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MARTIN PADAR

# Enteral nutrition, gastrointestinal dysfunction and intestinal biomarkers in critically ill patients

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## Original studies

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V. Padar, M., Starkopf, J., Starkopf, L., Forbes, A., Hiesmayr, M., Jakob, S. M., Rooijackers, O., Wernerman, J., Ojavee, S. E., & Reintam Blaser, A. (2021). Enteral nutrition and dynamics of citrulline and intestinal fatty acid-binding protein in adult ICU patients. *Clinical Nutrition ESPEN,* 45, 322-332.

## Literature reviews

VI. Padar, M., Reintam Blaser, A., Talving, P., Lipping, E., & Starkopf, J. (2019). Abdominal compartment syndrome: improving outcomes with a multidisciplinary approach – a narrative review. *Journal of Multidisciplinary Healthcare*, 12, 1061–1074.

VII. Reintam Blaser, A., Padar, M., Tang, J., Dutton, J., & Forbes, A. (2019). Citrulline and intestinal fatty acid-binding protein as biomarkers for gastrointestinal dysfunction in the critically ill. *Anaesthesiology Intensive Therapy*, 51(3), 230–239.

**Contributions by Martin Padar**

In studies I–III and V Martin Padar participated in study design, data analysis and writing of the manuscript. In study IV, Martin Padar conducted the study in one study centre and participated in data analysis. In review articles, Martin Padar wrote the chapters on the pathophysiology and nonsurgical management of IAH/ACS (publication VI) and on the physiology and pathophysiology of I-FABP (publication VII).

# ABBREVIATIONS

| | |
|---|---|
| ACS | abdominal compartment syndrome |
| AGI | Acute Gastrointestinal Injury grading |
| APP | abdominal perfusion pressure |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| BMI | body mass index |
| CI | confidence interval |
| EN | enteral nutrition |
| EEN | early enteral nutrition |
| EEN/ON | early enteral or oral nutrition |
| ELISA | enzyme-linked immunosorbent assay |
| ESICM | European Society of Intensive Care Medicine |
| FI | feeding intolerance |
| GI | gastrointestinal |
| GIDS | Gastrointestinal Dysfunction Score |
| GIF | gastrointestinal failure |
| GRV | gastric residual volume |
| IAH | intra-abdominal hypertension |
| IAP | intra-abdominal pressure |
| ICU | intensive care unit |
| I-FABP | intestinal fatty acid-binding protein |
| LMM | linear mixed models |
| MAP | mean arterial pressure |
| MODS | Multiple Organ Dysfunction Score |
| OR | odds ratio |
| PaO2 | partial pressure of oxygen in arterial blood |
| PEEP | positive end-expiratory pressure |
| PN | parenteral nutrition |
| RASS | Richmond Agitation-Sedation Scale |
| SAPS | Simplified Acute Physiology Score |
| SOFA | Sequential Organ Failure Assessment |

# 1. INTRODUCTION

In intensive care units (ICU), care is provided to critically ill patients requiring intensive and specialised medical and nursing treatment, enhanced monitoring and multiple modalities of physiologic organ support to sustain life during a period of life-threatening organ system insufficiency (Marshall et al., 2017). Naturally, multiple organ dysfunction is a frequent cause of morbidity and mortality in intensive care patients. In health, the integration of different organ systems maintains homeostasis, while an acute or chronic dysfunction of any organ may cause dysregulation in another through a series of complex interactions (Armutcu, 2019). Several examples of such organ cross-talk are well described and acknowledged, e.g., the cardiorenal and hepatorenal syndromes, hepatic encephalopathy and others. Similarly, the theory of gut as a motor for multiple organ failure originates from already 35 years ago, initially focusing on hyperpermeability and bacterial translocation into the circulation (Carrico, 1986). More recently, other pathways of gut-derived distant organ damage have been brought to light, including the gut lymph hypothesis, increased enterocyte apoptosis and alterations in the microbiome (Klingensmith & Coopersmith, 2016). Despite recent rapid advances in the diagnosis, treatment and replacement therapies of other organs, the clinical assessment of gastrointestinal (GI) function in critically ill patients continues to rely on the time-tested, but unstructured and operator-dependent clinical examination. The GI tract is not incorporated in any of the currently used disease severity and multiple organ dysfunction assessment scores, hindering research in the field. Accordingly, treatment options targeting the gut in critically ill patients, outside enteral nutrition (EN), are scarce.

The present dissertation concludes studies performed in the fields of enteral nutrition, intra-abdominal hypertension (IAH) and gastrointestinal dysfunction in critically ill patients. Research in this dissertation is a continuation of the work done in the field of gastrointestinal problems in intensive care, carried out over the last decades in the Department of Anaesthesiology and Intensive Care of the University of Tartu and the Tartu University Hospital.

# 2. REVIEW OF THE LITERATURE

To gain insight into the management of gastrointestinal problems in intensive care, relevant aspects of nutrition, abdominal and gastrointestinal signs and symptoms as well as biomarkers need to be reviewed.

## 2.1. Nutrition in critical illness

Normal oral nutrition is seldom possible in critically ill patients (Bendavid et al., 2017). Inability to eat is often caused by disorders of consciousness or swallowing or treatments such as sedation and mechanical ventilation. An important consideration in this regard is also the sickness-associated anorexia, a concept recognised in humans and other animals already for centuries (van Niekerk et al., 2016a). Indeed, loss of appetite seems prevalent in intensive care patients with only around 30% reporting hunger or a desire to eat (Bendavid et al., 2017).

