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# TEMPORARY PORTACAVAL SHUNT IMPROVES THE OUTCOME OF CONTINUOUS NORMOTHERMIC LIVER ISCHEMIA

**By**

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***Warm liver ischemia is induced whenever hepatic pedicle clamping performed during liver surgery to minimize operative blood loss. The contributory role of intestinal congestion and injury, that follows prolonged hepatic pedicle occlusion, in aggravating liver ischemic injury and in inducing remote organ injury is underscored. The hepatic pedicles of twelve dogs were continuously interrupted for 90 minutes. In six dogs portacaval shunts were constructed prior to hepatic pedicle occlusion. Two dogs in the control group and all dogs in the shunt group survived for 24 hours after reperfusion ($p < 0.05$). Serum ALT concentrations at 1 and 24 h after reperfusion were significantly higher ($p < 0.001$) in the control versus shunt group. Significantly more severe histologic injuries were demonstrated in the liver (grade 4 versus grade 1 respectively, $p < 0.005$) and the intestine (grade 7 versus grade 1 respectively, $p < 0.005$) of the control versus the shunt group. The lung and kidney showed morphologic features of acute inflammatory injury in the control but not in the shunt group. We conclude that portacaval shunts, by preventing gut congestion and injury, improve tolerance of the liver to prolonged continuous warm ischemia and prevent its systemic effects on distant organs.***

## INTRODUCTION

Hepatic vascular inflow occlusion is used during liver surgery to prevent massive blood loss. This normothermic inflow interruption is detrimental to the liver and is related to the duration and continuity of the occlusion time [1-6]. The subsequent reperfusion exacerbates the development of ischemic liver injury [7-9]. During hepatic pedicle occlusion, gut congestion develops and intestinal injury from venous hypertension, stasis and ischemia ensues. This results in failure of the intestinal barrier function and leads to increased permeability to bacteria and toxins from the lumen [7, 10]. In addition to the local release of acute reactant cytokines in the liver [9, 11, 12], the postischemic gut produces inflammatory mediators [7, 13, 14], endothelins[15-20], and activate a variety of cellular elements [21-23], which are released into portal blood during reperfusion and aggravate hepatic ischemic injury. The ischemia-reperfusion (I/R) injury is not limited to the liver and intestine. Injury to distant organs has been documented in animals subjected to extended hepatic [3, 21] or to intestinal ischemia [13, 24-26]. Therefore, the ability to improve tolerance to prolonged hepatic pedicle occlusion would be clinically important.

The purpose of this study was to determine the degree of contribution of gut congestion to the detrimental effects of prolonged continuous normothermic hepatic inflow interruption on local (liver, intestine) and remote (lung, kidney) vital organs, and to demonstrate improved tolerance of the liver and prevention of the systemic effects of prolonged continuous warm liver ischemia with temporary portacaval shunt. A dog model of warm liver ischemia with and without portacaval shunt to decompress the splanchnic blood into the systemic circulation was used in this study. Liver resection was not carried out in the present study in order to evaluate the sole contribution of gut congestion to normothermic hepatic I/R injury [7].

## MATERIAL AND METHODS

### *Animal Model & Experimental Design*

Twelve adult mongrel dogs of both sexes weighing 15 to 25 kg were used for the experiment. The animals were kept for at least 1 week before use and were fed on commercial food and water *ad libitum*. The dogs were fasted for 12 hours before the procedure. All surgical procedures were performed at the same hour to avoid circardian variations. The dogs were divided into two groups. Group 1 (control) had 90 minutes of continuous hepatic pedicle occlusion while group 2 (shunt) had a temporary portacaval shunt performed followed by 90 minutes of continuous hepatic pedicle occlusion. Previous studies have shown that animals subjected to prolonged continuous hepatic inflow interruption for more than 60 minutes develop various injuries to the liver, lung, and intestine and had limited survival [3, 27, 28]. Other studies that used a pump-driven splanchnic-to-systemic venous bypass demonstrated that 100% of dogs survived 60 minutes of warm liver ischemia while 50% of dogs did not tolerate 180 minutes of portal triad occlusion [29, 30]. Studies on intestinal I/R demonstrated that significant intestinal injury occurs predictably following 60 minutes of ischemia [17, 25]. Moreover, 90 minutes of continuous hepatic pedicle occlusion is the usual duration required to perform most clinical liver resections [1,2,6,11]. Therefore, a 90-minute continuous hepatic inflow interruption will produce both local and systemic effects, but it will not be long enough to be lethal to the shunt group. The animals received humane care in compliance with the NIH guidelines for the use of experimental animals.

