Non-renal causes of acute kidney injury

The compartment syndrome

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Intra-abdominal hypertension (IAH) and the abdominal compartment syndrome (ACS)

• Deleterious effects on renal function of high IA pressure is known for many years: Wendt E (1876, oliguria)

• Main anatomic areas subjected to a compartment syndrome

- Intracranial cavity
- Orbital globe
- Leg
- Abdomen
Basic problems in 3 main steps

1. acute ↑ volume of the contents of a specific anatomic compartment (edema, h+m)  
   *Other: extrinsic compression*

2. ↓ arterial flow, secondary ischemic injury

3. +/- inflammation

Compartment with unyielding barrier (bone, fascia)
Principles of treatment

1. Fluid
   - Extraction (eg. puncture, diuretics)
   - ↓ production (eg. Glaucoma, ascites)

2. Tissue excision
   (eg cancer)

3. Removal of some part of the confining wall
   (eg craniectomy, laparotomy)

4. Anti-inflammatory
   (eg. Corticosteroids)

Management of the etiologic problem
Compartmental pressure relief

Designed to ↓ the absolute intracavitary volume/pressure
Intra-abdominal hypertension +12 mmHg

Consensus definition of IAH

Normal < 5 mmHg (varies with respiration)

Abdominal compartment syndrome +20 mmHg = late consequence

Intra-abdominal hypertension +12 mmHg

Organ dysfunction

Ruptured aneurysm
IAH & ACS (World Society for ACS, 2006)

• ACS
  • Refers to a clinical constellation resulting from IAP
  • Common: oliguria, decreased pulmonary compliance and metabolic acidosis
  • Mortality: 40-100%

• Intraabdominal hypertension
  • Grade 1 = 12-15 mmHg
  • Grade 2 = 16-20 mmHg
  • Grade 3 = 21-25 mmHg
  • Grade 4 >25 mmHg

Oliguria and renal dysfunction may already occur: Indicate that AKI may be present in much larger population of critically ill patients*

How to define/measure IA pressure?

• **Physical examination?** Highly subjective, poor sensitivity (40-60%)

• **Gold standard?** Transduction of urinary bladder pressure
  • strongly correlated with IAP
  • simple, cost-effective, safe procedure

• **Abdominal Perfusion Pressure (APP)**
  • APP = MAP – IAP (mmHg)*
  • ≃ cerebral perfusion pressure
  • ≥50-60 mmHg
  • If ↓ = independent predictor of AE

* > even if MAP is constant, any rise in IAP would result in lower APP
Urinary catheter

Side port for injection

Monitoring line with pressure transducer

Syringe attached to 3-way-taps

Adapted from DD Yeh and SG Simon in Bedside Procedures in the ICU, 2012, Springer Ed.
Renal arterial resistive index response

Kirckpatrick AW et al, Crit Care Med 2007;35;207
How to define/measure IAP pressure?

• **IAP measurements should be**
  - mmHg (1 mmHg = 1.36 cm H2O)
  - end-expiration
  - supine position
  - Zeroed: mid-axillary line
  - instillation volume <25 mL of warmed saline (bladder)
  - 30-60 sec. after instillation (bladder)

• **Several measurements**
  - every 4-6h
  - Cf. clinical appearance (abdomen) and on the clinical situation
Decreased renal output

Dogs with inflatable intraperitoneal bags

Resuscitated the dogs to normal CO but the renal function remained impaired until the abdomen was decompressed.

80% decrease

Frequent anuria

Nb. No role of ureteral compression
### Predisposing conditions and risk factors

<table>
<thead>
<tr>
<th>↓ abdominal wall compliance</th>
<th>↑ intra-luminal contents</th>
<th>↑ abdominal contents</th>
<th>Capillary leak / fluid resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Abdominal surgery with primary fascial closure</td>
<td>• Gastroparesis, gastric distension, ileus</td>
<td>• Acute pancreatitis</td>
<td>• Acidosis, Hypotension, Polytransfusion</td>
</tr>
<tr>
<td>• Major trauma/burns</td>
<td>• Colonic pseudo-obstruction</td>
<td>• Hemo- or pneumoperitoneum</td>
<td>• Massive fluid resuscitation or positive fluid balance</td>
</tr>
<tr>
<td>• Prone position</td>
<td>• volvulus</td>
<td>• Intra-abdominal infection, abscess, tumors</td>
<td>• Oliguria, Sepsis...</td>
</tr>
<tr>
<td>• ARDS, especially with ↑ intrathoracic pressure</td>
<td></td>
<td>• Ascites / liver dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peritoneal dialysis</td>
<td></td>
</tr>
</tbody>
</table>

*Others: Age, bacteremia, coagulopathy, ↑ head of bed angle, obesity, mechanical ventilation, PEEP >10*
# Common consequences