On the other hand, the critical state brought on by, for example, a severe infection, trauma or single or multiple organ failure is often accompanied by intense catabolism and increased energy expenditure. With no significant protein reserves in the human body, proteins mainly from the skeletal muscle are degraded into amino acids, and used to satisfy the needs for regeneration of tissues and synthesis of acute phase proteins. Over the last decades, developments in intensive care medicine have made it possible to sustain life longer than ever before, ultimately reducing mortality, but at the same time, for some patients prolonging the critical illness and catabolic state. Indeed, the development of large cumulative caloric and protein deficits during the stay in ICU has been observed to associate with infections, longer length of stay, and mortality (Villet et al., 2005; Dvir et al., 2006; Alberda et al., 2009; Weijs et al., 2019). Therefore, the question arises whether artificial nutrition can counteract the catabolic state and diminish wasting of the body reserves.

Closely tied to sickness-associated anorexia and likely promoted by it is autophagy, a cellular reparation and recycling process in which damaged organelles, proteins and macromolecules are degraded, ensuring endogenous energy production and substrates for biosynthesis (van Niekerk et al., 2016b). Autophagy plays a key role in energy homeostasis, immune regulation and a generic response to various stressors (van Niekerk et al., 2016a), thereby also mediating organ function recovery in critical illness (Van Dyck et al., 2018). Discovery and acknowledgement of the process of autophagy has had significant implications on the nutrition of critically ill patients. Autophagy is thought to be especially important in the early phase of acute severe illness to assure clearance of cellular damage, and is suppressed by nutrition. This is thought to be one explanation for the results of the EPaNIC study showing early full nutrition being associated with clinically significant complications, including muscle weakness, more frequent infections and longer length of stay in ICU (Casaer et

al., 2011; Van Dyck et al., 2018). Furthermore, the endogenous energy production sustained by stress hormones cannot be abolished with exogenous nutrients (Preiser et al., 2014), possibly resulting in overfeeding if early high volume nutrition is attempted. These findings together have led to the hypothesis that restrictive energy provision or trophic feeding is beneficial in the early stages of critical illness, confirmed by several randomised controlled trials comparing restrictive caloric intake to full energy provision in this setting (Arabi et al., 2011; Braunschweig et al., 2015; van Puffelen et al., 2018). Even if no significant differences in terms of mortality could be demonstrated (Rice et al., 2011, 2012; Arabi et al., 2015), the studies show that early trophic feeding is better tolerated (Rice et al., 2011, 2012). Full enteral nutrition in critically ill patients with shock may be associated with more frequent GI symptoms and life-threatening bowel ischaemia (Reignier et al., 2018).

Most intensive care patients require artificial nutrition, i.e. enteral or parenteral nutrition or a combination thereof (Bendavid et al., 2017). EN refers to the administration of food into the stomach (prepyloric) or more distal parts of the GI tract (postpyloric), while with parenteral nutrition (PN) nutrients are delivered intravenously. EN is considered the optimal method when eating is not possible, being more physiological and cheaper. EN is acknowledged to attenuate stress and modulate the immune response (Windsor et al., 1998; Bear et al., 2017). PN has historically been associated with more frequent bacterial and fungal infections compared to EN, resulting in significant morbidity and mortality (Koretz et al., 2001), but these findings were not confirmed in the most recent large trial (Harvey et al., 2014). Currently, early enteral nutrition (EEN), defined as EN started within 48 hours of admission to ICU, is advocated in the societal guidelines, with a low starting dose and later use of supplemental parenteral nutrition if protein and caloric needs are not met by EN alone (McClave et al., 2016; Reintam Blaser et al., 2017; Singer et al., 2019). A benefit of EEN over delaying EN seems to be a lower incidence of infectious complications (Reintam Blaser et al., 2017).

Although research in the last decade has cautioned against early high volume feeding of critically ill patients and slow initiation of feeding is a standard of care in most patients, underfeeding continues to be a major problem, especially among those at high risk of complications as demonstrated by Heyland and co-authors. In this observational study including 3390 mechanically ventilated patients from 26 countries, the prevalence of underfeeding, defined as failure to achieve 80% of energy targets during up to 12 days of ICU stay, was 65% among long-staying patients (ICU stay >7 days) and nearly 80% in patients with a modified Nutrition Risk in Critically Ill score of ≥5 (Heyland et al., 2015).

Practically, EN is administered as a continuous infusion, starting with low rates of 10–20 ml/h with careful attention to abdominal and gastrointestinal symptoms. The desired infusion rate should be achieved between days 3 and 7, with 70%–100% of resting energy expenditure considered adequate (Singer et al., 2019). The suggested standard in determining the energy expenditure of a critically ill patient is indirect calorimetry (Singer et al., 2019). In real practice,

the caloric prescription is predominantly based on values calculated with predictive equations or weight-based formulae (Heyland et al., 2015). Such approach is particularly inaccurate, achieving a result of ±10% of energy expenditure measured by IC in only a third of patients (Zusman et al., 2019), Thus, over- and underfeeding becomes frequent if IC is not used.

