

Renal Dysfunction Associated with Intra-abdominal Hypertension and the Abdominal Compartment Syndrome

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ABSTRACT

Once considered mostly a postsurgical condition, intra-abdominal hypertension (IAH) and the abdominal compartment syndrome (ACS) are now thought to increase morbidity and mortality in many patients receiving medical or surgical intensive care. Animal data and human observational studies indicate that oliguria and acute kidney injury are early and frequent consequences of IAH/ACS and can be present at relatively low levels of intra-abdominal pressure (IAP). Among medical patients at particular risk are those with septic shock and severe acute pancreatitis, but the adverse effects of IAH may also be seen in cardiorenal and hepatorenal syndromes. Factors predisposing to IAH/ACS include sepsis, large volume fluid resuscitation, polytransfusion, mechanical ventilation with high intrathoracic pressure, and acidosis, among others. Transduction of bladder pressure is the gold standard for measuring intra-abdominal pressure, and several nonsurgical methods can help reduce IAP. The role of renal replacement therapy for volume management is not well defined but may be beneficial in some cases. IAH/ACS is an important possible cause of acute renal failure in critically ill patients and screening may benefit those at increased risk.

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The deleterious effects of high intra-abdominal pressure (IAP) on the function of kidneys and other organs have been known for over a century.¹ In recent years both intra-abdominal hypertension (IAH) and the abdominal compartment syndrome (ACS)—the severe, advanced stage of IAH characterized by organ system failure—have increasingly been associated with morbidity and mortality in critically ill patients.²

Oliguria and renal dysfunction are among the earliest signs of increasing IAP.^{3,4} Although multiorgan failure is also well recognized in ACS, what is much less appreciated and what some recent data suggest is that kidneys may be particularly at risk with much lower lev-

els of IAP than would be seen in fully established ACS. These findings indicate that acute renal failure (ARF) resulting, at least in part, from lesser degrees of IAH may be present in a much larger population of critically ill patients than believed previously.^{5–9}

DEFINITIONS

IAH/ACS appears over a wide range of persistent IAP with large variability in the manner of clinical presentation. The lack of standardized definitions has hampered efforts to study this problem, and recognizing this, the World Society for Abdominal Compartment Syndrome (WSACS), an

international multispecialty consortium, published consensus definitions of IAH/ACS in 2006 based on current evidence and expert opinion.² IAP in critically ill adults ranges from 4 to 7 mmHg. IAH is defined as sustained or repeated pathologic elevation of IAP ≥ 12 mmHg. Sustained elevation of IAP of >20 mmHg associated with new organ dysfunction defines ACS.

Abdominal perfusion pressure (APP) is also a novel, clinically measurable parameter that has been introduced to explain the circulatory compromise in the abdominal cavity in the presence of IAH/ACS.² APP, similar to the familiar concept of cerebral perfusion pressure, is defined as the difference between the mean arterial pressure (MAP) and the IAP, and implies that as the IAP rises, the perfusion of organs or vessels in or near the abdomen falls even in the absence of a drop in MAP. APP is an independent predictor of adverse outcomes in patients with IAH/ACS. In a retrospective study of 144 surgical patients treated for IAH, abdominal perfusion pressure was statistically superior to both MAP and

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IAP in predicting patient survival from IAH/ACS with area under the curve representing receiver operating characteristics significantly greater than that of both MAP and IAP ($P < 0.001$).¹⁰ Maintenance of an APP of at least 50 mmHg seems to maximize both the sensitivity (76%) and specificity (57%) of APP as a predictor of patient survival.

Several studies describe predisposing conditions and risk factors for developing IAH.¹¹ In addition to trauma, major burns, and abdominal surgery several other factors are extremely common in critically ill patients. These include situations that lead to diminished abdominal wall compliance (mechanical ventilation, obesity, and elevation of the head of bed), increased intra- and extraluminal abdominal contents (ileus and ascites), and factors that increase capillary permeability and interstitial fluid accumulation (acidosis, sepsis, large volume resuscitation, polytransfusion, pancreatitis, and coagulopathy).

