Abdominal compartment syndrome and colonic ischaemia after abdominal aortic aneurysm repair in the endovascular era

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Abstract
Ersryd, S. 2020. Abdominal compartment syndrome and colonic ischaemia after abdominal aortic aneurysm repair in the endovascular era. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1689. 96 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1029-9.

Abdominal Compartment Syndrome (ACS) and colonic ischaemia (CI) are serious and potentially lethal complications after open (OSR) and endovascular repair (EVAR) of ruptured (rAAA) and intact (iAAA) abdominal aortic aneurysms. The aims of this thesis were to investigate the incidence, outcome, and risk factors associated with ACS (**Papers I-III**) and to evaluate extraluminal colonic tonometry for postoperative surveillance of colonic perfusion (**Paper IV**).

   Papers I-III combined data from the nationwide Swedish vascular registry (Swedvasc) (2008-2015) with case records and radiologic imaging. **Paper I** investigated incidence and outcome of ACS. The incidence was approximately 7% for both EVAR and OSR after rAAA and 1.6% after OSR and 0.5% after EVAR for iAAA. ACS was associated with a more than two-fold (59% vs 27%) 90-day mortality after rAAA and six-fold (19% vs 3%) after iAAA. **Paper II** investigated risk factors and outcome among subgroups. Risk of death could not be attributed to a specific main pathology of ACS: CI, postoperative bleeding and general oedema, nor to timing of decompressive laparotomy in relation to AAA surgery. However, the duration of intra-abdominal hypertension (IAH) predicted the need for renal replacement therapy. **Paper III** investigated risk factors after EVAR for rAAA. ACS was rare without pronounced pre- or intraoperative physiologic derangement associated with circulatory instability. Aortic morphology did not impact ACS development, nor did presence of a patent inferior mesenteric and lumbar arteries, known risk factors for type II endoleak. **Paper IV** studied patients operated on for iAAA/rAAA (n=27), and demonstrated extraluminal colonic tonometry safe, reliable and indicative of CI among all affected patients (n=4).

   In conclusion, ACS was common after rAAA repair, with poor outcome irrespective of AAA repair technique and indication for repair. Outcome did not differ depending on the main pathophysiological finding associated with ACS development, while a longer duration of IAH increased the risk of renal replacement therapy. ACS after EVAR for rAAA was largely associated with pre- and intraoperative physiologic factors. These findings highlight the importance of vigilant intra-abdominal pressure measurement after rAAA repair and in case of haemodynamic instability, as well as timely interventions to treat IAH. Extraluminal colonic tonometry appears promising for surveillance of postoperative colonic perfusion.

Keywords: Aortic aneurysm-abdominal, Intra-abdominal pressure, Intra-abdominal hypertension, Abdominal compartment syndrome, Rupture, Open ab-domen treatment, Colonic ischaemia, Endovascular aneurysm repair

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To Linda, Anabelle, August and Liv

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Ersryd S, Djavani Gidlund K, Wanhainen A., Björck M.
    Editor's Choice - abdominal compartment syndrome after surgery for abdominal aortic aneurysm: a nationwide population based study. Eur J Vasc Endovasc Surg 2016; **52**: 158-165.

II. Ersryd S, Djavani Gidlund K, Wanhainen A, Smith L, Björck M.
    Editor's Choice - Abdominal Compartment Syndrome after Surgery for Abdominal Aortic Aneurysm: Subgroups, Risk Factors and Outcome. Eur J Vasc Endovasc Surg 2019; **58:** 671-679.

III. Ersryd S, Baderkhan H, Djavani Gidlund K, Björck M, Gillgren P, Bilos L, Wanhainen A.
    Risk factors for abdominal compartment syndrome after endovascular repair for ruptured abdominal aortic aneurysm: A case-control study (Submitted manuscript).

IV. Ersryd S, Djavani Gidlund K, Wanhainen A, Björck M.
    Surveillance to detect colonic ischemia with extraluminal pH measurement after open surgery for abdominal aortic aneurysm (Submitted manuscript).

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Contents

Abbreviations

AAA	Abdominal aortic aneurysm
ACS	Abdominal compartment syndrome
BP	Blood pressure
CI	Colonic ischaemia
CO	Cardiac output
CT	Computed tomography
DL	Decompressive laparotomy
EAF	Entero-atmospheric fistula
EVAR	Endovascular aneurysm repair
FFP	Fresh frozen plasma
iAAA	Intact abdominal aortic aneurysm
IAH	Intra-abdominal hypertension
IAP	Intra-abdominal pressure
ICP	Intra-cranial pressure
ICU	Intensive care unit
iEVAR	Intact endovascular aneurysm repair
IFU	Instructions for use
IQR	Interquartile range
iOSR	Intact open surgical repair
MAP	Mean arterial pressure
mmHg	Millimeters Mercury

NPWT	Negative pressure wound therapy
OAT	Open abdomen treatment
OR	Odds ratio
OSR	Open surgical repair
pHe	Extraluminal intestinal pH
pHi	Intraluminal intestinal pH
pRBC	Packed red blood cells
rAAA	Ruptured abdominal aortic aneurysm
rEVAR	Ruptured endovascular aneurysm repair
ROC	Receiver operator characteristics
rOSR	Ruptured open surgical repair
RRT	Renal replacement therapy
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
T2EL	Type II endoleak

Introduction

"In four patients with ruptured abdominal aortic aneurysms increased intra-abdominal pressure developed after repair. It was manifested by increased ventilator pressure, increased central venous pressure, and decreased urinary output associated with massive abdominal distension not due to bleeding. This set of findings constitutes an intra-abdominal compartment syndrome caused by massive interstitial and retroperitoneal swelling." (Fietsam 1989)

With this introduction, Fietsam et al gave name to the syndrome described in all but name by Kron et al five years earlier (Kron 1984, Fietsam 1989). Abdominal compartment syndrome (ACS) was born.

However, already at the beginning of the 20th century, there were physicians concerned about intra-abdominal pressure (IAP) and the lack of attention thereof. In 1911, Emerson noted that

"The standard text-books of obstetrics, gynaecology and surgery treat of the matter so rarely, and when it is mentioned so inaccurately, that no information is to be had from them… Most of the textbooks of physiology fail to mention intra-abdominal pressure at all." (Emerson 1911)

ACS refers to the stage when severe intra-abdominal hypertension (IAH) causes organ dysfunction or failure, and is the subject of this thesis. This thesis also details colonic ischaemia (CI), which refers to when impaired circulation leads to ischaemia of one or more layers of the colonic bowel wall. While ACS, and to a lesser extent CI, may develop after a wide variety of diseases, the thesis will focus on their development after abdominal aortic aneurysm (AAA) repair.

AAA

AAA is a pathological enlargement of the abdominal segment of the aorta, the main artery in the human body. As the diameter of the AAA increase, so does the risk of rupture. Unless diagnosed beforehand, an AAA usually remains asymptomatic until rupture, an event with great risk of death. Diagnosis can be the result of a focused screening examination or as an incidental finding on a medical imaging modality e.g. computed tomography (CT), performed for other medical reasons. Treatment consists of an operation, either open surgical

repair (OSR) or endovascular aneurysm repair (EVAR). EVAR (iEVAR) is less invasive and has an early survival benefit over OSR (iOSR) for intact AAA (iAAA) (Greenhalgh 2004, Prinssen 2004). With time, survival is evened out and after eight years, iOSR for iAAA shows better survival (Blankensteijn 2005, Greenhalgh 2010, Patel 2016). In case of AAA rupture, an immediate operation is necessary. Without surgery, mortality is close to 100% and even with surgery, mortality is still high, about 28-38% (Mani 2013, Sweeting 2015, Lilja 2017). In an epidemiological study from Malmö, the overall mortality after AAA rupture was estimated to 74%; 70% in men and 92% in women (Acosta 2006).

History

The knowledge of aneurysms existed already in Greece centuries B.C. In the sixteenth century, the Belgian physician and anatomist Andreas Vesalius was among the first to give a clinical description of AAA (Fortner 1984). During the first half of the twentieth century several methods of surgical treatment were tested (Matas 1903, Abbott 1949), before Freeman et al in 1951 reported a successful AAA reconstruction with vein homograft (Freeman 1951). The use of human homograft was eventually replaced in favour of synthetic prostheses (DeBakey 1958). Then, in 1986, the Ukrainian surgeon Nikolay Volodos et al reported (in Russian) on their experience with a new minimally invasive endovascular technique (Volodos 1986). Five years later, the first report (in English) on EVAR was published by Parodi et al (Parodi 1991). EVAR has since gained in popularity and is now the dominant method of treatment for iAAA (Budtz-Lilly 2017, Lilja 2017).

Definition

A universally recognized definition as to when an aortic widening is considered an aneurysm does not exist. A widely used definition was described by McGregor et al in 1975, and defined an AAA as an infrarenal aortic widening with a diameter of at least 30 millimeters (McGregor 1975). Another popular and widely used definition states an AAA being a localized dilatation of the aorta having at least 50% increase compared to the expected normal infrarenal diameter (Johnston 1991).

ACS

The negative physiological effects of elevated intra-abdominal pressure were already described in the beginning of the twentieth century (Wendt 1876, Emerson 1911). However, the term ACS is relatively recent, and was first used by Fietsam et al in 1989 (Fietsam 1989). Fietsam and co-workers described

this in four patients operated on for ruptured AAA (rAAA) who received massive amounts of fluid resuscitation. During the first postoperative day they deteriorated physiologically and were subsequently treated with decompressive laparotomy (DL), resulting in dramatic physiological improvement.

While not using the term ACS, Kron et al had five years earlier reported on treatment with DL in the paper "The Measurement of intra-abdominal Pressure as a Criterion for Abdominal Re-exploration". The paper described seven patients, the majority of whom had undergone AAA repair, where DL was performed on the basis of IAP >25 millimeters Mercury (mmHg) in association with organ dysfunction (Kron 1984). This resulted in prompt increase of urinary output. Four patients who were not decompressed all developed renal failure and died.

Definition

After ACS was established as a separate diagnosis, a uniformly recognized definition was still lacking. While the threshold for AAA diagnosis might vary between different definitions, there is no uncertainty among those treated. With ACS, various reports differed in terminology and criteria for the diagnosis. There was also a lack in standard for the very fundament of ACS diagnosis, IAP measurement.

In 2004, a group of concerned physicians formed WSACS – The abdominal compartment society, an international society devoted to research, education and improved outcome in patients with ACS. Consensus definitions were published in 2006 (Malbrain 2006), followed by consensus recommendations a year later (Cheatham 2007). The consensus definitions were updated in 2013 with inclusion of clinical practice guidelines (Kirkpatrick 2013).

In the consensus definitions, ACS is defined as a sustained IAP >20 mmHg (with or without an abdominal perfusion pressure below 60 mmHg) that is associated with new organ dysfunction or failure.

ACS can be primary, as in the source of IAH/ACS originating from abdominopelvic region, or secondary, as in the source not originating from the abdominopelvic region. Recurrent IAH/ACS refers to a re-developing IAH/ACS following previous treatment of the condition (Kirkpatrick 2013).

Normal IAP

Normal IAP in healthy adults is approximately 2 mmHg in the supine position. The corresponding IAP in a hospitalized patient population is 5-7 mmHg, but specific patient populations such as those with obesity may have higher resting IAP (De Keulenaer 2009). Exercise and physical activity will increase IAP, with coughing and jumping generating maximum increase, while lifting light weights generate minor increase (Cobb 2005).

IAH

Sustained or repeated elevation of IAP ≥12 mmHg is defined as IAH. The WSACS guidelines divide IAH into four grades depending on the IAP level (Kirkpatrick 2013):

Grade I: IAP 12-15 mmHg

Grade II: IAP 16-20 mmHg

Grade III: IAP 21-25 mmHg

Grade IV: IAP >25 mmHg

IAH has been associated with worse outcome in multiple reports (Malbrain 2005, Vidal 2008).

Risk factors

Many different risk factors for IAH/ACS have been identified in various patient populations. Some will only apply to a specific population, whereas others are more universal. There are risk factors that have been identified in other study populations, which are also valid for AAA patients and vice versa. In the WSACS guidelines, risk factors are divided into five categories depending on their mechanism of action. Identified factors are presented in Table 1, and it is clear that AAA patients are at risk for, or naturally meet, factors in every category. The clinical practice guidelines recommend measurement of IAP when one or more of the listed risk factors are present (Kirkpatrick 2013).

Diminished abdominal wall compliance

Abdominal compliance is the measure of the ease of abdominal expansion in relation to the change in IAP. The elasticity of the abdominal wall and the diaphragm determines the level of this compliance. A laparotomy affects abdominal compliance, resulting in an increased risk for IAH among those having undergone laparotomy (Dalfino 2008, Reintam Blaser 2011).

Increased intraluminal contents

Increased intraluminal contents contribute to IAH by way of increasing intra-abdominal volume. Patients having undergone major surgery, such as OSR for AAA, are prone to developing gastroparesis and paralytic ileus in the early postoperative phase (Sicard 1995).

Increased intra-abdominal contents

As the name suggests, increased intra-abdominal contents also contribute to IAH through increasing intra-abdominal volume. Patients operated on for rAAA are likely to have a retroperitoneal hematoma as a space occupying lesion.

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Table 1. *Risk factors IAH and ACS shown in five categories*

Risk factors

1. Diminished abdominal wall compliance	**4. Capillary leak/Fluid resuscitation**
Abdominal surgery	Acidosis
Major trauma	Damage control laparotomy
Major burns	Hypothermia
Prone positioning	Increased APACHE-II or SOFA score
	Massive fluid resuscitation
2. Increased intraluminal contents	Positive fluid balance
Gastroparesis/gastric distention	Polytransfusion
Ileus	
Colonic pseudo-obstruction	**5. Others/Miscellaneous**
Volvulus	Age
	Bacteremia
3. Increased intra-abdominal contents	Coagulopathy
Acute pancreatitis	Increased head of bed angle
Distended abdomen	Massive incisional hernia repair
Hemo- and pneumoperitoneum	Mechanical ventilation
Intra-peritoneal fluid collections	Obesity or increased body mass index
Intra-abdominal infection/abscess	Positive end expiratory pressure >10
Intra-abdominal or retroperitoneal tumors	Peritonitis
Laparoscopy with excessive insufflation	Pneumonia
Liver dysfunction/Cirrhosis with ascites	Sepsis

Capillary leak

Both iAAA and rAAA repair have been shown to trigger systemic inflammatory response syndrome (SIRS) (Bown 2003), which is a reaction of the human body to a non-specific insult. As one of several consequences of SIRS, pro-inflammatory cascades lead to disruption of endothelial tight junctions, resulting in capillary leak by allowing fluid and leukocytes entrance to the interstitial space. It in turn leads to tissue swelling and oedema, which may contribute to IAH.

In rAAA, the stress of haemorrhagic shock is added to the stress of surgery, as haemorrhagic shock is too a driver of SIRS and is widely reported as a risk factor for IAH (Balogh 2003, Malbrain 2006). When the haemorrhage is located in the abdominal cavity it also acts as a space occupying lesion. Acidosis and ischaemia-reperfusion response are effects of aortic cross-clamping (Zammert 2016), but can also follow on episodes of pronounced hypotension. Hypothermia is frequently observed during rAAA repair and is also a known risk factor for ACS (Balogh 2003).

Massive fluid and blood resuscitation

Massive blood- and fluid resuscitation both increase the risk of IAH/ACS (Balogh 2003, Malbrain 2005, Dalfino 2008). A universal threshold for when a transfused fluid volume is considered massive does not exist. The WSACS consensus recommendations cites a threshold of >5 litres fluid/24 hours, while others have demonstrated a risk at lower levels of >3.5 litres fluid/24 hours (Malbrain 2005, Cheatham 2007). Regarding transfusions, more than 6-10 units of packed red blood cells (pRBC) have been found to be a risk factor. (Cheatham 2007, Mayer 2009).

Risk factors from studies on AAA patients

A handful of reports have explored risk factors for ACS after AAA repair. Rasmussen et al reported several pre- and intraoperative risk factors for ACS (n=10) after OSR (rOSR) for rAAA: severe anaemia, prolonged shock (<90 mmHg), preoperative asystole, massive fluid resuscitation (>3.5 litres per hour of operation), hypothermia (<33° Celsius) and severe acidosis (Rasmussen 2002). Whereas Rasmussen reported on rOSR, Mehta et al reported on risk factors for ACS (n=6) after EVAR (rEVAR) for rAAA: aortic occlusion balloon, coagulopathy, conversion from bifurcated to uni-iliac device and massive transfusion (Mehta 2005). Rubenstein et al reported both on ACS after rOSR (n=15) and ACS after rEVAR (n=6). They found that aortic balloon occlusion, massive transfusions and massive intraoperative fluid infusions were associated with ACS after rEVAR, but only transfusions of fresh frozen plasma (FFP) and platelets were associated with ACS after rOSR (Rubenstein 2015).

IAP measurement

A necessity for detecting and managing patients with IAH/ACS is repeated reliable IAP measurements. Clinical examination is the simplest method, but unfortunately shows poor sensitivity and accuracy for identifying IAH (Kirkpatrick 2000, Sugrue 2002). More accurate and more reliable measurements require some form of aid, most often in the form of a urinary catheter. Measurements can be direct or indirect and intermittent or continuous, as shown in Table 2 (Sugrue 2015). The direct route uses a catheter placed in the abdominal cavity, and the indirect route, a catheter placed in an intra-abdominal hollow viscus through its natural orifice, e.g. bladder or stomach. Another indirect pathway is through a catheter placed in the inferior vena cava (Lacey 1987).

Table 2. *Techniques for measuring intra-abdominal pressure*

Route	Type & availability	References
Indirect		
Bladder	Continuous & intermittent	Iberti 1987, Lacey 1987, Balogh 2004
Gastric	Continuous & intermittent	Sugrue 1994, Davis 2005
Rectal	Experimental	Obeid 1995
Vaginal	Experimental	Coleman 2012
Inferior vena cava	Continuous	Lacey 1987, Gudmundsson 2002
Direct		
Intraperitoneal	Continuous	Schachtrupp 2003

The standard for IAP measurement, adopted by the WSACS consensus guide-lines, is the intra-vesical technique, *Figure 1* (Kirkpatrick 2013). Due to its simplicity, low cost and reliable results, this technique has been widely adopted (Malbrain 2004). In order to obtain reproducible IAP measurements with this technique, the following criteria need to be met (Sugrue 2015):

- Expressed in mmHg
- Patient in supine position
- Priming volume <25 mL of saline (children less than 20kg: 1mL per kg)
- Interval of 30-60 sec after saline instillation to allow relaxation of bladder detrusor muscle
- Level zero at iliac crest in mid-axillary line
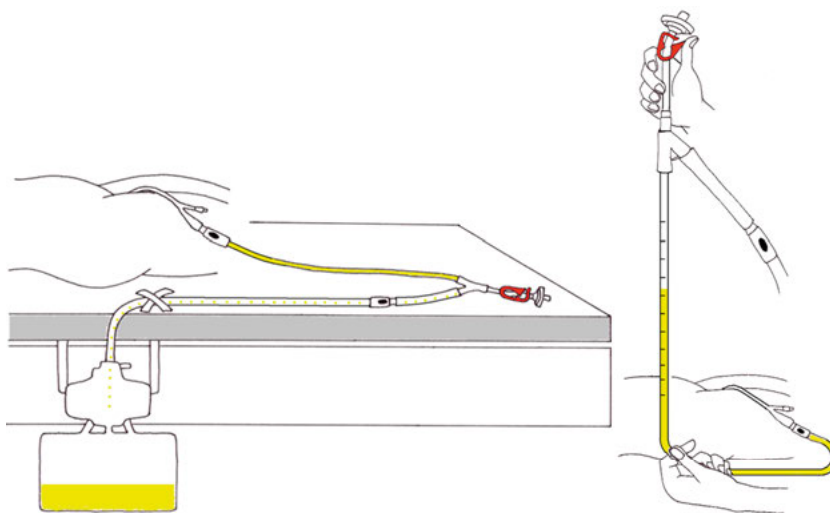- Measurement at end-expiration in absence of abdominal muscle contraction

Figure 1. FoleyManometer method of measuring IAP

Incidence

The incidence of ACS will inevitably depend on the studied population. ACS in relation to AAA surgery will depend on case-mix, resuscitation and transfusion protocols, and in the case of OSR also the rate of prophylactic open abdomen treatment (OAT). Awareness of the condition and whether routine IAP measurement is employed is likely also of importance. Illustrating this variance, the incidence of ACS after rAAA has been reported between 2-34% after rOSR and 5-21% after rEVAR (Fietsam 1989, Rasmussen 2002, Mehta 2005, Djavani 2006, Mehta 2006, Acosta 2007, Veith 2009, Djavani Gidlund 2011, Reimerink 2013, Karkos 2014, Powell 2014, Desgranges 2015, Rubenstein 2015).

