jiancheng Bioengineering Co.Ltd, Nanjing, China). (2) Naphthol ASD chloroacetate esterase (Sigma Chemical Co., St. Louis, MO). (3) IL-6 ELISA assay kit (Quantikine，MN, USA). (4) TNF-α ELISA assay kit (Quantikine, MN, USA).

2.2 Part I: Liver transplantation and determination of peak production of posthepatic ROS after transplantation

2.2.1 Surgical procedures, experimental groups and sample harvesting

The animals were anesthetized with intraperitoneal injection of 4% chloral hydrate. Orthotopic liver transplantation was performed by Kamada's two-cuff technique (Huguet et al., 1994) (Kamada et al., 1983). Blood was taken at 5 min, 20 min, 30 min, 1 h, 2 h, 6 h after reperfusion respectively (n=7 for each time point). Pure posthepatic blood and IH-VC blood were sampled by the method described in previous study (Jia et al., 2008). Sera were separated for lipid peroxide detection. Median cold ischemia time in all transplantation procedures in this study including in Part I and Part II was 50.22 min.

2.2.2 Lipid peroxide assay

The amount of oxidative stress was assessed by determining serum levels of malonaldehyde (MDA). Serum MDA was determined by the thiobarbituric acid reaction. Sera were isolated then MDA was detected according to manufacturer's instructions.

2.3 Part II: Posthepatic manipulative blood extraction on liver transplant I/R injury and hepatic cold I/R induced lung injury

2.3.1 Surgical procedures, experimental groups and sample harvesting

Rats were randomly divided into four groups and subjected to the following treatments.

IR control group (IR, n=5): The first group involved liver transplantation but without any intervention after transplantation.

Two percent of body weight posthepatic manipulative blood extraction with blood transfusion group (PB, n=7): One hour after transplantation, two percent of body weight posthepatic manipulative blood extraction with blood transfusion was performed by the method described in previous study (Jia et al., 2008). After isolation of IH-VC, a 7# silk suture was placed just above the level of right adrenal vein behind the IH-VC. All the structures in the portal triad were clamped by a Bull-dog clamp. Fresh abdominal aorta blood was collected from other SD rats and was anti-coagulated using heparin. The syringe

containing fresh blood was connected to a 5.5# scalp needle and was place on microinfusion pump. Right external jugular vein of the tested rats was exposed and the scalp needle was inserted into it. The pipeline was maintained by small flow of blood transfusion (1 ml/h). To obtain pure and immediate SH-VC blood after 1 h of reperfusion, an indwelling intravenous line (BD Vialon Biomaterial) was cannulated in the IH-VC with the catheter tip positioned between the liver and diaphragm. A slipknot around the indwelling intravenous line was tied using the pre-placed 7# silk suture to separate blood between both sides of the suture. Then SH-VC was occluded at the level of diaphragm and blood transfusion was sped up to 90ml/h at the same time. Then pure SH-VC blood was drawn-out through the catheter with the speed matching that of transfusion. The bleeding volume is 2% of body weight. After the blood extraction SH-VC and IH-VC was orderly unblocked followed by the catheter withdrawn. A schematic representation for blood extraction and transfusion is shown in Figure 1.
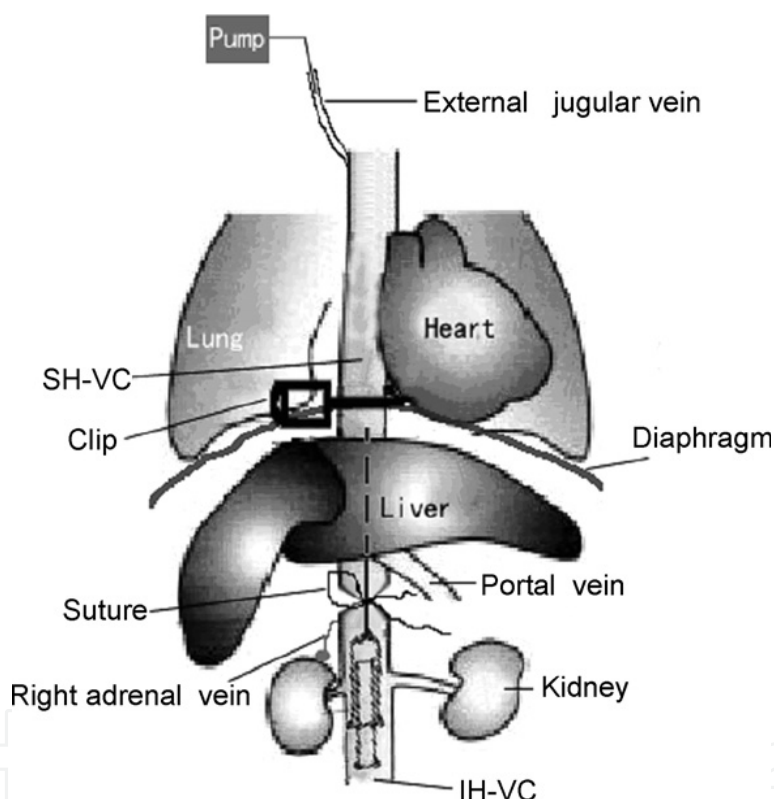

Fig. 1. Schema of blood extraction in SH-VC, blood transfusion in external jugular vein and sites of vascular occlusion.
To obtain pure and immediate SH-VC blood, the vena cava was occluded between the liver and the right atrium and between the liver and right adrenal vein. Pure SH-VC blood was drawn-out through the catheter with the speed matching that of transfusion.
(From Jia C, et al. Suprahepatic vena cava manipulative bleeding alleviates hepatic ischemia-reperfusion injury in rats. Dig Liver Dis, 2008, 40(4):285-292).

Two percent of body weight IH-VC manipulative blood extraction with blood transfusion group (IB, n=6): One hour after transplantation, two percent of body weight IH-VC manipulative blood extraction with blood transfusion was performed by the method described in previous study (Jia et al., 2008).

Two percent of body weight posthepatic manipulative blood extraction with Ringer's lactate solution transfusion group (PR, n=5): Ringer's lactate solution was used for transfusion while posthepatic manipulative blood extraction.

In IR group, a section of the liver was sampled and fixed in 10% formaldehyde, and blood samples were taken from IH-VC at 7 h after transplantation to meet the time course of other groups. In PB, IB and PR group, a section of the liver was sampled and fixed in 10% formaldehyde, and blood samples were taken from IH-VC at 6 h after blood extraction. A section of lung was sampled and fixed in 10% formaldehyde for pathological examination at 6 h after blood extraction. Another section of lung was sampled for the analysis of cytokine and tissue edema.

2.4 Myeloperoxidase and lipid peroxide assays

Sera were isolated and detected for MPO and MDA, an indicator of oxidative injury. Serum MPO contents were measured to analyze degree of neutrophil sequestration and activation. Serum MDA and MPO were assessed according to manufacturer's instructions.

2.5 Liver function

To assess hepatocellular injury in liver transplant, ALT and AST levels in Sera were measured using an Olympus AU600 Analyser (Olympus Optical, Tokyo, Japan).

2.6 Measurement of serum IL-6 level

We use commercially available ELISA kits for the determination of serum IL-6 level according to the manufacturer's instructions.