### *Operative Procedure*

The experiments were conducted at room temperature. Animals were premedicated by an intravenous injection of 0.05 mg/kg atropine sulphate and 0.5 mg/kg diazepam. Anesthesia was introduced by slow intravenous injection of 5-10 mg/kg of ketamine hydrochloride and 0.5 mg/kg of xylazine and repeated as necessary [22,31]. During the operation glucose/saline solutions were infused at a rate of 30 ml/kg/h for fluid replacement. Blood pressure and heart rate were monitored using a femoral arterial line. Laparotomy was carried out through a right subcostal incision. A wedge biopsy of the liver was taken as a control for histological evaluation. The hepatic pedicle was dissected and liver ischemia was induced by clamping the hepatic pedicle for 90 minutes [32,33]. In the shunt group, a side-to-side anastomosis between the portal vein and the infrahepatic inferior vena cava was performed. Two Satinsky vascular clamps were used for partial occlusion of the portal vein and inferior vena cava during construction of the shunt. The hepatic pedicle was then clamped between the shunt and the liver for 90 minutes. After 90 minutes of continuous liver ischemia, reperfusion was established and the shunt was ligated on the inferior vena cava side so as not to constrict the portal vein [34]. The abdomen was closed and the animal was returned to its cage. Heparin was not used. After 24 h of reperfusion, blood samples were withdrawn and the animals were killed. All specimens were kept at -20° C until the time of analysis.

### *Biochemical Analyses*

Serum ALT values were determined before clamping of the hepatic pedicle and at 1 and 24 hours after reperfusion by using commercially available kits.

### *Histological Examination*

Wedge liver biopsies were taken before hepatic pedicle occlusion. Autopsy was performed immediately on death; animals that survived were killed 24 hour after reperfusion and specimens were harvested from the liver, kidneys, intestine and lungs. All specimens were fixed in 10 per cent formalin and embedded in paraffin. The harvested intestinal segments were distended with fixative [35]. Sections 5 μm thick were stained with hematoxylin and eosin (H & E) and were evaluated for severity of injury. Hepatic injury was estimated using an ordinal scale modified from Camargo et al [36] (Table 1). The histologic grading for small bowel epithelial damage was assessed as described by Park et al (Table 2) [37]. The morphologic evidences of injury in the lung and kidney sections were described.

**Table (1):** ***Histologic grading of liver injury***

| *Grade* | *Description* |
|---|---|
| 0 | No apparent injury on light microscopic examination |
| I | Hepatocyte swelling |
| II | Cytoplasmic vacuolization, nuclear pyknosis, apoptosis |
| III | Cytoplasmic hypereosinophilia, loss of intercellular borders, focal necrosis |
| IV | Midzonal necrosis, disorganization of hepatic cords, neutrophil infiltration |
| V | Massive necrosis of whole hepatic cords & hemorrhage |

**Table (2):** ***Park's histologic grading of small bowel epithelial damage***

| *Grade* | *Description* |
|---|---|
| 0 | Normal mucosa |
| 1 | Subepithelial space |
| 2 | Extended subepithelial space |
| 3 | Epithelial lifting along villous side |
| 4 | Denuded villi |
| 5 | Loss of villous tissue |
| 6 | Crypt layer infarction |
| 7 | Transmucosal infarction |
| 8 | Transmural infarction |

***Statistical Analysis***

Results are entered in SPSS for Windows 8.0 (SPSS Inc., Chicago, IL). Continuous variables (serum ALT concentrations) are expressed as the mean ± SEM. Means of different groups were compared using a one-way analysis of variance (ANOVA) and Scheffe's (post hoc) test. The medians of ordinal variables (histologic grading of the liver and intestine) were compared by the nonparametric Mann-Whitney U test. The survival rates were statistically tested using the $\chi 2$ test. A p value < 0.05 is considered statistically significant.

## RESULTS

***Survival.***

Two dogs in the control group and all six dogs in the shunt group survived for 24 hours after reperfusion ($p < 0.05$, chi-square test).