Incidence of ACS after rOSR for rAAA

In the paper by Fietsam et al, where the term ACS was coined, 4 of 104 (4%) patients developed ACS (Fietsam 1989). Rasmussen et al compared outcome between prophylactic OAT and fascial closure after rAAA. Among those who had fascial closure, 11% received a DL due to IAH. Two Swedish studies, the first of which focused on ACS, reported incidences of 26% (Djavani 2006) and 7.5% (Acosta 2007). Three recent European randomized controlled trials comparing rOSR and rEVAR also detailed the incidences of ACS: 3.4% in AJAX (Reimerink 2013), 5.3% in IMPROVE (Powell 2014) and 2% in ECAR (Desgranges 2015). The same year as ECAR, Rubenstein et al reported an incidence of 34% in a single centre observational study (Rubenstein 2015).

Incidence of ACS after rEVAR for rAAA

In some of the earliest published data on ACS after rEVAR for rAAA, Mehta et al reported incidences of 20% and 18% in two consecutive studies (Mehta 2005, Mehta 2006). The following year Acosta et al reported an incidence of 5.3% (Acosta 2007). In a report with the ambitious title "Collected World and Single Center Experience with Endovascular Treatment of Ruptured Abdominal Aortic Aneurysms", with data from selected centres using EVAR whenever possible, the mean incidence of ACS was 12% (Veith 2009). A group from Zurich described an incidence of 20% and in another Uppsala study, 10% developed ACS (Mayer 2009, Djavani Gidlund 2011). A recent systematic review and meta-analysis, including some of the mentioned studies above, found a pooled ACS rate of 8%. When solely including studies with a clear definition of ACS, the incidence rose to 17% and when selecting those focusing on ACS, the incidence rose further to 21% (Karkos 2014). In the randomized rAAA trials the incidences of ACS after rEVAR were 8.8% in AJAX (Reimerink 2013), 5.4% in IMPROVE (Powell 2014) and 14.3% in ECAR (Desgranges 2015). Finally, Rubenstein et al reported an incidence of 20.7% in 2015 (Rubenstein 2015).

Incidence of ACS after iOSR and iEVAR for iAAA

There are numerous publications on the incidence of ACS after rAAA repair, however, this is not the case after iAAA repair. In the early report by Kron, two of the four patients who formed the very basis for the ACS hypothesis were treated for iAAA (Kron 1984). Yet after that, reports on ACS are based on patients treated for rAAA. ACS does not appear to be nearly as common after iAAA as after rAAA repair, and consequently meaningful studies would require a much larger patient population. In a study investigating OAT, 3 of 303 (0.9%) required OAT after iOSR for iAAA and 2 of 455 (0.4%) after iEVAR (Sorelius 2013). Among these five patients, four were decompressed due to ACS and one due to IAH. Thus, ACS after iAAA repair seems to be an infrequent event, which is twice as likely after iOSR than after iEVAR. However, there is little published data and certainly no population-based data.

Physiological effects of IAH

The body consists of several compartments enclosing their respective organs. The brain is enclosed in the scull, the heart and lungs are enclosed by the rib-cage, vertebral column and the diaphragm, and the abdominal cavity is enclosed by the pelvic floor, the diaphragm, the abdominal muscles and the vertebral column. IAH/ACS does not only affect the intra-abdominal organs, but can be transmitted to organs in other compartments (Malbrain 2014, Blaser 2015).

Renal effects

One of the first negative effects of elevated IAP to be described was on renal function (Wendt 1876). In 1947, Bradley et al reported how elevated IAP reduced renal blood flow and glomerular filtration rate in human volunteers (Bradley 1947). Several studies have shown the association between oliguria/anuria and elevated IAP (Harman 1982, Richards 1983, Kron 1984, Sugrue 1999). There also seems to be a dose-dependent relationship between increased IAP and renal impairment (Sugrue 1999, Biancofiore 2003).

Elevated IAP affects the kidneys in a number of ways, several of which have also been suggested to be the mechanism by which renal function is impaired: decreased cardiac output (CO), decreased renal perfusion pressure, increased renal venous pressure, decreased glomerular filtration gradient, decreased microcirculation and direct compression of the renal cortex (De Laet 2007, Cheatham 2009).

Cardiovascular effects

Increased IAP displaces the diaphragm in a cranial direction, effectively increasing intra-thoracic pressure (Robotham 1985). Venous return flow to the heart is thereby reduced, resulting in a reduced CO (Barnes 1985). In a study

on pigs subjected to haemorrhage and then resuscitation, CO was reduced when IAP rose above 10 mmHg (Simon 1997). Hypovolemia also exacerbates the decrease in CO observed with elevated IAP (Kashtan 1981, Friedlander 1998), where resuscitation with intravenous fluids will increase CO, but not to the same extent as DL (Cullen 1989). The increased intra-thoracic pressure can also cause hypokinesia of the heart as measured by echocardiography (Huettemann 2003).

Pulmonary effects

IAP and intra-thoracic pressure are closely related, exemplified by the variations in IAP during the respiratory cycle. Clinically, it is known that elevated IAP impairs respiratory function (Cullen 1989, Ridings 1995). Pulmonary physiology is affected by elevated IAP in the same way as cardiovascular physiology. The cranially displaced diaphragm increases intra-thoracic pressure, compressing the pulmonary parenchyma, causing atelectasis and perfusion mismatch (Mutoh 1991). The increased IAP reduces chest wall compliance, which means that higher ventilator pressures are required to deliver equivalent oxygenation. Exceedingly high ventilator pressures can then cause acute lung injury (Gattinoni 2010). The negative effect on oxygenation by increased IAP is exacerbated by preceding haemorrhage and resuscitation (Simon 1997).

In addition to sheer mechanical effects, elevated IAP also affects pulmonary function through humoral pathways, with release of pro-inflammatory cytokines, inducing pulmonary inflammation and alveolar oedema (Rezende-Neto 2002).

Splanchnic circulatory effects

Splanchnic circulation and abdominal wall blood flow has been shown to decrease already at IAP $\geq$10 mmHg (Diebel 1992). The greater the increase in IAP, the greater the decrease in splanchnic blood flow (Diebel 1992). The reduction is not automatically accompanied by a lowered mean arterial pressure (MAP), making detection and monitoring more elusive (Diebel 1997). At IAP levels of 20 mmHg, decreases in blood flow can be measured in nearly every splanchnic organ (Caldwell 1987, Djavani 2009). The reduction of blood flow to the superior mesenteric artery, after haemorrhage in combination with elevated IAP, is more pronounced than the reduction of CO itself. This suggests that restoring CO may be insufficient in terms of also restoring blood flow (Friedlander 1998). Alongside reductions in venous return and outflow, mechanical compression of intra-abdominal capillaries and veins also contribute to venous stasis, which in turn will increase intestinal oedema and further accelerate the negative cycle (Caldwell 1987, Schilling 1997).

Central nervous system effects

Several normal physiologic functions such as coughing, vomiting and defecation, transiently increase intracranial pressure (Josephs 1994). IAH may contribute to elevated intracranial pressure and decreased cerebral perfusion pressure by raising intra-thoracic pressure, which is known to impede cerebral venous outflow (Bloomfield 1997, Citerio 2001). This mechanism is similar to the way that positive expiratory end pressure can increase intra-cranial pressure during mechanical ventilation (Burchiel 1981).

Outcome

Outcome of ACS after rOSR for rAAA

Mortality with ACS after rOSR was first reported in the two landmark papers from the 80s (Kron 1984, Fietsam 1989). In the paper by Kron et al, three of the eleven described patients were operated on for rAAA. The first patient, who was not decompressed died, while the two who were decompressed survived (Kron 1984). In the report by Fietsam et al, three of the four patients who developed ACS after rOSR for rAAA died, despite the fact that all were decompressed (Fietsam 1989). In 2002, Rasmussen et al published a case-control study where patients who received prophylactic OAT after rAAA repair were matched with controls who had their abdomens closed. In-hospital mortality was 7 of 10 (70%) among the controls who developed ACS (Rasmussen 2002). The ECAR trial reported a mortality of 1 of 1 (100%) with ACS while the AJAX and IMPROVE trials did not report the specific outcome of ACS, despite having reported the incidence (Reimerink 2013, Powell 2014, Desgranges 2015) Another recent study, which focused specifically on ACS, reported an in-hospital mortality of 8 of 15 (53%) (Rubenstein 2015). In summary, mortality with ACS development after rOSR for rAAA ranges from 33-100%.

Outcome of ACS after rEVAR for rAAA

One of the earliest studies on ACS after rEVAR reported an in-hospital mortality of 4 of 6 (67%) (Mehta 2005). In an extended study the following year, which focused on establishing a protocol for rEVAR, the same authors reported a mortality of 4 of 7 (57%) (Mehta 2006). In 2009, Mayer et al presented a large single centre experience with a 30-day mortality of 6 of 20 (30%) (Mayer 2009), and two years later Djavani et al reported a mortality of 1 of 3 (33%) (Djavani Gidlund 2011).

Recently, several studies and a systematic review and meta-analysis have been published. The meta-analysis reported, with data available on 76 of 108 patients, a mortality of 35 of 76 (47%) (Karkos 2014). The ECAR trial reported a 30-day mortality of 4 of 8 (50%), and Rubenstein et al described an in-hospital mortality of 5 of 6 (83%) (Desgranges 2015, Rubenstein 2015).

Based on these reports, mortality in patients with ACS after rEVAR for rAAA is 30-83%.

Outcome of ACS after iOSR and iEVAR for iAAA

As noted previously, data on the incidence and outcome of ACS after iAAA repair is virtually non-existent. While Sörelius et al reported on the incidence of OAT after iAAA repair, outcome for this specific group was not detailed (Sörelius 2013).

Treatment of IAH/ACS

The WSACS consensus definitions and clinical practice guidelines contain a general management algorithm and a specific medical management algorithm. Medical and minimally invasive treatment is recommended with IAP ≥12 mmHg. Treatment can be divided into different categories depending on the intended effect. The WSACS guidelines recommended that treatment is undertaken in a step-wise fashion, where the steps for each category is detailed therein (Kirkpatrick 2013). All measures described in the step-wise algorithm is detailed below. Not all measures described are supported by evidence, but are then supported by expert opinion.

Evacuation of intraluminal contents

1. Nasogastric and/or rectal tube

Studies have not shown better outcome with routine use of postoperative nasogastric tubes. However, evacuation of gastrointestinal contents by either a nasogastric or rectal tube is theoretically appealing, as it offers a minimally invasive measure that can reduce the intra-abdominal volume.

2. Gastrointestinal pro-motility agents

Treatment with neostigmine has shown to decompress the colon in pseudo-colonic obstruction, why treatment is recommended if IAH is associated with colonic pseudo-obstruction (Ponec 1999).

3. Minimize enteral nutrition

Minimizing enteral nutrition will reduce the amount of intraluminal contents. Although such a regime can be strategically negative since enteral nutrition will result in earlier bowel emptying. If early enteral nutrition is used the gastric content should be emptied once or twice a day.

4. Administration of enemas

In the same way that orally given pro-motility agents may help in stimulating bowel movements, rectal administration of enemas may help emptying the colon.

5. Colonoscopic decompression

Colonoscopic decompression can be used in colonic pseudo-obstruction to de-compress a dilated colon (De Giorgio 2009), and is recommended if IAH is accompanied by colonic dilatation.

Evacuation of intra-abdominal space occupying lesions

1. Percutaneous catheter drainage

Percutanous drains offer a minimally invasive alternative to reducing intra-abdominal fluid collections. Successful reports have been published (Corcos 2001, Latenser 2002), why drains are recommended when deemed feasible.

2. Surgical evacuation of lesions

When evacuation of a lesion is warranted and percutaneous catheter drainage is not feasible, surgical evacuation should be considered.

Improve abdominal wall compliance

1. Optimal analgesia

Optimal analgesia is a cornerstone of modern medicine and is recommended as initial treatment of IAH. IAP is affected by abdominal muscle contractions, which in turn are affected by adequate pain relief. An effective pain relief may reduce IAP considerably.

2. Remove constrictive dressings

Constrictive dressings such as abdominal girdles are commonly used after AAA repair. In the event of IAH, the removal of constrictive dressings should be considered. However, among unselected patients after laparotomy, IAP was not significantly increased by the use of an elastic girdle (Clay 2014).

3. Optimizing body position

There is often a trade-off between optimizing respiration, which may require elevation of the chest, and reducing IAP. Different body positions have the potential to either increase or decrease IAP. Prone positioning shows small increases in IAP, although decreasing IAP is considered possible with a tailored prone positioning technique (Kirkpatrick 2010). A head elevation of 15-30 degrees results in a significant IAP increase and abdominal perfusion pressure decrease (Cheatham 2009, Yi 2012).

4. Neuromuscular blockade

Neuromuscular blockade is the last step of medical management aiming to improve abdominal compliance. Neuromuscular blockade has been shown to reduce IAP among patients with IAH as well as during laparoscopy (De Laet 2007, Van Wijk 2015). Higher fascial closure rates have also been reported

with postoperative neuromuscular blockade among trauma patients receiving OAT (Abouassaly 2010).

Optimization of fluid balance

    1.   Fluid balance

A positive cumulative fluid balance is associated with IAH (Malbrain 2005, Cordemans 2012), and in trauma patients, profuse crystalloid infusion is associated with ACS (Balogh 2003). WSACS guidelines suggest avoidance of positive fluid balance after acute resuscitation is finished.

    2.   Fluid removal through diuresis

Diuretics are widely used to improve fluid balance. The WSACS guidelines make no suggestions regarding their use for IAH/ACS but include them in the algorithm.

    3.   Renal replacement therapy

Renal replacement therapy (RRT) also offers the possibility of augmenting fluid balance. As with diuretics, the WSACS guidelines give no recommendations regarding RRT, but the algorithm includes consideration of RRT as the final step of fluid balance optimization.

Optimization of systemic and regional perfusion

    1.   Goal-directed fluid resuscitation

Early goal-directed therapy was described in a landmark paper on sepsis (Rivers 2001), where treatment was directed by a bundle of goals. Although goal directed therapy has come under debate in recent years, benefits with goal-directed therapy have recently been reported in cardiac surgery (Osawa 2016).

    2.   Haemodynamic monitoring guiding resuscitation

Positive effects of using haemodynamic monitoring to guide fluid resuscitation have been reported, and is the second step of perfusion optimization (Bednarczyk 2017)

DL

The early studies (Kron 1984, Fietsam 1989) described how DL resulted in dramatic physiological improvement, and Kron et al also reported that four patients who did not undergo DL died. While clear evidence is lacking as to whether DL actually reduces mortality, many studies describe pronounced physiological improvement after decompression, Table 3. DL is considered the golden standard therapy and is recommended in the WSACS guidelines when overt ACS is present (Kirkpatrick 2013).

Table 3. *The physiological effects of DL*

Reference	Physiological effects
Kron 1987	Improved renal function
Fietsam 1989	Improved renal function, central venous pressure, ventilator pressure, oxygenation and arterial carbon dioxide tension
Platell 1990	Improved renal function
Meldrum 1997	Improved renal function, cardiac index, oxygen delivery and decrease in pulmonary capillary wedge pressure, systemic vascular resistance and peak airway pressure
Chang 1998	Improved preload, respiratory function and visceral perfusion
Sugrue 1998	Improved renal function, improved dynamic lung compliance
Ertel 2000	Improved cardiac index, renal function, tidal volume. Decreased heart rate, central venous pressure, pulmonary artery occlusion pressure, peak airway pressure and lactate
Biffl 2001	Improved systolic pressure and renal function and decreased peak airway pressure
McNelis 2002	Improved renal function, cardiac index and reduced peak inspiratory pressure
Balogh 2003	Improved renal function, MAP, cardiac index, systemic vascular resistance index, mixed venous oxygen saturation, base deficit, arterial pH and respiratory function
Joseph 2004	Decreased intracranial pressure among patients with elevated intracranial pressure after traumatic brain injury
Batacchi 2009	Improved SOFA score and lactate decrease
Mentula 2010	Improved renal or respiratory function
De Waele 2010	Organ function quantified by SOFA score improved
Pearson 2010	Improved oxygenation and MAP, less fluid requirements, less vasopressor requirement and lactate decrease.
Zhou 2010	Increased aerated lung volume
De Waele 2016	Improved oxygenation and renal function

CI

CI is the result of impaired circulation to the colon, affecting one or more layers of the colon wall. Grading the severity into three grades was proposed by Tollefson et al (Tollefson 1991):

I	Mucosal ischaemia
II	Mucosal and muscular ischaemia
III	Transmural ischaemia

The mucosa, which receives the majority of the blood supply to the bowel, is most sensitive and therefore the first layer to be affected by hypoperfusion. With longer duration and greater severity of hypoperfusion, the muscularis layer is affected and finally also the serosa. Transmural ischaemia, also known as full thickness ischaemia, will result in loss of the structural integrity of the bowel wall (Haglund 1987, Haglund 1999). The sigmoid colon is the part of colon most frequently affected by ischaemia after AAA surgery (Björck 1996).

Incidence

The incidence of CI after AAA repair depends on whether treatment is for iAAA or rAAA and whether performed with OSR or EVAR. After iAAA repair, the incidence is 0.5-3% (Björck 1997, Van Damme 2000, Dadian 2001, Geraghty 2004, Maldonado 2004, Ultee 2016), and after rAAA repair it is 6-15% (Björck 1997, Perry 2008, Ultee 2016). When postoperative colonoscopic surveillance is performed after rAAA repair, higher incidences of 23-36% have been reported (Champagne 2004, Champagne 2007).

Risk factors

IAH is common after AAA repair and especially after rAAA repair (Platell 1990, Papavassiliou 2003). As previously described, IAH is associated with reduced splanchnic circulation, where reduced colonic circulation has been specifically reported (Djavani Gidlund 2011). Patients operated on for AAA are even more vulnerable for CI since the inferior mesenteric artery, which provides circulation to the left colon, is normally ligated (if patent) during OSR and covered by the stentgraft during EVAR.

