Acute obstructive jaundice and chronic cirrhosis protect against the adverse renal effects of pneumoperitoneum: role of nitric oxide

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Abstract

Background Obstructive jaundice and cirrhosis are associated with impaired renal function. Previously we demonstrated that increased intra-abdominal pressure (IAP, pneumoperitoneum) in normal rats induced renal dysfunction. This study investigated the renal effects of pneumoperitoneum in rats with acute jaundice and cirrhotic rats.

Methods Following a baseline period, rats with obstructive jaundice or cirrhosis induced by acute or chronic bile duct ligation (BDL), respectively, and their sham-controls were subjected to consecutive IAPs of 10 and 14 mmHg for 45 min each. Urine flow (V), Na$^+$ excretion ($U_{Na}V$), glomerular filtration rate (GFR), renal plasma flow (RPF), and urinary NO metabolites ($U_{NO_2+NO_3}$) and cGMP (U_{cGMP}) were determined.

Results: Elevating IAP from 0 to 10 and 14 mmHg in normal rats caused IAP-dependent reductions in V, $U_{Na}V$, GFR, RPF, $U_{NO_2+NO_3}$, and U_{cGMP}. Basal renal function and hemodynamics were lower in rats with obstructive jaundice. In contrast to normal rats, application of elevated IAP of 10 and 14 mmHg significantly improved V, $U_{Na}V$, GFR, RPF, and MAP along with increased $U_{NO_2+NO_3}$ and preserved U_{cGMP}. Similarly, when identical IAP conditions were applied to cirrhotic rats, no deleterious changes in V, $U_{Na}V$, GFR or RPF were observed.

Conclusions Application of pneumoperitoneum to rats with acute BDL improves kidney function and renal hemodynamics. Likewise, increased IAP does not exert adverse renal effects in cirrhotic rats. These effects are distinct from the deleterious renal consequences of increased IAP in normal rats. Perturbations in the generation of NO/cGMP during IAP in normal rats but not in rats with BDL or cirrhosis may contribute to these differences.

Keywords Pneumoperitoneum · Kidney · Jaundice · Cirrhosis · Renal hemodynamics · Rat

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List of abbreviations

BDL	Bile duct ligation
cGMP	Cyclic guanosine monophosphate
GFR	Glomerular filtration rate
IAP	Intra-abdominal pressure
MAP	Mean arterial blood pressure
NO	Nitric oxide
RPF	Renal plasma flow
V	Urine flow
$U_{Na}V$	Urinary sodium excretion

Minimally invasive laparoscopic surgery is rapidly replacing the open approach in many areas of surgery, owing to its advantages including lesser pain and shorter postoperative hospital stay [1]. However, this procedure requires induction of pneumoperitoneum, an increased intra-abdominal pressure (IAP), which adversely affects kidney function; For instance, pneumoperitoneum at pressure above 10 mmHg has been shown to produce transient oliguria and deterioration in glomerular filtration rate (GFR) [1–5]. Likewise, most studies have identified a decrease in renal blood flow (RBF) [1, 6–12]. The exact mechanisms underlying these adverse effects are not fully understood. Nevertheless, the deleterious renal effects induced by pneumoperitoneum are affected by the level of IAP [12, 13], volume status, degree of hypercarbia, positioning, and individual hemodynamic and renal reserves [9, 11, 14]. Additional factors that may contribute to renal dysfunction include direct compression of the renal parenchyma and renal vein [1, 6, 12, 15], increased resistance in the renal vasculature [16], and release of various vasoconstrictors [1, 17]. Although the transient renal dysfunction during laparoscopy has no permanent effects, some suggestions have been offered to overcome the negative renal effects of pneumoperitoneum, including aggressive hydration, using IAP lower than 14 mmHg [18, 19], and preconditioning consisting of 10 min of pneumoperitoneum followed by 10 min of deflation [20]. Nevertheless, none of these approaches completely abolish the deleterious consequences of pneumoperitoneum on renal perfusion/function. An additional unmet concern is whether pneumoperitoneum-induced kidney dysfunction is influenced by the presence of background diseases. This issue is of particular importance since a considerable portion of the patients who undergo laparoscopic surgery suffer from comorbid conditions and metabolic disturbances, including jaundice and cirrhosis. Previously, we demonstrated that rats with experimental heart failure and impaired kidney function exhibited increased sensitivity to IAP-induced renal deleterious effects as compared with normal animals [21]. The question of whether patients who suffer from jaundice or cirrhosis are susceptible to the adverse renal effects of pneumoperitoneum has not been addressed yet. Interestingly, decreases in RBF and GFR are among the most common pathophysiological alterations in clinical and experimental jaundice and cirrhosis [22–24], suggesting that these clinical conditions may display an exaggerated renal vulnerability to increased IAP. In this context, Bostanci et al. [25] have demonstrated that 12 mmHg pneumoperitoneum for 60 min in a rat model of obstructive jaundice resulted in moderate but nonsignificant increases in serum liver enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin values. Unfortunately, this report did not refer to the renal effects of increased IAP in rats with obstructive jaundice. Therefore, the present study was designed to examine the effects of pneumoperitoneum on kidney function and renal hemodynamics in rats with either acute obstructive jaundice or chronic liver cirrhosis.