***Liver Enzymes.***

Changes in serum levels of ALT in the control and shunt groups, before liver ischemia and at 1 and 24 hours after reperfusion are depicted in (Table 3). The serum levels of ALT before hepatic pedicle occlusion were similar in the control and shunt groups. At 1 hour after reperfusion, serum ALT of both the control (730.3% increase) and shunt (419.6% increase) groups increased significantly ($p<.001$) compared with the pre-ischemic values. However, The ALT values of the shunt group at 1 hour were significantly ($p < 0.001$) lower than those of the control group. At 24 hours after reperfusion, the serum concentrations of ALT of both the control and shunt groups, although were lower than those levels at 1 hour, were still statistically higher ($p<0.001$) than the pre-ischemic levels (566.5% and 255.2%, respectively). Again the ALT levels of the shunt group at 24 hours after reperfusion were significantly ($p<0.001$) lower than those of the control group.

**Table (3):** ***Serum values of ALT.***

| | *ALT (U/L)* | |
|---|---|---|
| | *Control* | *Shunt* |
| Pre-ischemia | 29.3±4.7 | 25.5±3.1 |
| 1 h after reperfusion | 214±6.3† | 107±1.8*† |
| 24 h after reperfusion | 166±15† | 65.1±2 *† |

Table 3. Serial changes in means (SEM) of ALT in the control and shunt groups before hepatic pedicle occlusion (pre-ischemia), at 1h and 24h after reperfusion. The number of observation in each group = 6 except in control group at 24 h = 2. Four dogs of the control group died within 24 h. Data were evaluated by ANOVA.
*$p < 0.001$ versus control
†$p < 0.001$ versus pre-ischemia level

***Histological Findings***

**Liver.** Light microscopic evaluation of liver specimens from dogs subjected to 90 minutes of continuous hepatic pedicle occlusion without portacaval shunt showed severe degree of hepatocyte necrosis (median grade 4) (Fig. 1, B). However, dogs subjected to 90 minutes of continuous inflow occlusion with prior portacaval shunt presented with significantly less injury (median grade 1) than the control group ($p < 0.005$) (Fig. 1, A).

**Intestine.** In the control group, the bowel became congested, edematous and bluish in color following hepatic pedicle clamping. All dogs in the control group had bloody diarrhea postoperatively. At autopsy, the bowel wall was still bluish in color while the lumen contained dark blood. (Fig. 2, B) demonstrates the small intestine of the control group with transmucosal infarction (median grade 7). In the shunt group, the intestine morphology did not change after hepatic pedicle clamping following construction of the portacaval shunt during operation and at autopsy. None of the dogs in the shunt group had bloody diarrhea postoperatively. (Fig. 2, A) illustrates the small intestine of the shunt group with significantly less injury (subepithelial space, median grade 1) compared with the control group ($p < 0.005$).

**Lung**. In the control group, the lung showed congestion of the perialveolar capillaries and pulmonary blood vessels and thickening of alveolar septa which is infiltrated with inflammatory cells (Fig. 3, B). The shunt group had normal lung histology (Fig. 3, A).

**Kidney**. In the control group, the glomerular tufts showed hypercellularity that included proliferation of endothelial and mesangial cells with leukocytic infiltration. Excessive amount of albuminous filtrate accumulated in the Bowman's capsule. The proximal and distal convoluted tubules showed swelling of their epithelial lining (Fig. 4, B). In the shunt group, only intraluminal albuminous droplets in the renal tubules were seen (Fig. 4, A).