Several studies have explored risk factors for CI after AAA repair and found that some are related to the preoperative physical status of the patient while others are related to the AAA repair. Björck et al identified rupture, renal disease, age, aorto-bifemoral graft, operating time, cross-clamping time and ligation of one or both hypogastric arteries as independent factors (Björck 1997). Becquemin et al found that rupture, duration of operation and creatinine >200 mol/l affected the risk for CI (Becquemin 2008). In a recent study,

the need for intra- or postoperative transfusions, aneurysm rupture, renal failure requiring RRT, proximal extension of aneurysm, diabetes and female sex all predicted CI (Moghadamyeghaneh 2016). The same study also found that age and CI requiring surgical treatment predicted mortality. Another recent study found rupture to be the most important predictor followed by OSR. Other associated factors were advanced age, female sex, hypertension, heart failure, smoking, unilateral hypogastric artery occlusion, prolonged operating time, blood loss >1 litre and a femoral anastomosis (Ultee 2016).

Diagnostics

In clinical routine, a sigmoidoscopy/colonoscopy is recommended when CI is suspected (Chaikof 2018, Wanhainen 2019). The endoscopy can, however, only disclose the presence of CI and cannot differentiate between mucosal and transmural ischaemia (Houe 2000).

Several methods have been evaluated for measuring colonic perfusion and identifying hypoperfusion. A report from the 1970s advocated measurement of inferior mesenteric artery stump pressure for predicting the risk of CI (Ernst 1978). The authors concluded, based on one patient with "ischemic colitis", that CI did not develop when IMA stump pressure was above 40 mmHg or when IMA had a pre-existing occlusion. However, later papers have reported CI during those settings (Schiedler 1987, Piotrowski 1996). Other methods for measurement of colonic circulation have also been reported: pulse oximeter probe placed in colon (Ouriel 1988), inferior mesenteric vein sampling (Avino 1995) and laser Doppler flowmetry (Ahn 1986).

Another available method for measurement of colonic perfusion is colonic tonometry. The first device was described in 1972 (Ninikoski 1972) and the technique was further developed ten years later (Fiddian-Green 1982). The technique utilizes a catheter with a small balloon placed in the part of the gastrointestinal tract of interest. The balloon is gas permeable, allowing CO_2 in the gastrointestinal lumen to equilibrate with CO_2 in the balloon, where samples are then intermittently collected. With the addition of arterial bicarbonate concentration, intraluminal pH (pHi) can be calculated by using the Henderson-Hasselbalch equation. In 1986, Fiddian-Green et al evaluated colonic tonometry in patients subjected to aortic surgery (Fiddian-Green 1986). Twenty-five high-risk patients for CI were subjected to pHi measurement after aortic surgery, six of whom developed early ischaemic values. Among all six, the ischaemic values were noted on the same day as the operation and they later developed clinical signs of CI. In another study, intraoperative pHi of the sigmoid colon was measured. Three patients with pHi <6.86 developed severe CI and seven patients with pHi down to 6.99 developed mild CI (Schiedler 1987). Björck et al reported how pHi <7.10 served as a warning of impending CI and that pHi <6.86 predicted endoscopically detectable CI (Björck 1994). In another study by Björck et al, patients who developed CI had pHi <7.1 for 16-

80 hours, while those with pHi <7.1 for less than five hours neither developed ischaemic lesions nor experienced adverse outcome (Björck 2000).

There are, however, several drawbacks with intraluminal colonic tonometry. Catheter placement requires sigmoidoscopy, which can be complicated by diverticulosis, a common feature in the elderly population. Some patients have large amounts of faeces in the colon, preventing correct measurement, and bowel movements may also displace the catheter. Extraluminal colonic tonometry is a new and less explored method, which utilizes extraluminal measurement of pH (pHe). The catheter is placed adjacent to the sigmoid colon in the abdominal cavity at the end of AAA surgery. This technique does not have the same disadvantages as pHi measurement. Djavani et al compared pHe and pHi and found pHe useful as a screening test and that pHe <7.2 indicated CI (Djavani Gidlund 2011).

Treatment

CI without full-thickness involvement, equal to grade I and II, can be treated conservatively, while CI engaging all layers of the colon requires surgical resection (Björck 2000, Becquemin 2008, Chaikof 2018). Conservative treatment include physiologic optimization and measures to treat and reduce IAH (Djavani 2009, Kirkpatrick 2013, Chaikof 2018).

Outcome

Mortality is considerable when AAA repair is complicated by CI. After iAAA repair mortality with CI is 20-50%, strikingly high compared to when CI does not develop, and after rAAA repair mortality with CI is 30-50% (Dadian 2001, Geraghty 2004, Maldonado 2004, Ultee 2016).

Rationale

ACS and CI are severe complications after AAA surgery. As such they warrant attention with efforts to improve for those at risk and those affected. The vascular research group in Uppsala, which has a wide interest in aortic disease, has also had a special interest in ACS and CI for more than twenty years.

While there are studies that have reported on ACS, they are not many and most include few ACS patients. Also, the endovascular revolution has changed the landscape of vascular surgery, so that existing data risk becoming irrelevant. Larger studies require multi-centre data, which is not easily gathered. In that regard, a registry covering many centres or an entire population can make an important contribution. Although many centres in Sweden are small by international standards, all centres dutifully report to Swedvasc. So, when Swedvasc incorporated ACS as a variable, it provided access to population-based data from a population of 10 million people, and opened up for unique opportunities in studying ACS. In this context, aspects of ACS can be reported using nationwide data, which means that outstanding issues can be addressed and the nature of ACS in the endovascular era can be explored.

Despite the very serious nature of ACS, there is a developed easy-to-use monitoring system for IAH/ACS used in hospitals around the world, namely repeated IAP measurements. However, there is no corresponding widely established method for monitoring postoperative colonic circulation. Ideally, such a method should facilitate early detection of colonic malperfusion and enable feedback from any undertaken countermeasures. A possible solution to this methodological problem may be extraluminal colonic tonometry. The method involves a catheter placed trans-abdominally at the end of surgery, in contact with the sigmoid colon serosa. pH of the colonic bowel wall is then measured for the desired time of observation, after which the catheter is withdrawn. Standalone extraluminal colonic tonometry has not been studied and warrants further evaluation for feasibility and efficacy.

Aims

The overall aim of this thesis was to investigate ACS and CI after repair of iAAA and rAAA. The specific aims were:

- To describe the incidence, treatment and outcome of ACS after AAA repair in Sweden (Paper I)

- To investigate the outcome and prognostic factors for ACS and OAT after AAA repair, with emphasis on the significance of the underlying main pathophysiological finding, the timing of DL and the duration of IAH before decompression (Paper II)

- To investigate morphological, radiological and physiological risk factors for ACS after rEVAR for rAAA (Paper III)

- To evaluate the feasibility and safety of postoperative extraluminal pH measurement using colonic tonometry in surveillance for CI after AAA repair (Paper IV)

Patients and methods

Study designs

The first three studies in this thesis were retrospective, nationwide or multi-centre, and based on patients identified through the Swedish vascular registry (Swedvasc). Study III utilized a nested case-control design with all centres eligible for participation. Seven centres had patients matching inclusion criteria, why the study was termed as multi-centre. Study IV was a prospective, single-centre study performed at Gävle County Hospital. The study designs are shown in Table 4.

Table 4. *Designs of the studies in the thesis*

Study	Design	Period	Patients	Centres	Sources
I	Retrospective national cohort study	2008-2013	AAA n=6634	Nationwide (31 centres)	Swedvasc and Medical records (validation)
II	Retrospective national cohort study	2008-2015	ACS n=120	Nationwide (24 centres)	Swedvasc, Swedish Intensive care registry and Medical records
III	Retrospective nested case-control multi-centre study	2008-2015	ACS n=40 Controls n=68	Multicentre (7 centres)	Swedvasc, Medical records and radiologic imaging
IV	Prospective single centre study	2013-2019	Monitored n=27	Gavle County Hospital	Medical records and monitoring protocol

Registries

Swedvasc is the national vascular registry in Sweden. It was established in January 1987 and reached nationwide coverage by 1994. Several validations have been performed, confirming validity of well more than 90% (Troeng 2008, Venermo 2015). The registry has undergone a number of revisions and in 2008 came to include separate variables for ACS and DL. This change made it possible to identify patients with ACS in the registry. Swedvasc is also

cross-linked with the national population registry, why survival data in Swedvasc is near absolutely correct.

The Swedish Intensive Care Registry is the national quality registry of intensive care in Sweden and monitors the quality of care. It was established in 2001 with coverage of all units performing intensive care in Sweden.

Patients

Studies I-III identified patients based on examination of AAA repairs registered in Swedvasc. For study I, all 7417 AAA repairs between May 2008 and December 2013 were examined. For studies II & III the starting point was the same but the study periods were prolonged until September 2015 in order to include more patients, resulting in 8765 examined AAA repairs.

Study I included all 6634 identified AAA repairs in Swedvasc. Study II and III employed a two-step approach for inclusion. All patients eligible for inclusion were first identified in Swedvasc and selected for individual case record review. Patients whose case records confirmed the inclusion criteria for each study were then included. In study II, 179 patients registered for both AAA repair and ACS were identified and selected for case record review. Among those, 120 patients had ACS diagnosis confirmed during review and they were included in the study.

In study III, 39 patients with ACS after rEVAR were identified in Swedvasc and each patient was matched with two controls without ACS. Matching was performed by centre and repair date, so that both controls were treated with rEVAR at the same centre, and the first control being the previously treated patient and the second being the following treated patient. In the event that sequential patients developed ACS, the two patients treated in closest proximity in time were chosen as controls. After case record review, 40 ACS patients and 68 controls were finally included. Consort diagrams for respective study are shown in *figure 2, 3 and 4*.

Patients found with repair for other indications than infra- or juxta-renal AAA were excluded, as were those with AAA repair at Sahlgrenska University hospital, in order not to compete with an ongoing study on prophylactic OAT at that hospital. The second and third study excluded those where ACS was not confirmed in the case records. The most common reason for exclusion was prophylactic OAT, which was found among 26 patients. Another seven patients had OAT due to wound dehiscence, and although IAH may have played a part, poor fascial edges was stated as the main reason for OAT. The third study also excluded controls with experimental local thrombolysis for IAH and those where rEVAR for rAAA was not confirmed. Furthermore, in the third study, three patients assigned as controls were found to have developed ACS, despite not being registered, and were then allocated to the ACS study group.
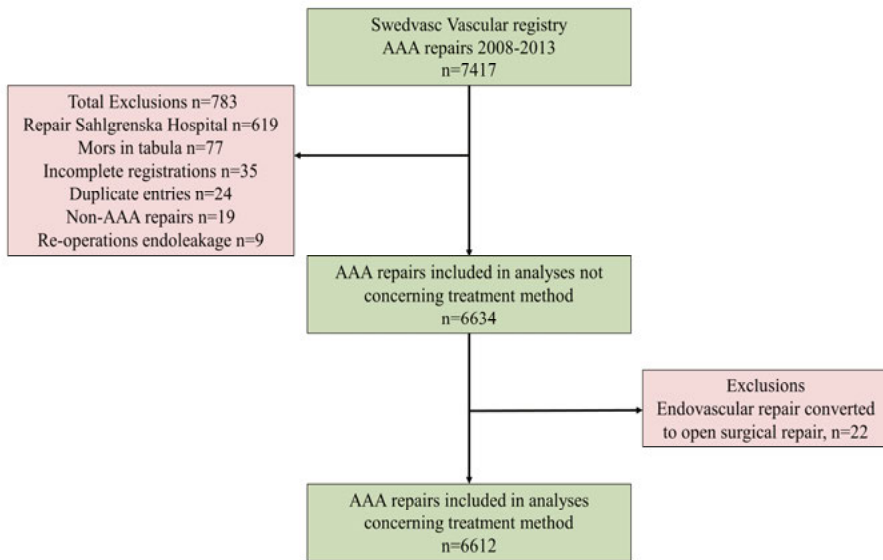
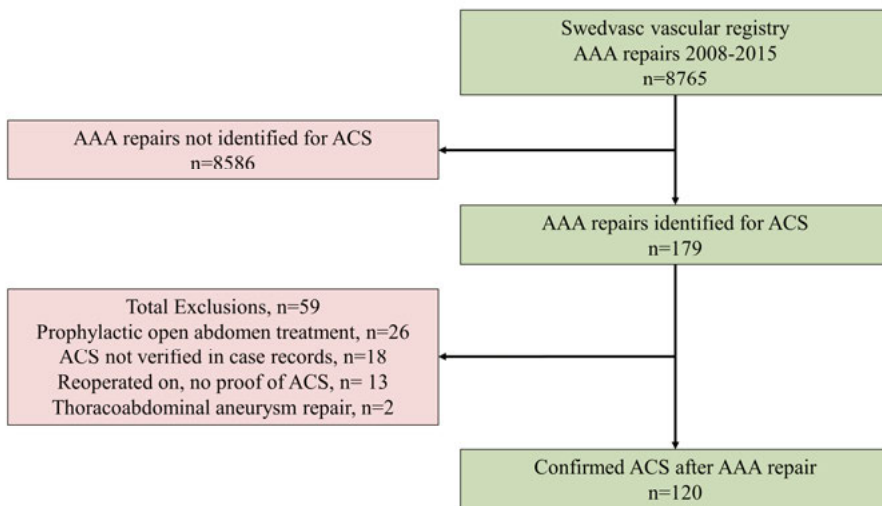*Figure 2.* Consort diagram study I. Modified from paper I.

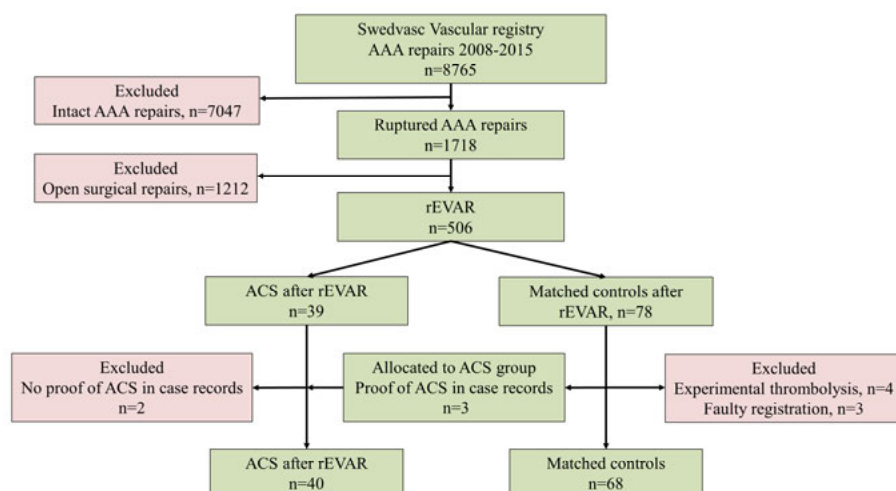*Figure 3.* Consort diagram study II. Modified from paper II.

Figure 4. Consort diagram study III. Reproduced from paper III.

The fourth study included 27 patients operated on for iAAA or rAAA at Gavle County Hospital during 2013-2019. A number of eligible patients were not included. Ruptured AAA patients not included mainly belonged to time periods when the primary investigator (S.E) was on leave for a fellowship or on administrative leave. Intact AAA patients were included at the same rate as rAAA, as there was an effort to have equally sized groups. The iAAA repairs with more complex anatomy and being at a higher at risk for CI were selected for inclusion, while those with very low risk were not.

Methods

The definition of ACS was according to the Abdominal Compartment Society's consensus definitions and clinical practice guidelines (Kirkpatrick 2013).

Study I

Risk factors and outcome were compared between those who developed ACS and those who did not, with analyses separate for rAAA and iAAA repair. Among ACS patients, outcome was also compared for treatment modality, EVAR or OSR, and whether DL was performed or not.

Patients (n=22) whose repair consisted of conversion of previous EVAR to OSR were excluded from analyses related to treatment method.

Among patients treated with OSR for rAAA (n=965), a validation from 300 of the case records was performed to identify the rate of prophylactic OAT.

Study II

Patients were grouped according to main pathophysiological finding at DL (bowel ischaemia, postoperative bleeding or oedema), the timing of DL (early: within 24 hours, intermediate: 24-48 hours and late: after 48 hours) and depending on method of treatment (OSR or EVAR). Analyses of duration of IAH utilized two fixed levels of IAP, ≥ 15 mmHg and ≥ 20 mmHg.

Survivors and non-survivors at 90 days after AAA repair were compared for risk factors. Outcome was analysed with respect to subgroups, where the analyses on treatment modality were performed separate for rAAA and iAAA repair. In addition to the timing of DL being used to group patients, the timing of DL was also compared for survivors versus non-survivors, EVAR versus OSR and for main pathophysiological finding at DL. Outcome analysis included mortality and morbidity, where mortality was analysed at 30 days, 90 days and at one year, while morbidity included the rate and duration of RRT, and the duration of mechanical ventilation.

When analysing the time from symptoms to arrival at hospital and arrival at hospital to surgery, patients referred from another hospital were excluded due to missing information. Analysis of postoperative transfusions excluded those who did not survive the entire period of respective (24 hours or 48 hours) analysis. Analyses related to RRT excluded those who died within 48 hours with respect to competing risk.

Study III

ACS patients and controls were compared for perioperative and radiologic imaging risk factors, which included risk factors for type II endoleak (T2EL) and aortic morphology.

For the same reasons as in study II, referred patients were excluded from the specific analyses of time to hospital and time to surgery, while postoperative transfusion analysis excluded those who did not survive the whole 24 or 48 hour duration of respective analysis.

Significant physiological risk factors were plotted in receiver operator characteristics (ROC) curves. Preoperative blood pressure (BP) and intraoperative pRBC were dichotomized and combined with aortic balloon occlusion and tested in models with two or three factors together.

Radiologic imaging assessment

Analysis of radiologic imaging was performed with blinding of individual patient group affiliation by two experienced vascular surgeons: Examiner N°1: S.E. in Gavle and examiner N°2: H.B. in Uppsala. All CT images were evaluated by examiner N°1. All borderline measurements, relating to each device's specific instructions for use (IFU), were then analysed by examiner N°2. Des-

ignation of borderline measurement was according to the following conditions: The proximal neck having a 5-15% diameter increase (inverted funnel) along the required neck length (the maximum recommended diameter increase is 10%), the iliac artery having a 5-15% inverted diameter increase (funnel) in the distal landing zone, and the proximal neck's alpha and beta angulations being within 15 degrees of the recommended maximum angulation. Measurements diverging between examiners were jointly re-measured to obtain consensus. Measurements were then dichotomized as either being in compliance with device specific IFU, inside IFU, or not in compliance with IFU, outside IFU.

Measurements not eligible for borderline classification were assessed by one examiner and included preoperative internal iliac artery occlusion, aneurysm rupture site, visible active extravasation and patency of the inferior mesenteric and lumbar arteries.

All radiologic imaging analysis was performed with dedicated software for imaging reconstruction, Vital Images in Gävle and 3mensio Medical Imaging in Uppsala.

