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Review Article

Deleterious Effects of Increased Intra-Abdominal Pressure on Kidney Function

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Elevated intra-abdominal pressure (IAP) occurs in many clinical settings, including sepsis, severe acute pancreatitis, acute decompensated heart failure, hepatorenal syndrome, resuscitation with large volume, mechanical ventilation with high intrathoracic pressure, major burns, and acidosis. Although increased IAP affects several vital organs, the kidney is very susceptible to the adverse effects of elevated IAP. Kidney dysfunction is among the earliest physiological consequences of increased IAP. In the last two decades, laparoscopic surgery is rapidly replacing the open approach in many areas of surgery. Although it is superior at many aspects, laparoscopic surgery involves elevation of IAP, due to abdominal insufflation with carbonic dioxide (pneumoperitoneum). The latter has been shown to cause several deleterious effects where the most recognized one is impairment of kidney function as expressed by oliguria and reduced glomerular filtration rate (GFR) and renal blood flow (RBF). Despite much research in this field, the systemic physiologic consequences of elevated IAP of various etiologies and the mechanisms underlying its adverse effects on kidney excretory function and renal hemodynamics are not fully understood. The current review summarizes the reported adverse renal effects of increased IAP in edematous clinical settings and during laparoscopic surgery. In addition, it provides new insights into potential mechanisms underlying this phenomenon and therapeutic approaches to encounter renal complications of elevated IAP.

1. Introduction

Under normal conditions the intra-abdominal pressure (IAP) is usually below 4 mmHg and even in most obese subjects it does not exceed 8 mmHg [1, 2]. Elevated IAP occurs when the abdomen becomes subject to increased pressure. Sustained or repeated elevation of IAP above 12 mmHg, called intra-abdominal hypertension (IAH), is considered an important mortality risk factor in intensive care unit (ICU). When not treated, IAH has a series of consequences, explicitly, leading to abdominal compartment syndrome (ACS), where IAP increases over 20 mmHg, causing multisystem organ failure, and finally death. Elevated IAP could take place in various clinical settings including trauma, major burns, abdominal surgery, severe heart failure, hepatorenal syndrome, and critically ill patients [2]. The latter are prone to develop elevated IAP as a result of risk factors such as (i) diminished abdominal wall compliance due to mechanical ventilation, obesity, and patient position, (ii) increased intra- and extraluminal abdominal contents, and (iii) enhanced capillary permeability and interstitial fluid accumulation due to acidosis, sepsis, large volume resuscitation, pancreatitis, and disturbed coagulation [1, 2]. Additional clinical condition characterized by elevated IAP is pneumoperitoneum during laparoscopic surgery [2–4].

Although the deleterious effects of increased IAP are known for decades, the interest in this field has been revisited recently most likely due to the increasing number of

subjects undergoing laparoscopic surgery on one hand and the continuous increase in decompensated heart failure and cirrhosis prevalence on the other. Increased IAP adversely affects several vital systems including the cardiac, pulmonary, gastrointestinal, and the renal system, due to diminished blood flow to these organs. The deleterious effects of elevated intra-abdominal pressure (IAP) on the kidneys are widely recognized in the setting of abdominal compartment syndrome or other surgical conditions involving visceral edema [5], as well as during laparoscopic surgery [3–5]. The kidney seems to be extremely sensitive to the harmful consequences of increased IAP even at low levels [5, 6]. In this context, data from patients in intensive care unit indicate that an IAP cutoff value of 12 mmHg has the best sensitivity to specificity ratio for predicting the development of acute kidney injury (AKI) [7]. Although elevated IAP negatively affects multiple physiological systems, the present review will focus only on the kidney, which is preferentially vulnerable to this highly common clinical condition. Specifically, we will review the deleterious impact of increased IAP due to decompensated heart failure, hepatic failure, or pneumoperitoneum on kidney function.

2. The Kidney in Heart Failure

CHF is the major cause of morbidity and mortality in the western world, thus posing a major health and economic burden [8]. Despite the continuous progress in our understanding of the pathogenesis of CHF and its management, the mortality remains high.

Generalized edema formation, the clinical hallmark of ECF volume expansion, represents fluid accumulation in the interstitial compartment and is invariably associated with renal Na^+ and water retention. It occurs most commonly in response to CHF and other edematous disease states (cirrhosis and nephrotic syndrome), where the effector mechanisms that normally act to maintain normal Na^+ balance are exaggerated and continue to preserve salt despite expansion of ECF volume.

The syndrome of CHF encompasses pathophysiological alterations related to a reduction of the effective blood volume and those that are related to increase in the volume of blood and the filling pressures in the atrium and great veins, behind the failing ventricle. In response to these changes, a series of adjustments occur that result from the operation of circulatory and neurohumoral compensatory mechanisms (Figure 1). The importance of vasoconstrictor neurohormonal systems in the pathogenesis of CHF is well recognized [9–11]. Numerous studies in patients and experimental models of CHF have established the important role of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) in the progression of cardiovascular and renal dysfunction in CHF (Figure 1). Prolonged activation of the SNS and RAAS enhances Na^+ retention and has direct deleterious actions on the myocardium, independent of their systemic hemodynamic effects [9–11]. Specifically, norepinephrine and angiotensin II (ang II) have been shown to stimulate myocyte hypertrophy and to enhance fibrosis and apoptosis, leading ultimately to progressive remodeling and further deterioration in cardiac performance [12]. The concept that CHF is also a "neurohormonal disorder" has led to the use of angiotensin converting enzyme (ACE) inhibitors, ang II receptor blockers, and aldosterone antagonists, as well as β-blockers, that are now central to the treatment of CHF [10, 12, 13]. Yet, the RAAS and SNS comprise only two of the three major components originally proposed to link neurohormonal activation to CHF. The third component of the neurohormonal axis in CHF is arginine vasopressin (AVP), whose circulating levels are also elevated in patients with CHF [14]. Likewise, endothelin (ET) signaling is a common network activated during both cardiac and renal dysfunctions [15]. Concomitant with the stimulation of the vasoconstrictor neurohumoral systems, compensatory vasodilatory/natriuretic systems are also activated in CHF, serving to counterbalance the actions of the opposing vasoconstrictor systems. Among these vasodilatory/natriuretic agents, those particularly studied in both patients and animals with heart failure are the natriuretic peptides, primarily atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and the nitric oxide (NO) system [16, 17] (Figure 1). However, the lusitropic, antihypertrophic, and natriuretic effects of ANP and BNP are significantly attenuated in CHF despite a considerable apparent increase in plasma concentrations [16, 17]. The imbalance between the antinatriuretic vasoconstrictor systems and natriuretic vasodilatory mechanisms in favor of the former leads to avid Na^+ and water retention (Figure 1(b)). Thus, chronic CHF entails a complex interaction between the heart and the kidneys that represents the pathophysiological basis for a new clinical entity called the cardiorenal syndrome [15, 18]. Worsening of renal function is frequently observed in patients hospitalized for acute decompensated heart failure (ADHF) at the time of admission [18]. The ability to sustain filtration and tubular functions of the kidneys during therapeutic interventions in patients with ADHF is vital to successful alleviation of congestion. Therefore, understanding the mechanisms involved in the deterioration of renal function in this setting may allow targeting therapies that protect the kidneys and improve clinical outcomes [18].