2.7 Measurement of TNF-α level in lung

We use commercially available ELISA kits for the determination of lung TNF-α level according to the manufacturer's instructions.

2.8 PMN infiltration in the transplant and in the lung

PMN infiltration in the transplant and lung was evaluated by staining for naphthol ASD chloroacetate esterase, a neutrophil specific marker. PMNs were identified by positive staining and were counted in 5 high-power fields under a light microscope (×400).

2.9 Lung edema assay

After resection, lung samples were weighed and then placed in an oven at 60°C until a constant weight was obtained. In this determination, edema is represented by an increase in the wet-to-dry weight ratios(Peralta et al., 1999).

2.10 Histopathological analysis

Liver and lung tissues were fixed with 10% neutral formalin and were stained with hematoxylin and eosin. The degrees of sinusoidal congestion, cytoplasmic vacuolization and

necrosis of parenchymal cells were evaluated semiquantitatively according to Suzuki's criteria (Suzuki et al., 1993).

2.11 Statistical analysis

These data are expressed as mean ± SD. Calculations were made using the SPSS 13.0 for windows computer software (SPSS Inc., Chicago, IL). Statistical comparisons were performed using one-way analysis of variance (ANOVA) and the LSD t-test for blood MDA, IL-6, liver PMNs, TNF-α and enzyme levels. P-values less than 0.05 were considered statistically significant.

3. Results

3.1 Time course and peak level of posthepatic MDA after transplantation

Figure 2 represents the kinetic changes of MDA in all time points in experiment Part I. In this study MDA concentration within SH-VC peaked at 1 h after transplantation. MDA concentration at 1 h was significantly higher than that at other time points except for 5 min. Furthermore, MDA concentrations in SH-VC were significantly higher than that in IH-VC at 20 min，30 min，1h (*P*<0.05) and slightly higher at all other time points. MDA concentration within IH-VC peaked at 2 h after transplantation.
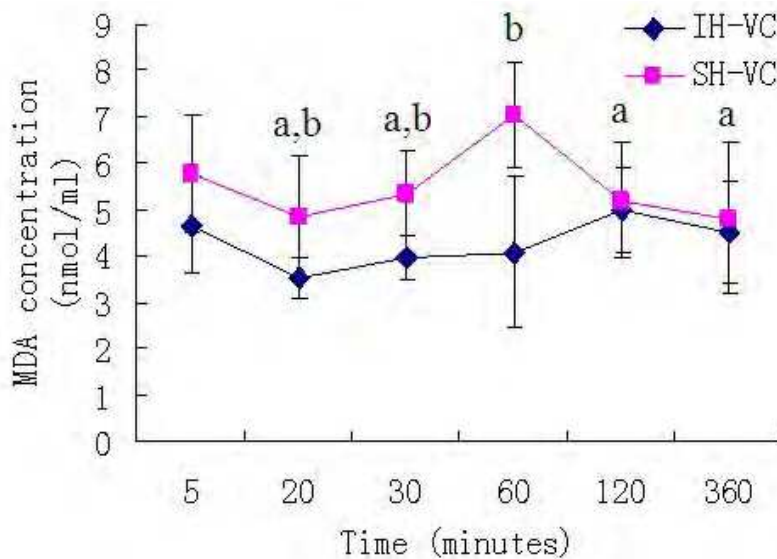
Fig. 2. Time course and peak level of MDA after liver transplantation in Part I
SH-VC represents the group that blood was taken form SH-VC. IH-VC represents the group that blood was taken form IH-VC. [a]*P* < 0.05 vs. 60 min within SH-VC. [b]*P* < 0.05 vs. IH-VC.

3.2 MDA and PMO levels in the sera

In experiment Part II, serum MDA level at 6 h after transplantation was slightly lower in PB, IB and PR group than in IR group but no statistically significant. Whereas serum MPO level in PB and PR groups (48.78±9.36 pg/ml and 49.36±18.32 pg/ml, respectively) were significantly lower than that in IR group (71.34±22.14) (*P*=0.022, *P*=0.045, respectively). Serum MPO level in IB group was not significantly lower than that in IR group (Figure 3).
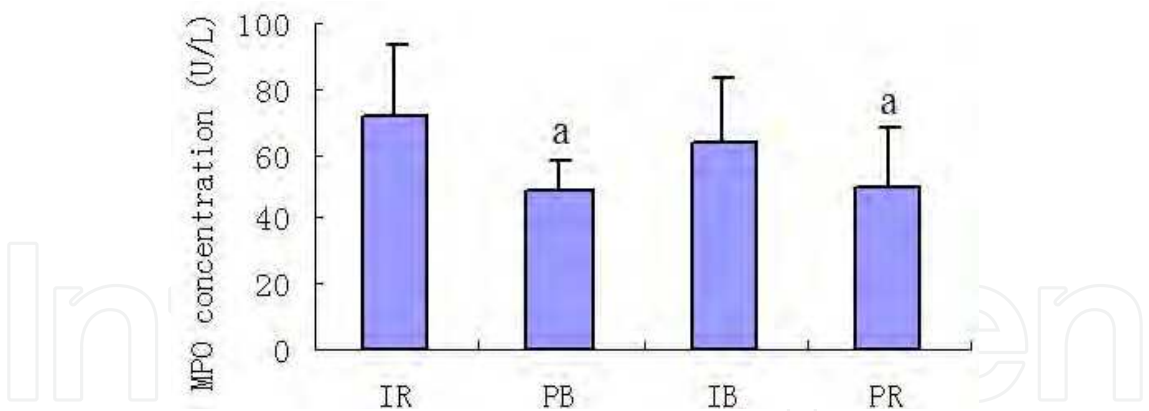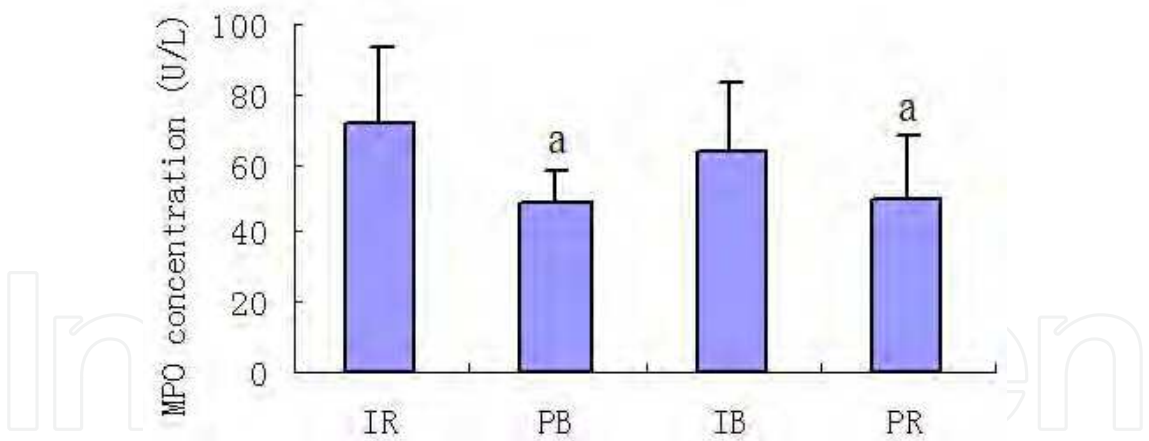
Fig. 3. Serum MPO level in all groups in Part II
IR: IR control group. PB: Two percent of body weight posthepatic manipulative blood
extraction with blood transfusion group. IB: Two percent of body weight IH-VC
manipulative blood extraction with blood transfusion group. PR: Two percent of body
weight posthepatic manipulative blood extraction with Ringer's lactate solution transfusion
group. aP < 0.05 vs. IR.