The use of feeding protocols is encouraged by several societies to achieve early initiation, slow and gradual increase of EN together with a protocolised management of possible GI problems (McClave et al., 2016; Reintam Blaser et al., 2017; Singer et al., 2019). Usual features of feeding protocols include a time and indication to start feeding, a target feeding rate, details on feed advancement strategies, instructions on how to handle gastric residual volumes (GRV) and details on when to decrease or stop nutrition or consider an alternative feeding route. An increase of nutrients administered is a common observation in studies evaluating the effects of feeding protocols (Arabi et al., 2004; Compton et al., 2014; Doig et al., 2008; Mackenzie et al., 2005), with also a positive effect on treatment outcome in some studies (Martin et al., 2004; Taylor et al., 1999; Heyland et al., 2013).

Contraindications to oral and enteral nutrition include several severe general and gastrointestinal conditions where feeding may be harmful. The list includes uncontrolled shock, uncontrolled hypoxemia and acidosis, large gastric aspirate (>500 mL in 6 hours), continuing upper GI bleeding, bowel ischaemia or obstruction, abdominal compartment syndrome (ACS) and a high-output fistula in the absence of a distal feeding access (Reintam Blaser et al., 2017; Singer et al., 2019).

Feeding intolerance (FI) is a clinical scenario where enteral feeding is not tolerated. FI is considered present if EN has to be stopped due to any clinical reason or at least 20 kcal per kilogram of body weight per day cannot be achieved within 3 days after the start of the feeding attempt (Reintam Blaser et al., 2012). Considerable variation exists in definitions of FI used in clinical studies (Reintam Blaser et al., 2014b). Most often it is diagnosed on the basis of large GRV alone, with a median value of 250 mL used across studies (Reintam Blaser et al., 2014b). Prevalence of FI depends significantly on the definition but is in the range of 24–45% of all ICU patients (Reintam Blaser et al., 2014b; Hu et al., 2017; Heyland et al., 2021). Several studies with GI symptom-based definitions of FI have demonstrated an association between FI and poor treatment outcome (Mentec et al., 2001; Lam et al., 2007; Nguyen et al., 2007; Reintam et al., 2008a; Shimizu et al., 2011; Gungabissoon et al., 2015; Heyland et al., 2021), highlighting the importance of GI symptoms in assessment of GI function.

Taken together, nutrition of a critically ill patient is a complex topic, with many questions still insufficiently answered. EEN with gradual progression towards the goal is the suggested standard. However, there is no consensus regarding the optimal calorie target in the acute phase of critical illness and methods to reach it.

In study I nutritional practices, complications and outcomes were compared before and after implementing an enteral feeding protocol in mechanically ventilated ICU patients at the 1st ICU of the Tartu University Hospital.

## 2.2 Gastrointestinal signs and symptoms

Gastrointestinal signs and symptoms are frequent, with at least one symptom occurring in around 60% of patients (Reintam et al., 2009; Reintam Blaser et al., 2013). Reported prevalences of single symptoms vary considerably, partly owing to different definitions, for example 20–83% for constipation and 3.3–78% for diarrhoea (Hay et al., 2019).The symptoms can be related to the abdominal pathology that necessitated admission to ICU, or may indicate GI dysfunction/failure developing as a part of multiple organ dysfunction during intensive care. The occurrence GI symptoms on admission day or their development later during ICU stay are both associated with impaired outcome in several observational studies (Reintam et al., 2009; Reintam Blaser et al., 2013).

GI symptoms have been historically a cornerstone in recognizing and diagnosing of GI dysfunction in critically ill patients. However, these symptoms are often nonspecific, and their assessment subjective and poorly reproducible. Additional difficulty in this field has been the absence of uniform definitions. In 2012, the Working Group on Abdominal Problems of the European Society of Intensive Care Medicine (ESICM) aimed to overcome the latter issue by standardizing the definitions of common GI symptoms (Reintam Blaser et al., 2012). List of these symptoms with definitions and brief overview of their significance is given below.

*Vomiting* is the occurrence of any visible regurgitation of gastric content irrespective of the amount (Reintam Blaser et al., 2012). In intensive care patients, vomiting (an active forceful event) is often indistinguishable from regurgitation (a passive effortless event), therefore these two should be assessed together (Reintam Blaser et al., 2012). A frequent adverse event among postoperative patients admitted to intensive care units is postoperative nausea and vomiting, occurring in 30% of the overall surgical population and as much as 80% of patients with risk factors (Gan et al., 2020). Other well-known causes for vomiting in critically ill patients are various abdominal and central nervous system pathologies and use of certain medications, e.g. chemotherapy or opioids (Gan et al., 2020; Reintam Blaser et al., 2015b). The incidence of vomiting in critically ill patients is 15–38% (Reintam et al., 2009; Reintam Blaser et al., 2013; Virani et al., 2019). Nausea and vomiting are associated with patient discomfort, but also serious complications such as dehydration, malnutrition, electrolyte and acid base disorders and surgical site disruption (Thompson, 1999; Gennari & Weise, 2008). An immediately life-threatening complication is tracheal aspiration of gastric contents, potentially leading to aspiration pneumonitis or pneumonia, acute respiratory failure and death (Raghavendran et al., 2011).