Materials and methods

Studies were conducted on a local strain of male Sprague–Dawley rats (Harlan Laboratories, Ltd., Jerusalem), weighing ~ 300 g. The animals were kept in individual metabolic cages in a temperature-controlled room, and were fed standard rat chow containing 0.5 % NaCl and tap water ad libitum. All experiments were performed according to the guidelines of the committee for the supervision of animal experiments, Technion, IIT.

The experimental model of jaundice

After skin shaving, the abdominal wall was cleaned with 10 % povidone iodine solution and a midline laparotomy was performed. The common bile duct (CBD) was isolated, and two ligatures were passed around the bile duct and tightly ligated. Then the abdominal incision was closed and the animals were allowed to recover. Four days after CBD ligation, jaundice was confirmed by blood chemical analysis, and only animals that showed increased serum bilirubin concentrations were included in the study.

The experimental model of cirrhosis

Cirrhosis was induced by CBD ligation as described above, with the exception that the CBD was cut within the two sutures. The animals were allowed to recover and housed in metabolic cages for 4 weeks. The cirrhotic changes were confirmed by histological analysis and development of ascites as described by Kountoura et al. [26]. Liver tissues were fixed in 10 % buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin (HE). Blind analysis was performed on all samples by a pathologist based on the criteria of sinusoidal congestion and vacuolization, necrosis of parenchymal cells, and proliferation of bile ducts [25].

The experimental model of pneumoperitoneum

A small incision in the lower third between the xiphoid and pubis was made, through which a regular Veress needle was inserted into the abdominal cavity. Sequential pneumoperitoneum of 10 and 14 mmHg each for 45 min was established with CO_2 gas supply to maintain IAP at the desired level using a special insufflator (Aesculap,

Tuttlingen, Germany) connected to the Veress needle (Fig. 1). The muscle layer and skin layer of the abdominal wall were closed separately by silk sutures in an airtight manner.

Clearance studies

Normal rats ($n = 23$), rats with acute jaundice ($n = 7$), and animals with chronic cirrhosis ($n = 7$) were prepared for clearance studies as described previously [21, 27]. After a 60-min equilibration period, two baseline clearance periods of 30 min each were obtained (IAP = 0). Then the animals were subjected to increasing IAP of 10 and 14 mmHg during 45 min for each pressure. After completing the last IAP, namely 14 mmHg, the abdominal cavity was deflated

and a urinary collection was obtained for an additional 1-h period (recovery). One clearance period was obtained during each IAP and two during the recovery period. Blood samples were obtained in the middle of every clearance period (Fig. 1).

One the day of experiment, rats were anesthetized with Inactin (100 mg/kg, i.p.), placed on a thermoregulated (37 °C) surgical table, and prepared for hemodynamic and clearance studies [21, 27]. After tracheotomy, polyethylene (PE_{50}) tubes were inserted into the carotid artery and jugular vein for blood pressure monitoring and infusion of various solutions, respectively. The abdomen was opened by a small midline incision, and the urinary bladder was catheterized with PE_{50} for urine collection. A solution of 2 % inulin and 0.5 % p-aminohippurate (PAH) in 0.9 % saline was continuously