Most ADHF hospitalizations stem from congestion in patients refractory to oral diuretics [19–21]. Despite use of intravenous diuretics in the overwhelming majority of these patients, the average hospitalization for ADHF is 4.3 days, with 42% of the patients discharged with unresolved symptoms, 50% losing ≤5 pounds, and 20% gaining weight during the hospitalization [19]. The unresolved congestion likely contributes to high readmission rates and mortality among ADHF subjects. Specifically, the development of worsening renal function in this setting has been consistently associated with greater short- and long-term all-cause and cardiovascular mortality [22–26] and with accelerated progression to more advanced kidney disease [27]. The pathophysiology of kidney dysfunction in evolved CHF is complex. Classical mechanisms include extrarenal hemodynamic changes such as low cardiac output and venous congestion, neurohormonal activation and release of vasoactive substances resulting in low renal perfusion, intrarenal microvascular and cellular dysregulation, and oxidative stress [18, 28, 29]. However,

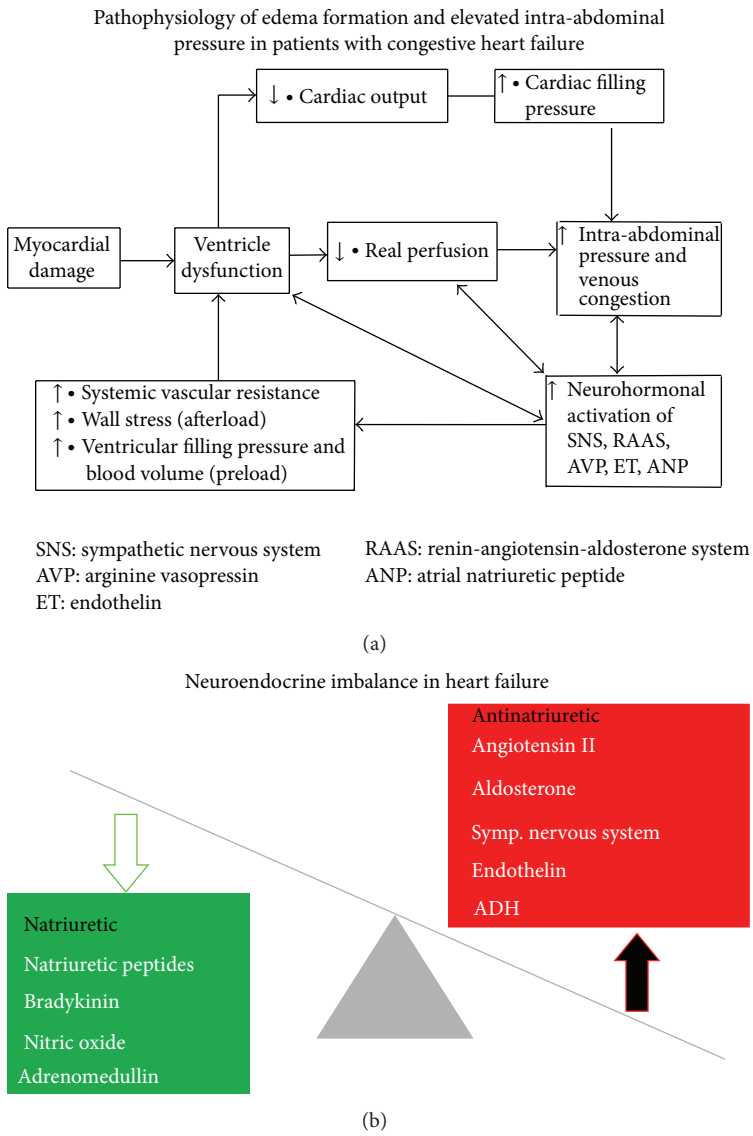

Figure 1: (a) Pathophysiology of edema formation and elevated intra-abdominal pressure in patients with congestive heart failure and (b) imbalance between natriuretic and antinatriuretic neurohormonal systems in congestive heart failure, in favor of the former.

recent evidence suggests that the abdominal compartment might contribute significantly to renal dysfunction in ADHF [30]. Similarly, vigorous fluid overload and resultant visceral edema are a risk factor for increased IAP, which has increasingly been associated with acute kidney injury (AKI) in critically ill patients [2, 31]. The normal intra-abdominal pressure (IAP) ranges from 4 to 7 mmHg. However, in a study of 40 patients with ADHF, Mullens et al. reported that 24 (60%) of patients admitted with advanced heart failure had elevated IAP (≥8 mmHg) and 4 (10%) demonstrated intra-abdominal hypertension (IAP > 12 mmHg) [32]. In patients with evolved heart failure, already small increases in IAP, in the range of 8 to 12 mmHg, are associated with impaired renal function [32]. Patients with IAP ≥ 8 mmHg had higher serum creatinine levels (2.3 ± 1.0 mg% versus 1.5 ± 0.8 mg%) as compared with patients with normal IAP [32]. The mechanism underlying the elevated IAP-induced kidney dysfunction in patients with ADHF is not fully characterized. However, some of the adverse effects overlap with those of venous congestion. For instance, there is a direct compression of abdominal contents on the renal parenchyma and renal vein [2, 31]. This results in prominent reduction in renal plasma flow and elevation in renal parenchymal and renal vein pressures. Under normal physiological condition, the hydrostatic pressure in Bowman space is low (~10 mmHg) promoting glomerular filtration. However, elevated IAP increases the pressure in bowman space and proximal tubule resulting in reduced GFR [2, 33, 34]. Moreover, it has been shown that increased IAP was associated with activation of the RAAS [35], which is known for its deleterious effects on kidney function and renal hemodynamics. Specifically, angiotensin II via AT1 receptors exerts multiple direct intrarenal influences, including

renal vasoconstriction, stimulation of tubular epithelial Na^+ reabsorption, augmentation of tubular-glomerular feedback (TGF) sensitivity, modulation of pressure natriuresis, and stimulation of mitogenic pathways. Therefore activation of the RAAS during elevated IAP may contribute to the reduced GFR obtained in this setting.

Since higher IAP is characterized with worse impaired renal function, reduction of IAP resulted in improvement in renal function after medical therapy. In a small prospective study of diuretic resistant ADHF patients with mild intra-abdominal hypertension, Mullens et al. showed that ultrafiltration or paracentesis (if ascites was present) produced a significant reduction in IAP and serum creatinine with an increase in urine output [36], suggesting that IAH may be responsible for diuretics resistance. The improvement in kidney function following reduction of IAP could also be attributed to relief in venous return and enhanced cardiac output [2, 37–39].

Collectively, treating the signs and symptoms of heart failure while preserving or improving renal function is a crucial therapeutic goal. This could be achieved at least partially by reducing IAP, which without a doubt contributes to kidney dysfunction in advanced CHF.

3. Hepatorenal Syndrome

Avid Na^+ and water retention are very common in cirrhosis and may lead to ascites, a common complication of this disease and a major cause of morbidity and mortality, with the occurrence of spontaneous bacterial peritonitis, variceal bleeding, and development of the hepatorenal syndrome [40–42]. In CHF and cirrhosis with ascites, the primary disturbance leading to Na^+ retention does not originate within the kidney, but from extrarenal mechanisms that regulate renal Na^+ and water handling.

