Intra-abdominal hypertension and abdominal compartment syndrome in critical illness

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CHAPTER 8

Summary, discussion
and future perspectives
Summary

In this thesis we aimed to investigate the prevalence and outcome of increased intra-abdominal pressure (IAP) in critically ill patients, to investigate the relationship between IAP, biomarkers of acute kidney injury (AKI) and intestinal injury and to explore the relationship between IAP, body mass index (BMI) and central obesity.

Chapter 2 is a narrative review which focuses on the pathophysiology, risk factors and outcome of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) and on therapeutic strategies such as non-operative management, surgical decompression and management of the open abdomen. Future steps are discussed including propositions of what a future guideline should focus on.

Chapter 3 describes a retrospective series of patients with severe acute pancreatitis admitted to the ICU of the University Medical Center Groningen, a tertiary academic teaching hospital, between January 2005 and May 2011. IAP had been measured in just over half of the patients (29/59). All of these patients had IAH and 13/29 patients (44.8%) met the criteria for ACS. Ten patients with ACS underwent decompressive laparotomy. This study confirmed that IAH and ACS are common in patients with severe acute pancreatitis. As a novel finding, a high incidence of intra-abdominal ischemia was observed in patients with pancreatitis and ACS (61.5%). Mortality was high. One of the conclusions of this study was that national and international guidelines need updating to include routine IAP measurements as standard of care for patients with severe acute pancreatitis in the ICU.

The addendum to chapter 3 contains a letter to the editor of the American Journal of Gastroenterology as a response to the publication of the American College of Gastroenterology Guideline on Management of Acute pancreatitis in 2013. [1] Although this guideline included 34 recommendations, none of these mentioned IAP, IAH or ACS. There was no recommendation to monitor IAP in order to diagnose IAH or ACS. In the letter to the editor, we recommended that the American College of Gastroenterology would include measurement of IAP in all patients with acute pancreatitis and signs of organ failure in future guidelines.

In chapter 4 the results of a human model of mild IAH (of 12 mmHg) were reported. In this prospective randomized clinical trial, 50 living kidney donors were randomly assigned between hand-assisted laparoscopic nephrectomy and open nephrectomy. In the laparoscopic group a carbon dioxide pneumo-peritoneum of 12 mmHg was induced during the procedure. The open nephrectomy group was the control group.
In this study, C-reactive protein (CRP) and interleukin-6 (IL-6), markers of systemic inflammation, were determined in both groups peri-operatively. Neutrophil gelatinase-associated lipocalin (NGAL), a marker of AKI, was determined in plasma and urine in both groups at the start of the procedure and just before extraction of the donor kidney. CRP and IL-6 were higher postoperatively in the laparoscopy group. NGAL in plasma was 1.2 times higher just before extraction of the kidney than at the start of the operation in the laparoscopy group. Although procedure time was shorter, there was an increase in markers of systemic inflammation and serum NGAL in the laparoscopic nephrectomy group (with IAP of 12 mmHg) compared to open nephrectomy.

**Chapter 5** is a prospective, observational study which included 186 cardiothoracic surgical patients. The aims in this study were to find the range in values of IAP in cardiothoracic patients, to investigate the relationship between central obesity, BMI and IAP and to investigate the relationship between IAP, inflammation and renal function in this population.

The range in IAP in these patients was wide (0-26 mmHg). IAP ≥ 12 mmHg was observed in 50 patients (26.9%); 39 of these patients were either overweight (BMI between 25 and 29.9 kg/m²) or obese (BMI ≥ 30 kg/m²). There was a positive correlation between IAP and BMI, but correlations between IAP and indices for central obesity were not significant. In a multiple regression model BMI was a better predictor of IAP than waist-hip ratio. There were no correlations between pre- and postoperative CRP and serum creatinine and IAP.

The addendum to chapter 5 contains a letter to Critical Care Medicine. Danziger et al. convincingly showed that obesity is associated with AKI in critically ill patients.[2] The authors speculate about the underlying mechanisms, that are probably multifactorial. We suggested that increased IAP may be one of the mechanisms involved in the development of AKI in obesity. We hypothesized that obese patients may benefit from more aggressive monitoring and treatment of IAH in order to avoid any additional increase in IAP and secondary complications.

After the retrospective series on pancreatitis described in chapter 3 we performed a prospective, observational study to investigate the prevalence and outcome of IAH and ACS in a cohort of high risk patients admitted to the ICU. This included the exploration of the relationship between IAP and biomarkers of AKI and intestinal injury. The results of this study are reported in chapter 6 and chapter 7.