Fig. 1 Experimental protocol in rats with acute bile duct ligation (BDL), rats with cirrhosis, and their sham-controls. U1–U6, urine collection periods; B1–B4, collection of blood samples
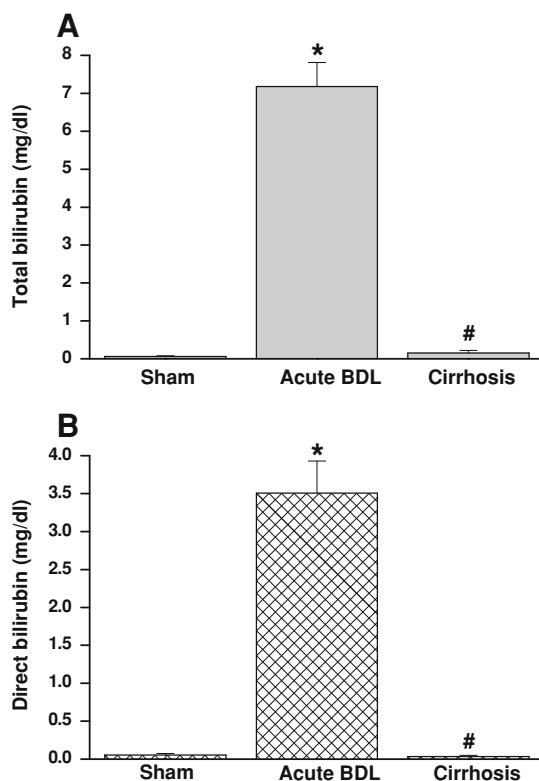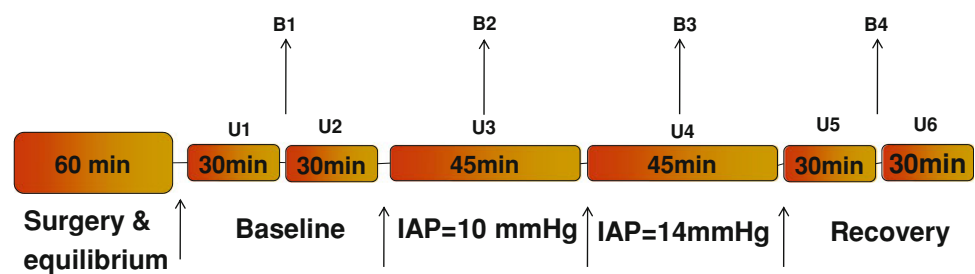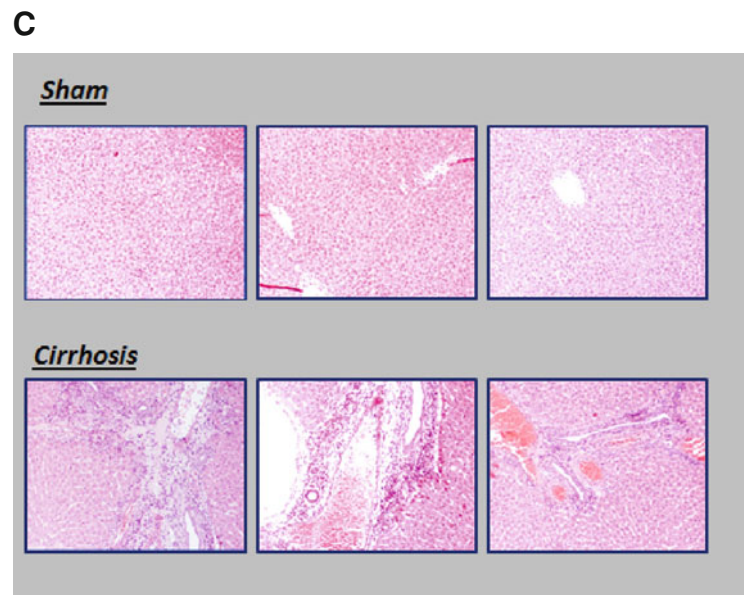

Fig. 2 (A) Total bilirubin levels and (B) direct bilirubin serum concentrations in rats with acute BDL and cirrhotic rats and their sham-controls. *$P < 0.05$ versus baseline of each group, #$P < 0.05$ versus sham-controls. (C) Representative histological sections of liver stained with HE from normal rats and cirrhotic animals

infused at a rate of 1.0–1.5 % of body weight per hour throughout the experiment. Arterial blood pressure was continuously monitored with a pressure transducer (model 156PC05GWL; Microswitch, Freepoint, IL) connected to the carotid arterial line.

Chemical analysis

Urine volume was determined gravimetrically. Blood samples were separated by centrifugation, and the concentrations of sodium in plasma and urine were determined by a flame photometer (model IL 943; Instrumentation Laboratory). Concentrations of inulin and PAH in plasma and urine samples were measured by colorimetric methods. Renal plasma flow (RPF) and GFR were estimated as the infusion clearance of PAH ($C_{PAH} = U_{PAH} \times V/P_{PAH}$) and inulin ($C_{in} = U_{in} \times V/U_{in}$), respectively. Bilirubin was determined by automated analyzers using appropriate kits (Dimension® Clinical Chemistry Systems, Kearneysville, WV, USA). NO metabolites (NO_2 and NO_3) in the urine samples from the various experimental groups were determined with the Griess method using a commercially available colorimetric kit (Calbiochem, Darmstadt, Germany).

Urine flow was calculated by dividing urine volume by time of urine collection; urinary sodium excretion ($U_{Na}V$) was calculated by multiplying urinary sodium concentration (U_{Na}) by urinary flow rate (V); fractional sodium excretion (FE_{Na}) was calculated according to the following formula: $FE_{Na} \% = U_{Na} \times V/P_{Na} \times GFR$, where U_{Na} is urinary sodium concentration, V is urinary flow rate, P_{Na} is plasma concentration of sodium, and GFR is glomerular filtration rate.

Statistical analysis

One-way analysis of variance (ANOVA) for repeated measures, followed by the Dunnett or Tukey test, was used for comparison of treatment values with baseline in each group or with corresponding values in control group. A value of $P < 0.05$ was considered statistically significant. Data are presented as mean ± SEM.

Results

The total bilirubin levels and direct bilirubin concentrations in rats with acute BDL were significantly higher than the corresponding values of the sham-operated controls (7.2 ± 0.6 vs 0.06 ± 0.02 mg/dl, $P < 0.05$; 3.5 ± 0.4 vs 0.06 ± 0.02 mg/dl, $P < 0.05$) (Fig. 2A, B). In contrast, cirrhotic rats did not display significant changes in direct or total bilirubin levels. However, these rats exhibited typical

histopathological changes seen in cirrhosis, including sinusoidal congestion and vacuolization (Fig. 2C).