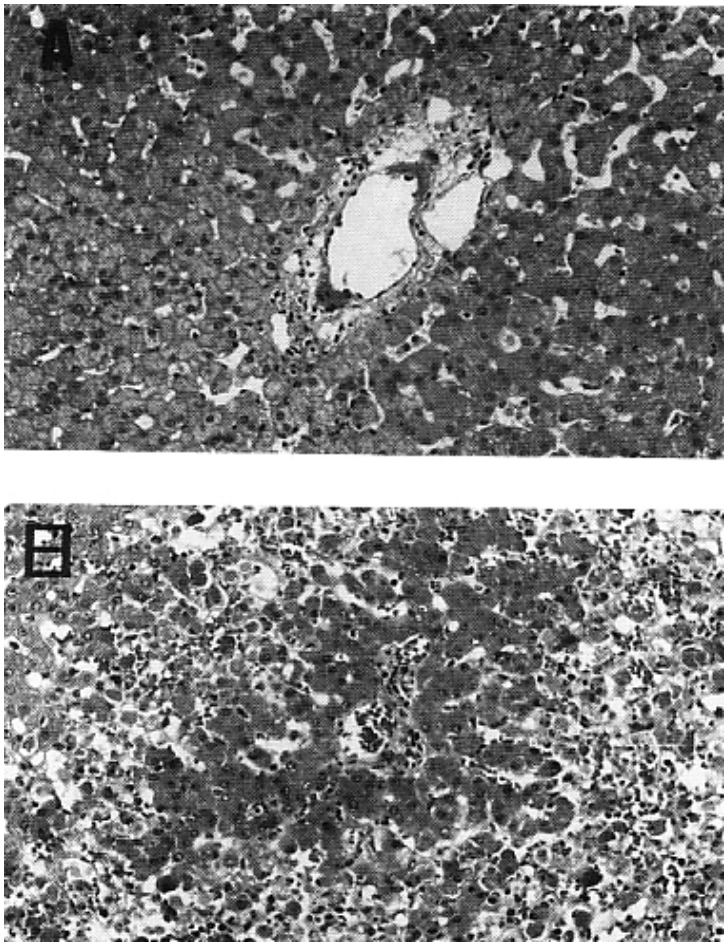


**Fig. (1).** ***Photomicrograph of liver specimens obtained from the shunt group (A) and the control group (B). Panel A shows hepatocyte swelling; grades 1 liver injury. Panels B shows midzonal necrosis, disorganization of hepatic cords, and neutrophil infiltration; grades 4 liver injury. (magnification ×200).***