Several formulations have been proposed over the years to explain the mechanism(s) by which patients with cirrhosis develop positive Na^+ balance and ascites formation. Two major theories put forward to explain the mechanisms of Na^+ and water retention in cirrhosis are the "overflow" and the "underfilling" theories of ascites formation [43]. While the occurrence of primary renal Na^+ and water retention and plasma volume expansion prior to ascites formation was favored by the "overflow" hypothesis, the classical "underfilling" theory posits that ascites formation causes hypovolemia that further initiated secondary renal Na^+ and water retention [44]. The importance of NO as a cardinal player in the hemodynamic abnormalities that mediate vasodilation and salt and water retention in cirrhosis became increasingly evident [45]. Decreases in RBF and GFR are among the most common pathophysiological alterations in clinical and experimental cirrhosis [46, 47]. Kidney hypoperfusion in decompensated hepatic failure is attributed to intense renal vasoconstriction caused by imbalance between the vasodilatory/diuretic mechanisms and vasconstrictory retaining system in favor of the latter [44]. The increase in Na^+ and water retention along enhanced permeability of the abdominal capillaries contributes to the elevation in IAP. Increased IAP in liver disease aggravates the impaired kidney function. This concept is further supported by the finding that reduction in IAP from 22 mmHg to 10 mmHg following the placement of LeVeen shunt resulted in improvement of kidney function at the excretory and hemodynamic levels [48]. Umgelter et al. [49] have shown that the improvement in kidney function in patients with hepatorenal and tense ascites following reduction of IAP via paracentesis and albumin substitution stems from enhanced renal blood flow as reflected by decreasing renal resistive index in Doppler ultrasound. Collectively, cirrhotic patients with ascites display an exaggerated renal vulnerability to increased IAP. Relief of the latter results in prompt reversal of kidney dysfunction.

4. Pneumoperitoneum and Kidney Function

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]. Moreover, laparoscopic donor nephrectomy has the potential to increase the number of living kidney donations by reducing donor morbidity and therefore lower the threshold of donating a kidney [4]. However, laparoscopic procedure requires induction of pneumoperitoneum, an increased IAP, which adversely affects kidney function [3]. For instance, pneumoperitoneum at a pressure above 10 mmHg has been shown to produce transient oliguria and deterioration in glomerular filtration rate (GFR) [2, 50–53]. Likewise, most of the studies identified a decrease in renal blood flow (RBF) and renal cortical perfusion [2, 54–60]. Elevated IAP secondary to pneumoperitoneum (15–20 mmHg) causes significant renal hypoxia in association with decreased RBF [61]. The most prominent consequence of pneumoperitoneum is transient oliguria [2]. Despite much research in this field, the systemic physiologic consequences of CO_2 pneumoperitoneum and the mechanisms underlying its adverse effects on renal excretory function and hemodynamics are not fully understood. Nevertheless, it is well hypothesized that pneumoperitoneum-induced renal dysfunction is a multifactorial phenomenon. For instance, the severity of the reduction in renal function following pneumoperitoneum is affected by the level of IAP [57], baseline volume status [59], degree of hypercarbia [62], positioning [57], and individual hemodynamic and renal reserve. Contradictory results have been reported in studies of cardiac output and release of vasopressin and endothelin in combination with pneumoperitoneum [63–66], whereas compression of the urethra has now been ruled out as a factor contributing to the oliguria [52, 53, 60]. Additional factors that may affect renal function during pneumoperitoneum include direct compression of the renal parenchyma and renal vein [54, 67], increased resistance in the renal vasculature [68], neurohormonal responses due to increases in hormones release such as vasopressin, endothelin, hormones of the renin-angiotensin-aldosterone system (RAAS), and catecholamines [69], and, to a lesser extent, the negative effects of absorbed CO_2 on cardiac contractility [67]. In the last few years, there is an increasing body of evidence, mainly from animal studies, that the pneumoperitoneum-induced decrease in splanchnic perfusion is associated with

oxidative stress. The contribution of pneumoperitoneum-associated oxidative stress to the pathogenesis of kidney dysfunction during this clinical procedure is still awaiting further research.

Although the transient renal dysfunction during laparoscopy has not been shown to have any permanent effects on the donor [56, 70], concerns have been raised that these negative renal effects may predispose to altered allograft function in the recipient [71].

Therefore, some suggestions were offered to overcome the negative renal effects of pneumoperitoneum such as avoidance of treatment inhibiting the RAAS and aggressive hydration [72, 73]. Preconditioning consisting of 10 min of pneumoperitoneum followed by 10 min of deflation decreases the oxidative stress induced by sustained pneumoperitoneum in the plasma, liver, and kidney and other organs [74]. Nevertheless, the precise consequences of pneumoperitoneum on renal perfusion and function require further studies, especially developing new approaches to minimize the adverse effects of the laparoscopic surgical procedure.

Experimental evidence has accumulated in recent years suggesting that locally produced vasoactive substances, such as nitric oxide (NO), play a fundamental role in the regulation of systemic and intrarenal hemodynamics, pressure natriuresis, release of sympathetic neurotransmitters and renin, and tubular solute and water transport [2, 75, 76]. The involvement of NO system in the adverse effects of pneumoperitoneum on renal perfusion and function was studied by our group where we have used an experimental model of pneumoperitoneum. The latter was induced via a small incision in the lower third between the xiphoid and pubis of normal rats, through which a regular Veress needle was inserted into the abdominal cavity. A pneumoperitoneum of 7 or 14 mmHg was established with CO_2 gas supply to maintain IAP at the desired level using a special insufflator connected to the Veress needle. The muscle layer and skin layer of the abdominal wall were closed separately by silk sutures in an airtight manner.

As depicted in Figures 2(a) and 2(b), there were no significant changes in GFR and RPF during 7 mmHg insufflation. However, substantial reductions in these parameters were observed when 14 mmHg was applied: GFR decreased from 1.6±0.12 to 0.9±0.09 mL/min and RPF from 8.15±0.87 to 3.8±0.16 mL/min, $P < 0.05$. When the animals were pretreated with NTG, the adverse effects of IAP of 14 mmHg on GFR and RPF were improved by ~40% (Figures 2(c) and 2(d)). In line with this notion, pretreatment with L-NAME remarkably aggravated the hypoperfusion/hypofiltration associated with pneumoperitoneum (Figures 2(e) and 2(f)). These results clearly show that elevated IAP pressure to 14, but not 7 mmHg, decreased kidney function and perfusion. These effects are most likely related to impairment of NO system and could be partially ameliorated by pretreatment with nitroglycerine. Support for this concept came from experimental study in swine, where some of the animals were subject to insufflation with CO_2 alone or CO_2 containing fixed amounts of ethyl nitrite (1–300 ppm) [79]. Insufflation with CO_2 alone produced declines in splanchnic organ blood flows and it reduced circulating levels of S-nitrosohemoglobin (i.e., nitric oxide bioactivity); these reductions were obviated by ethyl nitrite. Moreover, preservation of kidney blood flow with ethyl nitrite kept serum creatinine and blood urea nitrogen concentrations constant whereas in the CO_2 alone group both increased as kidney blood flow declined. The data indicate ethyl nitrite can effectively attenuate insufflation-induced decreases in organ blood flow and nitric oxide bioactivity leading to reductions in markers of acute tissue injury. This simple intervention provides a method for controlling a major source of laparoscopic-related morbidity and mortality: tissue ischemia and altered postoperative organ function [79].

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 cardiovascular and metabolic diseases, including diabetes, heart failure, jaundice, and cirrhosis. Interestingly, decreases in RBF and GFR are among the most common pathophysiological alterations in clinical and experimental CHF [9]. Previously, we demonstrated that rats with aortocaval fistula (ACF), an experimental model of volume-overload CHF, closely mimic the neurohumoral, renal, and cardiac manifestations of patients with CHF [80, 81]. These include increased activity of neurohormonal systems such as renin angiotensin aldosterone system (RAAS), sympathetic nervous system (SNS), antidiuretic hormone (ADH), and atrial natriuretic peptide (ANP); decreases in RBF and GFR with sodium retention; and a marked degree of cardiac hypertrophy [80–82].