**Chapter 6** describes the prevalence and outcome of 503 high risk patients admitted to the ICU. IAH developed in 164 patients (33%). In this group, 18 patients (3.6%) developed ACS. Highest prevalence of ACS occurred in pancreatitis (57%), orthotopic liver transplant...
(7%) and abdominal aorta reconstruction (5%). Length of intensive care stay increased by a factor 4 in patients with IAH and a factor 9 in ACS, compared to patients with normal IAP. Both intensive care mortality and 90-day mortality were significantly higher in IAH (4.8% and 15.2%) and ACS (16.7% and 38.9%) compared to normal IAP (1.2% and 7.1%). Body mass index (BMI), mechanical ventilation at admission and Apache IV score were independent risk factors for the development of IAH or ACS. The patient most at risk of IAH or ACS in this high-risk cohort has a BMI > 30 kg/m² and was admitted to the ICU after emergency abdominal surgery or with a diagnosis of pancreatitis.

In chapter 7 we investigated whether biomarkers of intestinal injury (serum fatty acid binding proteins (FABPs), citrulline, claudin-3) and AKI (NGAL in serum and urine) correlate with IAP in the same population as in chapter 6. Groups with normal IAP, IAH and ACS were compared.

None of the intestinal biomarkers showed significant differences between the groups. NGAL in serum and urine were significantly increased in IAH and ACS. Post-hoc comparisons showed significant differences between all 3 groups for NGAL in serum and urine. Further study on biomarkers for prognostication of secondary complications of IAH should focus on AKI biomarkers like NGAL.

Discussion and future perspectives

This part of the chapter consists of a general discussion of the studies performed in this thesis and expands on the future steps described in chapter 2. This thesis originated in 2011, when data collection started for the retrospective study in patients with severe acute pancreatitis reported in chapter 3. In chapter 3 IAP had been measured in 29/59 patients with severe acute pancreatitis. All 29 patients had IAH. At this time, there was no IAP monitoring protocol in place in our intensive care unit (ICU). This first study led to the introduction of an IAP monitoring protocol in our department and also to the design of the subsequent studies. In the prospective study described in chapter 6, IAH was present in 33% of high risk patients and the prevalence of ACS was 3.6%. This is in line with other recent studies.[3, 4] Compared to the more historical data summarized in table 2 of the narrative review in chapter 2, ACS is decreasing for most diagnoses. Pancreatitis is a notable exception. This decrease may be caused by multiple factors. Meticulous attention to hemostasis perioperatively (for example during liver transplantation), the implementation of mass transfusion protocols and more individually tailored fluid requirements preventing massive fluid overload play an important role in preventing ACS. Early recognition and management of IAH may contribute also. [5]
When is an increase in IAP detrimental?
This question is fundamental for a better understanding of IAH and ACS and to optimize treatment for patients with an increased IAP. According to the WSACS, the definition of normal IAP is approximately 5-7 mmHg in critically ill adults [6], but baseline levels are higher in morbidly obese patients between 9-14 mmHg. [7] A possible explanation for higher pressures in the obese is a direct mass effect of the abdominal adipose tissue on the measurement of IAP. [7] It is not clear whether higher values should be used for defining IAH in obese patients.

Our findings are that there is a positive correlation between IAP and BMI (chapter 5) and that BMI is an independent risk factor for IAH or ACS (chapter 6). Furthermore, IAP of only 12 mmHg may already have a detrimental effect (chapter 4). Therefore, we do not recommend using higher values for defining IAH in obese patients. We suggest (as we wrote in the addendum to chapter 5) that obese patients may benefit from more aggressive monitoring and treatment of IAH in order to avoid any additional increase in IAP and secondary complications.

The results of the studies in chapter 4, 5 and 6 provide evidence in support of the statement by Reintam Blaser that it does not seem logical to accept higher IAP values in obese patients in shock. [8]

Remaining questions are: When should IAH be treated? Does treatment of IAH prevent ACS? Does treatment of IAH improve outcome?

We propose to design a prospective randomized multi-center trial with multiple treatment arms: Bundles of medical management are applied in an ICU population starting at different IAPs (for example 12 mmHg, 15 mmHg, 18 mmHg). Preferably, the included patients have a high risk of IAH and are homogeneous (for example pancreatitis patients).

Update guidelines
Besides an update in the guideline by the American College of Gastroenterology on management of acute pancreatitis [1,9] we recommend updating of the World Society of Abdominal Compartment Syndrome (WSACS) consensus definitions and clinical practice guidelines. [6] Several recommendations are included in chapter 2 and include allowing (and correcting) for IAP measurement in a position other than the supine position. Additionally, the definition “normal IAP is approximately 5-7 mmHg in critically ill adults” may be deleted, since baseline IAP varies. [7] The definitions of IAH and ACS need adaptation to reflect more clearly that they are not separate entities, but belong to the same spectrum. We propose: “IAH and ACS are a disease continuum of increased IAP. IAH has been arbitrarily defined as sustained IAP ≥ 12 mmHg and ACS > 20 mmHg that
is associated with new organ dysfunction or failure. However, the clinical circumstances of the individual patient more than any one IAP measurement determine whether (an escalation of) therapy is required.”