PREVALENCE AND EFFECT ON OUTCOMES

Studies of mixed populations in medical and surgical intensive care units (ICUs) show a prevalence of IAH and ACS of up to 64 and 12%, respectively.⁸ The highest prevalence of both IAH and ACS is found in two critically ill medical populations. In a prospective study of 40 patients with septic shock who received >5 L of volume resuscitation in the first 24 hours, 34 patients (82.7%) developed IAH and 10 (25%) developed ACS.¹² Al-Bahrani *et al.* also reported that, in their cohort of patients with severe acute pancreatitis, more than half developed ACS.¹³

The development of IAH is associated with worse clinical outcome. In the largest study to date comprising 265 patients from 14 ICUs in 6 countries, Malbrain *et al.* found that IAH developing during an ICU stay is an independent predictor of mortality (RR = 1.85, 95% CI 1.12 to 3.06; $P = 0.01$).¹⁴ A large prospective observational study established IAH (defined as an IAP ≥ 18 mmHg) as an independent cause of renal impairment in

patients who were in an ICU after abdominal surgery with an odds ratio of 2.96 (95% CI 1.62 to 5.42; $P = 0.004$).¹⁵ Dalfino *et al.*⁶ prospectively investigated the relationship between IAH and ARF using RIFLE criteria¹⁶ in all patients admitted to a general ICU over a period of 6 months. After shock, IAH ($P = 0.002$) and low APP ($P = 0.046$) were the best predictive factors for developing ARF. Their analysis of receiver operating characteristics data indicate that an IAP cut-off value of 12 mmHg has the best sensitivity (91.3%) to specificity (67%) ratio for predicting the development of ARF. In another prospective cohort of 83 ICU patients,⁸ those with IAH have significantly higher mortality (53 *versus* 27%; $P = 0.02$) and higher incidence of renal dysfunction by Sequential Organ Failure Assessment renal subscore (58 *versus* 27%; $P = 0.006$). In addition, APP and IAH were independent predictors of mortality. Biancofiore *et al.*¹⁷ also report a higher incidence of ARF in patients after liver transplantation whose IAP is >25 mmHg compared with those with IAP <25 mmHg.

Some very intriguing recent data concerns the possible effect of elevated IAP on renal function in patients admitted with acute decompensated heart failure (ADHF). In a group of 40 patients with ADHF, those with elevated baseline IAP (≥ 8 mmHg) had higher serum creatinine levels (2.3 ± 1.0 *versus* 1.5 ± 0.8 mg/dl, $P = 0.009$) compared with those with normal IAP.⁹ The improvement in kidney function after intensive medical therapy did not correlate with hemodynamic improvements in cardiac index or left- and right-sided filling pressures, but did correlate with reduced IAP ($r = 0.77$, $P < 0.001$).

PATHOPHYSIOLOGY

Local and Systemic Effects

At higher levels of IAP, not only is there direct compression of abdominal contents but also pressure is transmitted to the thoracic cavity and has even been shown to cause elevation in the intracranial pressure.¹⁸ But more importantly,

there is compression of the intra-abdominal and intrathoracic blood vessels, resulting in compromise of microvascular blood flow.¹⁹ As IAP increases, intestinal and mesenteric vascular venous congestion, ischemia, and edema ensue because of diminished venous drainage.²⁰ This results in a vicious cycle that further increases IAP. For most patients, the critical IAP at which microcirculatory disturbance is observed is 10 to 15 mmHg.²

Effacement of the inferior vena cava (IVC) also causes reduction in venous return. As the duration and intensity of IAH increases, direct compression of heart, lungs, and aorta results in a variety of effects, including decreased cardiac output, potentially misleading elevations in central venous pressure and pulmonary arterial occlusion pressure, increased intrathoracic pressure, decreased chest wall compliance, and worsening atelectasis and hypoxia.¹⁹ Respiratory failure usually accompanies ACS but even at IAPs of approximately 16 mmHg, about a 50% reduction in pulmonary compliance can be seen.²¹ Because there is a concomitant increase in systemic vascular resistance,²² systemic arterial BP is often maintained despite significant reduction in cardiac output.