The importance of locally released vasoactive substances in the regulation of RBF and systemic hemodynamics, in particular the endothelial nitric oxide (NO) synthase (eNOS) pathway under normal conditions and during CHF, has been extensively studied [83, 84]. Several studies have clearly documented an impaired endothelium-dependent vascular response in CHF, such as a markedly attenuated response to acetylcholine [12, 85]. Since the adverse renal and hemodynamic consequences of increased IAP were studied extensively under normal conditions [3, 4], but not in the presence of background diseases such as CHF. We examined whether rats with CHF of various severities are vulnerable to the adverse renal effects of increased IAP and the potential involvement of the NO system in this susceptibility. Basal renal function and hemodynamics were lower in CHF rats in correlation with disease severity. Decompensated CHF rats that were subjected to 10 and 14 mmHg exhibited aggravated declines in urine flow, urinary sodium excretion, GFR, and RPF (Figure 3). In contrast, no adverse renal effects were observed in compensated CHF under identical IAP conditions. When compensated CHF rats were pretreated with the NO synthase inhibitor L-NAME, they exhibited worsened renal function in response to pneumoperitoneum (Figure 4). These findings indicate that decompensated CHF rats are susceptible to the adverse renal effects of pneumoperitoneum, a phenomenon which may involve alterations in the renal NO/cGMP system. To explore in depth this possibility we examined whether phosphodiesterase 5 (PDE5) inhibition

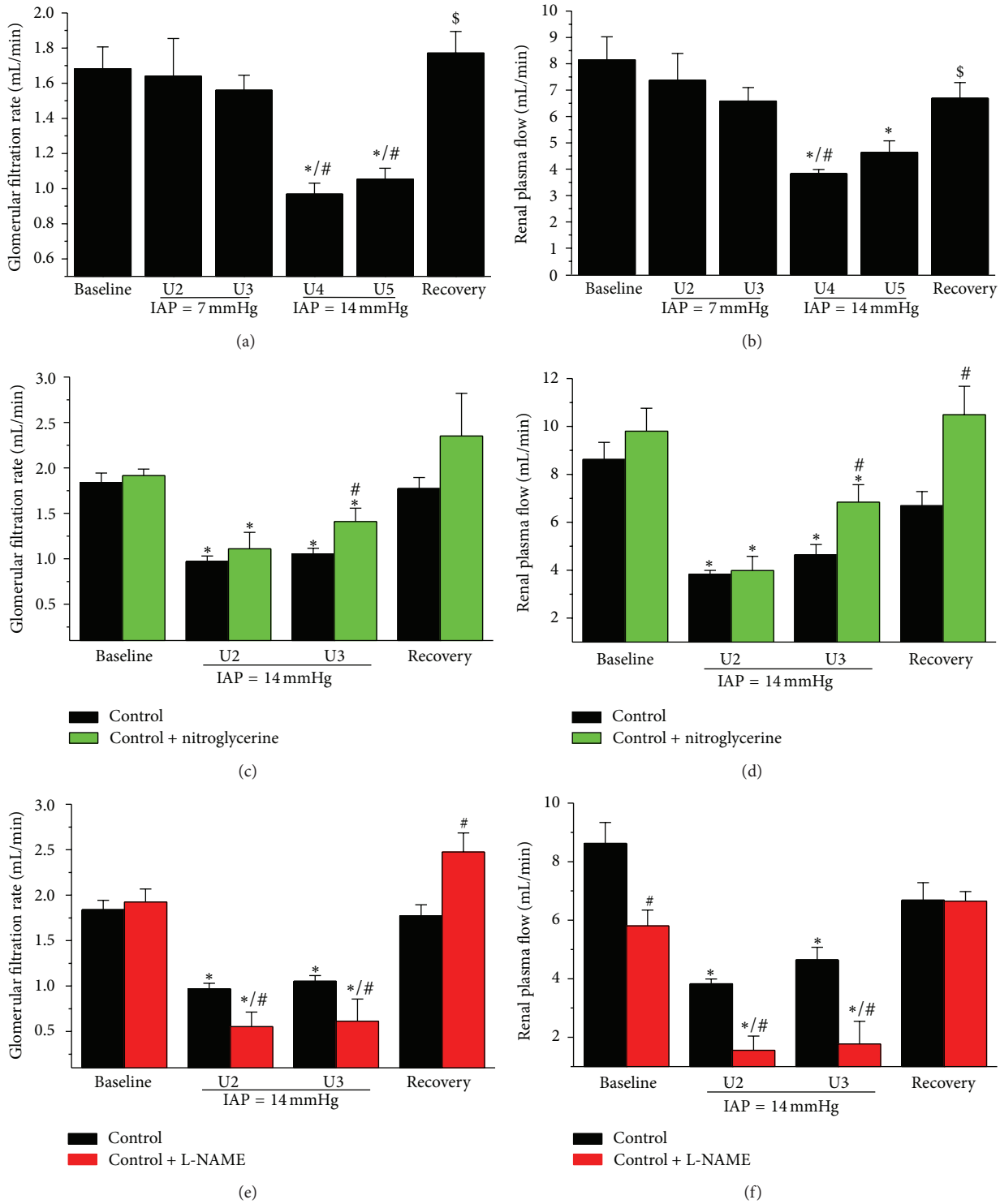

Figure 2: Effects of 7 and 14 mmHg insufflations with CO_2 on glomerular filtration rate (GFR) (a) and renal plasma flow (RPF) (b). Note that only IAP of 14 mmHg was effective in attenuating IAP-induced renal hemodynamics alterations. (∗) $P < 0.05$ versus baseline, (#) $P < 0.05$ versus U2-7 mmHg, ($) $P < 0.05$ versus U3-7 mmHg, Effects of nitroglycerine on pneumoperitoneum- (IAP = 14 mmHg) induced renal hemodynamic alterations. Glomerular filtration rate (GFR) (c) and renal plasma flow (RPF) (d) in nitroglycerine treated rats as compared with untreated animals (controls). Note that nitroglycerine was effective in attenuating the pneumoperitoneum-induced reduction in renal hemodynamic alterations. (∗) $P < 0.05$ versus baseline; (#) $P < 0.05$ versus untreated pneumoperitoneum. Effects of L-NAME on pneumoperitoneum- (IAP = 14 mmHg) induced renal hemodynamic alterations. Glomerular filtration rate (GFR) (e) and renal plasma flow (RPF) (f) in L-NAME treated rats as compared with untreated animals (controls). Note that L-NAME treatment aggravated the pneumoperitoneum-induced reductions in GFR and RPF. (∗) $P < 0.05$ versus baseline; (#) $P < 0.05$ versus untreated pneumoperitoneum [5, 6].