Effects of increased IAP on renal clearance and hemodynamics in rats with jaundice

Figure 3 depicts V, $U_{Na}V$, and MAP of sham-controls that were subjected to incremental increases in IAP. There were slight nonsignificant declines in these parameters during 10 mmHg insufflations. However, remarkable reductions in V and $U_{Na}V$ were observed when IAP of 14 mmHg was applied: V decreased from 9.31 ± 0.68 to 7.48 ± 0.82 and 6.01 ± 0.58 μl/min ($P < 0.05$), respectively, and $U_{Na}V$ decreased from 0.82 ± 0.16 to 0.58 ± 0.18 and 0.51 ± 0.12 μEq/min, respectively, without affecting MAP (Fig. 3). In addition, increasing the IAP to 10 and 14 mmHg resulted in decreases in GFR from 1.93 ± 0.09 to 1.29 ± 0.19 and
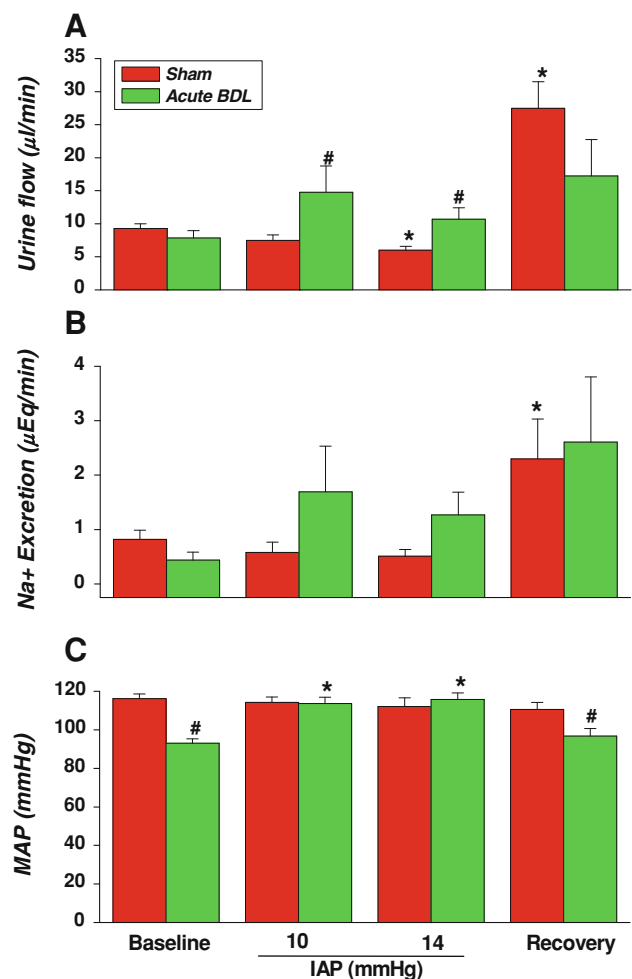

Fig. 3 Effects of 10 and 14 mmHg insufflations on: (**A**) urinary flow (V), (**B**) urinary sodium excretion ($U_{Na}V$), and (**C**) mean arterial blood pressure (MAP) in rats with acute bile duct ligation (BDL) versus sham-controls. *$P < 0.05$ versus baseline of each group, #$P < 0.05$ versus sham-controls
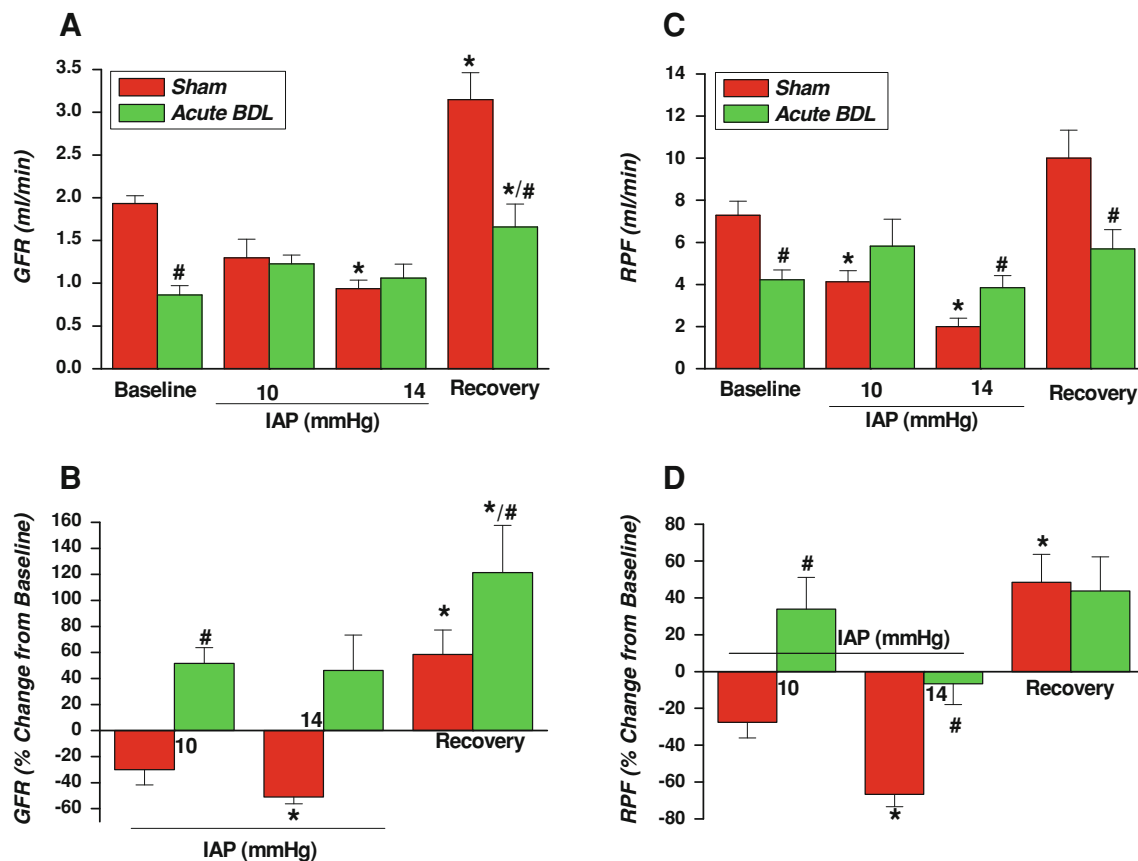
Fig. 4 Effects of 10 and 14 mmHg insufflations on: (**A**) GFR, (**B**) percentage change in GFR from baseline, (**C**) renal plasma flow (RPF), and (**D**) percentage change in RPF from baseline, in rats with acute bile duct ligation (BDL) and sham-controls. *$P < 0.05$ versus baseline of each group, #$P < 0.05$ versus sham-controls