Study IV

Extraluminal colonic tonometry was performed using the following procedure: prior to completion of the AAA operation, right before abdominal closure, a balloon catheter was tunnelled through the left fossae abdominal wall and placed adjacent to and in contact with the sigmoid colon. To detect and prevent dislodgement, the catheter was marked with a pen and anchored to the skin with a stitch. If there was doubt as to the stability of the position, the catheter was anchored with a loose suture to the peritoneum beside the sigmoid colon.

In the intensive care unit (ICU), the catheter was connected to a Tonocap device (GE Healthcare, Helsinki, Finland) which measured the extraluminal partial pressure of pCO_2 at intervals of 10 minutes. The measurements were combined with values from arterial blood gas samples. Extraluminal pH was calculated using the Henderson-Hasselbalch equation. Every four hours the measurements were recalibrated and repeated. This was continued for the duration of the ICU stay or until a maximum of 48 hours, upon which the catheter was removed.

If measurements fell below pHe 7.2, the threshold indicative of colonic malperfusion in previous work (Björck 2000, Djavani Gidlund 2011), the vascular surgeon was contacted. Measurements were then subjected to intensification if considered necessary, along with appropriate treatment in consultation with the intensivist physician in charge. Simultaneous to all pHe measurements, IAP was measured using the FoleyManometer device (Holtech, Medical, Charlottenlund, Denmark).

Clinically significant CI was defined as CI equal to Grade II-III according to the classification proposed by Tollefson et al (Tollefson 1991). In this classification grade I is defined as mucosal ischaemia, grade II as mucosal and muscularis layer ischaemia and grade III as transmural ischaemia.

All simultaneous IAP and pHe values were tested for correlation. Sensitivity and specificity analysis tested the ability of pHe to detect CI.

Statistics

The data management and statistical analyses for all studies and this thesis utilized SPSS Statistics version 22.0 to 25.0 (IBM, Armonk, NY, USA.)

Categorical data were shown as numbers and/or proportions expressed as percentage and comparisons were performed with Fisher's exact test or Chi-square, as appropriate. Continuous variables were in paper I shown as means and compared by Student's t-test, after testing for normality. Testing for normal distribution included visual assessment of histograms and the Shapiro-Wilk test. Continuous variables were in paper II-IV displayed as medians (interquartile range [IQR]) and compared using non-parametric tests: Mann-Whitney U-test for groups of two and Kruskal-Wallis test for groups of three.

Survival and outcome analysis was in paper I performed with the Kaplan-Meier method and Cox proportional hazards regression, and in paper II with the Kaplan-Meier method and multivariable logistic regression by forced entry. The latter was also used in paper III in analysis of risk factors. Associations in the logistic regression were expressed as odds ratios (OR) including 95% confidence intervals.

Correlations were, in studies III-IV, tested using Spearman's rank coefficient. Linear interpolation was used to obtain estimated hourly values of IAP (paper II) and pHe (paper IV), between two already existing measurements.

Missing data was in all studies handled by exclusion from respective analysis.

In paper I and III, the threshold for significance was set to *p<.01*, adjusting for multiple comparisons, while *p<.05* was considered significant in the remaining studies. The tests were two sided in all studies.

Ethical considerations

All studies were approved by the regional ethics review board in Uppsala. Earlier practice mandated individual informed consent for retrospective review of case records. This later changed on a national level and was an adjustment to the situation in other countries. Consequently, individual informed consent was not needed for studies I-III.

Study IV employed individual informed consent. Among patients operated on for iAAA, consent was collected prior to inclusion. Among patients operated for rAAA, written consent was collected as soon as feasible, in line with the mandate of the ethical approval. Patients were informed again at the time of discharge from the hospital. Among those where written consent was not feasible prior to AAA surgery, the relatives were informed as soon as possible. The ethical review boards in Sweden have repeatedly approved written consent being obtained after the emergency procedure (Djavani Gidlund 2011, Fröbert 2013). Waiving written informed consent prior to the emergency procedure is also not unique to Swedish Ethics Committees, and an example of this is the IMPROVE trial (Powell 2014). In many situations, it is the patients who have the most to gain from new evidence, who at the same time are those who (due to the circumstances) are the least able to give that consent. It is obvious that it is an extremely delicate and complex subject that requires the full consideration of the review boards. Not all countries have reached the same conclusion, but different solutions have emerged in different countries.

Results

Study I

There were 5271 repairs for iAAA and 1341 repairs for rAAA (20.4%). OSR was performed in 2206 (41.9%) of the iAAA repairs and 965 (72.0%) of the rAAA repairs, while the other repairs were performed with EVAR.

The study population exhibited some baseline differences. In the iAAA group, those treated with iEVAR were older (74.0 years versus 69.9, $p<.001$), less often women (14.9% versus 17.6%, $p=.009$), had more cardiac disease (43.7% versus 36.7%, $p<.001$) and higher preoperative creatinine (98.6 μmol/L versus 90.2, $p<.001$), compared to iOSR patients. In the rAAA group, those treated with rEVAR were older than rOSR patients (76.6 years versus 73.9, $p<.001$), Table 5.

Table 5. *Clinical characteristics of the study cohort. Adapted from paper I.*

	rAAA			iAAA		
	rOSR n=965	rEVAR n=376	p-value	iOSR n=2206	iEVAR n=3065	p-value
Age [years]	73.9	76.6	**<.001**	69.9	74.0	**<.001**
Female sex*	17.6	23.1	.025	17.6	14.9	**.009**
Cardiac disease*	36.5	42.6	.067	36.7	43.7	**.001**
Pulmonary disease*	22.6	26.7	.164	21.6	23.5	.120
Creatinine [μmol/L]	123.3	108.3	.191	90.2	98.6	**<.001**
Aneurysm width [mm]	79.4	73.1	.218	61.4	61.0	.400

L= Litres; mm= millimetres; Periop= Perioperative; Values are means. *Values are percentages.

The incidence of ACS after rAAA repair did not differ between rOSR and rEVAR (6.8% vs 6.9%, $p=1.0$) but the incidence was higher after iOSR than iEVAR for iAAA (1.6% versus 0.5%, $p<.001$).

Risk factors

Age and sex did not impact ACS development after rAAA repair nor iAAA repair, but several other risk factors were identified. Patients who developed ACS after rAAA repair had lower preoperative BP (61.4 mmHg versus 76.3, *p=.004*), more often episodes of preoperative unconsciousness (60.4% versus 44.9%, *p=.004*), more often intraoperative blood loss >5 litres (44.7% versus 22.1, *p<.001*) and were more frequently subjected to aortic balloon occlusion (61.5% versus 20.2%, *p<.001*), compared to those without ACS.

Among patients who developed ACS after iAAA repair, intraoperative blood loss >5 litres was more common (21.2% versus 2.4%, *p<.001*) as well as re-implantation of a renal artery (13.9% versus 3.5%, *p=.009*), compared to non-ACS patients.

Outcome

Outcomes among ACS patients, compared to non-ACS patients, were worse in nearly every measured outcome variable after both rAAA and iAAA repair, as shown in Table 6. After rAAA repair, the mortality rate with ACS versus without ACS was roughly two-fold at every measured point in time. After iAAA repair, the mortality rate was overall lower than after rAAA repair, but the difference between those with and without ACS was even higher, being six-fold at 90 days and more than four-fold at one year, Table 6.

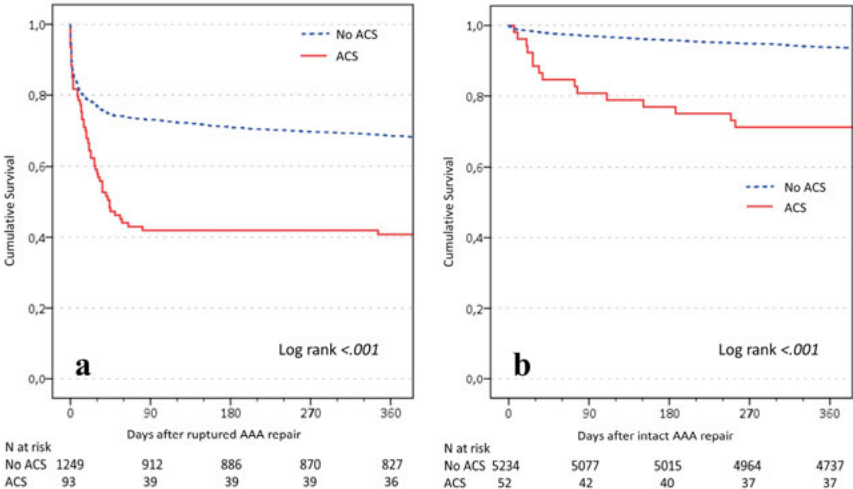Table 6. *Outcome with or without ACS after rAAA and iAAA repair. Adapted from paper I*

	rAAA			iAAA		
	ACS n=94	No ACS n=1253	p-value	ACS n=52	No ACS n=5235	p-value
AMI	14.6	4.4	**<.001**	5.9	1.6	.050
Renal failure	73.1	15.6	**<.001**	48.1	3.5	**<.001**
MOF	63.4	11.5	**<.001**	34.6	1.0	**<.001**
ICU care > 5 days	97.4	22.7	**<.001**	61.5	3.4	**<.001**
Bowel ischaemia	38.5	7.1	**<.001**	28.8	1.2	**<.001**
Bowel resection	28.7	3.6	**<.001**	25.0	0.7	**<.001**
Re-lap for bleeding	28.7	5.0	**<.001**	19.2	2.2	**<.001**
30-day mortality	42.4	23.5	**<.001**	11.5	1.8	**<.001**
90-day mortality	58.7	27.2	**<.001**	19.2	3.0	**<.001**
1-year mortality	60.7	31.8	**<.001**	27.5	6.3	**<.001**

AMI= Acute Myocardial Infarction; MOF= Multi Organ Failure; Re-lap= Re-laparotomy
Values are percentages.

Cumulative survival using Kaplan-Meier analysis was shown to be significantly worse with ACS versus without ACS for both rAAA and iAAA, *Figure 5a* and *5b*. After rAAA repair, it was evident that mortality stabilized first at 90 days, *Figure 5a*.

In a Cox proportional hazards regression model for rAAA repair, age (*p=.153*), sex (*p=.411*) and treatment modality (*p=.218*) did not influence mortality, nor was mortality influenced in a corresponding model for iAAA repair: age (*p=.097*), sex (*p=.227*) and treatment modality (*p=.496*).

Among ACS patients, outcome did not differ depending on whether DL was performed or not, Table 7, nor depending on treatment modality being EVAR or OSR, Table 8.

Figure 5. Kaplan-Meier curves for 1-year mortality with or without ACS after **a)** rAAA and **b)** iAAA repair. Reproduced from paper I.

Table 7. *Mortality among ACS patients depending on whether DL was performed or not after rAAA repair and iAAA repair. Reproduced from paper I.*

	ACS after rAAA repair			ACS after iAAA repair		
	DL n=74	No DL n=18	p-value	DL n=29	No DL n=23	p-value
30-day mortality	29 (39.2)	10 (55.6)	.288	4 (13.8)	2 (8.7)	.682
90-day mortality	44 (59.5)	10 (55.6)	.794	7 (24.1)	3 (13.0)	.482
1-year mortality	45 (60.8)	10 (55.6)	.790	10 (34.5)	5 (21.7)	.369

Values are numbers (percentages).

Table 8. *Outcome with ACS depending on treatment with OSR or EVAR for rAAA and iAAA. Adapted from paper I.*

	rAAA with ACS			iAAA with ACS		
	rOSR n=66	rEVAR n=26	p-value	iOSR n=35	iEVAR n=16	p-value
AMI	15.9	12.5	1.0	5.9	6.3	1.0
Renal failure	77.3	64.0	.200	51.4	37.5	.384
MOF	65.2	56.0	.471	42.9	12.5	.053
ICU care > 5 days	96.5	100	1.0	74.3	31.3	**.005**
Intestinal ischaemia	40.6	32.0	.479	22.9	43.8	.187
Intestinal resection	30.3	23.1	.610	17.1	43.8	.08
Re-lap for bleeding	25.8	34.6	.445	20.0	18.8	1.0
30-day mortality	37.5	50.0	.346	14.3	6.3	.651
90-day mortality	54.7	65.4	.481	20.0	18.8	1.0
1-year mortality	54.0	75.0	.090	20.6	43.8	.105

AMI = Acute Myocardial Infarction, MOF = Multi Organ Failure, Re-lap= Re-laparotomy
Values are percentages.

OAT

Among patients who developed ACS, the rate of DL did not differ between rOSR and rEVAR (77.3% versus 84.6%, p=.433), but DL was more common after iOSR than after iEVAR (68.6% vs 25.0%, p=.006).

The validation found that prophylactic OAT was performed on 31 of 289 (10.7%; 95% Confidence Interval 7.2-14.3) rAAA patients. Four of those patients (4/289, 1.4%) had erroneously been registered for ACS (the registry did not permit recording prophylactic OAT during the studied time period). In Swedvasc, 75 of 1347 (5.6%) rAAA patients were registered as having undergone DL. Adding together those with OAT due to ACS and those with prophylactic OAT and then subtracting those erroneously registered, the proportion of OAT after rAAA repair was approximately 14.9%.

Study II

There were 83 repairs for rAAA: 45 rOSR and 38 rEVAR, and there were 37 repairs for iAAA: 30 iOSR and 7 iEVAR. The clinical characteristics of the study cohort are shown in Table 9. Among rAAA patients, the incidence of ACS after rOSR was 45/1212 (3.7%), and after rEVAR 38/506 (7.5%). Among iAAA patients, the incidence of ACS after iOSR was 30/2859 (1.0%) and after iEVAR 7/4150 (0.2%).

DL was carried out within 24 hours in 56 (48.2%) patients, between 24 and 48 hours in 30 (26.3%) and after 48 hours in 29 (25.4%). ACS was associated with three main findings at DL: bowel ischaemia in 27 (23.5%), postoperative bleeding in 34 (29.6%) and general oedema in 54 (47%).

The patients who developed ACS after iEVAR for iAAA had an operating time of 233 (IQR: 180-345) minutes and an intraoperative blood loss of 0.8 (IQR: 0.4-3.0) litres. One patient received suprarenal aortic balloon occlusion, while none were reoperated on prior to ACS development.

Correspondingly, those who developed ACS after iOSR for iAAA had an operating time of 390 (IQR: 300-510) minutes and an intraoperative blood loss of 4.5 (2.7-9.0) litres. Fourteen (46.7%) patients had suprarenal aortic clamping and 9 (30.0%) patients underwent reoperation prior to ACS development.

Among rAAA patients, time interval to DL was shorter after rEVAR than after rOSR (2.8 hours (IQR: 0-12.0) vs 30.8 hours (14.1-58.2); $p<.001$). There was also a difference in time interval to DL depending on the main pathophysiological mechanism found at DL: 51.9 hours (IQR: 27.6-193.2) for bowel ischaemia, 11.4 hours (2.8-29.3) for postoperative bleeding and 29.2 hours (5.0-46.2) for oedema, $p<.001$.

Table 9. *Clinical characteristics of the study cohort. Modified from paper II.*

	rAAA n=83	iAAA n=37	p-value
Age [Years]	75 [68-80]	69 [66-76]	**.008**
Female sex*	20.5 (12.4-30.8)	16.2 (6.2-32.0)	.802
Max aneurysm [mm]	76 [70–85]	57 [55–65]	**<.001**
Cardiac disease*	34.9 (24.8-46.2)	43.2 (27.1-60.5)	.419
Pulmonary disease*	24.4 (15.6-35.1)	27.0 (13.8-44.1)	.821
Diabetes*	10.8 (5.1-19.6)	13.5 (4.5-28.8)	.760
Previous CVE*	7.3 (2.7-15.2)	16.2 (6.2-32.0)	.187
EVAR*	45.8 (34.8-57.1)	18.9 (8.0-35.2)	.752

CVE= CerebroVascular Event; mm= millimetres; Values are medians [IQR]. *Values are percentages (95% confidence interval).

Risk factors for mortality

Non-survivors at 90 days (n=60, 50.0%) were older (78 years vs 71, *p<.001)* and had larger aneurysms (70 millimetres vs 65, *p=.045)* compared with survivors, while comorbidities did not differ, Table 10.

Among rAAA patients, neither preoperative BP, unconsciousness, asystole nor preoperative time intervals differed between survivors and non-survivors.

Intraoperatively, non-survivors more often had suprarenal clamping/balloon occlusion (63.3% vs 31.7%, *p<.001*), received more transfusions of pRBC (12 units vs 7, *p=.002),* more FFPs (8 units vs 6, *p=.021)* and more platelets (8 units vs 0, *p=.009),* compared to survivors. Postoperative transfusions did not differ, neither did peak IAP, duration of IAP ≥15 mmHg and ≥20 mmHg before DL, nor time interval to DL. The ratios of pRBC:FFP transfusions were below two in both survivors and non-survivors, with the highest ratio among either group at 1.3 pRBC units per unit FFP. All data shown in Table 11.

Table 10. *Clinical characteristics among survivors and non-survivors at 90 days. Modified from paper II.*

	90-day Survivors n=60	90-day Non-survivors n=60	p-value
Age [Years]	71 [67–75]	78 [71–80]	**<.001**
Female sex*	13.3 (5.9–24.6)	25.0 (14.7–37.9)	.163
Max aneurysm width [mm]	65 [56–80]	70 [61–80]	**.045**
Cardiac disease*	38.3 (26.1–51.8)	36.7 (24.6–50.1)	1.0
Pulmonary disease*	23.3 (13.4–36.0)	26.7 (16.1–39.7)	.833
Diabetes*	6.7 (1.8–16.2)	16.7 (8.3–28.5)	.153
Previous CVE*	10.2 (3.8–20.8)	10.0 (3.8–20.5)	1.0
Ruptured aneurysm*	56.7 (43.2–69.4)	81.7 (69.6–90.5)	**.005**

CVE= CerebroVascular Event; mm= Millimeters; Values are medians [IQR]. *Values are percentages (95% confidence interval)

Table 11. *Perioperative risk factors among survivors and non-survivors at 90 days. Reproduced from paper II.*

	90-day Survivors n=60	90-day Non-survivors n=60	p-value
Preoperative			
Interval: Symptoms-Hospital	2.5 [1.5-10.0]	2.0 [1.3-8.0]	.578
Interval: Hospital-Surgery	2.3 [1.4-3.6]	1.5 [1.0-2.0]	.480
Unconsciousness*	46.9 (29.1-65.3)	54.2 (39.2-68.6)	.651
Lowest preop blood pressure	63 [50-75]	70 [50-80]	.484
Preop asystole*	5.9 (0.7-19.7)	2.1 (0.1-11.1)	.567
Intraoperative			
EVAR*	30.0 (18.8-43.2)	45.0 (32.1-58.4)	.131
Suprarenal aortic control*	31.7 (20.3-45.0)	63.3 (49.9-75.4)	**<.001**
Operating time [minutes]	270 [184–360]	225 [180–366]	.467
Operative bleeding [Litres]	4.3 [2.7–6.5]	5.9 [2.7–10.0]	.268
pRBC [units]	7 [4–11]	12 [7–17]	**.002**
FFP [units]	6 [2–9]	8 [4–15]	**.021**
Platelets [units]	0 [0–8]	8 [0–16]	**.009**
Ratio pRBC:FFP	1.3 [1.0–1.8]	1.3 [1.0–1.8]	.541
Ratio pRBC:Platelets	1.3 [1.0–1.8]	1.3 [1.0–2.0]	.947
Postoperative			
Duration IAP ≥20mmHg [hours]	1.0 [0-7.0]	3.0 [0-9.0]	.387
Duration IAP ≥15mmHg [hours]	7.0 [2.0-23.0]	13.0 [1.0-26.5]	.504
Interval AAA repair to DL [hours]	29.1 [7.5-56.0]	23.6 [4.7-45.6]	.387
Maximum IAP [mmHg]	21 [19-28]	22 [20-25]	.696
OAT*	96.7 (88.5-99.6)	81.7 (69.6-90.5)	**.016**
pRBC day 1 [Units]	2 [0–6]	6 [1–10]	.066
FFP day 1 [Units]	2 [0–7]	5 [2–9]	.064
Platelets day 1 [Units†	0 [0–8]	4 [0–8]	.631
Ratio pRBC:FFP day 1	1.0 [0.6–1.2]	1.0 [0.7–1.2]	.920
Ratio pRBC:Platelets day 1	0.8 [0.4–1.4]	1.1 [0.9–1.9]	.023
pRBC day 2 [Units]	1 [0–3]	2 [0–3]	.333
FFP day 2 [Units]	0 [0–3]	2 [0–5]	.057
Platelets day 2 [Units]	0 [0–0]	0 [0–4]	.126
Ratio pRBC:FFP day 2	0.7 [0.3–1.0]	0.5 [0.3–1.0]	.621
Ratio pRBC:Platelets day 2	0.5 [0.3–0.8]	0.4 [0.3–0.9]	.877

Values are medians [IQR]; *Values are percentages (95% confidence interval)

Outcome

Mortality did not differ depending on the main pathophysiological finding at DL, nor depending on whether DL was performed early, intermediate or late, *Figure 6a-b*.