3.3 Serum IL-6 level

As shown in Figure 4, IL-6 level at 6 h in Part II were significantly lower in PB and IB group
(470.88±101.36 pg/ml and 392.71±259.80 pg/ml, respectively) than in IR group
(1067.42±547.91) (P=0.017, P=0.008, respectively). IL-6 level at 6 h in PR group was not
significantly lower than in IR group.

Fig. 4. Serum IL-6 level in all groups in Part II
IR: IR control group. PB: Two percent of body weight posthepatic manipulative blood
extraction with blood transfusion group. IB: Two percent of body weight IH-VC manipulative
blood extraction with blood transfusion group. PR: Two percent of body weight posthepatic
manipulative blood extraction with Ringer's lactate solution transfusion group. aP < 0.05 vs. IR.

3.4 Liver function

Figure 5 showed posthepatic manipulative blood extraction significantly attenuated
hepatocellular injury, as compared with I/R control group. ALT and AST levels at 6 h were

significantly lower in PB and IB group (460.00±126.65UI/L and 766.00±165.02 UI/L, respectively) than in IR group (1494.00±1015.05UI/L and 1976.00±1262.79 UI/L, respectively) (*P*=0.043, *P*=0.043, respectively). ALT and AST levels at 6 h in IB and PR group were not significantly lower than in IR group.
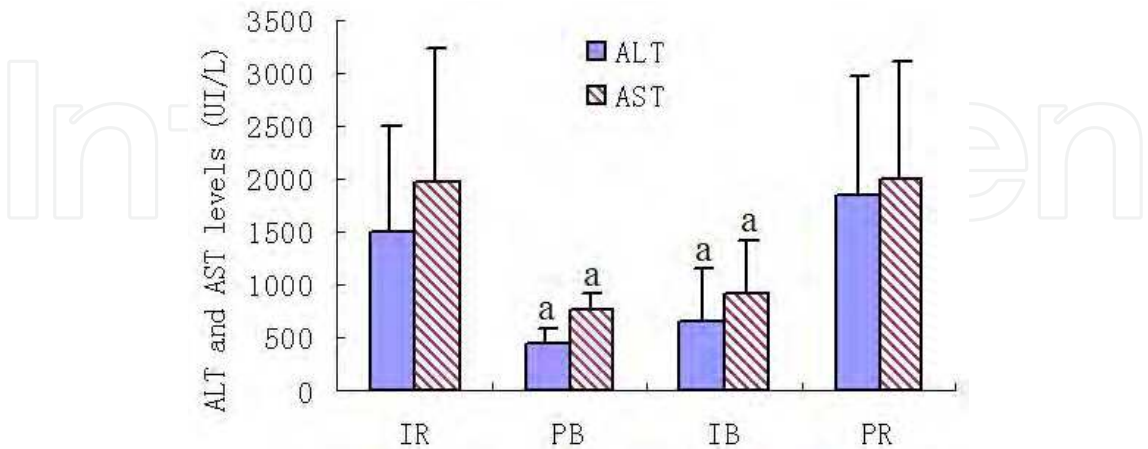

Fig. 5. ALT and AST levels in all groups in Part II
IR: IR control group. PB: Two percent of body weight posthepatic manipulative blood extraction with blood transfusion group. IB: Two percent of body weight IH-VC manipulative blood extraction with blood transfusion group. PR: Two percent of body weight posthepatic manipulative blood extraction with Ringer's lactate solution transfusion group. ᵃ*P* < 0.05 vs. IR.

3.5 TNF-α level in lung

As shown in Figure 6, lung TNF-α level at 6 h in Part II were significantly lower in PB group (21.01±7.87 pg/ml) than in IR group (47±19.62 pg/ml) (*P*=0.038). Lung TNF-α level in IB and PR group was not significantly lower than that in IR group.
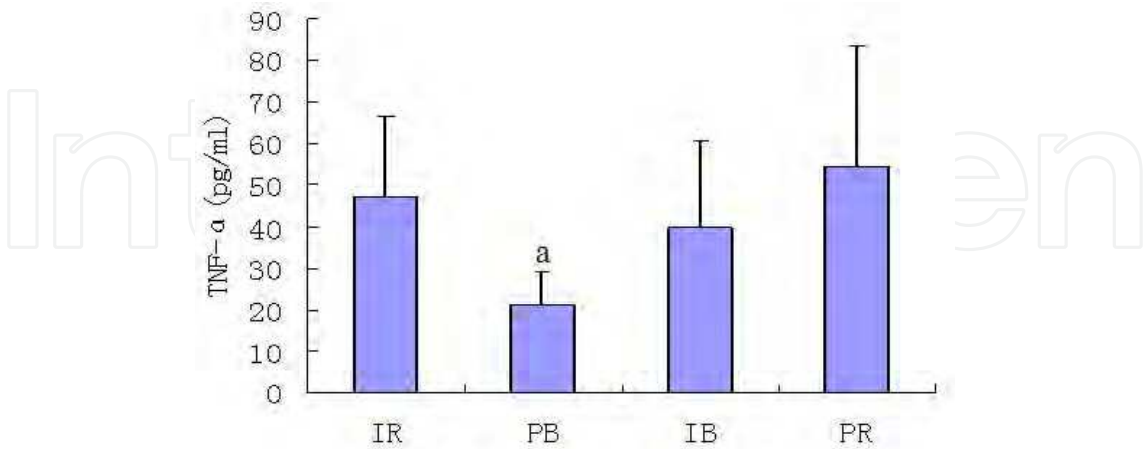

Fig. 6. Lung TNF-α level in all groups in Part II
IR: IR control group. PB: Two percent of body weight posthepatic manipulative blood extraction with blood transfusion group. IB: Two percent of body weight IH-VC manipulative blood extraction with blood transfusion group. PR: Two percent of body weight posthepatic manipulative blood extraction with Ringer's lactate solution transfusion group. ᵃ*P* < 0.05 vs. IR.