0.94 ± 0.09 ml/min ($P < 0.05$) (% change of GFR from baseline was −30.11 ± 11.8 and −51.2 ± 5.1 %, $P < 0.05$, respectively) and RPF from 7.29 ± 0.66 to 4.12 ± 0.53 and 1.99 ± 0.41 ml/min ($P < 0.05$), respectively (% change of RPF from baseline was −27.55 ± 8.55 and −66.72 ± 6.7 %, $P < 0.05$, respectively) (Fig. 4). Both the excretory and renal hemodynamic parameters returned to baseline and exceeded baseline values following a deflation period of 1 h (recovery) (Figs. 3, 4).

Rats with acute BDL have reduced baseline $U_{Na}V$, MAP, GFR, and RPF as compared with sham-controls (Figs. 3, 4). In contrast to normal rats, increased IAP to 10 and 14 mmHg in rats with acute BDL increased V, $U_{Na}V$, MAP, GFR, and RPF (Figs. 3, 4). Specifically, V increased from 7.23 ± 1.06 to 15.24 ± 4.47 and 11.06 ± 1.95 μl/min, respectively; $U_{Na}V$ increased from 0.37 ± 0.14 to 1.89 ± 0.92 and 1.35 ± 0.47 μEq/min, respectively; MAP increased from 93.7 ± 2.5 to 112.8 ± 3.4 and 115 ± 3.7 mmHg, respectively ($P < 0.05$) (Fig. 3). In addition, GFR increased from 0.86 ± 0.11 to 1.23 ± 0.1 to 1.06 ± 0.16 ml/min (% change of GFR from baseline was +51.5 ± 12.3 % and +46.2 ± 27.09 %, respectively) and

RPF from 4.22 ± 0.46 to 5.80 ± 0.1.28 and 3.84 ± 0.57 ml/min (% change of RPF from baseline was +33.88 ± 17.24 % and −6.61 ± 11.3 %, respectively) (Fig. 4).

Effects of increased IAP on renal clearance and hemodynamics in rats with cirrhosis

Basal V, $U_{Na}V$, and MAP were lower in rats with cirrhosis than their sham-controls (Fig. 5). Similarly, GFR and RPF were significantly lower in cirrhotic rats as compared with sham-controls (Fig. 5). When these animals were exposed to IAP of 10 and 14 mmHg, V increased from 6.12 ± 0.72 to 7.25 ± 1.3 and 6.66 ± 0.48 μl/min, respectively, and $U_{Na}V$ increased from 0.39 ± 0.19 to 0.81 ± 0.46 and 0.43 ± 0.24 μEq/min, respectively, with no significant effect on MAP (Fig. 5).