<table>
<thead>
<tr>
<th>Vascular beds</th>
<th>Lung function</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↓ venous return to the heart (↓ cardiac preload and output)</td>
<td>• 20% of the ↑ IAP is transmitted to the thoracic cavity</td>
<td>• Can ↑ intracranial pressure (head injured trauma patient)</td>
</tr>
<tr>
<td>• ↓ mesenteric blood flow and intestinal perfusion (bacterial translocation, sepsis)</td>
<td>• ↓ lung capacity and residual volume, barotrauma (↑ airway pressures), ↑ work of breathing</td>
<td>• Risk of thrombosis (stasis, edema)</td>
</tr>
<tr>
<td>• ↓ venous return from the kidney, decreased arterial perfusion</td>
<td></td>
<td>• Death (40-100% ACS)</td>
</tr>
</tbody>
</table>

Nb. BP is often maintained (concomitant ↑ in systemic vascular resistance)
Common early clinical manifestations of ACS

- **Oliguria (AKI)**
  - first reported in 1876 (Wendt)
  - Begins at **10 mmHg**
  - anuria common >20 mmHg*
  - < ⬆ parenchymal and vein pressure

- **Tense abdomen (not always...)**

- **Ventilation (Peak inspiratory pressure)**
  - difficult ventilation (>16 mmHg)

- **Others**

Contributing cause of morbidity eg. metabolic acidosis, decreased cardiac output

*Bradley JCI 1947
Intra-abdominal hypertension (IAH)

• **Incidences**
  - IAH: up to 64% (global population), 83% (sepsis, large volume resuscitation)
  - ACS: up to 12% (global population), 25% (sepsis, 5L+), 50% (acute pancreatitis)

• **Severe impacts**
  - IAH (± APP): independent predictor of mortality in medical ICU (RR 1.85), independent cause of renal impairment after abdominal surgery (>18 mmHg, OR 2.96) or OLTx (≥25 mmHg)

• **Different types**: acute vs. Chronic, many causes

• Under-recognized cause of AKI (critically ill)

Main categories of IAH/ACS

<table>
<thead>
<tr>
<th>Primary or acute IAH/ACS</th>
<th>Secondary IAH/ACS</th>
<th>Chronic/recurrent IAH/ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• intra-abdominal pathology is directly and proximally responsible for the ACS</td>
<td>• No visible intra-abdominal injury</td>
<td>• In presence of cirrhosis and ascite or related disease states – often in the later stages of the disease</td>
</tr>
<tr>
<td>• Frequently requires surgery of radiological treatment</td>
<td>• Injury outside the abdomen</td>
<td>• Inadequate decompression (eg. Temporary closure device is too tight)</td>
</tr>
<tr>
<td></td>
<td>• Association with severe capillary leak requiring resuscitation</td>
<td></td>
</tr>
</tbody>
</table>
### Main causes of IAH/ACS

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Chronic</th>
</tr>
</thead>
</table>
| • Penetrating trauma  
  • Intraperitoneal hm+  
  • **Pancreatitis**  
  • External compression  
  • Pelvic fracture  
  • Rupture of AAA  
  • Perforated peptic ulcer  
  • Liver Tx | • **Large volume resuscitation** (e.g. > 3L)  
  • Polytransfusions  
  • Large areas of full-thickness burns  
  • Penetrating/blunt trauma  
  • **Postoperative**  
  • Packing and primary fascial closure  
  • **Sepsis** | • **Peritoneal dialysis**  
  • **Morbid obesity**  
  • **Cirrhosis**  
  • Meigs syndrome  
  • Intraabdominal mass  
  • **Other?** |
Elevated Intra-Abdominal Pressure in Acute Decompensated Heart Failure

A Potential Contributor to Worsening Renal Function?

Wilfried Mullens, MD,* Zuheir Abrahams, MD, PhD,* Hadi N. Skouri, MD,*
Gary S. Francis, MD, FACC,* David O. Taylor, MD, FACC,*
Randall C. Starling, MD, MPH, FACC,* Emil Paganini, MD,† W. H. Wilson Tang, MD, FACC*

Cleveland, Ohio
Elevated IAP in ADHF...