*Diarrhoea* is defined as having three or more loose or liquid stools per day with a stool weight greater than 200–250 g/day (or greater than 250 ml/day) (Reintam Blaser et al., 2012). Several studies estimate the prevalence of diarrhoea in critically ill patients to be 13–22% (Reintam et al., 2009; Reintam Blaser et al., 2013; Thibault et al., 2013; Tirlapur et al., 2016), however a recent systematic review shows a range of 3–78%, demonstrating significant differences in patient selection and diagnostic criteria in available studies (Hay et al., 2019). Common causes for diarrhoea in the critically ill include infectious (mainly bacterial, notably *Clostridioides difficile*) and non-infectious conditions. Among the latter, enteral nutrition and drugs (prokinetic, antibiotics, laxatives) are the most frequent, whereas bowel ischaemia and hypoalbuminemia are also important causes of diarrhoea (Wiesen et al., 2006; Thibault et al., 2013; Tirlapur et al., 2016). Among 1207 ICU patients experiencing diarrhoea, an infectious cause was identified in only 9.2%, while the use of laxatives or enemas/suppositories preceded the development of diarrhoea in 20.2% and 13.1%, respectively (Tirlapur et al., 2016). Diarrhoea may develop as a result of EN, influenced by the composition of the feed as well as the site and method of EN (Wiesen et al., 2006). EN covering >60% of energy target has been identified as a risk factor for diarrhoea (Thibault et al., 2013). Diarrhoea is known to be associated to decreased delivery of nutrients via the enteral route and if left uncorrected, with fluid loss as well as acid-base and electrolyte disorders (Wiesen et al., 2006). Diarrhoea is independently associated with longer length of stay and a greater mortality in ICU (Tirlapur et al., 2016).

*Gastrointestinal bleeding* in the critically ill is defined as any bleeding into the GI tract lumen, confirmed by macroscopic presence of blood in vomited fluids, gastric aspirate or stool (Reintam Blaser et al., 2012). The prevalence is dependent on the extent or nature of bleeding. An earlier study revealed that most critically ill patients experience endoscopically detectable mucosal erosions and subepithelial haemorrhage within 24 hours of admission to ICU (Mutlu et al., 2001). In the current era of frequent proton pump inhibitor use, clinically important GI bleeding (defined as overt bleeding and at least one of the following: decrease in blood pressure ≥20 mmHg; need to start or increase vasopressor infusion by 20%; decrease of haemoglobin ≥20 g/L; transfusion of ≥2 units of red blood cells) occurs in around 2% of patients (Krag et al., 2015, 2018). The main risk factors for GI bleeding include co-existing severe diseases, liver failure and coagulopathy (Krag et al., 2015). While use of proton pump inhibitors in critically ill patients is associated with less frequent GI bleeding (2.5 vs 4.2%), there seems to be no effect on outcomes (a composite of clinically important gastrointestinal bleeding, pneumonia, Clostridium difficile infection, or myocardial ischaemia) (Krag et al., 2018). Accordingly, recent guidelines suggest limiting GI bleeding prophylaxis in the ICU to patients with the highest risk of bleeding (Ye et al., 2020).

*Paralysis of the lower GI tract* (paralytic ileus) refers to the inability of the bowel to pass stool due to impaired peristalsis (Reintam Blaser et al., 2012). In the absence of a mechanical obstruction, it can be diagnosed if stool is not passed for three or more consecutive days. Paralytic ileus affects 13–17% of patients undergoing major abdominal surgery (S. Iyer et al., 2009; Moghadamyeghaneh et al., 2016). Prolonged paralysis of the lower GI tract is seen in sedated and mechanically ventilated patients and those with increased intracranial or intra-abdominal pressure (IAP), infections and sepsis, fluid overload and use of catecholamine drugs (Fruhwald et al., 2008). Bowel paralysis may lead to bowel distension, the most severe form being acute colonic pseudo-obstruction, known as Ogilvie's syndrome (Ladopoulos et al., 2018). This syndrome is characterized by impaired colonic propulsion, which may resemble intestinal obstruction, but a mechanical cause is absent (Ladopoulos et al., 2018).

*Bowel dilatation* is defined as an increase in the diameter of the colon over 6 cm (greater than 9 cm for caecum) or the small bowel over 3 cm, diagnosed either on plain abdominal X-ray or computed tomography scan (Nicolaou et al., 2005; Krajewski et al., 2009). The most severe forms of bowel dilatation without obstruction are Ogilvie's syndrome and toxic megacolon(Reintam Blaser et al., 2015b). Ogilvie's syndrome is rare, occurring in 0.1% of ICU admissions (Ross et al., 2016), but carries a significant risk of colonic ischaemia and mortality of 40% if ischaemia and/or perforation of the bowel occurs (Wells et al., 2017). Ogilvie's syndrome has been associated with a variety of acute clinical conditions including medical and both abdominal and other surgical pathologies, but affects predominantly patients with chronic comorbidities and the elderly (Wells et al., 2017).

*Abdominal distension* is a sign arising from increased intra-abdominal volume, not necessarily related to a gastrointestinal pathology. With no uniform definition, it can be recognised as an increase in the sagittal diameter of the abdomen such that the anterior face of the abdomen extends higher than the imaginary line from the xiphoid process to the symphysis pubis in a supine patient (Reintam Blaser et al., 2015b). Causes may among others include ascites, bowel oedema or dilatation due to paralysis or obstruction (Reintam Blaser et al., 2015b). Being a general and nonspecific sign, abdominal distension should warrant further investigation toward its causes. Abdominal distension may point to the presence of intra-abdominal hypertension (Reintam Blaser et al., 2015b).