Application of IAP of 10 or 14 mmHg in cirrhotic rats caused a moderate decline in GFR and RPF (Fig. 6); GFR decreased from 1.29 ± 0.24 to 1.19 ± 0.19 and 0.94 ± 0.12 ml/min (% change of GFR from baseline was −4.9 ± 16.3 and −16.98 ± 11.7 %, respectively) and RPF from 6.01 ± 0.68 to 4.61 ± 1.15 and 3.83 ± 0.84 ml/min
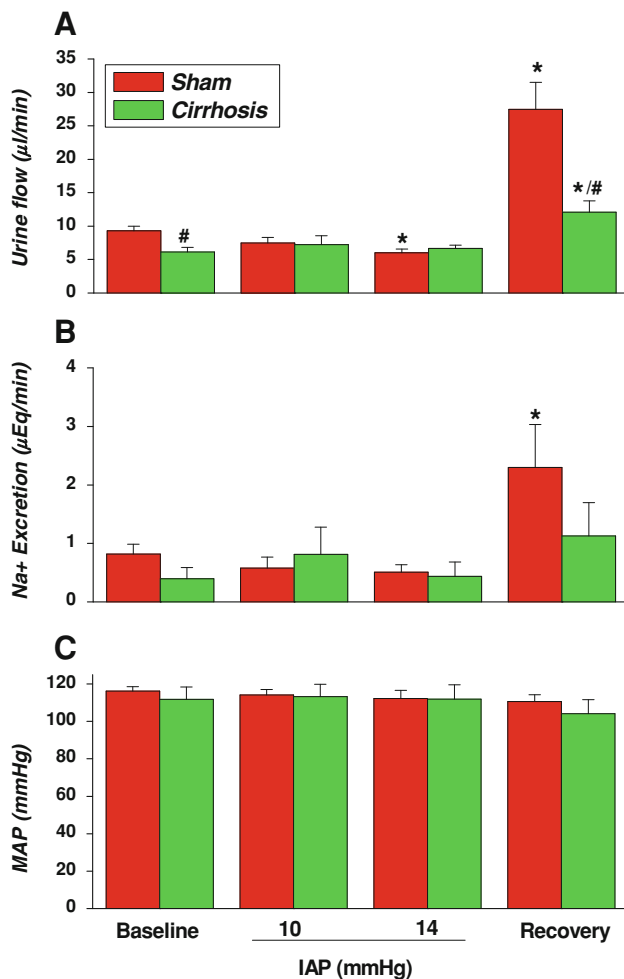
Fig. 5 Effects of 10 and 14 mmHg insufflations on: (**A**) urinary flow (V), (**B**) urinary sodium excretion ($U_{Na}V$), and (**C**) mean arterial blood pressure (MAP) in rats with cirrhosis versus sham-controls. *$P < 0.05$ versus baseline of each group, #$P < 0.05$ versus sham-controls

(% change of RPF from baseline was -25.14 ± 17.6 and -38.71 ± 8.32 %, respectively) (Fig. 6). However, the deleterious effects of increased IAP on renal perfusion/filtration were significantly to a lower extent than those obtained in normal rats that were subjected to similar IAP (Figs. 5, 6).

Effects of increased IAP on urinary excretion of NO and cGMP in the various groups

To assess the status of the renal NO and GMP production system in rats undergoing pneumoperitoneum, the urinary excretion of these vasodilatory second messengers was measured in normal rats, rats with acute BDL, and cirrhotic animals using urine samples taken during the clearance protocol. The effects of IAP on urinary excretion of NO and cGMP in these animals are depicted in Fig. 7. Elevation of

IAP from 0 to 10 and 14 mmHg caused pressure-dependent reductions in $U_{cGMP}V$, and $U_{NO_2+NO_3}V$ in sham-controls. While basal $U_{NO_2+NO_3}V$ was higher than controls, $U_{cGMP}V$ was lower in rats with acute BDL but not in cirrhotic rats. Rats with acute BDL exhibited progressive increases in $U_{NO_2+NO_3}V$ in response to IAP elevations, which were most profound during IAP of 10 mmHg. In contrast to sham-controls, no decline in $U_{cGMP}V$ was observed in either rats with acute BDL or in cirrhotic rats. Notably, this stimulatory effect of IAP on urinary excretion of NO and cGMP coincides with the beneficial actions of pneumoperitoneum on kidney function and renal hemodynamics.

Discussion

The present study provides new insights into the effects of pneumoperitoneum on kidney function in experimental jaundice and cirrhosis, as compared with normal rats. In contrast to the adverse response of normal rats, our data clearly show that IAP of 10 and 14 mmHg substantially improved kidney excretory functions and renal hemodynamics in rats with acute BDL, an experimental model of jaundice. These beneficial renal effects were associated with restoration of blood pressure in these rats to normal values. Similarly, application of IAP of 10 and 14 mmHg to rats with cirrhosis did not provoke deleterious effects on GFR or RPF as observed in normal rats. Collectively, these results indicate that rats with jaundice and cirrhosis are largely protected from the adverse renal effects of pneumoperitoneum.