Neither did mortality differ between rEVAR and rOSR, while it was higher after iEVAR than iOSR at one-year (6/7 (85.7%) vs 9/30 (30.0%); *p=.011*), Table 12.
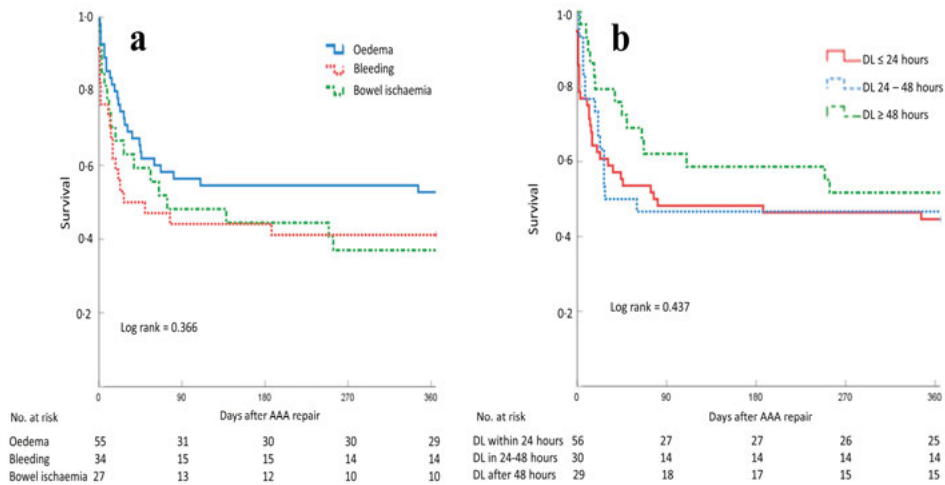
Figure 6. Survival after AAA repair and ACS depending on **a)** the main pathophysiological finding and **b)** timing of DL. Reproduced from paper II

Table 12. *Outcome among ACS patients depending on OSR or EVAR for rAAA and iAAA. Reproduced from paper II.*

	rAAA			iAAA		
	rOSR n=45	rEVAR n=38	p-value	iOSR n=30	iEVAR n=7	p-value
30-day mortality	44.4 (29.6-60.0)	50.0 (33.4-66.6)	.663	20.0 (7.7-38.6)	14.3 (0.4-57.9)	1.0
90-day mortality	55.6 (40.0-70.4)	63.2 (46.0-78.2)	.510	26.7 (12.3-45.9)	42.9 (9.9-81.6)	.403
1-year mortality	55.6 (40.0-70.4)	68.4 (51.3-82.5)	.264	30.0 (14.7-49.4)	85.7 (42.1-99.6)	**.011**
RRT	63.9 (46.2-79.2)	57.7 (36.9-76.6)	.792	65.5 (45.7-82.1)	66.7 (22.3-95.7)	1.0

Values are percentages (95% confidence interval)

The rate of RRT, the duration of RRT or duration of mechanical ventilation did not differ among subgroups.

In two logistic regression models with 1-year-mortality and RRT as end-points, age was the only predictor for mortality. Duration of IAP ≥20 mmHg as well as IAP ≥15 mmHg were predictors for RRT while rAAA repair and ACS due to postoperative bleeding were negative predictors for RRT, Table 12.

Table 13. *Multivariable logistic regression for mortality and need for RRT among patients with ACS after AAA repair. Reproduced from paper II.*

	1-year mortality OR (95% ConfI)	p-value	Need for RRT OR (95% ConfI)	p-value
Age [years]	1.08 (1.01–1.16)	**.026**	1.05 (0.97–1.13)	.233
rAAA vs iAAA	1.45 (0.47–4.44)	.515	0.20 (0.05–0.71)	**.013**
Intraop pRBC [units]	1.04 (0.97–1.11)	.139	1.03 (0.97–1.09)	.397
Suprarenal aortic occlusion	1.88 (0.70–5.07)	.109	2.05 (0.68–6.22)	.206
Time IAP ≥20mmHg [hours]	1.03 (0.99–1.08)	.281	1.10 (1.01–1.21)	**.031**
EVAR vs OSR	2.97 (0.96–9.19)	.073	1.51 (0.43–5.25)	.519
Bowel ischemia vs oedema	1.78 (0.54–5.86)	.342	0.34 (0.09–1.32)	.118
Postop bleeding vs oedema	2.51 (0.76–8.34)	.133	0.24 (0.07–0.86)	**.028**

ConfI= Confidence Interval; Intraop= Intraoperative; Postop= Postoperative; vs= versus

OAT

OAT was performed in 106 patients of whom 98 (92.5%) received negative pressure wound therapy (NPWT). This was in the majority also combined with mesh-mediated traction. Among 85 patients with NPWT who survived until the abdomen was closed, 81 (95.3%) achieved primary delayed fascial closure.

Study III

Baseline characteristics did not differ between ACS patients and controls, Table 14.

Table 14. *Clinical Characteristics of the study cohort. Reproduced from paper III.*

	Valid n	ACS n=40	Controls n=68	p-value
Age [Years]	108	78 [75-81]	79 [72-83]	.700
Female sex*	108	23 (11-39)	18 (10-29)	.617
Max aortic diameter [mm]	108	78 [70-85]	74 [64-87]	.332
Cardiac disease*	92	40 (25-57)	39 (25-53)	1.0
Pulmonary disease*	95	23 (11-39)	27 (16-40)	.811
Diabetes*	99	15 (6-30)	15 (7-27)	1.0
Previous CVE*	92	8 (2-21)	21 (11-34)	.140
Referrals*	108	45 (29-62)	57 (45-69)	.236

ConfI= Confidence interval; CVE= Cerebrovascular event; mm= Millimetres;
Values are medians [IQR]. *Values are percentages (95% confidence interval)

Clinical risk factors

Haemodynamic status prior to surgery was more affected among ACS patients than controls, evidenced by lower BP (70mmHg versus 97mmHg, *p<.001*) and more often episodes of unconsciousness (62.5% versus 32.3%, *p=.004*).

During surgery, ACS patients received aortic occlusion balloon to a higher degree than controls (55.0% versus 10.3%, *p<.001*), received more transfusions of pRBC and FFP (9 units pRBC versus 2 units pRBC and 5 units FFP versus 0 units FFP, both *p<.001*).

After surgery, the amount of transfusions were continued higher among ACS patients compared to controls (5 pRBC units day 1 versus 0 pRBC units day 1, *p<.001*). All values shown in Table 15.

Table 15. *Perioperative risk factors among ACS patients and controls after rEVAR for rAAA. Adapted from paper III.*

	Valid n	ACS n=40	Controls n=68	p-value
Preoperative				
Time: symptoms-hospital [Hours]	75	5.3 [1.5-13.6]	10.3 [2.1-29.4]	.244
Time: hospital-surgery [Hours]	88	2.1 [1.3-3.3]	3.4 [1.2-5.8]	.196
Lowest measured BP [mmHg]	92	70 [58-80]	97 [70-110]	**<.001**
Unconsciousness*	105	62.5 (47.5-77.5)	32.3 (20.9-43.7)	**.004**
Asystole*	106	2.5 (0.0-13.2)	3.0 (0.0-10.5)	1.0
Intraoperative				
Aortic occlusion balloon *	108	55.0 (38.5-70.7)	10.3 (4.2-20.1)	**<.001**
Operating time [Minutes]	105	183 [124-265]	130 [90-210]	.020
Operative bleeding [Litres]	49	1.8 [0.9-3.5]	0.4 [0.2-1.0]	**.002**
Total amount of fluids [Litres]	85	3.2 [3.0-4.0]	2.1 [1.6-3.3]	**<.001**
pRBC [Units]	101	9 [6-16]	2 [0-5]	**<.001**
FFP [Units]	101	5 [3-12]	0 [0-3]	**<.001**
Platelets [Units]	101	4 [0-12]	0 [0-0]	**<.001**
Postoperative				
pRBC day 1 [Units]	93	5 [2-12]	0 [0-3]	**<.001**
FFP day 1 [Units]	93	5 [1-10]	0 [0-0]	**<.001**
Platelets day 1 [Units]	93	4 [0-8]	0 [0-0]	**<.001**
pRBC day 2 [Units]	89	1 [0-3]	0 [0-1]	**.002**
FFP day 2 [Units]	89	0 [0-3]	0 [0-0]	**<.001**
Platelets day 2 [Units]	89	0 [0-4]	0 [0-0]	**<.001**

Values are medians [IQR]. *Values are percentages (95% confidence interval).

Radiologic risk factors

ACS patients and controls did not differ with regards to treatment outside IFU (57.7% ACS vs 54.4% controls, *p=.842*), patency of the inferior mesenteric artery (57.1% ACS vs 63.9% controls, *p=.522*), the number of visible lumbar arteries on preoperative CT (2 versus 4, *p=.014*), nor visible active extravasation on preoperative CT (55.6% ACS vs 45.0% controls, *p=.400*). All data shown in Table 16.

Table 16. *Radiologic risk factors among ACS patients and controls after rEVAR for rAAA. Adapted from paper III.*

	Valid n	ACS n=40	Controls n=68	p–value
CT with contrast*	108	90.0 (80.7-99.3)	88.2 (80.6-95.9)	1.0
Preop IIA occlusion*	96	2.9 (0.1-14.9)	7.1 (4.5-14.9)	.645
Proximal neck outside IFU*	108	45.0 (29.6-60.4)	33.8 (22.6-45.1)	.306
Neck Angulation outside IFU*	108	22.5 (9.6-35.4)	20.6 (11.0-30.2)	.812
Landing Outside IFU*	108	10.0 (0.7-19.3)	14.7 (6.3-23.1)	.565
Any Outside IFU*	108	57.5 (42.2-72.8)	54.4 (42.6-66.2)	.842
Patent inferior mesenteric artery*	96	57.1 (40.7-73.5)	63.9 (51.9-76.0)	.522
Patent lumbar arteries [count]	96	2 (1-4)	4 (2-5)	.014
>2 mm	96	1 (1-2)	2 (1-3)	.041
>1 mm	96	1 (1-2)	2 (1-3)	.137
Active Extravasation*	96	55.6 (39.3-71.8)	45.0 (32.4-57.6)	.400
Anterior rupture site*	55	47.8 (27.4-58.2)	28.1 (12.5-43.7)	.163

IIA= Internal Iliac Artery; IMA= Inferior mesenteric artery; Preop= Preoperative;
Values are medians [IQR]. *Values are percentages (95% confidence interval).

Characteristics of risk factors

ROC curves indicated that preoperative BP, intraoperative blood loss as well as intra- and postoperative 0-24h pRBC transfusions all had some ability to discriminate between ACS patients and controls. The area under curve value was highest for intraoperative pRBC transfusions with 0.857. ROC curves as shown in *Figure 7*.

Ninety-seven percent of ACS patients had a preoperative BP ≤90 mmHg and 44% had a preoperative BP <70 mmHg compared to 46% and 16% of controls, respectively. Eighty percent of ACS patients received >5 pRBC transfusions compared to 21% of controls, and 49% of ACS patients even received >9 pRBC transfusions compared to 3% of controls.

Among ACS patients, 97% had at least one of these three risk factors: preoperative blood pressure <70mmHg, aortic occlusion balloon during EVAR or transfusion of >5 pRBCs. Among controls, the corresponding rate was 38%. All three risk factors were present among 22-50% of ACS patients, depending on which cut-offs were used, while at most 5% of controls. All models are shown in Table 18.

In a multivariable logistic regression model testing these three risk factors, the number of intraoperative pRBC transfusions was independently associated with ACS development, as shown in Table 17.
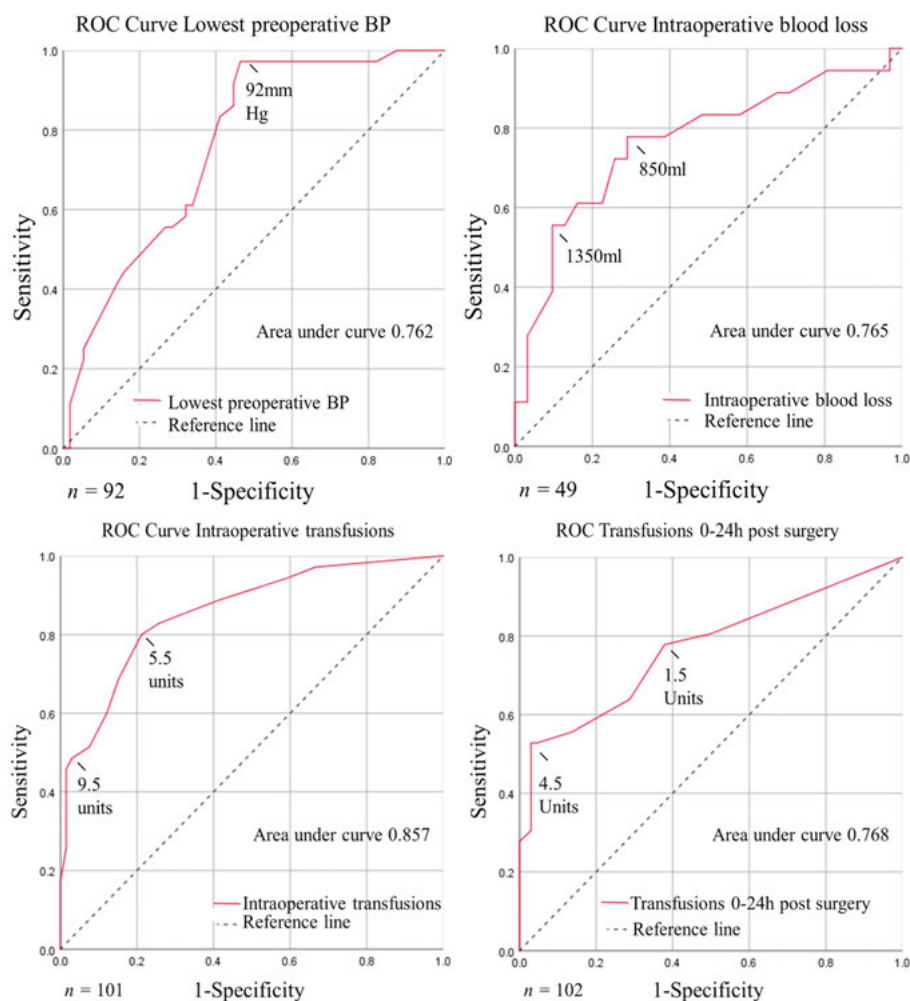
Figure 1. ROC curves of the accuracy of perioperative risk factors to discriminate between ACS patients and controls. Adapted from paper III.

Table 17. *Uni- and multivariable logistic regression of risk factors for ACS*

	Univariable OR (95% ConfI)	p-value*	Multivariable OR (95% CI)	p-value†
Preoperative BP (mmHg)	0.96 (0.94-0.98)	<.001	0.99 (0.96-1.01)	.320
Aortic balloon occlusion	10.65 (3.92-28.95	<.001	6.08 (1.36-27.21)	.018
Intraoperative pRBC transfusions	1.37 (1.2-1.56)	<.001	1.32 (1.13-1.54)	**<.001**

ConfI= Confidence interval; *p-values refer to univariable logistic regression
†p-values refer to multivariable logistic regression

Table 18. *Models of preoperative BP, aortic occlusion balloon and intraoperative pRBC transfusions among ACS patients and controls after rEVAR for rAAA. Reproduced from paper III.*

	Valid n	ACS n=40	Controls n=68	p-value
Individual factor analysis				
BP≤90mmHg	92	97 (86-100)	46 (33-60)	**<.001**
BP<70mmHg	92	44 (28-62)	16 (8-28)	**.004**
Aortic occlusion balloon (AOB)	108	55 (39-71)	10 (4-20)	**<.001**
>2 pRBC	101	89 (73-97)	41 (29-54)	**<.001**
>5 pRBC	101	80 (63-92)	21 (12-33)	**<.001**
>9 pRBC	101	49 (31-66)	3 (0-11)	**<.001**
Two factors combined analysis				
BP≤90mmHg + AOB	104	53 (36-69)	6 (2-15)	**<.001**
BP<70mmHg + AOB	104	29 (15-46)	3 (0-11)	**<.001**
BP≤90mmHg + >2 pRBC	93	88 (72-97)	20 (11-33)	**<.001**
BP≤90mmHg + >5 pRBC	96	73 (55-87)	13 (6-23)	**<.001**
BP<70mmHg + >2 pRBC	92	33 (18-52)	9 (3-19)	**.004**
BP<70mmHg + >5 pRBC	99	21 (9-38)	6 (2-15)	.043
AOB + >2 pRBC	101	57 (39-74)	6 (2-15)	**<.001**
AOB + >5 pRBC	105	47 (31-64)	5 (1-13)	**<.001**
Three factors combined analysis				
BP≤90mmHg + AOB + >2 pRBC	101	50 (33-67)	5 (1-13)	**<.001**
BP≤90mmHg + AOB + >5 pRBC	102	44 (28-62)	3 (0-11)	**<.001**
BP<70mmHg + AOB + >2 pRBC	102	25 (12-42)	3 (0-11)	**.001**
BP<70mmHg + AOB + >5 pRBC	103	22 (10-39)	3 (0-10)	**.003**
Any of the factors combined analysis				
BP≤90mmHg or AOB or >2 pRBC	100	97 (86-100)	68 (55-79)	**<.001**
BP≤90mmHg or AOB or >5 pRBC	97	97 (86-100)	58 (44-70)	**<.001**
BP<70mmHg or AOB or >2 pRBC	99	97 (86-100)	55 (42-68)	**<.001**
BP<70mmHg or AOB or >5 pRBC	97	97 (86-100)	38 (26-52)	**<.001**

AOB= Aortic occlusion balloon; Values are rounded to the nearest integer and show percentages (95% Confidence interval).