Renal Effects of Increased IAP

Oliguria in the presence of elevated intra-abdominal pressure was first reported by Wendt in 1876.¹ Animal studies in the 1920s and 1930s observed that oliguria commences at intrarenal pressures as low as 10 mmHg,²³ whereas animals become anuric with IAP of 30 mmHg.²⁴

In 1947, Bradley and Bradley published a seminal study of the renal effects of elevated IAP in humans.²⁵ Subjects underwent direct measurements of renal vein pressure, IVC pressure (as a surrogate marker for IAP), renal plasma flow, and glomerular filtration rates while the IAP was raised by external compression to approximately 20 mmHg. The effective renal plasma flow dropped, on average, by 24.4%, whereas the average drop in GFR was 27.5%. All patients became oliguric with an average reduction in urine flow of 57.4%. The absence of a

sudden increase in urine flow on release of pressure suggested that ureteral compression was unlikely the cause of oliguria; instead, elevation in renal vein pressure, which increased on average from 5.8 to 18.3 mmHg, was the likely cause of altered filtration. In a later animal model of renal failure in ACS, Harman *et al.*²⁶ showed that reversal of the accompanying reduction in cardiac output with volume expansion had little beneficial effect on renal function.

Although elevation of renal parenchymal and renal vein pressure had been suspected as the likely mechanisms of renal impairment in IAH/ACS, it was not clear how much, if at all, each contributed to the process. Doty *et al.* showed in pigs that isolated elevation of renal vein pressure to 30 mmHg results in a significant decrease in GFR from 26 to 8 ml/min with significant increase in serum aldosterone levels and plasma renin activity;²⁷ such changes were not seen with isolated elevation of intraparenchymal pressure.²⁸ However, recent studies in a 45-minute ischemia-reperfusion murine model demonstrate that preventing the rise in intracapsular pressure caused by interstitial edema, by making a small incision in renal capsule, attenuates the risk of functional renal impairment.²⁹ These findings suggest that although an isolated rise in parenchymal pressure may not be sufficient to cause renal dysfunction, it may contribute to the acute kidney injury caused by ischemic insult. Nephrosarcoma—severe interstitial edema of the kidney, causing physical compression and occlusion of tubules and blood vessels—has been proposed as a possible explanation of ARF seen in some patients with nephrotic syndrome from minimal change disease.³⁰ Interstitial edema, however, has been an inconsistent finding in biopsy series of patients suspected of having nephrosarcoma and there is lack of clinical data supporting this hypothesis.³¹

The postglomerular intrarenal vascular network is a low-pressure system. In 1983 Kon *et al.* reported in rats that hydrostatic pressure in the distal most peritubular capillaries averaged 8.1 ± 0.6 mmHg and under state of high renal per-

fusion 10.7 ± 0.7 mmHg.³² It is, therefore, not surprising that IAP of approximately 15 mmHg should lead to significant intrarenal venous congestion and impaired filtration rate.

Several other effects of IAH on renal function have been reported at higher ranges of IAP. Renal vascular resistance increases 555% (15 times the systemic vascular resistance) at IAPs of 20 mmHg.²⁶ In 1985, Barnes *et al.* demonstrated in dogs that renal artery blood flow diminishes in a linear fashion with increasing IAP to about 65% at 20 mmHg and about 50% at 30 mmHg.³³ This finding is consistent with the concept of APP described above. IAPs >20 mmHg also increase the circulating levels of a variety of inflammatory mediators.^{34,35}

It is plausible from the review of the myriad pathophysiological mechanisms described above that early in the course of IAH intrarenal vascular congestion due to elevated renal vein pressure may induce ARF. As the IAP approaches the range of ACS, additional factors—including reduction in cardiac output and elevated levels of catecholamines,³⁶ renin, angiotensin, and inflammatory cytokines—may also come into play, further worsening renal function.

Cardiorenal Syndrome

In a study of 145 patients with ADHF, Mullens *et al.* discovered that patients who develop worsening renal function have significantly higher central venous pressures (18 *versus* 12 mmHg; $P < 0.001$) than those that did not and venous congestion is a stronger predictor of worsening renal function than cardiac index.³⁷ In another study, even slight elevations in IAP were associated with reduced renal function.⁹ In the face of severe circulatory compromise with very low MAP, as is seen in ADHF, even slight elevations in IAP may lead to very low APP. Poor abdominal arterial perfusion, coupled with renal vein congestion from increased central venous pressure, may explain the sharp decline in urine output that is seen relatively early in the course of ADHF. These observations add IAH as a novel dimension to our evolving understanding of the pathophysiological mechanisms underlying cardiorenal syndrome.³⁸