3.6 Lung edema assay

Wet-to-dry weight ratio of the lung tissue in group PB was 4.25±0.79, which was significnagly lower than that in IR group (7.0±4.03) (*P*=0.039). Wet-to-dry weight ratio of the lung tissue in IB and PR group were not significantly lower than that in IR group (Figure 7).
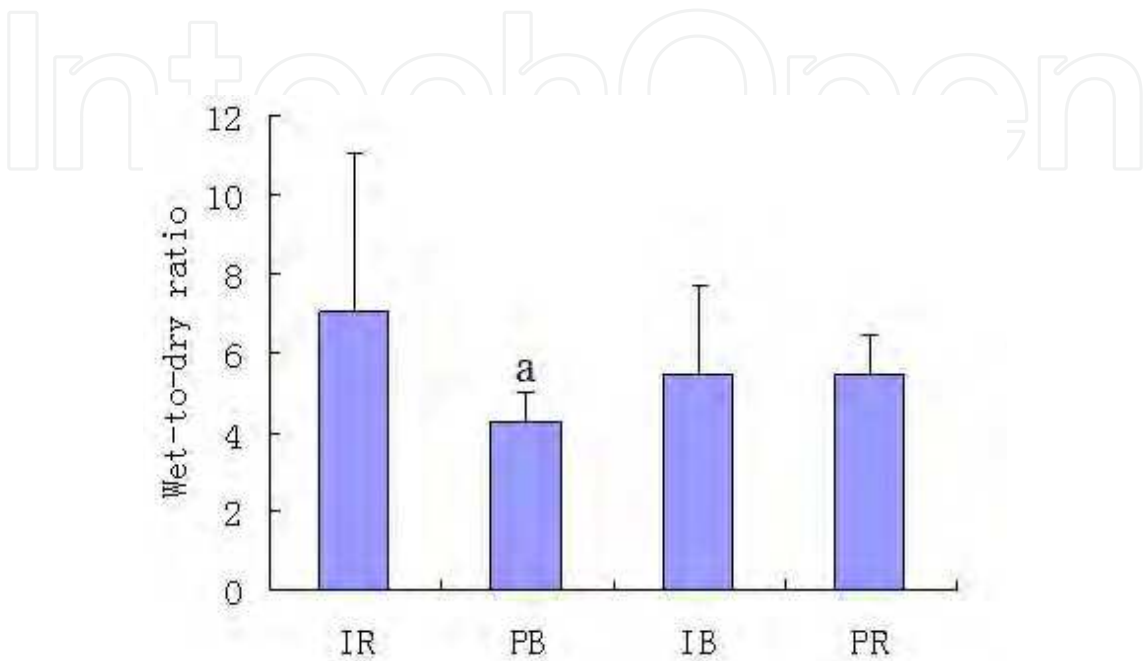

Fig. 7. Wet-to-dry weight ratio of the lung tissue in all groups in Part II
IR: IR control group. PB: Two percent of body weight posthepatic manipulative blood extraction with blood transfusion group. IB: Two percent of body weight IH-VC manipulative blood extraction with blood transfusion group. PR: Two percent of body weight posthepatic manipulative blood extraction with Ringer's lactate solution transfusion group. ᵃ*P* < 0.05 vs. IR.

3.7 PMN infiltration in the transplant and in the lung

To determine whether posthepatic manipulative blood extraction affected local leukocyte infiltration in transplant and lung, we assessed PMNs infiltration using naphthol ASD chloroacetate esterase staining. In this study, PMN counts in liver transplant were significantly lower in PB, IB and PR group (11.75±5.02 counts/HPF, 8.53±1.98 counts/HPF and 13.6±4.07 counts/HPF, respectively) than that in IR group (24.46±13.87 counts/HPF) (*P*=0.006, *P*=0.002, *P*=0.031, respectively) (Figure 8). PMN counts in lung were significantly lower in PB and IB group (44.13±19.29 counts/HPF and 56.57±9.10 counts/HPF, respectively) than that in IR group (82.8±25.01 counts/HPF) (*P*=0.001 and *P*=0.030, respectively). PMN infiltration in PR group was not significantly lower than that in IR group (Figure 9).
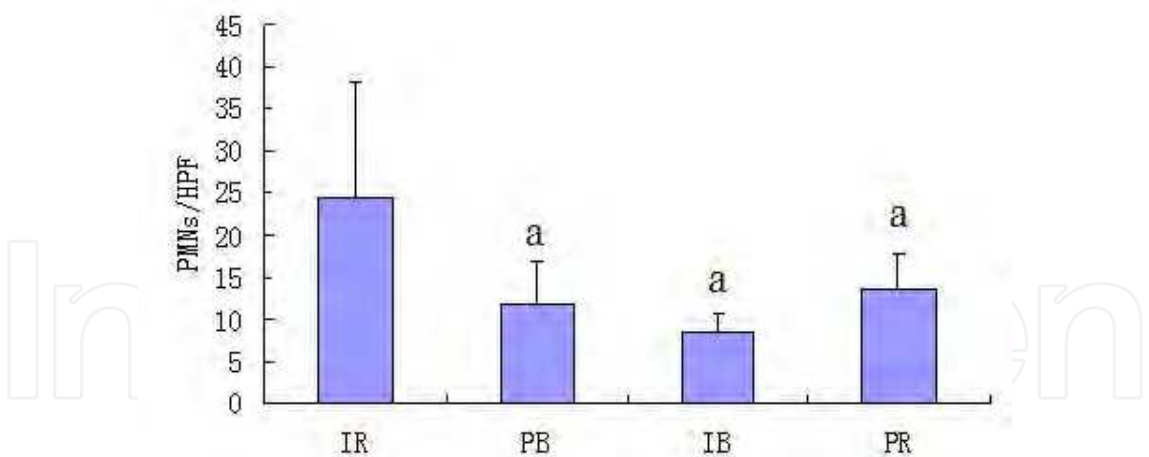
Fig. 8. PMN infiltrations in the transplants at 6 h after manipulation in Part II
PMN kinetics in the liver after reperfusion. IR: IR control group. PB: Two percent of body weight posthepatic manipulative blood extraction with blood transfusion group. IB: Two percent of body weight IH-VC manipulative blood extraction with blood transfusion group. PR: Two percent of body weight posthepatic manipulative blood extraction with Ringer's lactate solution transfusion group. [a]P<0.05 versus IR.