Study IV

All patients (n=27) underwent OSR for AAA, twelve patients for rAAA and fifteen for iAAA. Baseline characteristics of the studied patients are shown in Table 19.

Table 19. *Clinical characteristics of the monitored AAA patients. Modified from paper IV.*

	Ruptured AAA n=12	Intact AAA n=15
Age [Years]	79 [72-86]	68 [65-68]
Female sex*	2 (17)	2 (13)
Cardiac disease*	6 (50)	2 (13)
Hypertension*	12 (100)	11 (73)
Pulmonary disease*	4 (33)	2 (13)
Active Smoking*	3 (25)	5 (33)
Diabetes*	0 (0)	2 (13)
Previous CVE*	2 (17)	0 (0)
Renal insufficiency*	2 (17)	0 (0)

CVE= CerebroVascular Event; Values are medians [IQR]. *Values are numbers (percentages)

The overall pHe in the study population was 7.30 (IQR: 7.26-7.33) and the median number of pHe measurements per patient was 7 (IQR: 5-10). The lowest measured pHe for each patient was 7.23 (IQR: 7.15-7.28).

IAH was common: grade I (IAP 12-15mmHg) was present in six (22%) patients, grade II (IAP 16-20mmHg) in 11 (41%), and grade III (IAP 21-25mmHg) in 3 (11%). No patients had grade IV (>25mmHg) IAH. IAP was negatively correlated to pHe, r=-0.144 with *p=.044*. Monitoring and outcome are shown in Table 20.

Table 20. *Operative characteristics, monitoring and outcome among monitored AAA patients. Modified from paper IV.*

	rAAA n=12	iAAA n=15
Preoperative hypotension <90mmHg*	8 (66.7)	0 (0)
Bilateral patency internal iliac arteries*	9 (100)	12 (80.0)
Intraop internal iliac artery ligation*	0 (0)	0 (0)
Operating Time [Minutes]	161 [129-221]	227 [195-276]
Aortic Clamp Time [Minutes]	85 [60-114]	107 [70-120]
Reimplantation of IMA*	2 (13.3)	0 (0)
Operative Bleeding [Litres]	2.8 [2.0-5.2]	3.0 [1.8-4.5]
pHe measurements [count]	7 [3-10]	7 [5-10]
Overall pHe-value	7.30 [7.16-7.34]	7.30 [7.27-7.33]
Lowest pHe-value	7.16 [7.10-7.25]	7.25 [7.21-7.28]
IAH Grade 0-I IAP ≤15 mmHg*	7 (58)	6 (40)
IAH Grade II IAP 16-20 mmHg*	3 (25)	8 (53)
IAH Grade III IAP 21-25mmHg*	2 (17)	1 (7)
ACS*	3 (25)	1 (7)
CI*	5 (42)	0 (0)
30-day Mortality*	5 (42)	0 (0)
90-day Mortality*	5 (42)	0 (0)

IMA= Inferior Mesenteric Artery; Intraop= Intraoperative;
Values are Medians [IQR]. *Values are numbers (percentages).

CI

CI requiring bowel resection developed in four patients, all after rAAA repair. Two of these patients simultaneously developed ACS while the other two had prophylactic OAT. In all patients, the pHe values were indicative of CI. The classical cardinal symptom of CI, diarrhoea with or without blood, was absent in all four. In two of the patients, worsening pHe was the main indication for re-operation while the other two were re-operated due to both physiologic deterioration and worsening pHe. The pHe measurements alongside the temporal relationship to IAP and lactate are shown in figure 8 and 9.
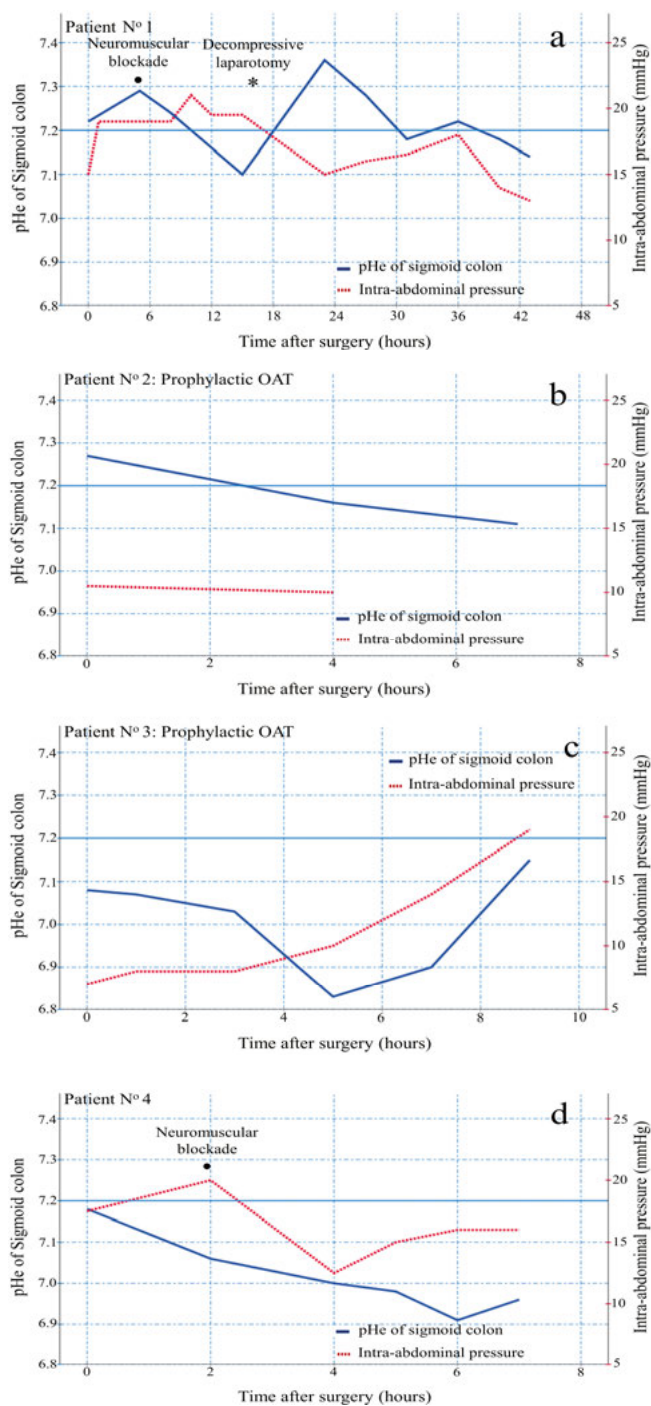
Figure 8. pHe measurements with simultaneous IAP in the four patients (a-d) who developed CI. Modified from paper IV.
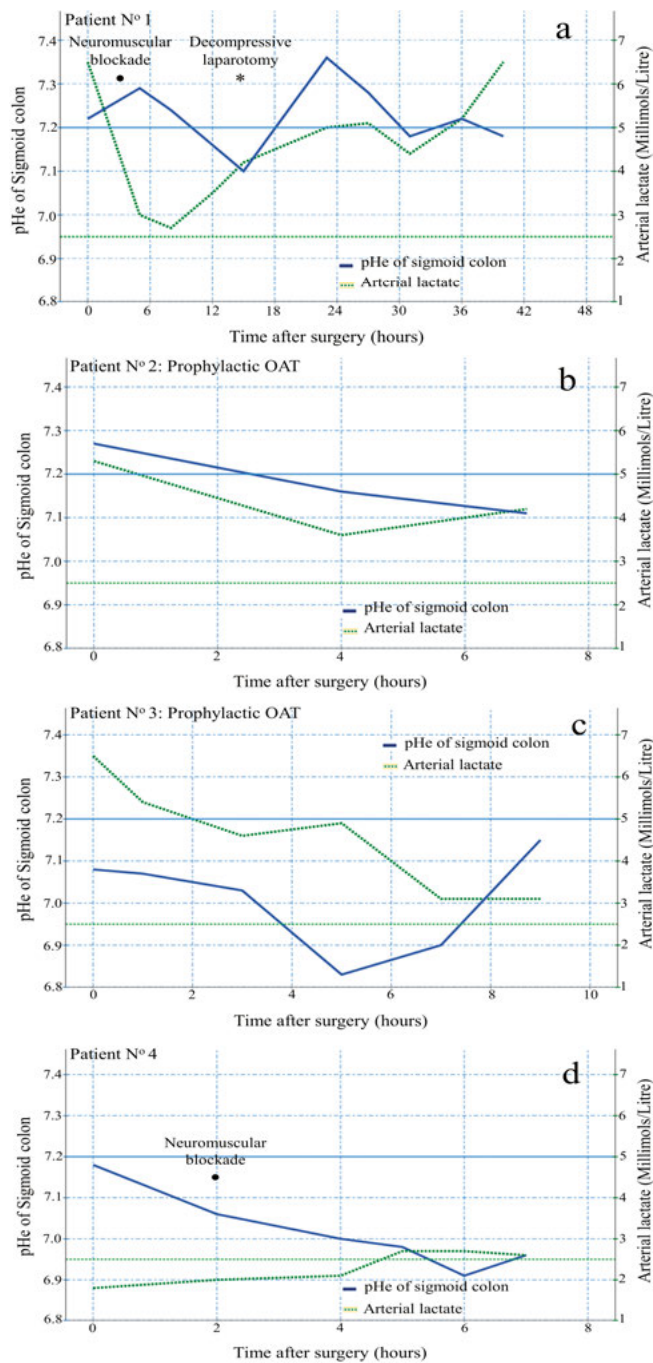
Figure 9. pHe measurements with simultaneous arterial lactate in the four patients (a-d) who developed CI. Modified from paper IV.

A fifth patient had recurring diarrhoea that started on postoperative day 2, after termination of pHe measurement. The lowest pHe during measurement was 7.21. As the symptoms were moderate in nature, a sigmoidoscopy was performed first on postoperative day 18, which revealed mild CI. Conservative management was successful and no further treatment was required.

In addition, brief episodes of pHe <7.2 were present in another seven patients. The duration was less than five hours in all and did not result in clinical symptoms of CI or any related adverse consequences. The sensitivity of pHe to detect clinically significant CI was 100%. The specificity of any pHe <7.2 in detecting CI was 70%, but increased to 100% with a threshold of the duration set at five hours.

ACS

Four patients developed ACS, three treated for rAAA and one for iAAA. Among those treated for rAAA, two also suffered CI and were described above. The third rAAA patient received neuromuscular blockade with success, with all pHe measurements indicating adequate colonic perfusion: minimum pHe 7.27 and median pHe 7.35. The patient who developed ACS after iAAA repair was treated with DL. The temporal relationship of pHe and IAP measurements in that patient is shown in *Figure 10*.
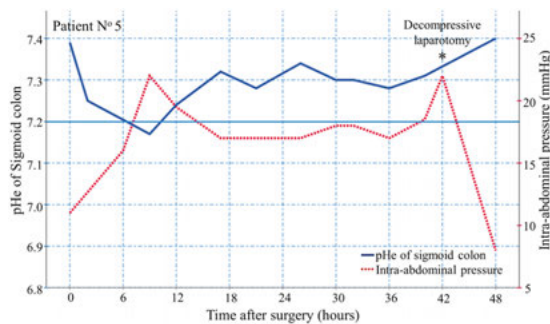
Figure 10. Simultaneous pHe and IAP in patient with ACS after iAAA repair. Reproduced from paper IV.

No complications affecting the patients were noted, but two patients had their catheters dislodged, which resulted in premature termination of the measurements. One catheter was inadvertently dislodged by the ICU staff during patient work and the other by the patient pulling on the catheter under the influence of confusion.

General discussion

Despite the fact that the deleterious effects of IAH have been known since the second half of the 19th century, ACS as a clinical entity is quite recent. The pioneering work of Kron et al was published in the 1980s (Kron 1984) and the "WSACS – the abdominal compartment society" was formed in the beginning of the 21st century. Many of the published studies on ACS have either been single-centre and/or included few patients, resulting in wide confidence intervals of the reported data and limiting the possibility of robust conclusions (Kron 1984, Fietsam 1989, Mehta 2005, Makar 2009, Djavani Gidlund 2011). But, that is often the case when studying an uncommon complication after common surgery, ACS after iAAA repair, or a frequent complication after infrequent surgery, ACS after rAAA repair. In this respect, Swedvasc offered a unique possibility to report on ACS. Swedvasc has had nationwide coverage since the mid-90's, with all vascular centres currently participating, and thus generate population based data from a population of 10 million people.

Incidence of ACS

ACS after rOSR for rAAA

The incidence of ACS has mainly been studied after rAAA repair, which is not surprising given that the incidence appears to be significantly higher after rAAA repair than after iAAA repair. The incidence varies considerably between reports, 2-34%, also not surprising since many reports, as described above, are single centre and/or include few patients (Fietsam 1989, Makar 2009, Desgranges 2015, Rubenstein 2015).

In the nationwide study I, the incidence of ACS after rOSR for rAAA was roughly 6.8%. In study II, with an extended time period and, more importantly, validation of data by means of individual case record review, the incidence decreased to 3.7%. The lower ACS incidence in study II compared to study I, was mainly due to detection and exclusion of those treated with prophylactic OAT.

During the study period, Swedvasc did not differentiate between OAT due to ACS and prophylactic OAT. Consequently, detection was only possible during case record review. This represents a misclassification in the registry, and while it highlights both one of the limitations of study I and registry data

as a whole, it also highlights the intimacy with which the incidence of ACS is associated to prophylactic OAT. The most physiologically deranged patients tend to be those selected for prophylactic OAT, and had they not been selected, a number of those patients would have been very likely to develop ACS. If all patients were to receive prophylactic OAT, a practice not recommended in the WSACS guidelines (Kirkpatrick 2013), the incidence of ACS would be virtually zero. However, such a practice would not mean that ACS had become irrelevant. The ultimate treatment of ACS would then have been applied in all patients, and with it all the burden and pitfalls associated with OAT.

In the validation performed as a part of study I, the overall rate of prophylactic OAT was 10.7% (95% Confidence interval 7.2-14.3). The incidence of ACS without any prophylactic OAT would therefore, by all reason, be significantly higher than the 3.7% found in study II. Thus, the incidence of ACS after rOSR will inevitably depend on the propensity to initiate prophylactic OAT, which differs among physicians and hospitals. Investigating OAT on the whole is definitely an interesting subject, and has recently been explored in several fine reports (Acosta 2017, Seternes 2017). However, it was beyond the scope of this thesis.

When comparing with other studies, the question is always which studies offer a relevant comparison of "real world" data on ACS. Ideally, studies suitable for comparisons should focus on ACS and include validated nationwide or large multicentre data. However, such trials regarding ACS do not exist. In their absence, the incidence of ACS after rOSR in study I and II can be compared to the European randomized controlled trials on rAAA. Although they do not include as many participants as study I and II, they offer what randomized trials have in common, a maximum controlled environment for reporting. The incidence of ACS after rOSR in respective trial was 5.3% in IMPROVE (Powell 2014), 3.4% in AJAX (Reimerink 2013) and 2.0% in ECAR (Desgranges 2015). The pooled incidence of ACS from these trials is 4.5%. It is worth noting that none of the trials reported the rate of prophylactic OAT. Taken together, this indicates that the contemporary incidence of ACS after rOSR for rAAA is approximately 4%.

As mentioned above, the case record review during study II revealed that the incomplete validity of the ACS registrations constituted a limitation. While validation of aortic registrations in Swedvasc have shown >95% external and internal validity (Venermo 2015), the specific validity of ACS had previously not been evaluated. Several factors likely contribute to the observed lower validity of ACS registrations compared to aortic registrations as a whole. ACS was introduced in Swedvasc in 2008, which was also the starting period of study I and II. WSACS the abdominal compartment society had formed only four years prior, with the first recommendations published the year prior. During that time, ACS was not as widely known as today. The configuration of Swedvasc also added some ambiguity, as it was obvious that all vascular surgeons did not know how to record prophylactic OAT. Although

unwanted, some degree of erroneous registration can be expected given the nationwide reporting to Swedvasc, and the accuracy of the registrations did have the courtesy of improving during the study period.

ACS after rEVAR for rAAA

The incidence of ACS was 6.9% in study I and 7.5% in study II. Based on the same premises as for rOSR, this can be compared to the incidences in the European rAAA trials: 5.4% in IMPROVE (Powell 2014), 8.8% in AJAX (Reimerink 2013) and 14.3% in ECAR (Desgranges 2015). The pooled incidence from these trials is 7.2%, similar to that of study I and II. In a registry study of more than 1200 rAAA repairs, Adkar et al reported that 7.2% required a concurrent laparotomy after rEVAR (Adkar 2017). The study used concurrent laparotomy as a surrogate metric for ACS development, as the authors concluded that the need predominantly occurs due to ACS. The authors had also excluded patients whose procedural codes implied other indications for laparotomy than ACS. Furthermore, the incidence is also similar to the pooled rate of 8% found in the meta-analysis by Karkos et al (Karkos 2014).

However, Karkos et al noted an increase to 21% in studies focusing on ACS. This figure was based on the following four studies: Mehta et al with ACS in 7/40 (18%) patients (Mehta 2006), Mayer et al with ACS in 20/102 (20%) (Mayer 2009), Djavani Gidlund et al with ACS in 3/29 (10%) (Djavani Gidlund 2011) and Horer et al with ACS in 32/101 (32%) (Horer 2012). The higher incidence in the study by Mayer et al may be explained by case-mix. Their rate included not only those who underwent DL due to clear ACS, but also those who underwent DL due to certain risk factors for ACS (Mayer 2009). The study by Horer et al described experimental local thrombolysis in thirteen patients with IAH/ACS after rEVAR, and gave no reference nor data on any other patients. The numbers attributed to Horer et al were acquired by Karkos et al through personal communication. The two remaining studies are small single-centre studies and accompanied by wider confidence intervals. Thus, it can be risky to accentuate individual studies with extreme values. Taken together, this indicates that the contemporary incidence of ACS after rEVAR is approximately 7-8%.

Registrations in Swedvasc related to ACS after rEVAR were largely spared from misclassification. However, a few faulty ACS registrations were found, which lowered the number of confirmed ACS cases compared to the number registered in Swedvasc. In contrast, case record review during study III revealed that 3 out of 78 rEVAR controls had actually suffered ACS, but had not been registered as such. If this sporadic misclassification is limited to the investigated hospitals, or is constant throughout the rEVAR cohort in Swedvasc, is unknown. However, it opens for the possibility of a slightly higher rate of ACS than found in study I and II. Contrary to OSR, there is no

ambiguity towards prophylactic OAT with rEVAR, as OAT is always an active decision after rEVAR.

Recent data indicate improved long term outcome after rEVAR compared to rOSR (IMPROVE Trial Investigators 2017). Adding the growing experience of performing rEVAR as well as improving perioperative logistics for rEVAR, the propensity to choose rEVAR over rOSR will likely increase. Consequently, by taking into account the higher rate of ACS after rEVAR compared to rOSR (with the use of selective prophylactic OAT), the future incidence of ACS after rAAA may very well rise.