Hepatorenal Syndrome

Hepatorenal syndrome is characterized by intense intrarenal vasospasm caused by the imbalance between vasodilatory and vasoconstrictive mediators seen in decompensated liver disease.³⁹ Although the precise role of IAH in hepatorenal syndrome remains incompletely understood,⁴⁰ it can be argued—given diminished glomerular perfusion—that venous congestion results in further decline of GFR. Cade *et al.* reported significant increases in urine flow rate and creatinine clearance after reduction in IAP from 22 to 10 mmHg with paracentesis in patients with cirrhosis.⁴¹ In their experiments, the most striking improvement in GFR coincided with LeVeen shunt placement, which resulted in significant reductions in IAP and IVC pressures. More recent work by Umgelter in patients with established hepatorenal syndrome showed improvement in GFR and urine output and decreased vascular resistance in the renal interlobar arteries as evidenced by lowering of resistive indices assessed by Doppler ultrasound after paracentesis to decrease IAP.⁴²

MEASUREMENT OF IAP IN CLINICAL MEDICINE

Physical examination, with sensitivity of 40 to 60.9%, is unreliable for diagnosing IAH/ACS.^{43,44} Although a variety of direct and indirect techniques for measuring IAP have been developed and validated over the years,^{45–47} transduction of urinary bladder pressure through an indwelling urinary catheter remains the gold standard for measuring and monitoring IAP.

The bladder pressure method has been shown—when performed appropriately—to strongly correlate with IAP measured directly,¹¹ while remaining cost-effective and safe, without any increased risk of catheter-associated urinary tract infection.⁴⁸ In many institutions, screening patients at risk of developing IAH and serial monitoring of IAP every 4 to 6 hours is common practice.⁴⁹ However, the optimal frequency for serial measurements has not been established and it is not clear whether continuous IAP monitoring offers

any advantage over intermittent measurements.⁵⁰

WSACS recommends that bladder pressure be measured in a supine position at end-expiration in the absence of active abdominal muscle contraction with the transducer zeroed at the iliac crest in the mid-axillary line.² No more than 25 ml of saline should be instilled and the operator should wait at least 30 to 60 seconds after instillation before recording the pressure to allow the detrusor muscle to relax. Several studies show that elevation of the head of the patient's bed $>20^\circ$,^{51–54} using >25 -ml instillation volume,⁵⁵ and not allowing the detrusor time to relax,⁵⁶ can result in falsely elevated bladder pressures. Obesity, chronic ascites, and peritoneal dialysis can result in mild but persistent elevations in the baseline IAP.⁵⁷

Several proprietary kits are available for measuring bladder pressure quickly and easily with a high degree of operator reliability.⁵⁸ A nasogastric IAP monitor has also been validated and can be used in patients in whom bladder transduction is not possible or misleading.⁵⁹ These include patients with neurogenic bladder, bladder trauma, tense hematomas, or fluid collections in the pelvis, pelvic adhesions, and bladder outflow obstruction.

TREATMENT

Nonsurgical Management

There was, in the past, little specific management of IAH until the patients developed ACS, at which point the most common strategy was emergent abdominal decompression.⁶⁰ In fully established ACS, decompressive laparotomy remains the treatment of choice. Early, rather than late, decompression is gaining more popularity and is associated with better outcomes⁶¹ without a negative effect on long-term physical or mental health perception.⁶²

With increasing recognition of early IAH, several nonoperative interventions have also been developed, many of which are of benefit in preventing organ dysfunction in IAH or preventing progression to ACS.¹¹ Table 1 lists some simple nonsurgical measures that can possibly

Table 1. Medical treatment options to reduce IAP

1. Improve abdominal wall compliance
 - Sedation and analgesia
 - Neuromuscular blockade
 - Avoid head of bed $>30^\circ$
2. Evacuate abdominal fluid collections
 - Paracentesis
 - Percutaneous drainage
3. Evacuate intraluminal contents
 - Nasogastric decompression
 - Rectal decompression
 - Prokinetic agents
4. Correct positive fluid balance
 - Avoid excessive fluid resuscitation
 - Diuretics
 - Colloids/hypertonic fluids (in patients with severe burns)
 - Hemodialysis/ultrafiltration
5. Organ support and reducing capillary leak
 - Maintain APP >60 mmHg with vasopressors
 - Optimize ventilation, alveolar recruitment
 - Antibiotic therapy in septic patients

Adapted with permission of WSACS from Cheatham ML: Abdominal compartment syndrome. *Curr Opin Crit Care* 15: 154–162, 2009.

reduce IAP to varying extents. These are aimed at improving abdominal wall compliance,^{63,64} gastrointestinal tract evacuation and decompression, draining any intra-abdominal fluid, abscess, or blood,^{65–69} and minimizing the capillary leak process with antibiotic therapy for sepsis.