(E)
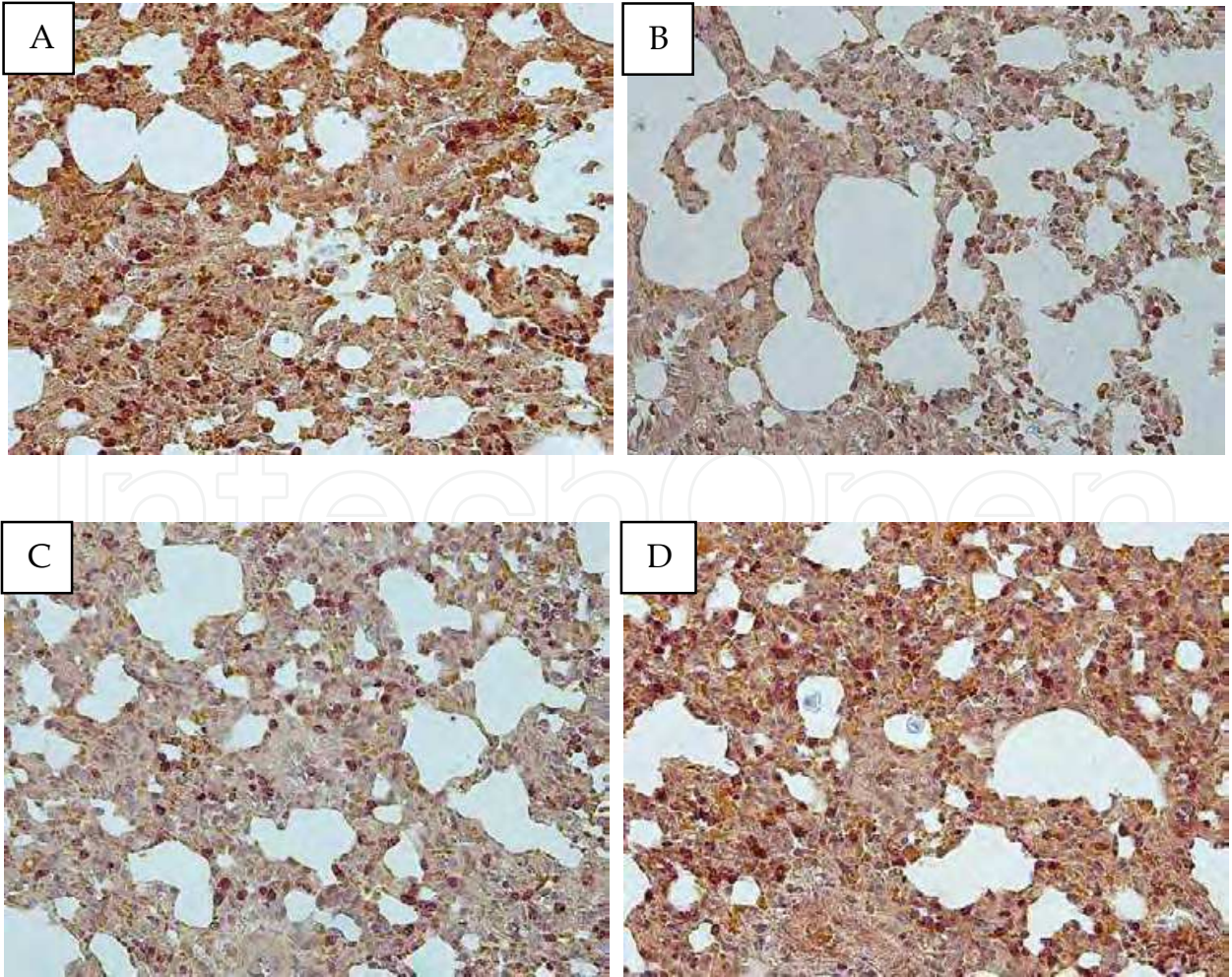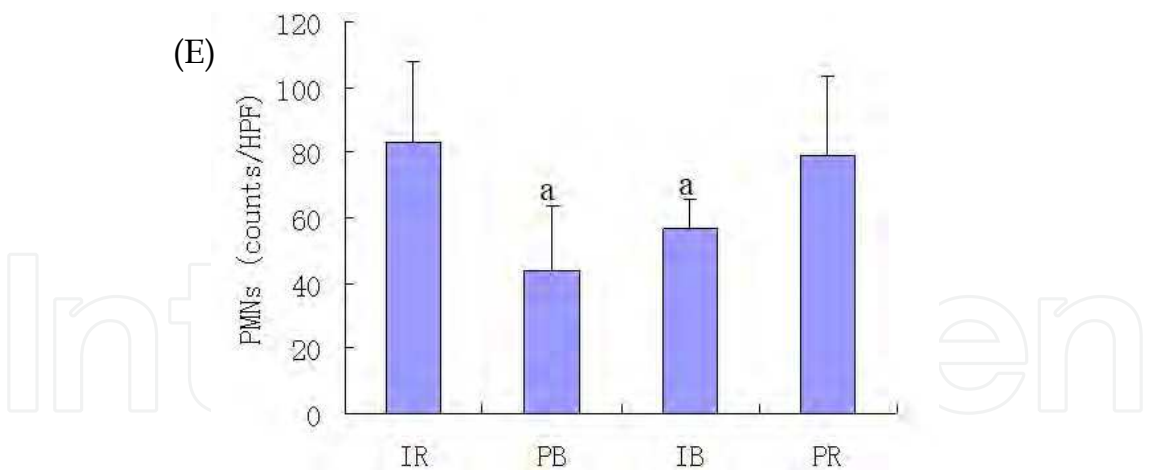
Fig. 9. PMN infiltration in the lung in all groups in Part II
PMNs were seen as deep-brown dots (original magnification ×400). A:IR group; B: PB group;
C:IB group; D: PR group. E: the comparison of PMN infiltration in the lung between groups.
IR: IR control group. PB: Two percent of body weight posthepatic manipulative blood
extraction with blood transfusion group. IB: Two percent of body weight IH-VC manipulative
blood extraction with blood transfusion group. PR: Two percent of body weight posthepatic
manipulative blood extraction with Ringer's lactate solution transfusion group. $^{a}P < 0.05$ vs. IR.