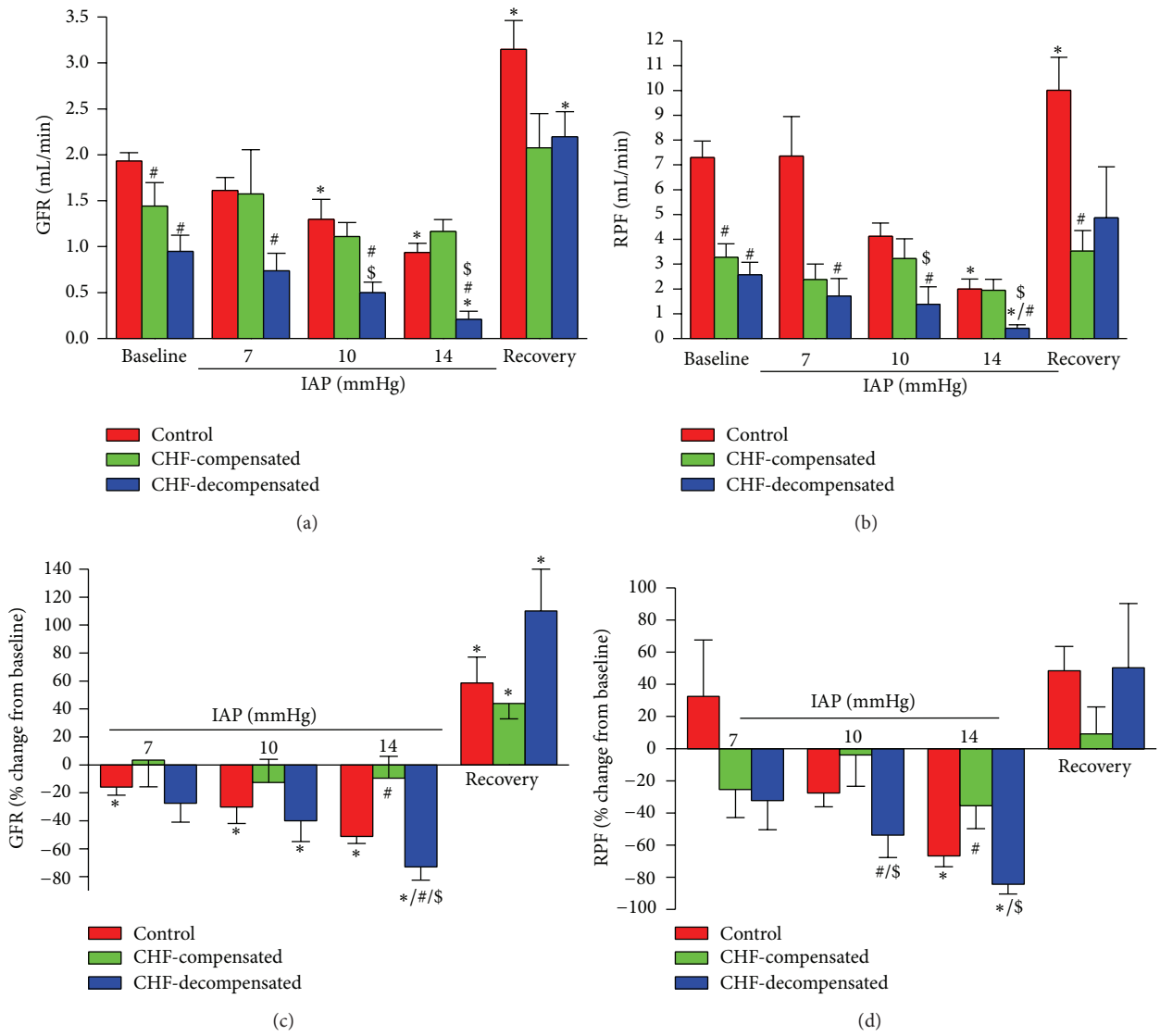

Figure 3: Effects of 7, 10, and 14 mmHg insufflations on (a) glomerular filtration rate (GFR) and (b) percentage change in GFR from baseline. (c) Renal plasma flow (RPF) and (d) percentage change in RPF from baseline in rats with compensated and decompensated CHF and sham controls. (∗) $P < 0.05$ versus baseline; (#) $P < 0.05$ versus sham. ($) $P < 0.05$ versus compensated [77].

via Tadalafil protects against the adverse renal effects of IAP in rats with congestive heart failure. Decompensated CHF rats induced by ACF that were subjected to 10 and 14 mmHg exhibited exaggerated declines in kidney function and renal hemodynamics as compared with sham controls (Figure 5). Pretreatment of decompensated CHF rats with Tadalafil ameliorated the adverse renal effects of high IAP, supporting a therapeutic role for PDE inhibition during laparoscopic surgery in decompensated CHF.

Similar to rats with ACF, basal renal function and MAP were lower in rats with MI compared with sham controls. Application of IAP of 7, 10, or 14 mmHg in these rats decreased renal hemodynamics (Figure 6). The most profound adverse renal effect was obtained when IAP of 14 mmHg was applied (Figure 6). The magnitudes of these deleterious effects were more severe than those obtained in sham controls, but similar to those observed in rats with decompensated CHF induced by ACF. Administration of Tadalafil to rats with MI prior to the induction of IAP protected the kidney from adverse consequences of high IAP. Specifically, PDE-I completely abolished the reduction in GFR and RPF induced by IAP of 14 mmHg (Figure 6).

It should be emphasized that not in all clinical settings increased IAP caused renal dysfunction. For instance, slightly elevated IAP may improve kidney function due to enhanced venous return and subsequently increase in CO in association with renal hyperperfusion. Most recently, we investigated the renal effects of pneumoperitoneum in rats with acute jaundice and cirrhotic animals. Interestingly, decreases in RBF and GFR are among the most common pathophysiological alterations in clinical and experimental jaundice and cirrhosis [46, 47, 86], suggesting that these clinical conditions may

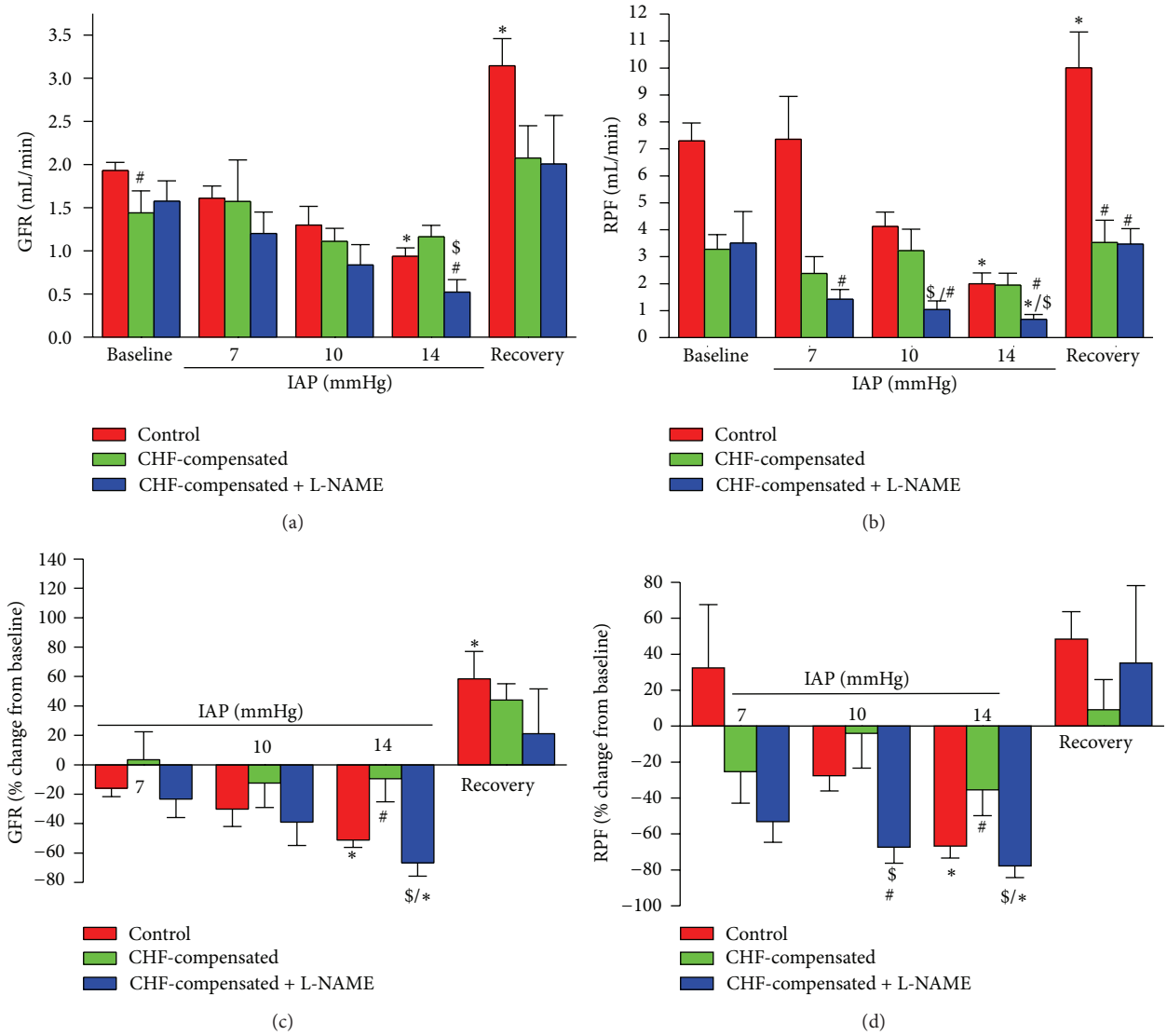

Figure 4: Effects of 7, 10, and 14 mmHg insufflations on (a) glomerular filtration rate (GFR) and (b) percentage change in GFR from baseline. (c) Renal plasma flow (RPF) and (d) percentage change in RPF from baseline in rats with compensated CHF pretreated with L-NAME. (∗) $P < 0.05$ versus baseline; (#) $P < 0.05$ versus sham. ($) $P < 0.05$ versus compensated [77].