Intermittent assessment of *gastric residual volume* is frequently used to guide enteral nutrition and assess its tolerance. The rationale of this practice lies in the acknowledgement that gastric emptying is often delayed in critically ill patients (Ladopoulos et al., 2018), resulting in large gastric volumes that may subject the patient to vomiting or regurgitation and subsequent complications. Detecting large GRV would then allow administration of prokinetic drugs and decreasing

or reducing EN, possibly preventing harm. However, it has been questioned whether GRV may adequately reflect gastric emptying rate. A recent study in 77 critically ill patients indeed established that GRV was moderately correlated to gastric emptying, assessed by 3-O-methylglucose pharmacokinetics, and that high GRV (>400 mL as one episode or two consecutive episodes of >250 mL) had a low specificity (47%), but high sensitivity (98%) in discriminating gastric emptying (Lew et al., 2021). The practice of assessing GRV is currently not standardised and highly variable in different centres, including differences in patient positioning, tube diameter, active aspiration vs passive outflow of gastric contents, discarding vs returning the gastric contents and other factors (Reintam Blaser et al., 2015b; Ladopoulos et al., 2018). In addition, variability exists in the interpretation of a given GRV, highlighted by a recent systematic review demonstrating that across 63 studies, the threshold for a large GRV ranged from 75 to 500 mL on a single measurement (median 250 mL) or 250 to 1000 mL during a 24 hour period (Reintam Blaser et al., 2014b). The ESICM Working Group on Abdominal Problems proposes to consider GRV increased if a single volume exceeds 200 mL (Reintam Blaser et al., 2012). Even though single measurement values above 200 mL are abnormal, pausing EN is not necessary based solely on a 200–500 mL single GRV (Reintam Blaser et al., 2012). In recent decades, the practice of measuring GRV through stopping EN and allowing for outflow of gastric contents has been subject to criticism. Several studies have suggested that measuring GRV with this method is associated with decreased nutrient delivery (Villet et al., 2005; Poulard et al., 2010). A randomised controlled trial comparing a GRV threshold of 200 vs 500 mL found that a use of a higher threshold was associated with more nutrients delivered during the first study week and a similar rate of complications (gastro-intestinal complications, ICU-acquired pneumonia, duration of mechanical ventilation and ICU length of stay) (Montejo et al., 2010). Subsequently, a study among mechanically ventilated patients receiving EEN demonstrated that abandoning GRV measurements in mainly medical patients with already established EN was not associated with an increased risk of ventilator-associated pneumonia compared to measuring GRV (Reignier et al., 2013). Similarly, a single-centre trial in medical ICU patients showed that not measuring GRV is associated with better nutrient delivery and a similar rate of gastric regurgitation as assessed by pH monitoring (Ozen et al., 2016). Current guidelines from the European Society for Clinical Nutrition and Metabolism support the use of GRV in assessing GI dysfunction and identifying intolerance to EN during initiation and progression of EN, stating that monitoring established EN with GRV measurements may not be necessary (Singer et al., 2019). The Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition guidelines suggest not using GRV to monitor patients receiving EN (McClave et al., 2016). However, if GRV is used, all guidelines state that EN should be delayed if GRV is >500 mL (McClave et al., 2016; Reintam Blaser et al., 2017; Singer et al., 2019).

Motor function of the GI tract is traditionally assessed using *auscultation of the abdomen*. Absent peristalsis is assumed if no bowel sounds are heard at cautious auscultation, while hyperperistalsis is considered present if excessive bowel sounds are heard (Reintam Blaser et al., 2012). More recently, ultrasound has been used to evaluate gastric volume and emptying as well as intestinal diameter, peristalsis and blood flow (Hamada et al., 2014; Haruma et al., 2008; Perez-Calatayud et al., 2018). Decreased bowel peristalsis is common among intensive care patients receiving analgosedation and catecholamine medications, with decreased or absent bowel sounds being present in half of the patients (Reintam Blaser et al., 2015b). Absence of bowel sounds has been shown to be independently associated to greater mortality rates (Reintam et al., 2008a; Reintam Blaser et al., 2013). Presence of excessive or tinkling bowel sounds may be a sign of bowel obstruction, a potentially life-threatening condition (Reintam Blaser et al., 2015b).

Although the importance of GI symptoms has been shown, several areas of uncertainty remain. It is not clear how to use GI symptoms in precise decision-making regarding nutrition, in assessment of the GI function as well as evaluating the course and severity of multiple organ dysfunction. Further, it is not straightforward when can GI symptoms and IAH be considered simply epiphenomenons of critical illness and when could their treatment improve outcomes. In study II, impact on outcomes of different etiologies of gastrointestinal failure (GIF), defined using a combination of GI symptoms, is evaluated.

## 2.3 Intra-abdominal hypertension

Intra-abdominal pressure refers to the static pressure within the abdominal cavity. Relevant consensus definitions of the Abdominal Compartment Society are listed in Table 1.