Obstructive jaundice affects multiple organs of the human body, including the heart and kidneys. Green et al. elegantly summarized the various effects of obstructive jaundice on the circulatory system as manifested by decreases in the peripheral resistance and blood pressure that does not match the extent of fluid loss [28]. At the cardiac level, jaundice induces cardiomyopathy, which is characterized by negative inotropic and chronotropic effects, i.e., "jaundiced heart." Padillo et al. [29] have shown that obstructive jaundice increased plasma levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) twofold to fourfold due to myocardial dysfunction. The effects of obstructive jaundice on kidney function are complex [28]. Both RBF and GFR are reduced in rats with acute jaundice. The renal dysfunction associated with obstructive jaundice could be related either to altered systemic hemodynamics such as hypotension and cardiac dysfunction or to a direct nephrotoxic effect of bile. Most studies, however, were unable to demonstrate kidney injury in the context of obstructive jaundice [28]. Therefore, we assume that hypotension characterizing rats with acute BDL is responsible for the impaired renal
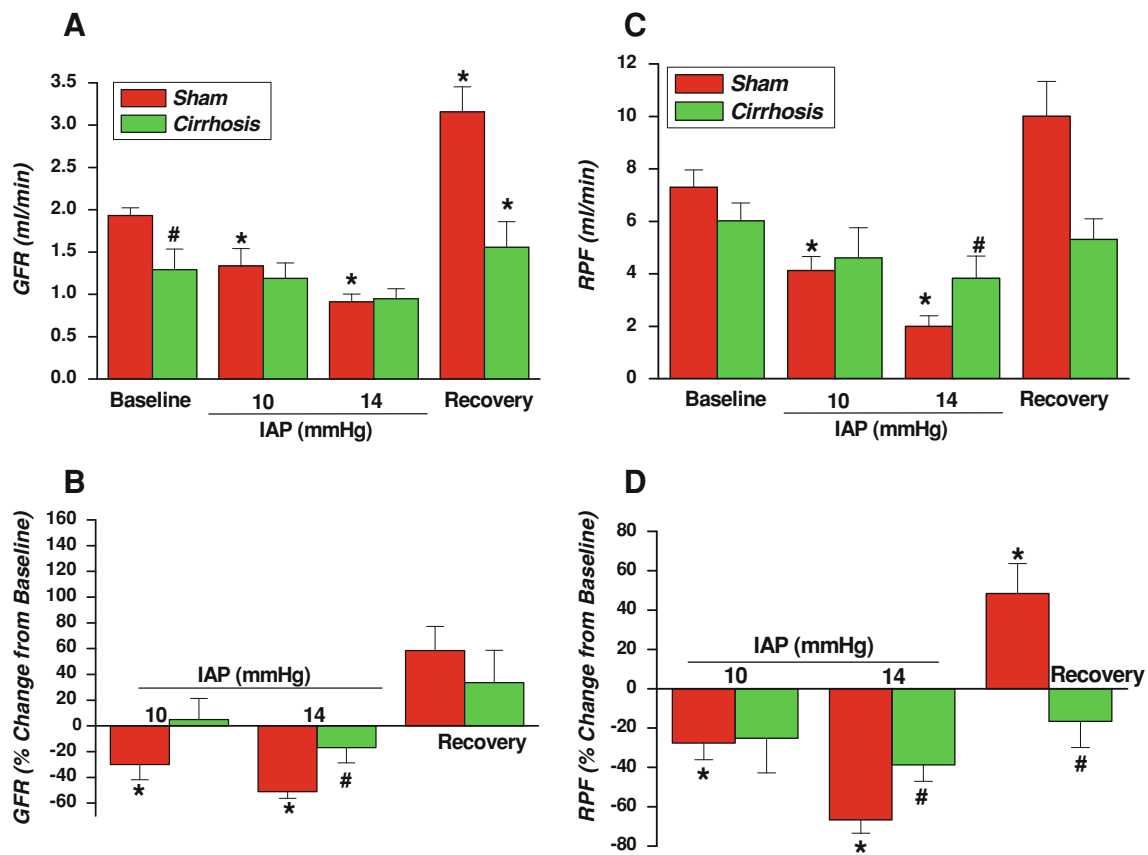
Fig. 6 Effects of 10 and 14 mmHg insufflations on: (**A**) GFR, (**B**) percentage change in GFR from baseline, (**C**) renal plasma flow (RPF), and (**D**) percentage change in RPF from baseline, in rats with cirrhosis and sham-controls. $*P < 0.05$ versus baseline of each group, $\#P < 0.05$ versus sham-controls
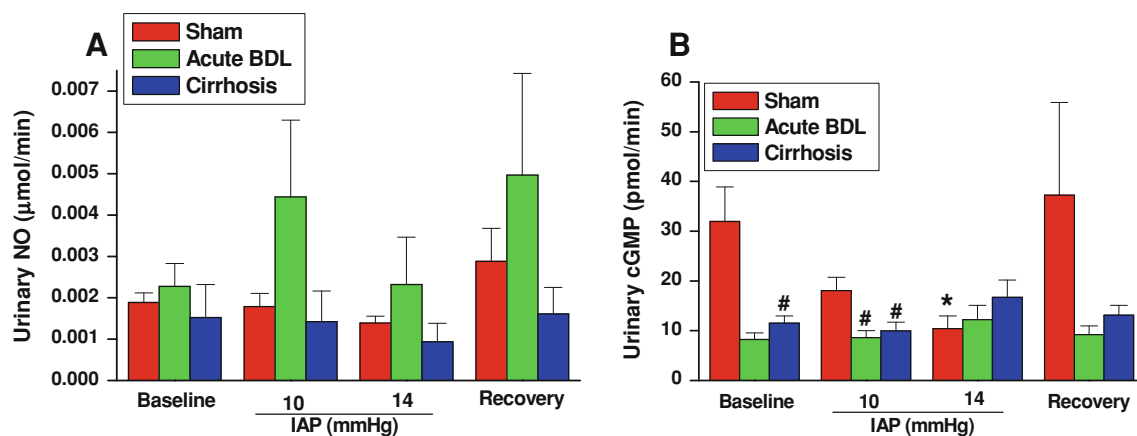