display an exaggerated renal vulnerability to increased IAP. In this context, Bostanci et al. [87] 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 AST, ALT, and total bilirubin values. However, this report did not refer to the renal effects of increased IAP in rats with obstructive jaundice. Therefore, our 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. 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 kidney excretory function and renal hemodynamics (GFR, RPF) (Figure 7). Similarly, when identical IAP conditions were applied to cirrhotic rats, no deleterious changes in these parameters were observed (Figure 7). These results are at odds with the deleterious consequences of elevated IAP observed in liver disease with ascites. The base for these differences between clinical situation and experimental models requires further investigation.

5. Additional Clinical Settings

Obesity. Obesity, a very prevalent health problem, is associated with increased morbidity and mortality, especially due to cardiovascular consequences [88]. Additionally, obesity contributes to the development of other comorbidities

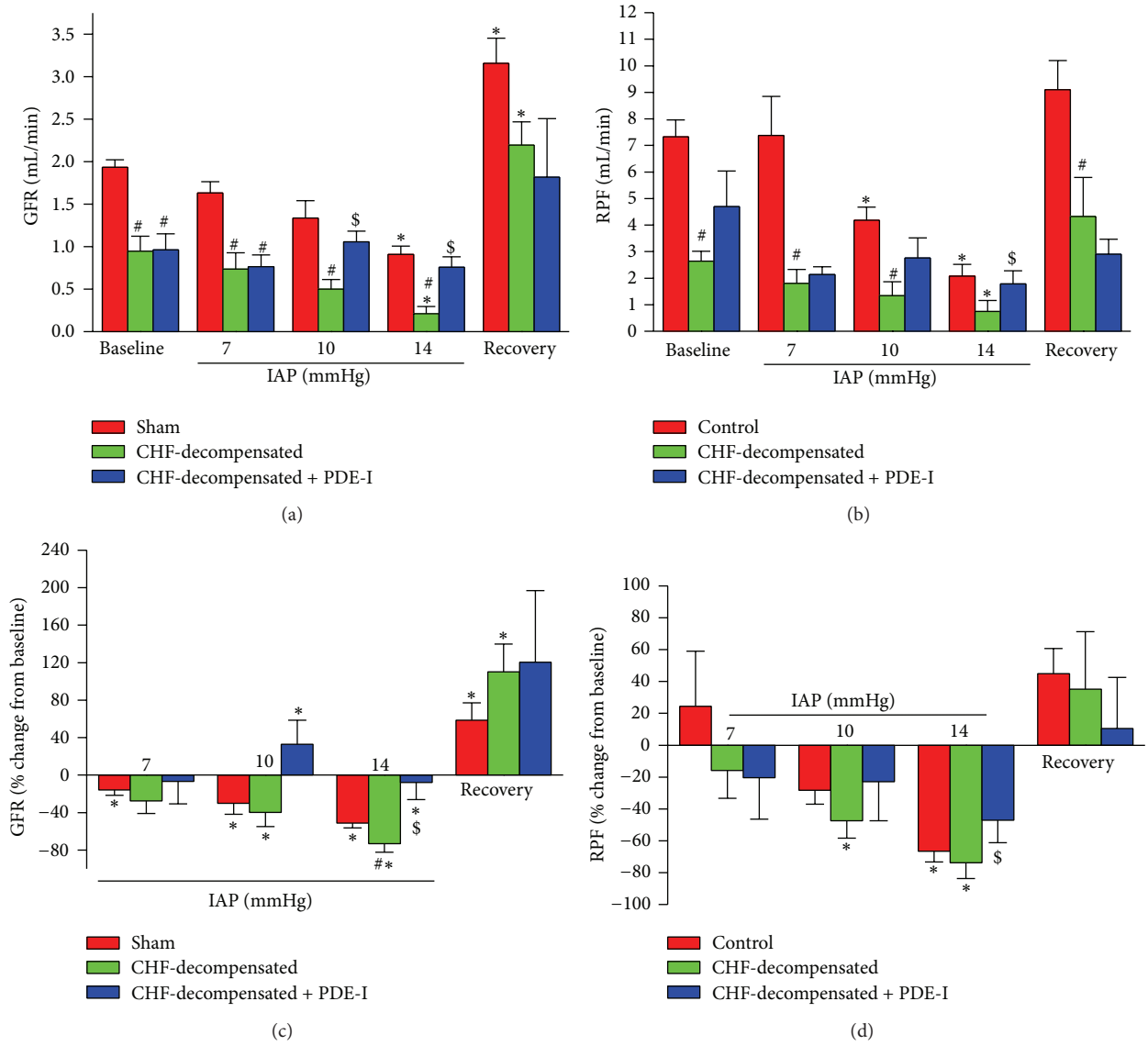

Figure 5: Effects of 7, 10, and 14 mmHg insufflations with CO_2 on (a) glomerular filtration rate (GFR), (b) percentage change in GFR from baseline, (c) renal plasma flow (RPF), and (d) percentage change in RPF from baseline, in sham controls with or without Tadalafil pretreatment and in rats with untreated decompensated CHF and animals with decompensated CHF pretreated with Tadalafil. (∗) $P < 0.05$ versus baseline of each group; (#) $P < 0.05$ versus sham controls [77].

including diabetes, hypertension, and hyperlipidemia, which are important risk factors for progressive chronic kidney disease (CKD) [89–91]. However, morbid obesity is also associated with increased intra-abdominal pressure (IAP) [92, 93]. In this context, Lambert et al. [92] have reported that the mean IAP in the morbidly obese patients (mean BMI $55 \pm 2\,kg/m^2$) was $12 \pm 0.8\,cmH_2O$, as compared to controls (IAP $= 0 \pm 2\,cmH_2O$). Does the increased IAP of morbid obesity contribute to kidney dysfunction? Such IAP is known to induce adverse renal effects as shown by us in experimental models of pneumoperitoneum [5, 6]. Moreover, kidney function at both the renal hemodynamic level and proteinuria has been improved in morbidly obese patients who underwent bariatric surgery, a useful way of losing weight in these subjects [94–96]. The mechanisms underlying the beneficial renal effects of bariatric surgery in severely obese patients are not known; however it could be attributed to improvement in glucose metabolism, cardiac function, hypertension, and probably reduction of IAP following the surgical procedure.