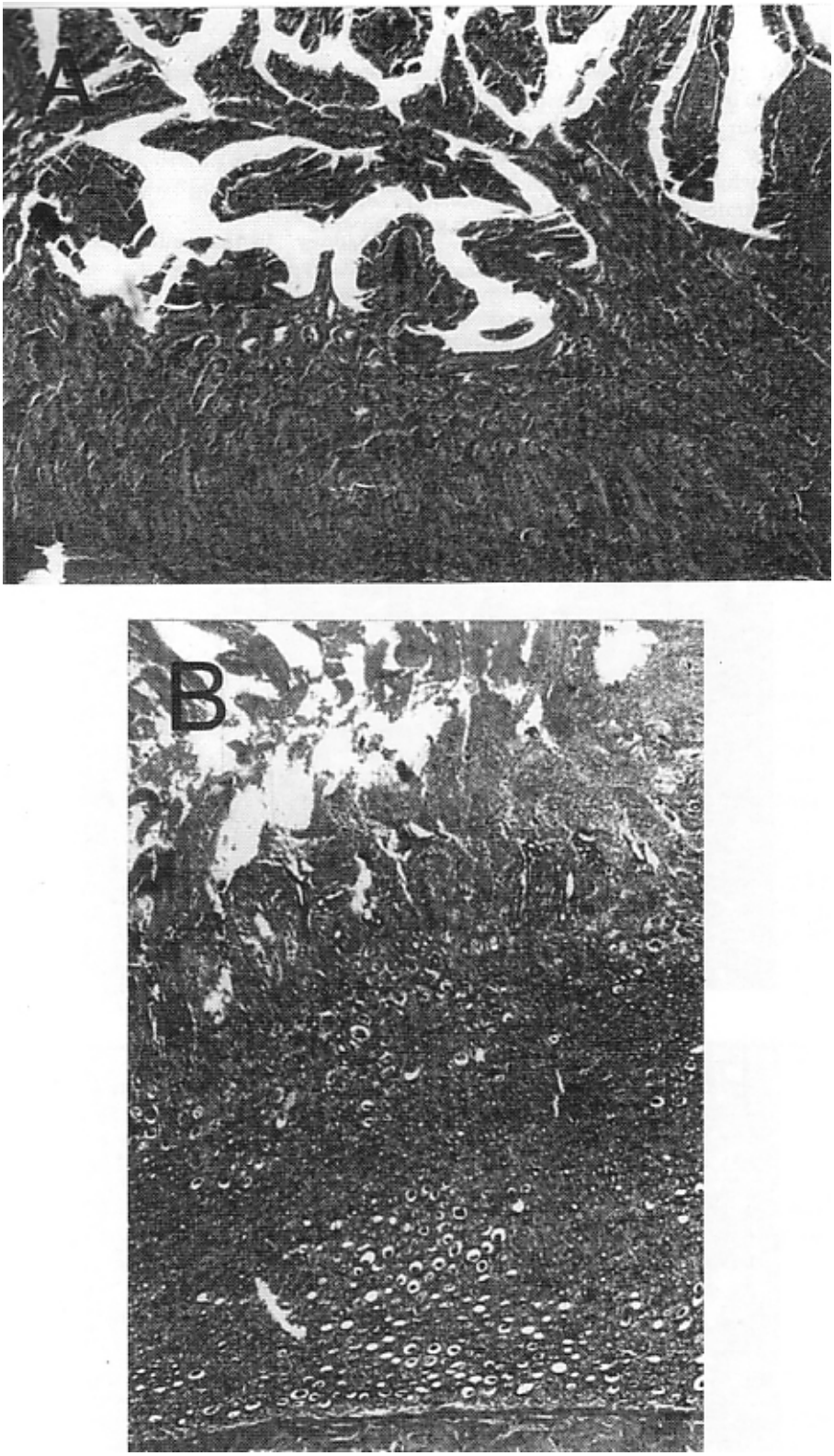


**Fig.(2).** ***Photomicrograph of intestine of the shunt (A) and control group (B). Panel A shows intestinal mucosa with subepithelial space (arrow). Panel B shows intestinal mucosa with transmucosal infarction. (magnification ×100).***