3.8 Histopathological findings in Part II

Histological changes of the transplant were in keeping with the aforementioned biochemical
observations. Liver sections of IR and PR rats at 6 h after manipulation showed sinusoidal
congestion, cytoplasmic vacuolization and conspicuously focal necrosis. Moderate severity
of necrosis and congestion were found in IB group. In marked contrast, liver sections in PB
rats showed significant preservation of the lobular architecture with ballooning of
parenchymal cells and minimal signs of hepatocyte necrosis (Figure 10). Four out of seven
rats in PB group showed + hepatic injury, 2 showed ++ and 1 showed +++, whereas rats in
other groups showed ++∼+++ hepatic injury according to Suzuki's criteria. The histological
study of the lungs revealed a diffuse interstitial thickening with marked edema and
polymorphonuclear infiltration 6 h after liver transplant in IR group. In contrast, mild
lesions were seen in PB group with discrete thickening of the alveolar septa and the
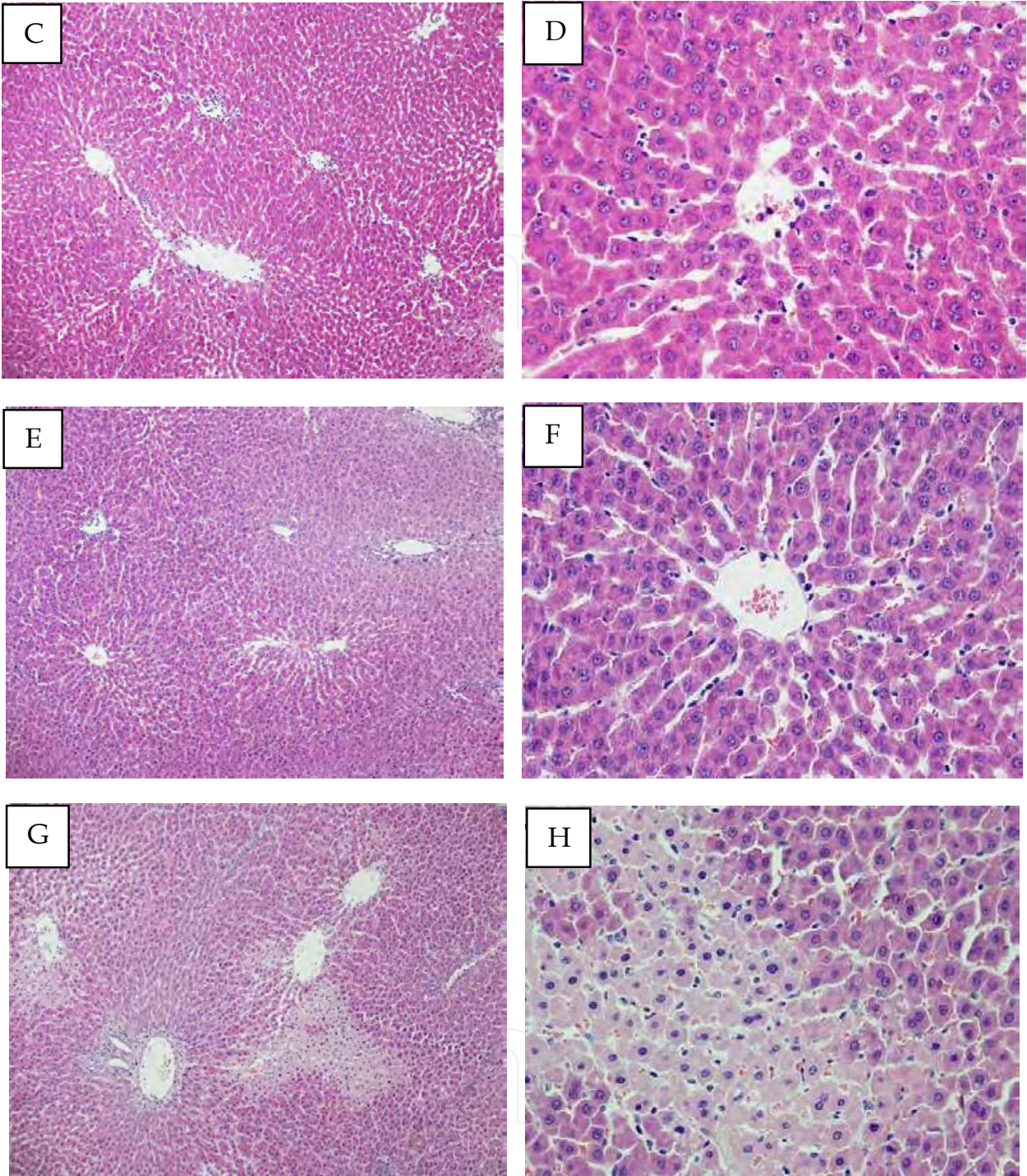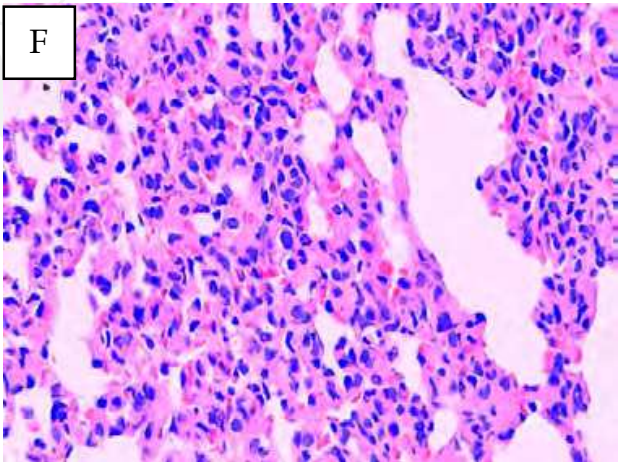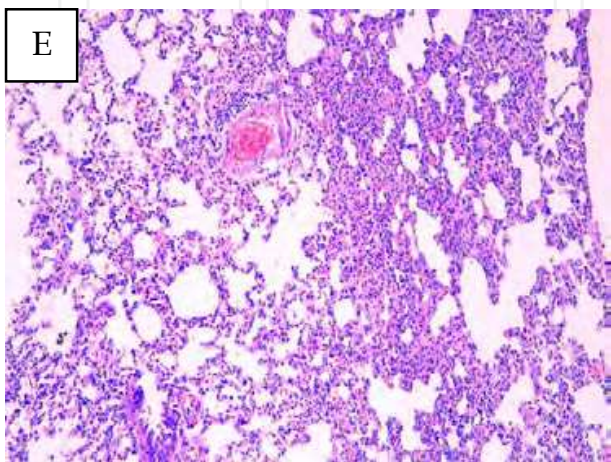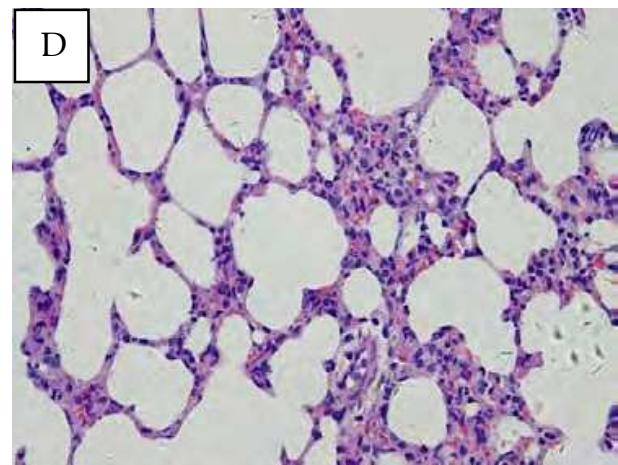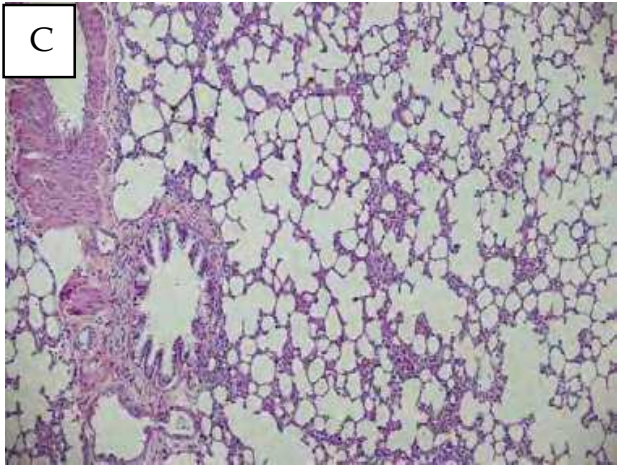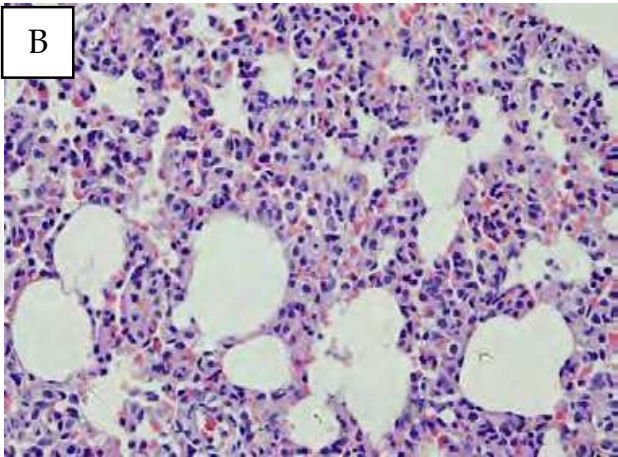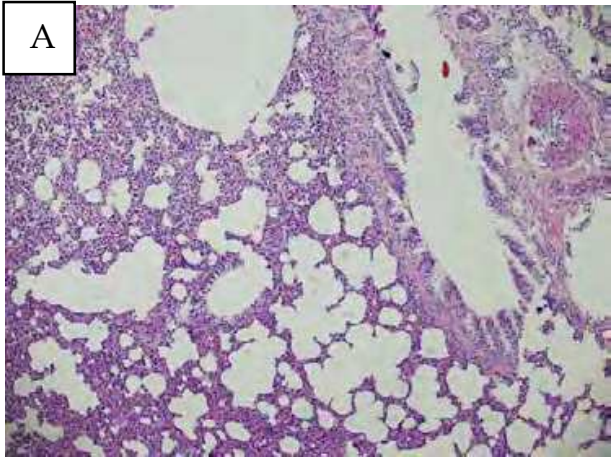presence of scattered inflammatory cells (Figure 11).
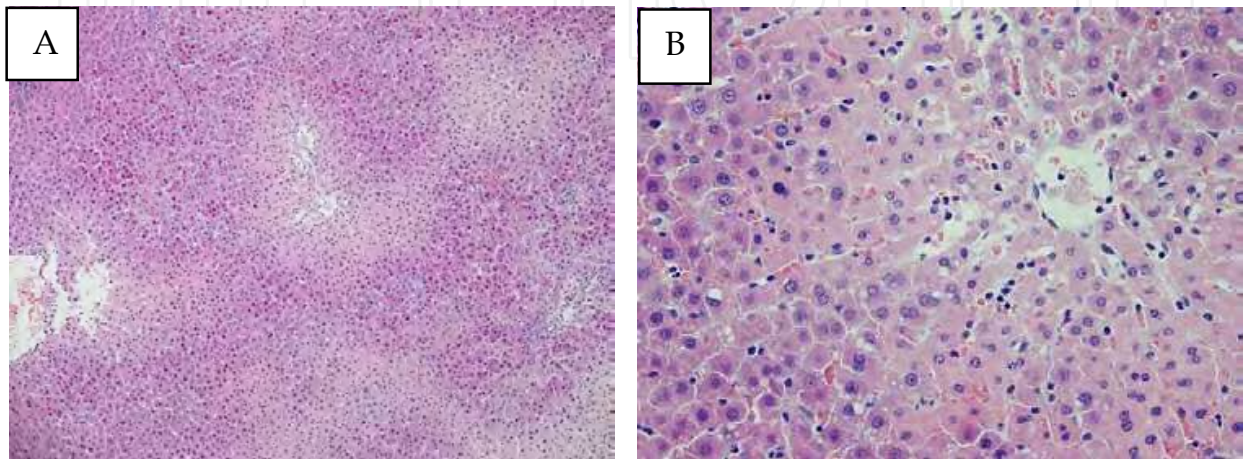
Fig. 10. Representative histologic findings in transplant at 6 h after manipulation.
At 6 h after transplantation, conspicuous necrosis and sinusoidal congestion were observed
in IR and PR group (A:IR group, original magnification ×100; B:IR group, original
magnification ×400; G:PR group, original magnification ×100; H:PR group, original
magnification ×400). Moderate severity of necrosis and congestion were found in IB group
(E:IB group, original magnification ×100; F:IB group, original magnification ×400). Only
ballooning of parenchymal cells and minimal necrosis were seen in PB group (C: original
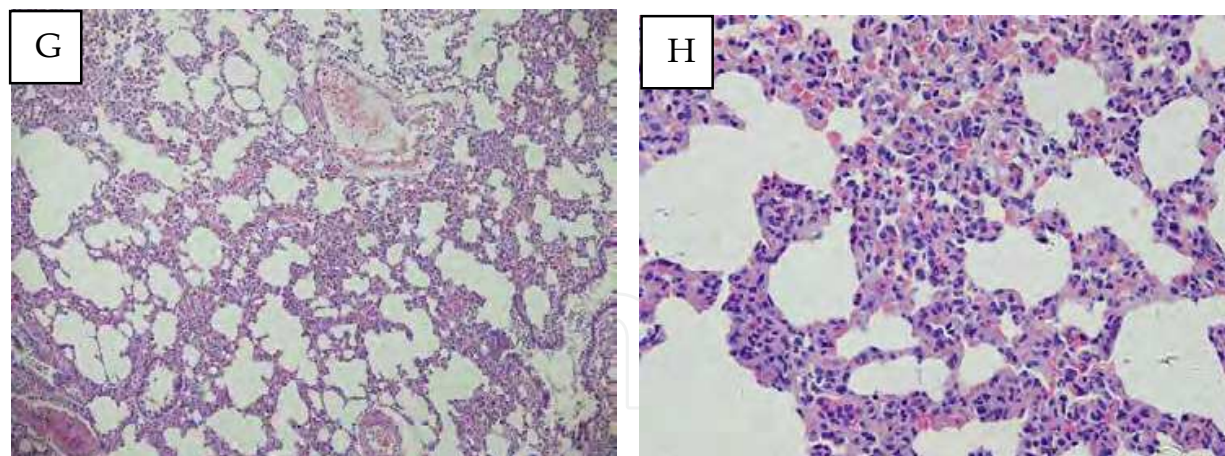magnification ×100; D: original magnification ×400).