Pregnancy. The normal values of IAP during pregnancy, in either healthy or complicated pregnancies, are poorly studied. However, transrectal measurement of IAP was higher in pregnant women compared to nonpregnant individuals, and values increased throughout the course of pregnancy. Most

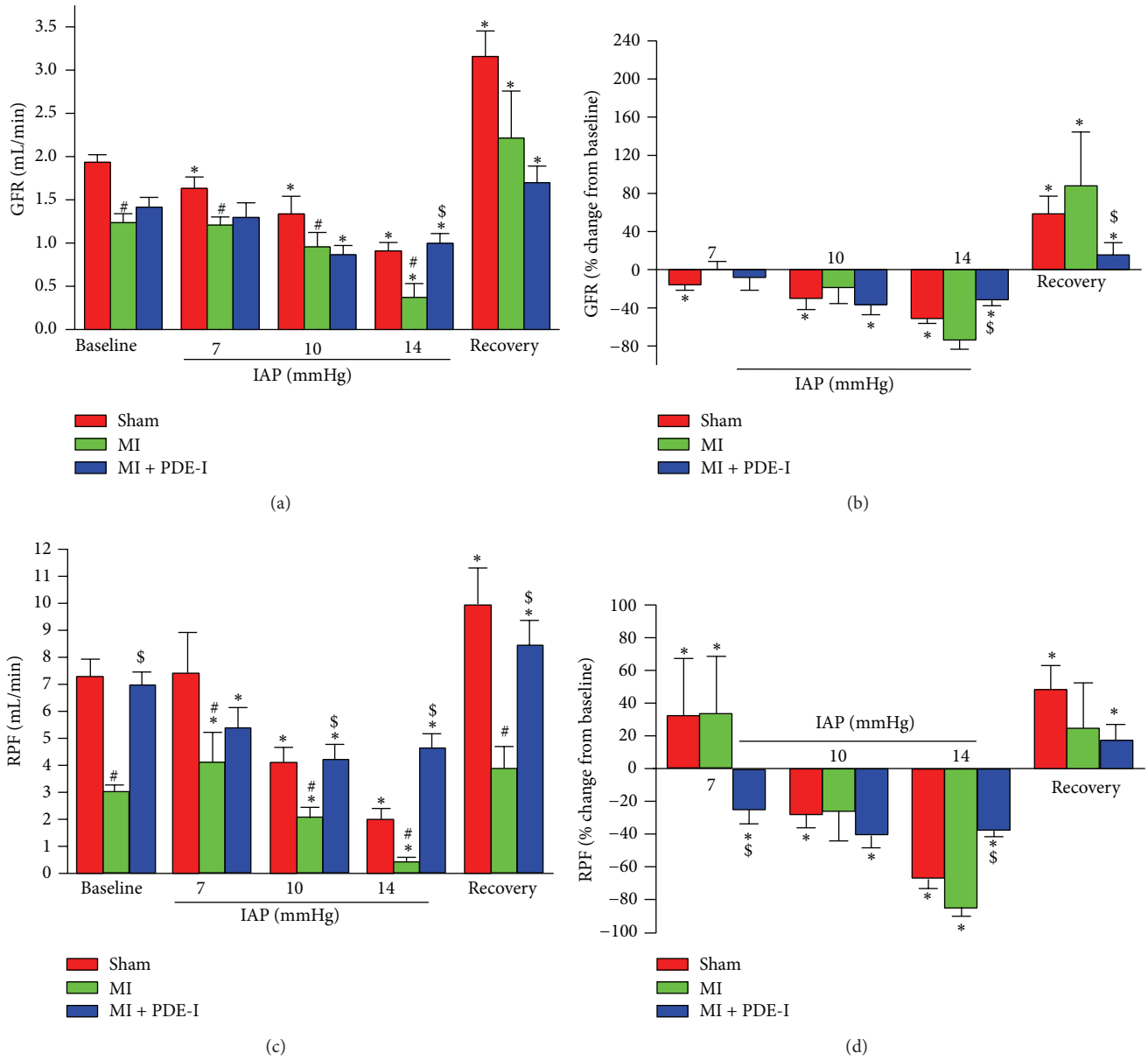

Figure 6: Effects of 7, 10, and 14 mmHg insufflations with CO_2 on (a) glomerular filtration rate (GFR), (b) percentage change in GFR from baseline, (c) renal plasma flow (RPF), and (d) percentage change in RPF from baseline, in sham controls with or without Tadalafil pretreatment and in rats with MI with and without Tadalafil pretreatment. (∗) $P < 0.05$ versus baseline of each group, (#) $P < 0.05$ versus sham controls, and ($) $P < 0.05$ versus untreated decompensated CHF.

recently, Staelens et al. [97] have demonstrated that IAP is increased in the range of intra-abdominal hypertension (>12 mmHg) in pregnant women and decreased to normal values after delivery. Moreover, few case reports have shown elevated IAP in preeclampsia to abdominal compartment syndrome range (>20 mmHg), suggesting a potential relationship between exaggerated IAP and maternal diseases such as preeclampsia-eclampsia, proteinuria, and liver complications and its potential impact on fetal development [98–101]. These findings underlie the importance of including IAP measurement in the differential diagnosis in pregnant women.

6. Conclusion

Elevated intra-abdominal pressure is a common phenomenon, which can occur in many clinical settings including decompensated heart failure, hepatorenal syndrome, and laparoscopic surgery. Although it has deleterious effects on various physiological systems, the kidney seems to be the most susceptible organ to the adverse consequences of increased IAP. IAP-induced kidney dysfunction is evident by oliguria and renal hypoperfusion. The mechanisms underlying the vulnerability of the kidney to elevated IAP are not fully known, but it could be attributed to hemodynamic,