• 60% ADHF patients with ↑ IAP (≥ 8 mmHg) despite the absence of overt abdominal symptoms; IAH was less frequent (10%)
  • ↑ IAP: more impaired renal function (2.3 vs 1.5 mg/dl, n=40)
• Medical therapy (inotropic support, vasodilators, diuretics)
  • ↑ renal function
  • ↓ IAP
  • without any changes in hemodynamic measurements

↑ IAP might contribute to the renal dysfunction commonly observed in patients with ADHF (↓ renal perfusion, ↑ renal vein pressure)
Venous congestion is the strongest hemodynamic determinant for worsening renal function in ADHF

Medical treatment options to reduce IAP

• preventive measures before a raised IAP develops into ACS

• Common sense:
  • **Improve abdominal wall compliance:** sedation and analgesia, neuromuscular blockade; removal of constrictive dressings (e.g. abdominal binders); trendelenburg position
  • **Evacuation of IA space-occupying lesions:** percutaneous aspiration and catheter drainage of IA fluid (e.g. Ascites, hemoperitoneum, IA abscess)
  • **Evacuation of intraluminal contents** (gastric decompression < nasogastric drainage, rectal enemas, temporary discontinuation of enteral feeding,...)
  • **Correct positive fluid balance** (avoid excessive fluid resuscitation, diuretics, HD/UF,..)
  • **Organ support and reducing capillary leak** (APP>60 mmHg, optimize ventilation, antibiotic therapy...)

Second-line options to reduce IAP

• RRT?
  • Few data, aggressive UF could help... but should not delay surgery

• Surgical decompression
  • Gold standard rescue therapy for IAP of 20-25 mmHg
  • Opening the abdominal wound and packing the wound open or closing it with as plastic dressing
  • Delayed closure can be done once the edema / bleeding has resolved
Is the kidney a compartment?

The renal compartment
A renal compartment?

- **Renal capsule**: unyielding fibrous structure (100 µm)
- Postglomerular intrarenal vascular network: low-pressure system (± 8 mmHg) > IAP of 15 mmHg is sufficient to cause venous congestion and impaired GFR

- *Theoretically*: a sudden increase in fluid volume inside the renal parenchyma can result in a substantial intrarenal pressure, and as consequence, a decrease in the renal perfusion pressure
  - Concept of « nephrosarca »
Renal compartment is a reality (theory)

Exponential relation between intrarenal pressure and volume in the intact kidney > indicative of a behavior commonly observed in organs confined by a (semi)rigid continent

Renal compartment syndrome in the clinical setting?

- **AKI**
  - Frequent increase in the kidney volume due to edema
  - Common hypoperfusion of the outer medulla

- **Renal edema**
  - Increased microvascular permeability (I/R)
  - Renal interstitial edema
  - Extrinsic compression of PT capillaries
  - Unresponsive to vasomotor tone

500,000-mol FITC-labeled dextran; From T. Sutton et al. Am Journal Physiol Renal Physiol 2003
Renal compartment syndrome in the clinical setting?

- Significant ↑ in the presence of acute inflammation (i.e. transplant rejection): 77% >40 mmHg.
- Scarce objective data in the literature...
  - Interstitial edema is an inconsistent finding in biopsy series
  - Lack of strong clinical data supporting this hypothesis

Salaman JR & PJA Griffin, Transplantation 1985
HH Stone and JT Fulenwider (1977): Renal decapsulation
Renal decapsulation

Native: Exponential relation
> Mechanical behavior common to confined organs

Decapsulation: Linear dependence, $R^2 = 0.95$
> Confirms that the renal capsule is a continent

The renal capsule: an old point of interest

- 1st kidney puncture: Harrison, 1878
- 1st full capsulotomy: Le Dentu, 1881
- 1st true decapsulation: Pousson, 1901
- 1st summary of the world experience: Abeshouse, 1944 (n=2307)
  - Efficient intervention is early (avoid renal cortical necrosis)
- 1945: introduction of PD and after HD...thoughts of capsule stripping were eclipsed...

**Table 7. Collection Review of Renal Decapsulation (Modified from Abeshouse—up to 1944)**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Improved</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute nephritis</td>
<td>246</td>
<td>176</td>
<td>71.5%</td>
</tr>
<tr>
<td>Chronic nephritis</td>
<td>565</td>
<td>390</td>
<td>69.0%</td>
</tr>
<tr>
<td>Acute or chronic nephritis</td>
<td>471</td>
<td>427</td>
<td>90.7%</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>112</td>
<td>61</td>
<td>54.5%</td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td>2</td>
<td>2</td>
<td>100.0%</td>
</tr>
<tr>
<td>Chronic perinephritis</td>
<td>62</td>
<td>62</td>
<td>100.0%</td>
</tr>
<tr>
<td>Degenerative nephrosis</td>
<td>108</td>
<td>73</td>
<td>67.6%</td>
</tr>
<tr>
<td>Toxic nephrosis</td>
<td>613</td>
<td>255</td>
<td>41.6%</td>
</tr>
<tr>
<td>Cortical necrosis</td>
<td>13</td>
<td>4</td>
<td>30.8%</td>
</tr>
<tr>
<td>Transfusion reaction</td>
<td>3</td>
<td>3</td>
<td>100.0%</td>
</tr>
<tr>
<td>Non-obstructive anuria</td>
<td>32</td>
<td>26</td>
<td>81.3%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>80</td>
<td>64</td>
<td>80.0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2307</strong></td>
<td><strong>1543</strong></td>
<td><strong>66.9%</strong></td>
</tr>
</tbody>
</table>