Other considerations
Since many patients have increased IAP upon admission to the ICU (chapter 6) [4], a future study where IAP measurements are performed before admission to the ICU, for example intra-operatively or in the emergency department, may inform us when increased IAP first occurs. In abdominal surgery, pre- and intraoperative IAP measurements may guide decision making on whether or not primary closure of the abdomen is performed.

There are several limitations to the study in cardiothoracic patients in chapter 5, which are important for data interpretation. Firstly, IAP was measured only once postoperatively in our study and by definition, this single IAP measurement did not allow us to diagnose IAH or ACS. Secondly, in the design of the study we assumed that the population of cardiothoracic surgery patients was not at risk of increased IAP. However, we now know that this assumption was inaccurate. Other studies have shown that IAP increased in 44% of patients undergoing CABG with extracorporeal circulation.[10,11] In a study of 69 cardiac surgery patients, IAH developed in 31.8% and was already evident 2 hours after the end of surgery. IAH was strongly associated with baseline IAP and a more positive fluid balance. A direct relationship between fluid balance and IAP was particularly significant in patients undergoing cardiopulmonary bypass.[12] Moreover, IAH was associated with a higher occurrence of postoperative AKI and longer duration of mechanical ventilation and ICU stay. However, IAP did not increase above 15 mmHg in any of the patients. This supports our findings that relatively mild increases in IAP may already have detrimental effects. The relationship between IAP and AKI, including the role of AKI biomarkers such as NGAL, deserves further study. This study could be performed in cardiac surgery patients.

Nurse involvement
Diagnosing and treatment of IAP increases is a multidisciplinary challenge, which should involve doctors as well as ICU nurses. Nurses at the bedside are of paramount importance since they are the ones who actually measure IAP. Many of the non-surgical interventions in ACS, such as nasogastric suctioning or repositioning of the patient are typically performed by nurses. Their role in diagnosing and treating this syndrome should increase. Implementation of nurse driven protocols may help. Additionally, involvement of nurses should also be encouraged and extended to areas such as research and education. For example, nurses should have a major role in investigating new or different measuring techniques, since they can experience first-hand which technique works best in their clinical practice. Subsequently, they should be involved in designing and
implementing IAP monitoring protocols on the workfloor and encouraging compliance with monitoring protocols within their teams.

IAP measurements are currently relatively time-consuming for nurses, an estimated 10 minutes to initiate and 5 minutes to perform one IAP measurement. Furthermore, a single high IAP measurement may not directly lead to an intervention. These factors may contribute to a decline in compliance with any monitoring protocol, especially in a busy workplace such as the ICU.

**Continuous IAP monitoring**
Facilitating IAP measurement and making its data management as easy as possible may help improve compliance with a monitoring protocol. As we discussed in chapter 2, continuous IAP monitoring may be beneficial. The multitude of data generated by continuous IAP monitoring may provide us with a better answer to the important question: when is an increase in IAP detrimental? Furthermore, trend monitoring will be easier and may resemble the monitoring of other vital signs in the ICU. In this way, IAP could become the “fifth vital sign”.

**Continued education**
In a repeat, international, cross-sectional survey of 559 respondents (mostly European physicians working in mixed ICUs), 73.2% were aware of WSACS the Abdominal Compartment Society, with a greater percentage being aware of the WSACS guidelines compared to the 2007 survey (60.2% vs. 28.4%). However, 18% of respondents never measure IAP. The most common reason given was reliance on physical examination. As the results of this survey illustrate, the importance of continued education for doctors and nurses, as well as for students of each profession cannot be overstated.

**Finally**
One major future challenge will be to elucidate whether treatment of IAH prevents ACS and improves patient outcome. Or, as J de Waele stated in 2015: “Understanding the subtle implications of modest IAH on all critically ill/injured patients and validating potential therapeutic interventions with sound evidence remain our biggest challenges.” Recognition of the patient at risk of IAH and its complications should improve further, as well as monitoring of IAP in order to diagnose IAH at an early stage. The clinical circumstances of the individual patient should dictate IAP management. Furthermore, IAP management should (continue to) be a multidisciplinary effort, where intensivists, ICU nurses, surgeons, anesthesiologists and gastroenterologists combine their expertise. At the end of this thesis, evidence is still lacking on many aspects of IAP increase and there is much more to learn. For now, the take home message is that clinicians and ICU nurses should have a high index of suspicion for IAP-related complications and a low
threshold for measuring IAP in all critically ill patients, especially when clinical signs are deteriorating, so that appropriate treatments may be implemented promptly.
References