ACS after iOSR for iAAA

Development of ACS after iOSR was found to be uncommon in study I and II. Unfortunately, there is very little data for comparison from other studies. Nevertheless, this should not be equated to the unimportance of IAH/ACS after iOSR. AAA repair represents major abdominal surgery, a known risk factor for IAH (Dalfino 2008, Reintam Blaser 2011), which in turn is associated with mortality (Reintam Blaser 2019). Add the even more unforgiving mortality with ACS observed in study I, and the need for addressing this issue should be clear. The only other larger study that has reported on ACS after iOSR for iAAA found an incidence of 0.9% (Sörelius 2013), similar to the 1.6% and 1.0% reported in study I and II, respectively.

ACS after iEVAR for iAAA

ACS after iEVAR was rare in both study I and II, with an in incidence of 0.5% in study I and 0.2% in study II. Despite a large data set of patients treated with iEVAR for iAAA (n=4150 in study II), only seven patients developed ACS. Regardless of the lack of corroboration from other studies, ACS after iEVAR must be concluded as a highly scarce entity. Such few cases will inherently limit conclusions regarding development. As described further in the section on risk factors, development of ACS after iEVAR were in all patients related to serious adverse perioperative events.

The continual increase of iEVAR as preferred treatment for iAAA will, given the lower incidence of ACS after iEVAR compared to iOSR, result in fewer patients who develop ACS. Paradoxically, the incidence of ACS after iOSR may very well increase. Patients with hostile anatomy unsuitable for EVAR or even fenestrated EVAR, may instead require complex and technically demanding iOSR, resulting in a case selection towards iOSR among those with increased risk for ACS.

Outcome of ACS

Outcome were among the main aims of study I and study II. Irrespective of indication for treatment and treatment method, morbidity and mortality were considerably worse in patients who developed ACS compared to those who did not. The studies in this thesis do not prove that ACS is the unequivocal cause of the observed impaired outcome among ACS patients, nor was there any conscious attempt to hold out such a prospect in the thesis. However, the studies do show that development of ACS after AAA repair is associated with worse outcome.

Mortality

Mortality with ACS was in study I and II, to put it short, dismal. It was evident in study I that mortality does not stabilize up until 90 days, why this time point offers a better reflection of the true perioperative period, compared to 30-day mortality. Consequently, 90-day mortality was chosen as the main mortality endpoint in study II, and should probably be considered in all studies evaluating mortality after AAA repair.

Mortality of ACS after rAAA repair

Although rAAA is intrinsically a deadly disease, the mortality with ACS was even in this context high, roughly two-fold at each measured time point (30 days, 90 days and 1 year). In study I, 59% of patients with ACS had died at 90 days compared to 27% without ACS. No matter how strikingly high it seems, it does not, however, stand out in comparison to most other reports, Table 19.

Many of the reported mortality rates are still close to the 75% reported in the pioneering article by Fietsam et al (Fietsam 1989), despite 15-30 years having passed. The report by Mayer et al show the lowest mortality rate of all studies with 30% (Mayer 2009). While the article evidences the importance of a large experience and exact treatment algorithms, and thus is inspiring as to what can be achieved, part of the explanation is probably a degree of case-mix. Other limitations hampering direct study comparisons are that several studies include few ACS patients, and the fact that mortality is measured at different time points. In study I and II, the mortality stabilized only at 90 days, why the mortality in studies reporting in-hospital or 30-day mortality could be expected to increase.

Table 21. *Mortality in different studies among patients with ACS after rAAA repair*

Author	Measured time point	Mortality with ACS
Fietsam 1989	In-hospital	3/4 (75%)
Rasmusson 2002	In-hospital	7/10 (70%)
Mehta 2005	In-hospital	4/6 (67%)
Mehta 2006	In-hospital	4/7 (57%)
Acosta 2007	In-hospital	9/11 (82%)
Mayer 2009	30d	6/20 (30%)
Djavani Gidlund 2011	30d	1/3 (33%)
Desgranges 2015	1y	5/9 (56%)
Rubenstein 2015	In-hospital	13/21 (62%)
Paper I	30d, 90d, 1y	40/94 (42%), 55/94 (59%), 57/94 (61%)
Adkar 2018	30d	55/90 (60%)
Aizawa 2018	In-hospital	1/3 (33%)
Miranda 2018	30d	2/3 (67%)
Paper II	30d, 90d, 1y	39/83 (47%), 49/83 (59%), 51/83 (61%)

d= days; y= year

In study I, there was at no point in time a difference in mortality among ACS patients depending on whether they had been treated with EVAR or OSR. Neither did multivariable analysis in study I and II indicate treatment method as an independent predictor of mortality. Thus, it seems as the mortality associated with ACS is largely driven by factors other than treatment modality. The IMPROVE trial showed improved survival with rEVAR as compared to rOSR. However, this was evident only at three years of follow-up and not in the initial publication investigating 30-day mortality, when ACS would be expected to play a role (Powell 2014, IMPROVE Trial Investigators 2017).

If survival among ACS patients has not improved significantly over time, despite the scientific achievements in medicine and the evolution in health technology, how can improved survival among ACS patients be achieved? The answer to this question probably lies as much, if not more, in the prevention of ACS rather than in the treatment of ACS. Emergency and intensive care have undergone important improvements in recent decades, exemplified by balanced resuscitation and massive transfusion protocols (Holcomb 2007, Mell 2010). However, these achievements, as well as awareness of IAH/ACS and the treatment of IAH outlined in the WSACS guidelines, primarily impact the prevention of ACS more than the treatment of already developed ACS. Consequently, the survival statistics of ACS patients may remain unchanged

even though there have been important improvements with regards to ACS prevention.

Mortality of ACS after iAAA repair

Not surprisingly, the mortality rate with ACS development after iAAA repair was not as high as after rAAA repair. However, the relative difference with and without ACS development was strikingly higher after iAAA repair, as shown in Table 6. In study I, the 90-day mortality was six-fold in the presence of ACS compared without (19.2% vs 3%, *p<.001*).

Unlike after rAAA repair, where mortality did not differ between rEVAR and rOSR, one-year mortality was higher after iEVAR than iOSR in study II (85.7% vs 30%, *p=.011*). One-year mortality did not significantly differ in study I, but the numerical difference (iEVAR 44% vs iOSR 21%, *p=.105)* suggested to a possible type-II statistical error. Study II also excluded a relatively large proportion of iEVAR patients included in study I due to discovered misclassification, which may also explain some of the observed difference. All registry data in study II was validated through cross-checking with medical records, making the data in study II more robust.

The finding that ACS was associated with higher relative mortality after iEVAR compared to iOSR may not be as surprising as one might first think. The minimally invasive nature of iEVAR, a procedure which can be performed under local anaesthesia, require the unfolding of virtually catastrophic adverse events to allow for ACS development (the events are detailed in the chapters on incidence and risk factors). OSR on the other hand represents major abdominal surgery, after which minor deviation from normal postoperative course can be enough to elicit ACS, and without the need for dramatic adverse events to also influence survival.

Morbidity

ACS was not only associated with worse survival, but also with worse morbidity. In study I, this was true for nearly every measured complication, and included acute myocardial infarction, renal failure, multi organ failure, bowel ischaemia and the proportion who needed intensive care >5 days, *figure 11*.

Several of the morbidities are such that they interact with IAH/ACS in a co-dependent fashion, with each potentiating the other: IAH is associated with reduced renal function and bowel perfusion, with any arisen bowel ischaemia and renal failure then increasing the inflammatory insult, furthering the inflammatory cycle.
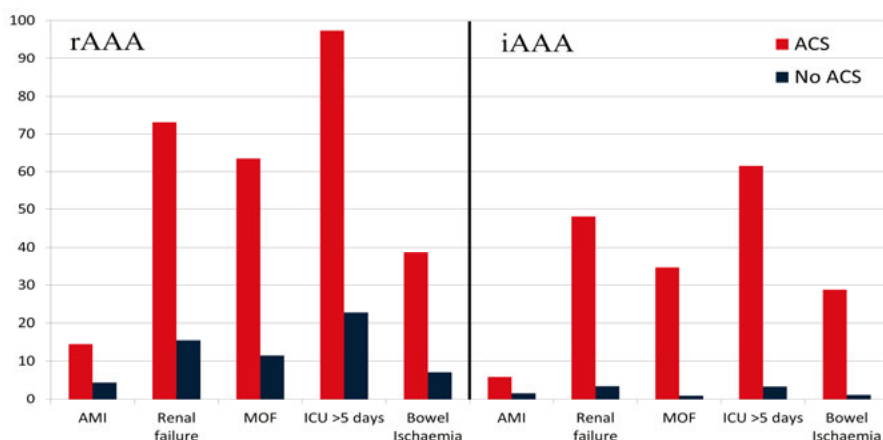
Figure 11. Morbidity among patients with and without ACS after rAAA and iAAA repair

Postoperative renal failure with need for RRT was seen in a majority of ACS patients in study II. RRT was temporary among most patients, median 9 (IQR: 0-23) days, but a handful of patients were transferred to the respective nephrology departments for prolonged or permanent RRT beyond 90 days.

The majority of patients with bowel ischaemia required bowel resection according to study I. Under those circumstances, creation of a bowel anastomosis is dissuaded and creation of a stoma is considered standard care. The stoma will then have to be reversed for an anastomosis at yet another procedure or be managed indefinitely, resulting in a significant reduction in the quality of life.

Risk factors for ACS

Studies I-III in the thesis addressed risk factors for ACS in various aspects. Risk factors can be divided between those that impact ACS development and those that impact mortality associated with ACS, with some factors naturally impacting both.

Study I found no association between comorbidity and ACS development. Instead, associated factors were largely those of pre- and intraoperative haemodynamic derangement and the complexity of the surgical procedure. Associated markers of haemodynamic derangement were preoperative unconsciousness, lower preoperative BP and use of aortic occlusion balloon during EVAR, while associated markers for complexity of the surgical procedure were intraoperative blood loss and, selectively for iOSR, re-implantation of a renal artery. The literature is consistent with these findings. Multiple studies

confirm the importance of haemodynamic compromise and surgical complexity in ACS development, while simultaneously rejecting the importance of comorbidity (Rasmussen 2002, Mehta 2005, Rubenstein 2015).

Due to the minimally invasive nature of iEVAR and the rarity of ACS thereafter, this clinical situation deserves a special mention. Study II showed that ACS, among the seven affected patients, was associated with either CI (3 of 7), perioperative bleeding events (3 of 7) or both (1 of 7). ACS developed earlier when associated with significant perioperative bleeding, and later when associated with CI. Thus, based on limited evidence, ACS after iEVAR seems to be the result of either massive bleeding, mimicking the situation of an AAA rupture, which in that sense seems logical, or the consequence of a rare and unexpected CI.

Study III examined factors associated with ACS specifically after rEVAR. In accordance with study I, there was no observed impact from comorbidities, but likewise an extensive association with pre- and intraoperative haemodynamic derangement. ACS development was highly unlikely without presence of either low preoperative BP, use of aortic occlusion balloon or multiple intraoperative transfusions.

To further explore on the predictive properties of these factors, they will here be described in terms traditionally associated with diagnostic tests: sensitivity, specificity and predictive values, Table 20. As this is not the standardized way of describing risk factors, it may not be suitable in an article, but is given accommodation within the context of this thesis. Positive and negative predictive values depend not only on the sensitivity and specificity of the tested variables, but also on the prevalence of the disease they aim to predict. To obtain predictive values for this analysis, the results of the controls were estimated to be valid for the whole rEVAR cohort in Swedvasc, e.g. aortic occlusion balloon among 10.3% of controls in study III were assumed to apply for 10.3% of whole rEVAR cohort (n=506) (without counting the ACS patients).

The presence of either BP <70mmHg, aortic occlusion balloon, or >5 intraoperative pRBC transfusions showed 97% sensitivity for ACS. The corresponding estimated positive predictive value was 17%, meaning that one in six patients fulfilling the criteria would actually be expected to develop ACS. The highest estimated positive predictive value, 55.5%, was obtained by using the combination of preoperative BP ≤90 mmHg, aortic occlusion balloon and >2 intraoperative transfusions of pRBC. This came at a cost of reduction in sensitivity to 50%.

The weakness of each analysis does not preclude usage, but instead, their respective strength and weakness render them useful in different ways. Analysis based on presence of ANY factors is better suited for prediction of who is at low risk of ACS, while analysis based on presence of ALL factors is better suited for who is at high risk of ACS.

Table 22. *Sensitivity, specificity and predictive values for ACS by using models of lowest preoperative BP, intraoperative pRBC transfusions and aortic occlusion balloon*

	Sensitivity (%)	Specificity (%)	Estimated PPV* (%)	Estimated NPV* (%)
Individual factor analysis				
BP≤90mmHg	97.2	53.5	13.9	99.6
BP<70mmHg	44.4	83.9	17.6	95.1
Aortic occlusion balloon (AOB)	55.0	89.7	31.4	95.9
>2 pRBC	88.6	59.1	14.0	98.6
>5 pRBC	80.0	78.8	22.1	98.1
>9 pRBC	48.6	97.0	54.9	96.2
Two factors combined analysis				
BP≤90mmHg + AOB	52.6	93.9	41.3	96.0
BP<70mmHg + AOB	28.9	97.0	44.0	94.4
BP≤90mmHg + >2 pRBC	87.9	79.7	23.5	98.9
BP≤90mmHg + >5 pRBC	78.8	87.3	30.5	98.3
BP<70mmHg + >2 pRBC	33.3	91.5	21.7	95.1
BP<70mmHg + >5 pRBC	20.6	93.8	19.5	94.2
AOB + >2 pRBC	57.1	93.9	41.3	96.7
AOB + >5 pRBC	47.4	95.5	46.2	95.7
Three factors combined analysis				
BP≤90mmHg + AOB + >2 pRBC	50.0	96.9	55.5	96.2
BP≤90mmHg + AOB + >5 pRBC	44.4	97.0	53.4	95.8
BP<70mmHg + AOB + >2 pRBC	25.0	97.0	39.2	94.4
BP<70mmHg + AOB + >5 pRBC	22.2	97.0	36.4	94.2
Any factors combined analysis				
BP≤90mmHg or AOB or >2 pRBC	97.4	32.3	10.5	99.3
BP≤90mmHg or AOB or >5 pRBC	97.4	42.4	12.1	99.0
BP<70mmHg or AOB or >2 pRBC	97.3	45.2	12.4	99.5
BP<70mmHg or AOB or >5 pRBC	97.3	61.7	16.8	99.7

AOB= Aortic occlusion balloon; Intraop= Intraoperative; NPV= Negative predictive value
PPV= Positive predictive value;
* Results of the control patients in paper III estimated upon the whole rAAA population treated with rEVAR

The focus on the importance of pre- and intraoperative haemodynamic compromise does not exclude involvement of other factors, e.g. type I endoleak, but the results indicate that severely deranged physiology is a requirement in most cases. A few patients who developed ACS in study III had prior been readmitted for an adjunctive EVAR procedure, due to haemodymaic instability caused by a type I endoleak. The contribution of such an event to ACS development cannot be overstated.

T2EL has been associated with aneurysm sac growth and adverse outcome (van Marrewijk 2004, Jones 2007) and current AAA guidelines recommend treatment of T2EL in the event of aneurysm sac expansion (Chaikof 2018, Wanhainen 2019). The degree of persistent T2EL has in turn been associated with specific patency of the inferior mesenteric artery and the number of patent lumbar arteries (Schlosser 2009, Lalys 2017). Therefore, it is possible that T2EL may contribute to ACS development through continuous bleeding from the ruptured aneurysm sac into the hematoma. This has previously been proposed by Mayer et al and Rubenstein et al among others (Mayer 2009, Rubenstein 2015). Study III does not give any evidence for this hypothesis, with neither a difference in patency of the IMA nor a greater number of visible patent lumbar arteries in patients with ACS. However, firm conclusions are limited by the fact that this is an indirect metric and not one measuring postoperative T2EL per se. Ideally, T2EL would be quantified on either completion angiograms or postoperative CTs and compared with prolonged transfusion need. Unfortunately, completion angiograms were unstandardized and of highly variable quality, making conclusions impossible, and postoperative CTs were not routinely performed in all patients. In the paper by Mayer et al, postoperative CTs were routinely performed, showing T2EL in 26 of 102 (25%) patients (Mayer 2009). Of these, one patient with combined T2EL and type 1b endoleak, and one patient with isolated T2EL (as the endoleak was considered large) were re-admitted for surgery and the remainder treated conservatively.

ACS patients received more postoperative transfusions than controls, where continued bleeding from T2EL is a possible source. However, it should be noted that postoperative transfusions were correlated to intraoperative transfusions (r=0.391, *p<.001*). Therefore, it is possible that a number of those who received many intraoperative transfusions were not normovolemic at the completion of rEVAR, with the transfusion need lagging into the postoperative period. Another caveat is that ACS patients also underwent a DL, which under these circumstances easily could result in a few extra given transfusions. Thus, despite an appealing hypothesis, existing data does not support that T2EL significantly contributes to ACS development.

Another aim in study III was to investigate whether hostile anatomy, i.e. treatment outside IFU, predicted ACS. Hostile anatomy has been associated with worse outcome (IMPROVE Trial Investigators 2015, Baderkhan 2016), which may also reflect upon the risk of ACS development. Hostile anatomy

may prolong the surgical procedure and predispose to type I endoleak. However, there was no difference in treatment outside IFU between ACS patients and controls. It may be that aneurysm seal, if only temporary, is sufficient with regards to ACS development. In the report by Baderkhan et al, challenging anatomy also did not influence 30-day mortality but rather long term mortality, and while early mortality was influenced by short aortic necks in the IMPROVE trial, it was not significant in the rEVAR cohort alone (IMPROVE Trial Investigators 2015, Baderkhan 2016).

Study II examined risk factors from a slightly different perspective, namely if certain risk factors among ACS patients impacted outcome: main pathophysiological finding at DL, timing of DL or duration of IAH before DL.

The main pathophysiological finding associated with ACS (bowel ischaemia, bleeding or oedema) was not associated with mortality. This was somewhat surprising as CI alone is a lethal complication, and would reasonably add to the burden of ACS. This implies that the main burden of ACS primarily lies within the ACS cohort as a whole and not with a specific pathophysiological subgroup. However, the Kaplan-Meier analysis pointed to a possible limitation in that the curves showed separation, visually favouring survival in ACS associated with oedema. The difference was statistically insignificant, and suggests a possible type-II statistical error.

The timing of DL has shown to impact outcome among trauma patients (Maxwell 1999, Balogh 2003) while the impact on AAA patients is unclear. Study II showed no difference in mortality depending on timing of DL. Survivors and non-survivors did not differ with regards to duration between AAA repair and DL, nor was there a survival difference between early (<24 hours), intermediate (24-48 hours) and late (>48 hours) DL. The Kaplan-Meier curves of early, intermediate and late DL separated initially but then converged within ¾ year. The conflicting results between study II and the trauma studies may in part reflect case-mix, but more likely the difference is due to improved treatment. Whereas the increased mortality in the earlier trauma studies likely reflect an unfavourable delay in diagnosis, due to lack of IAP measurement and tolerance of severe IAH before treatment, contemporary practice includes vigilant IAP monitoring and relatively prompt DL upon ACS diagnosis. Analysis of timing of DL is also confounded by the fact that earlier ACS development indicates a fundamentally more deranged physiology, resulting in an elevated mortality risk which conceals any negative impact of brief delay of DL. Furthermore, the results of study II include patients treated for both iAAA and rAAA, where iAAA patients have better outcomes but also develop ACS later.