Fig. 11. Representative histologic findings in lung at 6 h after transplantation.
The histological study of the lungs revealed a diffuse interstitial thickening with marked edema and polymorphonuclear infiltration in I/R, IB and PR group (A:IR group, original magnification ×100; B:IR group, original magnification ×400; E:IB group, original magnification ×100; F:IB group, original magnification ×400; G: PR group, original magnification ×100; H:PR group, original magnification ×400). In contrast, mild lesions were seen in PB group with discrete thickening of the alveolar septa and the presence of scattered inflammatory cells (C: original magnification ×100; D: original magnification ×400).

4. Discussion

Our results provided evidence for the role of ROS in the pathogenesis of liver transplant I/R. In Part I of this study, pure SH-VC and IH-VC blood were taken at multiple time points to determine the peak production of posthepatic ROS after transplantation. We found that serum MDA concentration in SH-VC increased and peaked at 1 h after transplantation. And the MDA concentrations in SH-VC were significantly higher than that in IH-VC at 20 min，30 min，1h ($P<0.05$). The phenomenon that MDA concentration increased slowly in the early stage after transplantation is due to its incomplete reflow and injured microcirculation including endothelial cell swelling (Vollmar et al., 1994), vasoconstriction (Marzi et al., 1994), leucocyte entrapment (Fondevila et al., 2003; Yadav et al., 1998) and possibly intravascular haemoconcentration (Menger et al., 1988). This process prolongs the period of hypoxia, with areas of the liver remaining ischemic after early period of transplantation. In the later stage, neutrophils infiltrate into the liver increased with time, so companied by increased ROS.