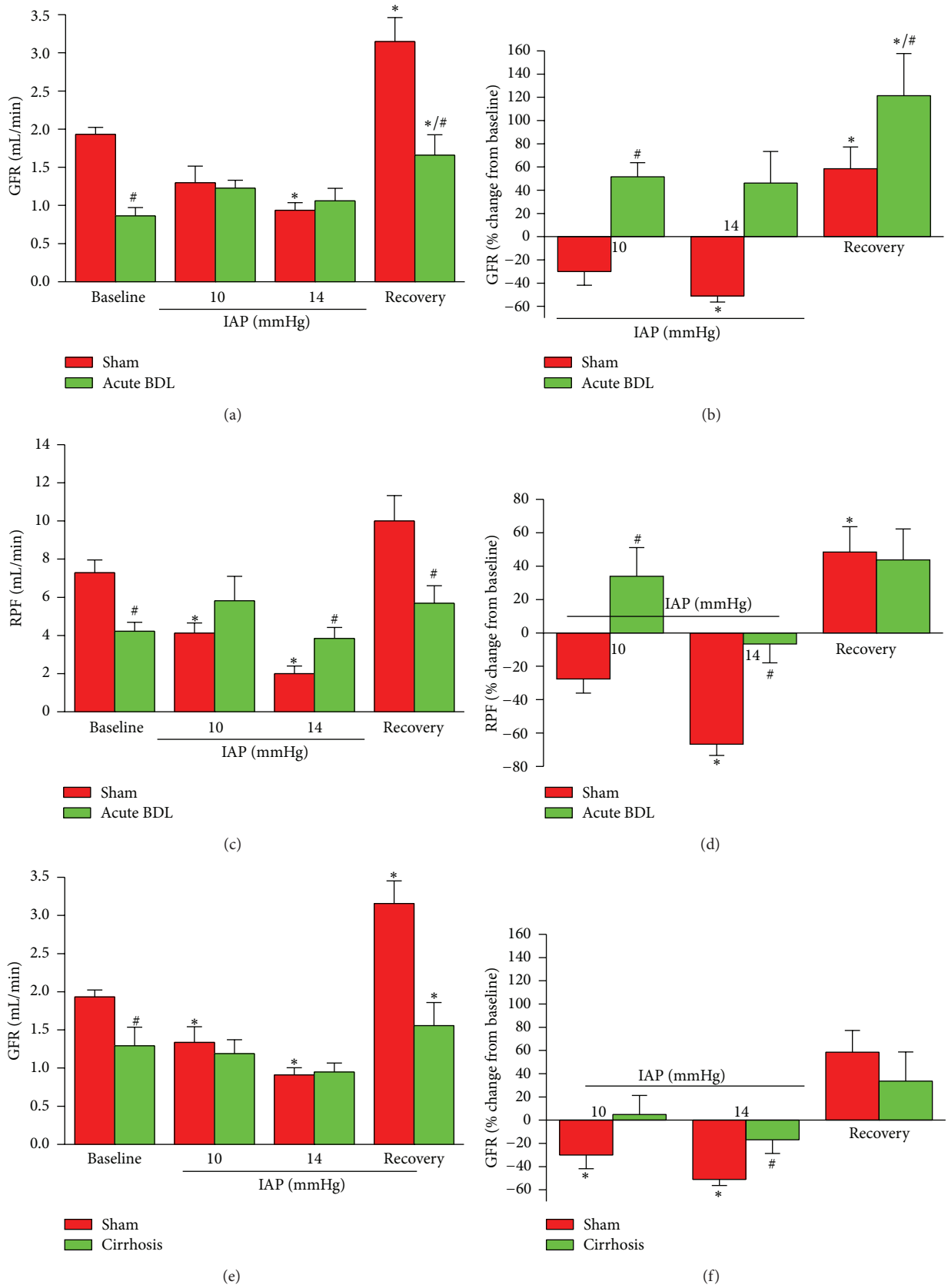

Figure 7: Continued.

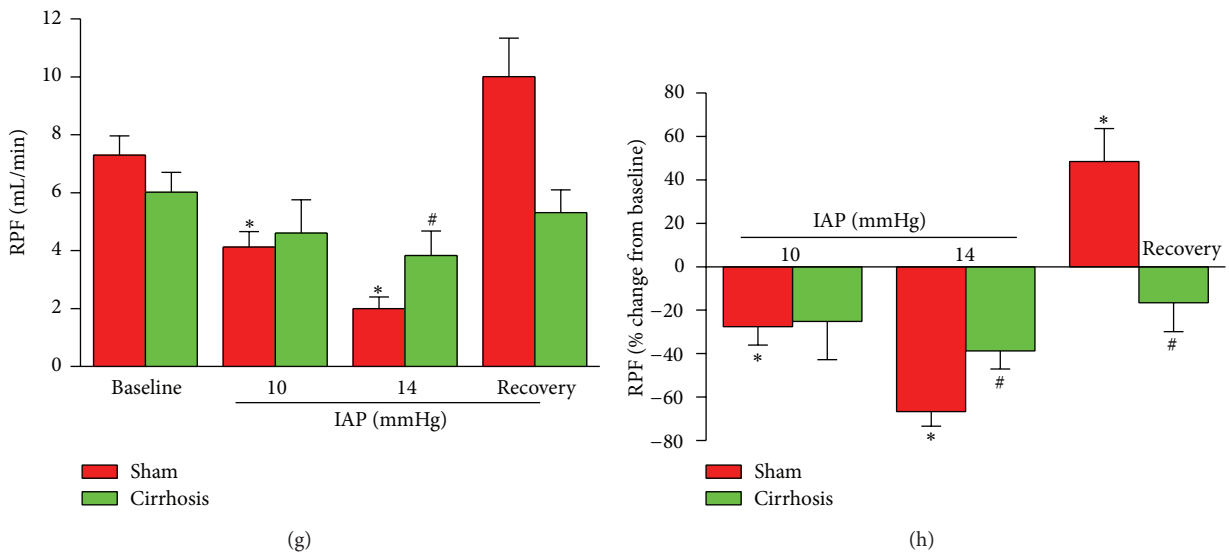

Figure 7: Effects of 10 and 14 mmHg insufflations on (a) glomerular filtration rate (GFR), (b) percentage change in GFR from baseline, (c) renal plasma flow (RPF), and (d) percentage change in RPF from baseline, in rats with acute bile duct ligation (BDL) and sham controls. (∗) $P < 0.05$ versus baseline of each group; (#) $P < 0.05$ versus sham controls. Effects of 10 and 14 mmHg insufflations on (e) glomerular filtration rate (GFR), (f) percentage change in GFR from baseline, (g) renal plasma flow (RPF), and (h) 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 [78].

respiratory, and metabolic alterations. Due to the poor understanding of this phenomenon, no beneficial therapeutic approaches are available to encounter the dangerous, even fatal, complications of increased IAP.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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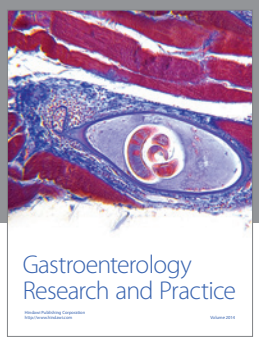

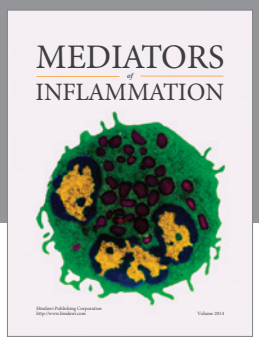

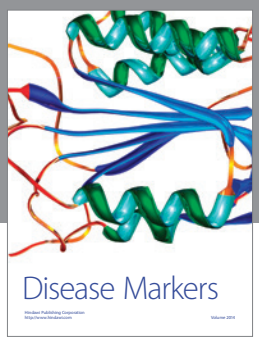

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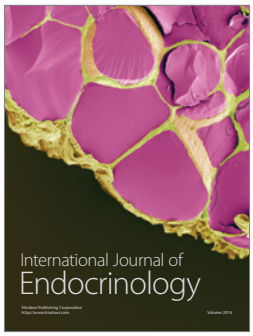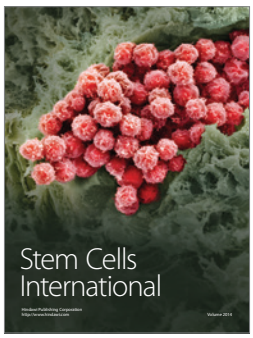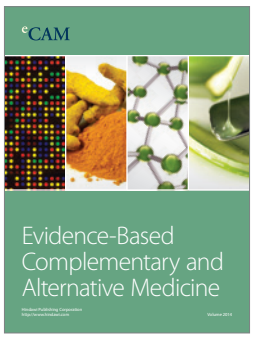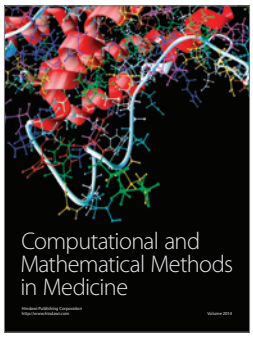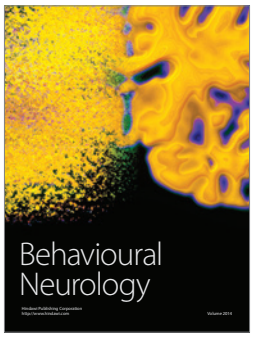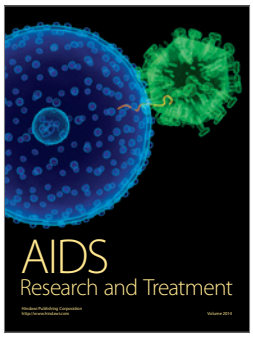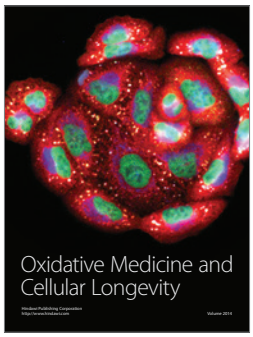
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