Fig. 7 Effects of 10 and 14 mmHg insufflations on urinary excretion of (**A**) $NO_2 + NO_3$ ($U_{NO2+NO3}V$) and (**B**) urinary cGMP ($U_{cGMP}V$) in sham-control rats, animals with acute bile duct ligation, and animals with cirrhosis. $*P < 0.05$ versus baseline of each group, $\#P < 0.05$ versus sham-controls

hemodynamics obtained in these animals. This notion is supported by our findings that elevation of IAP in rats with acute BDL improved both GFR and RBF along with restoration of MAP to normal values. The reduced MAP in

obstructive jaundice is largely attributed to the vasodilatory actions of renal prostaglandins E2 and I2 (PGE2 and PGI2) and NO in response to the increased levels of bile components [28]. In line with this concept, urinary excretion of

NO metabolites was preserved and even higher in rats with acute BDL as compared with sham-controls. In contrast, basal urinary excretion of cGMP, which derives from the cellular actions of NPs or NO, was significantly lower in rats with acute BDL. Taken into account that cGMP possesses vasodilatory and natriuretic properties, reduction in its availability in acute BDL may have contributed to the reduced basal renal hypoperfusion/hypofiltration characterizing these animals. Interestingly, when pneumoperitoneum was applied to rats with BDL, the urinary excretion of NO was elevated in parallel with improvement in diuresis/natriuresis and enhanced GFR and RPF, suggesting a cause and effect relationship between these parameters. Moreover, in contrast to normal rats, insufflation of rats with acute BDL did not decrease urinary excretion of cGMP. These findings may explain the beneficial or at least the lack of adverse effects of increased IAP on renal function/hemodynamics in rats with obstructive jaundice. An additional noteworthy finding is our observation that the excretory and renal hemodynamic parameters returned to baseline and even exceeded basal values following a deflation period of 1 h (recovery) (Figs. 3, 4). The mechanisms underlying this phenomenon are not known. However, it could be attributed to that deflation of pneumoperitoneum decompresses the abdominal venous system, thus increasing venous return and relieving renal vein congestion. Increasing venous return enhances ANP release from the right atrium, which is known to provoke substantial diuretic/natriuretic response [28, 29]. Most likely, the renal rebound is secondary to IAP release, since the diuretic and natriuretic responses to deflation started immediately after deflation. Additional studies are needed to address whether the renal rebound is a time- or pressure-dependent phenomenon.

In the present study, rats with cirrhosis displayed significant reductions in V, $U_{Na}V$, GFR, and RPF but not MAP. Renal function impairment is a common problem in hepatic cirrhosis. In this setting, the impairment of renal function might be a direct consequence of hepatic damage, or alternatively due to an insult damaging the liver and kidneys simultaneously [30]. Several types of renal damage can occur in the case of hepatic cirrhosis, namely prerenal azotemia, acute tubular necrosis, and hepatorenal syndrome [30]. Prerenal azotemia is the result of decreased effective blood volume that subsequently leads to decreased RBF. In the case of acute tubular necrosis, the tubular epithelium is damaged with resultant necrosis. Hepatorenal syndrome is a unique form of renal damage confined to patients with liver disease. The syndrome is characterized by oliguria and avid urinary sodium retention as the situation in prerenal azotemia but without the typical response to fluid challenge. The syndrome results, at least partially, from vasoconstriction of arterioles or small arteries of the kidneys, but the complete mechanism is far from being fully understood [30]. There is no information on renal function following pneumoperitoneum in patients with cirrhosis. Therefore, the current study sheds more light on this important clinical issue. Our results clearly show that, in contrast to normal rats, rats with cirrhosis are resistant to the adverse effects of increased IAP on GFR, V, and $U_{Na}V$. However, pneumoperitoneum induced a moderate pressure-related decline in RPF which is still lower than that observed in sham-controls. The lack of adverse hypofiltration/hypoperfusion response to elevated IAP in rats with cirrhosis could be again attributed to the increase in MAP during this procedure. At the cellular level, urinary excretion of NO metabolites and cGMP was not reduced during the application of increased IAP, suggesting that this phenomenon may play a compensatory role in the face of the adverse renal effects of increased IAP.

Conclusions

To the best of our knowledge, the present study is the first to show that pneumoperitoneum application to rats with acute BDL improves kidney function and renal hemodynamics. Noteworthily, increased IAP does not exert adverse renal effects in rats with cirrhosis. These effects are distinct from the deleterious renal consequences of increased IAP in normal rats. The mechanisms underlying these findings are not clear, however perturbations in the generation of NO and cGMP during IAP in normal rats but not in rats with BDL or cirrhosis may contribute to these differences. Clinical studies are needed to test whether similar behavior occurs in clinical settings and to explore the cellular and molecular mechanisms underlying this phenomenon.

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