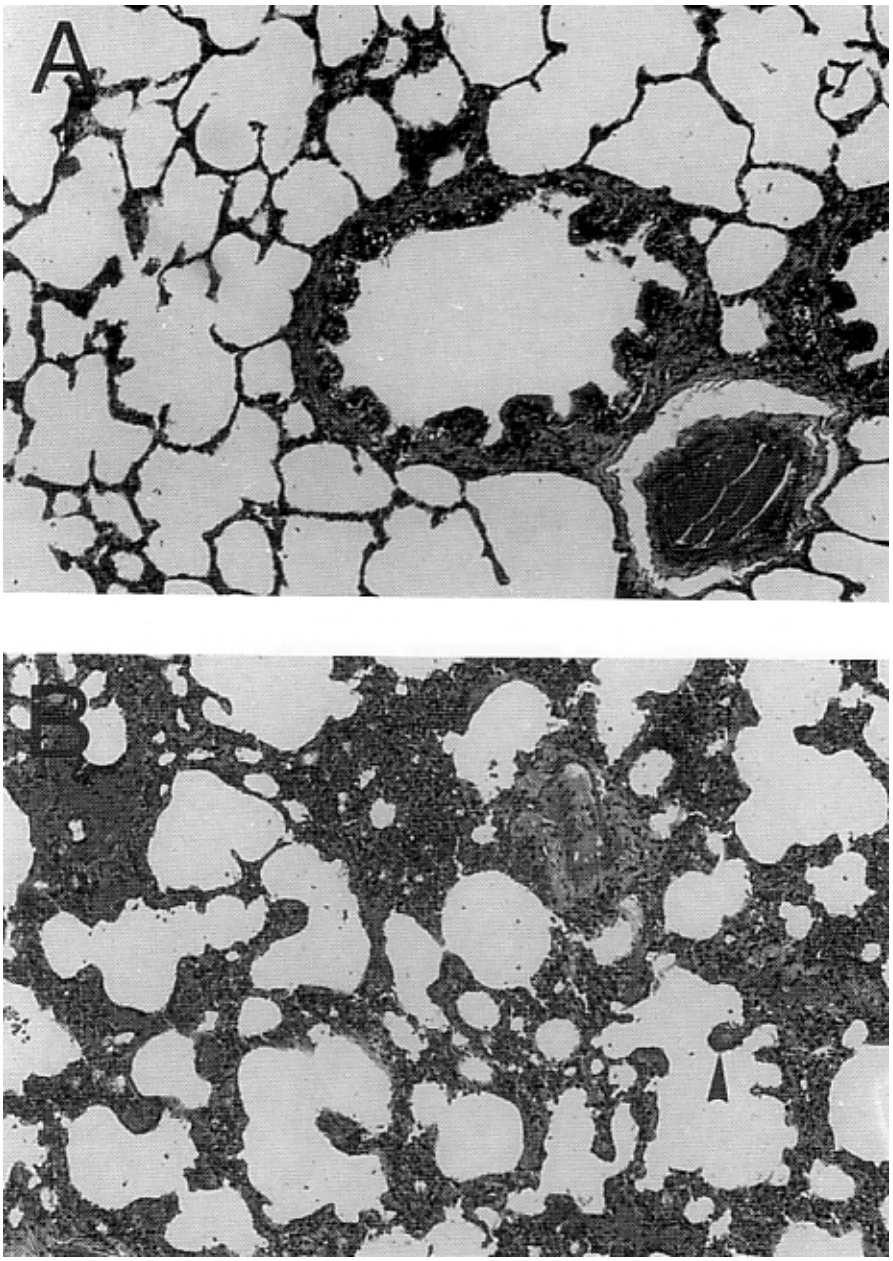


**Fig. (3).** ***Photomicrograph of lung specimens from the shunt (A) and control groups (B). Panel A shows normal lung architecture. Panel B shows congestion of perialveolar capillaries (arrow). Alveolar septa are thickened with inflammatory cell infiltrate. (magnification ×100).***

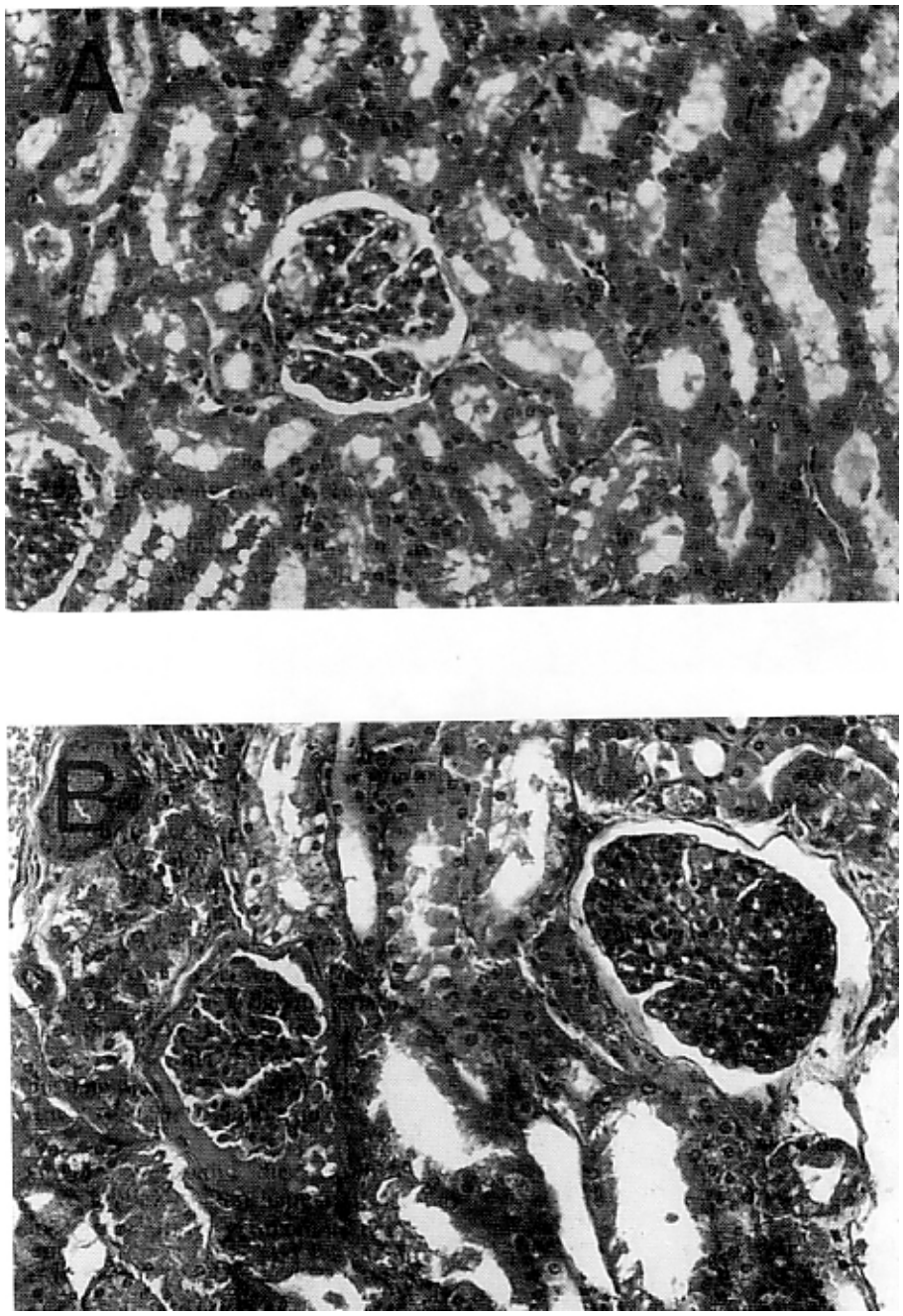


*Fig. (4). Photomicrograph of kidney specimens from the shunt (A) and control (B) groups. Panel A shows minimal albuminous filtrate. Panel B shows hypercellularity of the glomerular tufts, swelling of tubular epithelium, and severe albuminous filtrate. (magnification ×200).*