**Table 1.** Consensus definitions of the World Society of the Abdominal Compartment Syndrome (Kirkpatrick et al., 2013)

| | |
|---|---|
| 1 | IAP is the steady-state pressure concealed within the abdominal cavity |
| 2 | The reference standard for intermittent IAP measurements is via the bladder with a maximal instillation volume of 25 mL of sterile saline |
| 3 | IAP should be expressed in mmHg and measured at end-expiration in the supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the midaxillary line |
| 4 | IAP is approximately 5–7 mmHg in critically ill adults |
| 5 | IAH is defined by a sustained or repeated pathological elevation in IAP ≥ 12 mmHg |
| 6 | ACS is defined as a sustained IAP > 20 mmHg (with or without an APP < 60 mmHg) that is associated with new organ dysfunction/failure |
| 7 | IAH is graded as follows<br>Grade I, IAP 12–15 mmHg<br>Grade II, IAP 16–20 mmHg<br>Grade III, IAP 21–25 mmHg<br>Grade IV, IAP > 25 mmHg |
| 8 | Primary IAH or ACS is a condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or interventional radiological intervention |
| 9 | Secondary IAH or ACS refers to conditions that do not originate from the abdominopelvic region |
| 10 | Recurrent IAH or ACS refers to the condition in which IAH or ACS redevelops following previous surgical or medical treatment of primary or secondary IAH or ACS |
| 11 | APP = MAP − IAP |
| 12 | A polycompartment syndrome is a condition where two or more anatomical compartments have elevated compartmental pressures |
| 13 | Abdominal compliance is a measure of the ease of abdominal expansion, which is determined by the elasticity of the abdominal wall and diaphragm. It should be expressed as the change in intra-abdominal volume per change in IAP |
| 14 | The open abdomen is one that requires a temporary abdominal closure due to the skin and fascia not being closed after laparotomy |
| 15 | Lateralization of the abdominal wall is the phenomenon where the musculature and fascia of the abdominal wall, most exemplified by the rectus abdominus muscles and their enveloping fascia, move laterally away from the midline with time |

*IAP – intra-abdominal pressure; IAH – intra-abdominal hypertension; ACS – abdominal compartment syndrome; APP – abdominal perfusion pressure; MAP – mean arterial pressure.*

Intra-abdominal hypertension occurs in 40–50% of intensive care patients (D. Iyer et al., 2014; Murphy et al., 2018; Reintam Blaser et al., 2019). Mortality increases with increasing grade of severity, and the most severe form of IAH, ACS carries a mortality rate of 75–90% (D. Iyer et al., 2014; Murphy et al., 2018; Reintam Blaser et al., 2019).

IAP can increase as a result of either an increased intra-abdominal volume, a decreased abdominal compliance, or both (Reintam Blaser et al., 2015a). Relevant causes for increased intra-abdominal volume in critically ill patients include intra- or extraluminal gas or fluid (e.g., bowel obstruction, ascites, pneumoperitoneum), tissue oedema (e.g., abdominal inflammation or infection, fluid resuscitation) or solids such as fat, tumour or a pregnant uterus. Abdominal compliance influences the extent of increase in IAP in response to addition of a given intra-abdominal volume: with decreased compliance, a lower amount of added volume causes a greater increase in IAP (Reintam Blaser et al., 2015a). A low abdominal compliance cannot be measured at the bedside, but must be suspected in pathologies and conditions involving the abdominal wall, e.g. severe burn injuries, external constraints, previous abdominal surgery and massive fluid resuscitation with capillary leak (Reintam Blaser et al., 2015a).

Elevated IAP impairs the function of many organs, both close and distant. The diaphragm is displaced cephalad, causing compression of the thoracic organs, notably the lungs and the heart. Compression of the lungs provokes atelectasis, resulting in worsened intrapulmonary blood shunting with hypoxemia and hypercapnia, and reduced lung compliance (Obeid et al., 1995; Ridings et al., 1995) causing an increased work of breathing. Compression of the heart and the inferior vena cava is associated with decreased venous return and cardiac filling, leading to low cardiac output (Cheatham, 2009). Renal perfusion is reduced by compression of the renal vasculature, with ensuing oliguria and acute renal failure (Cheatham, 2009; Candan et al., 2020). Increased IAP likely impairs hepatic perfusion and/or function, assessed by plasma disappearance rate of indocyanine green (Malbrain et al., 2012). Abdominal wall muscle tissue ischaemia may occur already during short periods of modestly increased IAP of 12–13 mmHg (Maddison et al., 2012). In animal models, intra-abdominal hypertension from 15 mmHg has been shown to cause ischaemia of the small and large bowel resulting in bacterial translocation (Sertaridou et al., 2015).

The exact IAP value that should be considered abnormal and define IAH has been subject to debate for some time. An early classification was proposed by Burch and colleagues, with IAH grade I corresponding to 7.5–11 mmHg, based on physiological alterations becoming evident at these levels (Burch et al., 1996). The current IAH threshold of 12 mmHg originates from the first consensus definitions of the World Society of Abdominal Compartment Society, which took into account a large amount of accumulated data demonstrating that IAP as low as 10-15 mmHg may have negative effects on organ functions (Malbrain et al., 2006).

Abdominal compartment syndrome refers to a situation where reductions in organ blood flows due to increased IAP leads to organ failure(s). In addition to

organs in the abdominal cavity, a polycompartment syndrome is recognized, in which the head, chest and extremity compartments are affected as a result of increased IAP (Malbrain et al., 2014). This concept may involve both worsening of a primary injury in another compartment (e.g. traumatic brain injury) or a newly developing, secondary injury in a previously uninjured compartment (e.g. lower limbs) due to increased pressure in the abdomen (Malbrain et al., 2014).