HH. Stone, JT. Fulenwinder Ann Surg 1977
The renal capsule: a new point of interest

• **Experimental AKI (Ischemia-reperfusion)**
  • A rise in parenchymal pressure may contribute to the AKI caused by ischemic insult: impaired tubular excretion function, reduced blood flow, structural damage to the kidney
  • Controlled capsulotomy attenuates the risk of functional renal impairment
    • Significant reduction in IL-6, IL-1b, CCL-2 and cellular infiltration (CD4+, F4/80+)

• **New interest?** decompressive capsulotomy in preventing the rapid increase of intrarenal pressure in acutely injured kidneys
  • Transplant kidneys? Better function and lesser allogenicity?
  • Future studies needed... effect on RBF, renal oxygenation/perfusion, microcirculation, renal function, etc.

Renal decapsulation: the cons...

- Indication is not defined
- Not a standardized procedure
- Risk of:
  - uncontrolled rupture of the kidney capsule
  - Traction/compression of the incisional margins > microcirculatory impairment
  - Protrusion of renal parenchyma
  - hemorrhages
- Need for minimal puncture procedure
  - Drainage of interstitial fluid
  - Could serve as pressure compensating valve
An unsuspected role: a stem cell niche?

- Capsule= thin sheet of connective tissue containing fibroblasts, adipocytes, and blood vessels: inert barrier?
- Contains nestin-expressing cells in the renal capsule (mesenchymal stem cells) that may contribute to renal repair...

May contribute to the recovery of ischemia

The Intrinsic Renal Compartment Syndrome: New Perspectives in Kidney Transplantation

Tanja Herrler, Anne Tischer, Andreas Meyer, Serge Feiler, Markus Guba, Sebastian Nowak, Markus Rentsch, Peter Bartenstein, Marcus Hacker, and Karl-Walter Jauch

Purpose. Inflammatory edema after ischemia-reperfusion may impair renal allograft function after kidney transplantation. This study examines the effect of edema-related pressure elevation on renal function and describes a simple method to relieve pressure within the renal compartment.

Methods. Subcapsular pressure at 6, 12, 24, 48 hr, and 18 days after a 45 min warm ischemia was determined in a murine model of renal ischemia-reperfusion injury. Renal function was measured by 99mTc-MAG3 scintigraphy and laser Doppler perfusion. Structural damage was assessed by histologic analysis. As a therapeutic approach, parenchyma pressure was relieved by a standardized circular 0.3 mm incision at the lower pole of the kidney capsule.

Results. Compared with baseline (0.9 ± 0.3 mm Hg), prolonged ischemia was associated with a sevenfold increase in subcapsular pressure 6 hr after ischemia (7.0 ± 1.0 mm Hg; P < 0.001). Pressure levels remained significantly elevated for 24 hr. Without therapy, a significant decrease in functional parameters was found with considerably reduced tubular excretion rate (33 ± 3.5%, P < 0.001) and renal perfusion (64.5 ± 6.8%, P < 0.005). Histologically, severe tissue damage was found. Surgical pressure relief was able to significantly prevent loss of tubular excretion rate (62.5 ± 6.8%, P < 0.05) and renal blood flow (96.2 ± 4.8%; P < 0.05) and preserved the integrity of renal structures.

Conclusions. Our data support the hypothesis of the existence of a renal compartment syndrome as a consequence of ischemia-reperfusion injury. Surgical pressure relief effectively prevented functional and structural renal impairment and we speculate that this approach might be of value for improving graft function after renal transplantation.

Keywords: Transplantation, Compartment, Kidney, Renal function, Scintigraphy.

(Transplantation 2010;89: 40–46)
Capsulotomy of the ischemic renal transplant?

Increase in subcapsular pressure following renal IRI

- Capsulotomy
- Control
The renal capsule

The compartment

Fluid overload,
Edema,
Summary

• IAH: measurable, preventable, treatable
  • very common (critically ill)
  • could be underestimated in non-ICU settings
  • part of cardiorenal syndrome (CVP, IAP) or hepatorenal syndrome (ascites)
  • reversible AKI already at 10 mmHg IAP: oliguria, elevated RI

• ACS: end organ dysfunction
  • from untreated elevated IAP
  • High mortality rate
  • Indication of decompressive laparotomy (damage control)
Summary

• **Measurement of IAP is simple** (bladder technique),

• **Many unanswered questions... Renal compartment syndrome?**
  • Real entity but of unknown clinical relevance (remains speculative)
  • May be underestimated in particular situations (eg. transplant kidney, highly congestive cardiorenal syndromes,...)
Thank you!

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