## DISCUSSION

Clinical and experimental studies have consistently demonstrated that the preferable method of hepatic inflow vascular control is intermittent rather than continuous occlusion particularly in patients with abnormal liver parenchyma [1,4,5,35,38,39]. The final clinical outcome after hepatic inflow occlusion, whether continuous or interrupted, depends on both liver I/R injury and gut congestion-reperfusion injury. The role of gut congestion and injury in producing severe liver injury and multiple organ dysfunction following continuous hepatic pedicle occlusion is underscored.

This study demonstrates the significant contribution of gut congestion and injury during continuous hepatic pedicle occlusion in aggravating hepatic I/R injury and in inducing distant organ injury. First, the biochemical marker of hepatic injury (serum ALT values) are significantly elevated in the control group more than in the shunt group. Second, the histological findings in the control group of severe degrees of liver injury with a predominant midzonal necrosis compared with the minimal injury in the shunt group in the form of hepatocyte swelling and cytoplasmic vacuolization. These significant differences occurred despite the same duration of liver ischemia. Taken together, these data suggest that preformed cytotoxic mediators released from the congested and injured gut after reperfusion are responsible for the more severe hepatocyte injury incurred in the control group. Third, the morphologic evidence of acute lung injury was present only in the control group. Fourth, histological examination of the kidney showed evidence of acute injury affecting the glomerular tufts and the proximal and distal tubules with leukocytic infiltration in the control group only. Finally and most importantly, the survival rate is significantly improved in the shunt group.

Intestinal mucosal injury following outflow venous occlusion is identical with that described following inflow arterial occlusion of the gut [40]. In this study, continuous hepatic pedicle occlusion for 90 minutes resulted in severe intestinal congestion and injury with total necrosis of the intestinal mucosa. Many studies have demonstrated that intestinal I/R injury results in an inflammatory response that includes circulating plasma factors such as endothelin-1 [15-17], tumor necrosis factor [13,14,26], interleukin-1 [13], interleukin-6 [14], complement activation [13,14] and activated neutrophils [13,21,22,25,26], and Kupffer cells [23]. Additionally, failure of the intestinal barrier function when stasis-ischemia occurs results in increased permeability to, and subsequent translocation of, bacteria and toxins from the lumen [7, 10].

The liver plays a central role in the clearance of many cytokines from the circulation [11]. The hypoxic and energy depleted hepatocytes in case of prolonged hepatic pedicle clamping may be unable to withstand the stress of metabolizing these large amounts of mediators released from the injured gut after reperfusion with the resultant hepatocyte death and spillage of these mediators into the systemic circulation [24,39,41]. It has been shown that these factors generated by the injured intestine are involved in the development of hepatic dysfunction [26,42] and acute lung injury [24-26] after intestinal reperfusion. Moore, in a recent review of the role of the gastrointestinal tract in post-trauma multiple organ failure, concluded that reperfused gut becomes a source of proinflammatory mediators that cause acute lung injury, independent of bacterial translocation [43]. Certainly, acute liver and lung injury after intestinal I/R could be explained on the account that the vasculatures of these organs are coupled in series with the intestinal circulation [21,25,26]. Nevertheless, the role of gut I/R in inducing remote organ dysfunction is less emphasized. In our model of hepatic pedicle occlusion, we have demonstrated that gut congestion is associated with morphologically significant renal injury. Oldham et al reported both biochemical and morphological evidences of renal injury following sublethal intestinal I/R injury [14].

We demonstrated in this study that temporary portacaval shunt improved the survival rate of animals subjected to prolonged continuous warm liver ischemia. This improved survival is associated with significant reduction of hepatocyte injury. Moreover, portacaval shunt prevented the development of lung and kidney injuries seen after continuous liver ischemia without portacaval shunt.

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