The associations between IAH and GI symptoms and enteral nutrition have been investigated in few studies. Observations in intensive care patients suggest that majority of patients with IAH also experience GI symptoms, and IAH of higher grade of severity is associated with more simultaneous GI symptoms (Reintam Blaser et al., 2011a). Occurrence of IAH and GI symptoms together is frequent (36%) and associated with worse outcomes than occurrence of either IAH or GI symptoms or absence of both either (Reintam Blaser et al., 2011a). Likewise, simultaneously occurring IAH and FI have been shown to be associated with worst outcomes (Reintam et al., 2008a). In a study randomizing patients with severe acute pancreatitis to early (within 48 hours) or delayed (from the $8^{th}$ day) postpyloric EN, feeding intolerance was significantly more frequent in patients with early EEN, although no difference in the incidence of IAH was seen between the groups and surprisingly a trend towards less IAH was observed in those receiving EEN (Sun et al., 2013). In patients with IAP ≥15 mmHg, the incidence of FI during the first week was significantly higher compared to patients with IAP <15 mmHg (91% vs 45%) (Sun et al., 2013). In a prospective observational study involving 247 critically ill patients, it was shown that IAH frequently precedes development of FI, but no cut-off value for IAP to predict FI could be determined (Bordejé et al., 2019).

It is universally accepted that if IAH causes organ failure(s), ACS is to be diagnosed and treated. However, it is still not clear whether it is beneficial to intervene in case of mild to moderate increases of IAP. Previously, conflicting findings about the association between IAH as a yes-no phenomenon and mortality have been shown (Kim et al., 2012). However, more recent studies demonstrate better outcomes in those with lower and worse in those with higher grades of IAH (D. Iyer et al., 2014; Murphy et al., 2018; Reintam Blaser et al., 2019). Still, the causality of such associations and whether outcomes can be improved with treatment of IAH, remain unanswered without randomised studies evaluating the effect of different strategies in treating mild to moderate IAH.

Medical or minimally invasive treatment options are the first line in the management of IAH to prevent progression to ACS. Surgical decompression of the abdomen is often necessary in ACS and carries a high risk of complications; therefore, it would be desirable to avoid situations where it is inevitable. Decompressive laparotomy is recommended in ACS when medical management fails (Kirkpatrick et al., 2013). Management of ACS with the emphasis on surgical treatment is reviewed in detail in Paper VI.

*Nonsurgical management of IAH*

Management of IAH is aimed at reducing intra-abdominal volume, improving abdominal compliance and optimizing organ perfusion (Kirkpatrick et al., 2013). For example, evacuation of intraluminal fluid or gas may be achieved using nasogastric drainage in patients with bowel obstruction or ileus and using a rectal tube in patients suffering from acute colonic pseudo-obstruction, while abdominal compliance may be improved using neuromuscular blockade or analgesia and sedation (Kirkpatrick et al., 2013). However, the existing evidence is scarce and its quality low. Accordingly, most treatment options of IAH are either suggested with very low evidence or no recommendation could be made (Kirkpatrick et al., 2013). Therefore, new knowledge on the effectiveness of different proposed medical management options is essential. The impact and side effects of deepening of sedation as a mode of treatment of IAH are evaluated in study III.

## 2.4 Biomarkers of intestinal function and damage

Currently, there are no biomarkers in everyday clinical use that could help diagnose or manage Gl problems in intensive care patients. Such biomarkers would be very valuable to help make the assessment of the GI function more objective. Several potential candidates have been studied during the last years, with good pathophysiological rationale suggesting further investigations into some of them. Citrulline has been proposed as a marker of intestinal function while intestinal fatty acid-binding protein (I-FABP) is considered a biomarker of intestinal damage. The most important aspects of these biomarkers are described below, with a more detailed overview given in Paper VII. Other biomarkers reflecting gut injury/ischaemia, discussed below in short detail, include ileal lipid binding protein, D-lactate, ischaemia modified albumin, α-glutathione S-transferase and the smooth-muscle protein of 22 kDa. Ileal lipid binding protein is a cytosolic protein present specifically in the epithelial cells of the ileum, being responsible for the transport of bile acids. Similar to I-FABP, it is released to circulation in case of intestinal hypoperfusion and subsequent loss of cell membrane integrity (van Wijck et al., 2011). D-lactate is an isomer of lactate which is present in only low concentrations in human blood, originating from intestinal bacterial metabolism mostly in the large intestine and some foods. Alteration of mucosal integrity due to intestinal ischaemia has been proposed as a mechanism for increased D-lactate concentrations in blood (Montagnana et al., 2018). The metal binding capacity of human albumin (ischaemia modified albumin) is easily measured and is known to decrease in acute hypoxic conditions such as acute coronary syndrome, stroke, skeletal muscle ischaemia, but also acute mesenteric ischaemia (Montagnana et al., 2018). α-glutathione S-transferase is another biomarker of oxidative stress, but also lacks specificity, being present in both intestinal and hepatic cells (Montagnana et al., 2018). Smooth-muscle protein of 22 kDa is involved in the maturation of smooth muscle cells and is abundantly

expressed in case of smooth muscle injury, e.g. a transmural intestinal ischaemic injury (Montagnana et al., 2018). A recent systematic review and meta-analysis evaluating the diagnostic accuracy of the aforementioned biomarkers, excluding smooth-muscle protein of 22 kDa, found that highest specificity for acute mesenteric ischaemia was achieved with I-FABP (91%) and ischaemia modified albumin (86%) (Treskes et al., 2017).