Resuscitation and Fluid Management

Aggressive volume resuscitation is an independent predictor of developing secondary ACS.^{70–72} In addition, in the setting of IAH/ACS, fluid resuscitation may preserve cardiac output but may not prevent intra-abdominal organ compromise.⁷³ However, extracellular fluid volume depletion in mechanically ventilated patients worsens the effects of IAH/ACS.^{74,75} In patients with IAH, efforts should be made to maintain APP ≥ 60 mmHg,¹⁰ as low APP associates with poor survival. In patients with septic shock and IAH, use of norepinephrine may have a favorable effect on maintaining renal perfusion.⁷⁶ Judicious use of diuretics in hemodynamically stable and volume-overloaded patients is also reason-

able in an attempt to reduce intra-abdominal vascular and tissue congestion.¹¹ However, oliguria in ACS may be resistant to diuretics.⁴ Although WSACS recommends using hypertonic and colloid solution as an option for resuscitation,¹¹ their benefit in preventing ACS has been shown only in a very small number of patients with severe burns.^{77,78}

Role of Renal Replacement Therapy

Data concerning the use of dialysis in management of IAH/ACS is quite limited. In an uncontrolled study of 17 patients with severe acute pancreatitis, multiorgan failure, and high IL-6 levels, Oda *et al.* used cytokine dialysis—continuous hemodiafiltration using a polymethyl methacrylate membrane along with albumin infusion to maintain cardiac output—in an attempt to decrease IAP.⁷⁹ They showed significant reduction in IL-6 levels as well as IAP and were able to prevent the development of ACS in all 17 patients, and 94.1% of the patients in this cohort survived. Three cases of continuous venovenous hemodialysis (CVVHD) use with aggressive ultrafiltration (achieving net negative fluid balance of approximately 5 L or greater over 24 hours) for treatment of advanced ACS have been reported.^{80,81} In all three cases, there was substantial improvement in IAP with CVVHD with aggressive ultrafiltration. However, ACS and multiorgan failure were very advanced in all three cases, resulting in death of the patients. A recent report⁸² by Sood *et al.* highlights some important practical issues: when administering CVVHD through a femoral vein catheter, IAH can lead to access recirculation and poor clearance of solute in addition to inappropriate hemofilter removal of phosphate and potassium repletion solutions. Using any other central venous access for repletion can solve the latter problem.

Cardiorenal and Hepatorenal Syndromes

In a small prospective study of diuretic-resistant ADHF with mild IAH, Mullens *et al.*⁸³ showed that ultrafiltration ($n = 4$) and paracentesis (if ascites present; $n = 5$) to reduce IAP resulted in a significant reduction in IAP ($P = 0.001$) and serum

creatinine ($P = 0.01$) with a significant increase in urine output ($P = 0.01$) without a significant alteration of hemodynamic parameters. The CARRESS trial (NCT00608491) is currently exploring the safety and effectiveness of ultrafiltration versus standard medical therapy in improving kidney function and relieving congestion in patients hospitalized with ADHF and cardiorenal syndrome.

Studies are needed to define the normal range of IAP in patients with chronic ascites as well as to better define the contribution of IAH/ACS to the oliguria seen in hepatorenal syndrome and the role and optimal timing of paracentesis as a therapeutic intervention.

CONCLUSIONS

IAH/ACS are very common among critically ill patients that nephrologists are usually asked to see in consultation for ARF. It is important to be cognizant of these phenomena, screen for them in a timely fashion in patients at risk, and take an active role in helping guide management to prevent the multiple, potentially fatal, complications of IAH/ACS. Many questions remain unanswered and serious scholarly effort is needed from the nephrology community to better understand these phenomena.

DISCLOSURES

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