In Part II of this study, we evaluated the potential effects of posthepatic manipulative blood extraction and blood transfusion at 1 h after reperfusion on the liver transplant cold I/R injury and liver I/R induced lung injury. We found that 2% of body weight posthepatic manipulative blood extraction with blood transfusion (PB) significantly reversed the elevations in the serum MPO, IL-6, TNF-α, liver enzyme levels and dramatically decreased PMNs in the liver and lung. Oxidative and other environmental stress lead to an upregulation of proinflammatory mediators (Otterbein et al., 2000; Otterbein et al., 2003). Increased production of IL-6 is thought to be involved in the pathogenesis of cold hepatic I/R injury (Tomiyama et al., 2008; Uchida et al., 2009). IL-6 is considered a marker for liver

injury severity (Jin et al., 2006) and it has been demonstrated that IL-6 overexpression leads to detrimental effects in some studies (Monbaliu et al., 2007; Wustefeld et al., 2000). Here, prompt inflammatory response was evident in our model of cold hepatic I/R injury by the elevation of serum IL-6 level at 6 h of reperfusion. Then we have shown that posthepatic manipulative blood extraction reversed this elevation.

In Part II of this study, although serum MDA level was no statistically significant between groups, serum MPO levels in PB was significantly lower than that in IR group. Posthepatic manipulative blood extraction significantly reduced serum MPO level, indicating suppression of neutrophil accumulation and activation, which play important roles in I/R-induced ROS production (Parks et al., 1988; Zimmerman et al., 1990). This result shows the imbalance of oxidation/antioxidation and increase of lipid peroxide in vivo. So the protective effect of posthepatic manipulative blood extraction with blood transfusion was, in part, due to the inhibition of neutrophil infiltration and activation, which was further demonstrated by its suppression of PMNs accumulation in liver transplant and lung. Experimental evidence shows that there are two distinct phases of liver reperfusion injury (Jaeschke et al., 1990). The early phase covers the first 2 hours after reperfusion (Tamaki et al., 1996). So in the view of time course, we conclude that posthepatic manipulative blood extraction mainly alleviates liver IR injury in late phase in that it significantly decrease serum MPO, IL-6, liver enzyme levels and PMNs in the liver at 6 h after reperfusion.

Although IB group significantly reversed the elevations in the serum IL-6, liver enzymes and even PMN infiltrations in transplant, it did not exert significant protective effects in terms of serum MPO and did not improve transplant pathological injury. So we thought that the posthepatic manipulative blood extraction takes advantages over IH-VC manipulative blood extraction on attenuating hepatic cold I/R injury. Both blood/ROS extraction and fresh blood transfusion are indispensable in alleviating liver transplant I/R injury in our model. And the reason why PR group significantly decrease serum MPO and PMN infiltrations in the liver remains unclear. Blood dilution maybe at least one of the causes for this phenomenon.

The liver contains great concentration of Kupffer cells (Kamada et al., 1983). During the initial stage of hepatic ischemia, Kupffer cells are activated and these activated Kupffer cells released a lot of pro-inflammatory cytokines, and proteolytic enzymes. After reperfusion, activation products generated in the ischemic liver, including proinflammatory cytokines such as TNF-α, are released into the systemic circulation. Yoshidome et al demonstrated, in a rat hepatic I/R model, that hepatic-derived TNF-α plays a central role in the induction of lung neutrophil recruitment and tissue injury (Peralta et al., 1999). It initiates an inflammatory response both in liver and remote organs such as the lungs and kidneys (Rosen et al., 1998). These factors, after the reperfusion, can cause hepatocellular injury and hepatic microcirculation disorder. On the other hand, these active factors can reach to the pulmonary vascularity through systemic circulation to activate lung capillary endothelial cells, neutrophils and lead to the inflammatory reaction of the lung tissues, causing acute lung injury and increase the lung capillary permeability. This is because the pulmonary endothelium is sensitive to these cytokines, and because the pulmonary circulation represents the first vascular bed to which these mediators are delivered (Peralta et al., 1999). Furthermore, elevated levels of TNF-α are associated with neutrophil-dependent lung injury

after hepatic I/R (Suzuki et al., 1993). In this study, as decreased in serum MPO, TNF-α, a pleiotropic pro-inflammatory cytokine which can induce liver and lung injuries, was also decreased via posthepatic blood diacharge in that the liver by itself is also an important source for TNF-α release during liver I/R (Vollmar et al., 1994).

So in this study, the protective effect of posthepatic manipulative blood extraction was, in part, due to the inhibition of neutrophil infiltration and activation via its inhibition of tissue TNF-a production, which was further demonstrated by its suppression of PMNs accumulation in lung. In addition, we found that water content of the lung significantly increases after reperfusion. TNF-a and activated neutrophils contribute to the damage through the release of ROS. Increased accumulation of pulmonary TNF-a and neutrophil results in increased lung capillary permeability in that it can damage both vascular endothelium cells and lung epithelial cells. And the toxic lipid peroxidation reaction products mediated by ROS will furthermore cause cell injury and death (Marzi et al., 1994).

The protective mechanisms involved in PB were the direct decreasing in circulating MPO and pulmonary TNF-α via manipulative blood extraction. And the lung pathological findings parallel with biochemistry parameters mentioned above. So it demonstrated that posthepatic manipulative blood extraction alleviates lung injury induced by liver ischemia-reperfusion. Although other groups, compared with IR group, slightly reversed the elevations in the some parameters, it was not statistically significant.

In conclusion, we provided the first evidence that posthepatic ROS concentration elevated with time and peaked at 1 h after transplantation. Posthepatic manipulative blood extraction and blood transfusion alleviates liver transplant cold IR injury and lung injury induced by liver cold IR injury through its marked decrease in serum PMO, IL-6, inhibition neutrophil infiltration in transplant, so significantly attenuating hepatocellular injury. Our data strongly support that targeting posthepatic manipulative blood extraction with blood transfusion represents a useful approach to prevent IR injury in rats and maybe a potential way in human. It is possible to use this strategy clinically due to its facility and practicability. In human liver transplantation, for example, the posthepatic manipulatively extracted blood can be re-transfused after re-oxygenation and removal of ROS and pro-inflammatory cytokines. It might improve the overall success of liver transplantation and should be further investigated.

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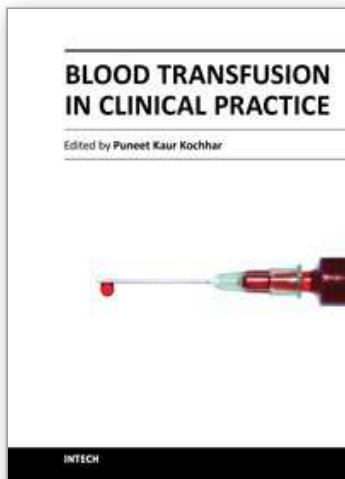
Blood Transfusion in Clinical Practice

Edited by Dr. Puneet Kochhar

Blood Transfusion in Clinical Practice focuses on the application of blood transfusion in different clinical settings. The text has been divided into five sections. The first section includes a chapter describing the basic principles of ABO blood group system in blood transfusion. The second section discusses the use of transfusion in various clinical settings including orthopedics, obstetrics, cardiac surgery, etc. The third section covers transfusion transmitted infections, while section four describes alternative strategies to allogenic blood transfusion. The last section speculates over immunomodulatory effects of blood transfusion.

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