An important finding in study II was that the need for RRT increased with longer duration of IAH before DL. This feature was evident in the multi-variable analysis for duration of both IAP ≥ 15 mmHg and ≥ 20 mmHg. The total median duration of IAP ≥ 20 mmHg before DL was brief, only 2 hours (IQR: 0-8), while the median duration of IAP ≥ 15 mmHg was longer, 8.5 hours (IQR: 2-24). The brief duration of IAP ≥ 20 mmHg is evidence, as discussed

above, of the contemporary aggressiveness when treating severe IAH and ACS.

As the study only included those affected by ACS, it is fair to wonder if the results also apply to a general population with IAH but without ACS. This may not pose a challenge regarding treatment of IAP ≥20 mmHg, where there is a consensus for aggressive treatment. But, how aggressively should slightly lesser IAH be treated, e.g. IAP 15-19 mmHg? In a study by Platell et al, IAP >18 mmHg was found to be a significant risk factor for renal failure (Platell 1990) and in a study by Papavassiliou et al, ≥15 mmHg was suggested as a cut-off value (Papavassiliou 2003). While these studies do not address the impact of duration of IAH, which was reported in study II, they address the severity of IAH.

Furthermore, several studies not focused on AAA patients, but on general ICU populations, have shown impaired outcome already with grade I IAH (≥12 mmHg) (Malbrain 2005, Reintam 2008, Vidal 2008, Reintam Blaser 2019). The step-wise treatment algorithm in the WSACS guidelines recommend initiation of medical management with IAP ≥12 mmHg and that therapy should be titrated to maintain IAP ≤15 mmHg (Kirkpatrick 2013). With the caveat that study II only focused on those with ACS and not all AAA patients, the finding that duration of IAP ≥15 mmHg impacted the need for RRT, speaks to the importance of the WSACS recommendation.

OAT

Study II reported on OAT due to ACS and found that all patients had at least been planned for OAT. However, not all ACS patients received OAT as 8% were switched to palliation prior to or during DL, and 3% had abdominal closure during the intended DL. Comparisons between surgical and medical treatment in registry based studies is hampered by the fact that medical management is more prone to underreporting, creating a selection bias. When going through a medical record to report to the registry, it is easier to overlook a shorter period of e.g. neuromuscular blockade, which might not even be properly noted in the medical records, than the patient having undergone a DL.

Among patients who ultimately received OAT, NPWT was used in 93% of the cases, which in most was also combined with mesh-mediated traction. The primary delayed fascial closure rate among survivors was 95%. In a nationwide setting including hospitals of all sizes, this is an impressive closure rate. However, it is not unique, since a recent Nordic study on OAT after aortic disease reported a delayed fascial closure rate of 92% (Acosta 2017). In another recent study from Norway, including both vascular and non-vascular patients treated with OAT using NPWT with mesh-mediated traction, the fascial closure rate was 84% (Seternes 2017).

The predominant technique of OAT in study II, NPWT with mesh-mediated traction, was first reported in two Swedish studies (Petersson 2007, Acosta 2011). This technique has evidently undergone widespread adaptation in Swedish centres, and is a reasonable explanation for the high delayed fascial closure rate observed in study II. Multiple trials utilizing NPWT but without mesh-mediated traction report lower closure rates in the range of 30-70% (Bee 2008, Rasilainen 2012, Cheatham 2013, Kirkpatrick 2015). None of the several other reported techniques for fascial traction (Wittmann 1990, Fortelny 2014, Mukhi 2014), were performed on the ACS patients in studies I-III.

Entero-atmospheric fistula

Entero-atmospheric fistula (EAF) is a feared complication to OAT. It was gratifying that the frequency of EAF in study II was a low 2%. In the paper by Acosta et al 5% developed EAF and in the paper by Seternes et al 8% (Acosta 2017, Seternes 2017). In a systematic review, the pooled rate of EAF with NPWT and mesh-mediated traction was 6% (Atema 2015). There are several explanations for the seemingly lower rate of EAF in study II. Firstly, the relatively limited sample size of studied OAT patients (Paper II, Acosta 2017, Seternes 2017) result in overlapping confidence intervals. Secondly, there was a significant different case-mix compared to the trials by Seternes et al and Atema et al, as both those trials included mostly non-vascular patients, whom for some reason may be more susceptible to EAF.

CI

Both ACS and CI are complications that may develop after aortic surgery, and both are associated with significant mortality (paper I, paper II, Ultee 2016). While surveillance for IAH and ACS, through repeated measurements of IAP, has become a standard procedure in intensive care units worldwide, surveillance for colonic malperfusion in whatever form, has not gained widespread clinical use.

Study IV further indicated extraluminal colonic tonometry as a useful method for surveillance of colonic malperfusion. All patients who developed significant CI also had pHe indicating malperfusion and ischaemia.

More than 30 years has passed since Fiddian-Green et al and Schiedler et al published their studies on intraluminal pH measurement for detection of CI after aortic surgery (Fiddian-Green 1986, Schiedler 1987). Their reports showed that CI developed early in the postoperative course and that pHi indicated CI before clinical signs and symptoms had developed. These findings were confirmed with pHe in study IV. Despite the promising surveillance capacity of intraluminal colonic tonometry, it has not been adopted in routine clinical practice. Why surveillance never became standard is hard to say, if

there even were any overarching reasons, but the somewhat laborious catheter placement procedure is probably part of the explanation.

Despite the lack of widespread clinical adaptation, there was some continuing research interest. In 1999, Koga et al showed good agreement between intraperitoneal tonometry, equating to extraluminal tonometry, and intraluminal tonometry in piglets subjected to shock (Koga 1999). Another twelve years passed before Djavani-Gidlund et al in 2011 compared intra- and extraluminal colonic tonometry after aortic surgery in humans (Djavani Gidlund 2011). Measurements, again, showed good agreement, although pHe did not reveal the true severity of CI as well as pHi. The threshold for CI was recommended at pHe <7.2, corresponding to the recommended threshold of pHi <7.1 (Björck 1994, Björck 2000). Study IV verified pHe <7.2 as an appropriate threshold for CI and all patients with significant CI had multiple measurements <7.2. However, this did not mean that all patients with a measurement of pHe <7.2 developed CI. Those with brief durations of pHe <7.2 did not experience clinical signs of CI. This was in line with the study by Björck et al, in which periods of 1-5 hours with pHi <7.1 were tolerated without adverse outcome (Björck 2000). Measurements of pHe <7.2 probably do reflect established CI, but one that can be fully reversible given the duration being brief. The early warning given by pHe offers a window of opportunity for the clinician, when efforts to improve colonic perfusion can be undertaken.

pHe was negatively correlated to IAP, as previously also shown by Djavani et al (Djavani 2009), meaning that increases in IAP were correlated to decreases in pHe. This further confirms the findings from previous studies of the negative physiological effects of IAH. Therefore, in situations of colonic malperfusion and IAH, it seems appropriate to vigorously apply the algorithm for reducing IAH presented in the WSACS guidelines (Kirkpatrick 2013).

Apart from correlation with IAP, pHe also correlated to MAP and arterial lactate. The correlation with MAP is expected and serves as a reminder of the importance of maintaining adequate perfusion among these patients. Elevated arterial lactate can be a marker for mesenteric ischemia and is commonly used in that respect. Compared to pHe, arterial lactate is more non-specific and it is also elevated in situations of general hypoperfusion without CI. Lactate can also be normal despite ongoing mesenteric ischemia, as seen at admission in those with superior mesenteric artery occlusion (Acosta 2012). The 2017 ESVS guidelines on mesenteric ischaemia also recommended against using lactate to diagnose or rule out mesenteric ischaemia.

The endovascular revolution temporarily brought a sense that OSR would soon be obsolete, with the natural inclination of a lesser need for associated research. In that regard the pendulum has partly swung back. The recent ESVS guidelines on AAA still recommend OSR in patients with long life expectancy. Thus, OSR will not be outdated in the near future and continued research in improving outcome for these patients is warranted. The poor outcome associated with CI after AAA repair makes improvements for this cohort

especially desirable. An effective method for surveillance, that not only enables early detection of CI in development, but also provides feedback to any applied countermeasures, could constitute such an improvement. Previous and present (study IV) work give promise to the feasibility of extraluminal colonic tonometry for surveillance of colonic perfusion.

Conclusions

- ACS and prophylactic OAT were common after rAAA repair and development of ACS did not differ depending on treatment with OSR or EVAR.

- ACS was associated with devastating outcome after both rAAA and iAAA repair, with no difference depending on the treatment modality being OSR or EVAR.

- Outcome was poor in patients with ACS after AAA repair irrespective of the timing of DL and whether the main pathopysiological finding at DL was bowel ischemia, postoperative bleeding or oedema.

- The duration of IAP ≥15mmHg and ≥20mmHg before treatment predicted the need for RRT.

- ACS after rEVAR was primarily associated with physiologic factors, and was unlikely without either pronounced preoperative hypotension, aortic balloon occlusion or multiple intraoperative transfusions. Treatment outside IFU and morphological factors could not be associated with ACS.

- Extraluminal pH measurement by colonic tonometry is a feasible technique for surveillance of CI after open AAA repair and was indicative of CI among all affected patients.

Future research perspectives

The nature of ACS makes it a somewhat difficult entity to study. A large population is required to ensure a large enough study cohort for meaningful statistical evaluation. Therefore, ACS is suited for investigation in a nationwide setting, or at least collaboration between several large centres. An even more ideal setting would that of a multi-national collaboration. The Vascunet reports are evidence that those collaborations are possible (Budtz-Lilly 2018, Grima 2020) and Nordic collaborations have already been performed for the adjoining subject of OAT (Acosta 2017). In such a setting it would be interesting to investigate whether the incidence of ACS differs between countries and over time, and whether measures such as hypotensive resuscitation and rEVAR under local anaesthesia has had an impact.

IAH is common after AAA repair and treatment of IAH is recommended in the WSACS guidelines. Previous work have shown negative effects of IAP >12 mmHg and higher. The treatment of IAH can require measures that are by themselves associated with risks, e.g. neuromuscular blockade. The optimal target level of IAP, that treatment should strive for in the postoperative AAA patient, remains to be elucidated and serves as another interesting question.

The possible impact of T2EL on ACS development was investigated in study III. This could be further investigated in a setting where all rEVAR patients undergo either an immediate postoperative CT or a highly standardized completion angiogram. Comparisons with postoperative transfusions could then be performed. Such a setup would facilitate a definitive answer to the hypothesis of T2EL involvement in ACS development. Some centres already include routine postoperative CT in their rEVAR algorithm, indicating the possibility to perform such a study.

Short term mortality is significantly increased with ACS and is described in several studies. On the other hand, the long term mortality of early survivors, has not been described and is an intriguing question. The long term morbidity of OAT, with regards to later hernia development and other issues, is also unclear. This may impact recommendations as to how a definitive closure of the open abdomen should be performed, why further evidence would have direct clinical consequences.

In line with the conclusion of study IV, extraluminal colonic tonometry should be evaluated in a larger study. Larger centres that perform a sufficient number of complex iAAA repairs and rAAA repairs with OSR would have

the caseload to perform such a study within a reasonable time frame. It would then be possible to also formulate a management algorithm.

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Populärvetenskaplig sammanfattning

Bukaortaaneurysm (AAA) uppstår till följd av en sjuklig vidgning av kropps-pulsådern i magen. I 65-årsåldern förekommer det hos ca 2% av alla män och hos ca 0,5% av alla kvinnor. Andelen som utvecklar AAA ökar med stigande ålder. AAA tenderar att växa i storlek över tid, där risken att det ska brista, ruptur, ökar med bråckets storlek. Rupturerat AAA är förenat med hög död-lighet och kräver omedelbar operation, med en trots det oviss utgång. För att förhindra ruptur rekommenderas i normala fall en förebyggande operation. Aktuella riktlinjer förespråkar operation för män när bråckdiametern når 55 mm och för kvinnor när den når 50 mm.

Det finns i huvudsak två olika operationsmetoder. Den ena, öppen operat-ion, genomförs öppet via snitt i buken där en konstgjord kärlprotes i tyg sys in och ersätter den sjuka delen av kroppspulsådern. Den andra, endovaskulär operation (EVAR), innebär att ett tygbeklätt metallnät s.k. stentgraft, förs in i kroppspulsådern via ljumskpulsartärerna och täcker över den sjukliga delen av kroppspulsådern.

Efter en operation, och då särskilt efter operation för rupturerat AAA, kan komplikationer tillstöta. Två fruktade komplikationer är bukkompartment-syndrom (ACS) och tarmischemi, som båda kan utvecklas var för sig eller tillsammans.

Diagnostik av ACS grundas på mätning av trycket i bukhålan, s.k. buk-tryck. Om buktrycket överstiger 12 mmHg klassificeras det som förhöjt tryck, s.k. intra-abdominell hypertension. Om buktrycket överstiger 20 mmHg och det uppstått organpåverkan klassificeras det som ACS. Obehandlat leder ACS nästan uteslutande till döden och trots behandling är dödligheten ansenlig. Be-handling av ACS syftar till att sänka buktrycket och sker i uttalade fall genom att buken öppnas kirurgiskt och s.k. öppen-buk behandling inleds.

Tarmischemi innebär att en del av tarmen skadas p.g.a. otillräcklig cirku-lation. Vid uttalad skada utvecklas gangrän, vilket kräver en operation för att ta bort den gangränösa delen av tarmen. I likhet med ACS är dödligheten bland drabbade patienter hög.

Syftet med denna avhandling var att kartlägga förekomst och utfall vid ACS, kartlägga vilka riskfaktorer som påverkar detta och att utvärdera en me-tod för att övervaka cirkulationen till tarmen efter AAA operation.

Delarbete I

I det första delarbetet kartlades förekomst och utfall vid ACS i Sverige under åren 2008 till 2013. Data inhämtades från det svenska kärlregistret, Swedvasc, och kompletterades med en validering från journaler på slumpmässigt utvalda patienter.

Efter operation av rupturerat AAA utvecklade 7% av patienterna ACS oavsett operationsmetod. Efter operation av intakt AAA utvecklade 1,6% av patienterna ACS med öppen operationsmetod och 0,5% efter EVAR.

ACS-patienter hade påtagligt sämre utfall jämfört med patienter utan ACS. Efter operation av rupturerat AAA var dödligheten hos ACS-patienter i stort sett dubblerad vid varje uppmätt tidpunkt jämfört med de utan ACS; 42% mot 24% vid 1 månad, 59% mot 27% vid 3 månader och 61% mot 32% vid 1 år. Dödligheten efter operation av intakt AAA var som förväntat lägre än efter operation av rupturerat AAA, men den relativa skillnaden mellan ACS-patienter och de utan ACS var större; 12% mot 2% vid 1 månad, 19% mot 3% vid 3 månader och 28% mot 6% vid 1 år. Operationsmetod påverkade inte dödligheten hos patienter med ACS oavsett om operationen genomfördes för rupturerat AAA eller intakt AAA.

Delarbete II

I det andra delarbetet undersöktes om utfallet hos ACS-patienter skiljde sig åt beroende på om ACS var associerat med tarmischemi, postoperativ blödning eller allmän svullnad, eller beroende på när i det postoperativa förloppet öppen-buk behandling inleddes. Vidare undersöktes om utfallet påverkades av tidslängden med förhöjt buktryck. Studieperioden förlängdes till september 2015 med nytt datauttag från Swedvasc. Därefter genomfördes journalgranskning av samtliga patienter som registrerats för ACS i Swedvasc. Totalt inkluderades 120 patienter i studien från sammanlagt 24 olika sjukhus.

I 83 fall uppkom ACS efter operation av rupturerat AAA, varav 45 fall efter öppen operation och 38 fall efter EVAR. I 37 fall uppkom ACS efter operation av intakt AAA, varav 30 fall efter öppen operation och 7 fall efter EVAR.

Överlevnaden skiljde sig inte åt beroende på om ACS var associerat med tarmischemi, postoperativ blödning eller allmän svullnad och inte heller beroende på när i det postoperativa förloppet som öppen-buk behandling initierades. I multivariat analys var ålder den enda enskilda faktor som kunde kopplas till försämrad överlevnad medan tidslängd med förhöjt buktryck påverkade risken att drabbas av dialyskrävande njursvikt.

Delarbete III

I det tredje delarbetet undersöktes bakomliggande faktorer till ACS efter EVAR för rupturerat AAA. Den undersökta tidsperioden omfattade i likhet med delarbete II åren 2008 till 2015. Studiepopulationen utgjordes av 40 patienter med ACS och 68 kontroll-patienter från sammanlagt sju olika sjukhus. ACS-patienter och kontroll-patienter matchades efter sjukhus och operationsdatum. Journalgranskning kombinerades med granskning av röntgenbilder.

Resultaten visade att cirkulatorisk påverkan och antalet blodtransfusioner innan och under operationen hade stor betydelse för utveckling av ACS. Det var mycket vanligt att ACS-patienter hade antingen lågt blodtryck innan operation (<70 mmHg), erhöll s.k. aortaballong-avstängning för att tillfälligt stänga av kroppspulsådern under operationen och/eller erhöll fler än 5 blodtransfusioner under operationen. Risken för ACS påverkades inte av huruvida de anatomiska förutsättningarna för stentgraft-placering var inom eller utom det rekommenderade intervallet. Inte heller hade ACS-patienterna fler öppetstående sidogrenar från den stentgraft-behandlade kroppspulsådern jämfört med kontroll-patienterna, vilket i tidigare studier kopplats till risk för betydande backblödning in i kroppspulsåderbråcket.

Delarbete IV

I det fjärde delarbetet utvärderas en metod, extern pH-mätning, för övervakning av cirkulationen till den delen av tjocktarmen (kolon sigmoideum) som är mest känslig efter AAA operation. Metoden innefattar att en tunn kateter lämnas kvar i bukhålan efter operationen. Katetern placeras i kontakt med utsidan på kolon sigmoideum, varefter man kan mäta pH i tarmväggen och tidigt upptäcka tarmischemi. Efter att mätningarna avslutas, vilket skedde efter som längst 48 timmar i den aktuella studien, kan katetern dras katetern smärtfritt.

Fyra patienter drabbades av allvarlig tarmischemi och i samtliga fall indikerades detta av pH-mätningarna innan specifika kliniska tecken utvecklats. Ytterligare sju patienter hade kortvariga episoder där pH-mätningarna indikerade begynnande tarmischemi, men episoderna var hos samtliga dessa patienter snabbt övergående och ledde inte till några komplikationer.

Sammanfattning: i några av de hittills största publicerade studierna om ACS efter aortakirurgi kunde förekomst och utfall kartläggas. Utfallet vid ACS var sämre i nästan samtliga mätta utfallsmått, med en påtagligt sämre överlevnad. Överlevnaden skiljde sig inte mellan olika subgrupper av ACS patienter, men en längre tid med högt buktryck påverkade behovet av dialys. De som utvecklade ACS efter EVAR av rupturerat AAA hade i mycket hög utsträckning varit uttalat cirkulatoriskt påverkade eller fått flertalet blodtransfusioner under operationen. Extern pH-mätning som metod för övervakning av cirkulationen till

tjocktarmen efter AAA operation visade lovande resultat. Det allvarliga utfallet vid ACS talar för vikten av noggrann postoperativ övervakning av buktrycket och tidiga åtgärder vid förhöjt buktryck.

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