### 2.4.1. Citrulline

Citrulline is a non-protein amino acid which is synthesised in many tissues of the human body, but the circulating citrulline originates almost exclusively from the gut (Curis et al., 2005). It is produced from glutamine in mature enterocytes of the small bowel and after being released in the circulation, is taken up and metabolised in the kidneys to arginine (Curis et al., 2005), being an important source of the latter. Therefore, citrulline plasma concentration reflects a balance between synthesis in the gut and uptake in the kidneys. In health, citrulline plasma concentration is about 40 μmol/L , while 20 μmol/L seems to be the most frequent cut-off between low and normal values in studies involving critically ill patients (Fragkos & Forbes, 2018; Papadia et al., 2018). However, some authors argue that a cut-off value for "normal" citrulline likely does not exist in critically ill patients due to a variety of confounders and that it may be appropriate to interpret values of 10–20 μmol/L as a grey area (Piton & Capellier, 2015).

Plasma citrulline concentrations have been shown to be strongly correlated to the remaining small bowel length in patients with short bowel syndrome (Fragkos & Forbes, 2018), associating citrulline with bowel mass. Increasing data suggests that the same may be true for bowel function. Meta-analysis of studies evaluating the association of citrulline levels with intestinal absorption shows a moderate positive correlation (Fragkos & Forbes, 2018). Further, citrulline is negatively correlated with severity of disease in enteropathies (e.g. coeliac disease, mucositis, acute rejection in transplantation and others) (Fragkos & Forbes, 2018), while treatment of patients with short bowel syndrome with teduglutide, a glucagon-like peptide-2 analogue which promotes mucosal growth, is associated with an increase in citrulline levels (Fragkos & Forbes, 2018). The aforementioned findings suggest that citrulline may be associated not only with enterocyte mass but also function, justifying studies in intensive care patients, in whom predominantly the function of enterocytes may be impaired in a variety of conditions.

Among critically ill patients, low levels of citrulline have been described in subsets of patients with cardiac arrest (Grimaldi et al., 2013; Piton et al., 2015) and septic shock (Crenn et al., 2014; Luiking et al., 2009) as well as in the general ICU population (Piton et al., 2010; Noordally et al., 2012; Piton et al., 2013; Piton, Cypriani, et al., 2015; Poole et al., 2016; Piton et al., 2019). Associations between low citrulline levels and poor outcomes have been

reported in several studies (Piton, Belin, et al., 2015; Piton et al., 2010, 2013). Proposed mechanisms for low citrulline values in critically ill patients include intestinal hypoperfusion resulting in mucosal ischaemia and reduced intestinal villi length and sepsis-associated glutamine deficiency and reduced de novo citrulline synthesis (Piton & Capellier, 2016).

In studies investigating the temporal dynamics of citrulline in ICU patients (Piton et al., 2010; Grimaldi et al., 2013; Piton et al., 2019), a common finding is a U-shaped curve – an initial decrease in the first few post-admission days is followed by an increase by the end of the first week. It has been discussed that such dynamics may correspond to an initial period of damage followed by a period of renewal of enterocytes (Piton & Capellier, 2016; Piton et al., 2019).

Low values of citrulline have also been described in critically ill patients with clinically apparent GI dysfunction. Fagoni et al. demonstrated that gastrointestinal failure, defined as the concomitant presence of IAH and feeding intolerance (Reintam et al., 2008a), was associated with very low citrulline values of less than 10 µmol/L. Noordally et al. reported low citrulline values of < 15 µmol/L in patients with intestinal dysfunction, defined as presence of feeding intolerance, ileus, diarrhoea or GI bleeding (Noordally et al., 2012). Yet, in a small observational study investigating glucose absorption in critically ill patients, no correlation between fasting citrulline concentration and subsequent absorption of glucose could be demonstrated (Poole et al., 2016).

Attention should also be paid on renal function when interpreting values of citrulline in critically ill patients. As the vast majority of citrulline is degraded in the kidneys, chronic renal dysfunction is associated with higher values of citrulline (Lau et al., 2000; Pironi, Guidetti, et al., 2015). Higher values of citrulline compared to controls with normal renal function have been shown if creatinine clearance is less than 50 mL/min (Pironi, Guidetti, et al., 2015). Several studies investigating citrulline in critically ill patients have a priori excluded those with chronic renal failure. Yet, in studies reporting citrulline in patients with acute renal failure, no differences to controls have been demonstrated (Noordally et al., 2012; Piton et al., 2010; Grimaldi et al., 2013).

### 2.4.2. Intestinal fatty acid-binding protein

I-FABP, also known as FABP2, is a small protein in the family of fatty acid binding proteins which participate in the uptake, metabolism and transport of long-chain fatty acids (Smathers & Petersen, 2011). This protein is found exclusively in mature enterocytes of the small and large intestine – mainly in the duodenum and jejunum and much less in the ileum and colon (Pelsers et al., 2005). The normal life cycle of an enterocyte ends with apoptosis and shedding into the intestinal lumen with no release of intracellular contents. Accordingly, the levels of I-FABP in plasma are very low or undetectable in healthy individuals (Pelsers et al., 2005; de Haan et al., 2009). Owing to a low mole-

cular weight, circulating fatty acid binding proteins are rapidly cleared via kidneys with an elimination half-life of 11 minutes (van de Poll et al., 2007).

When enterocyte membrane is disrupted, I-FABP is released into the circulation (Schellekens et al., 2014). As mature enterocytes are present at the tips of intestinal villi, a location especially vulnerable to ischaemia, I-FABP has been of great interest as a marker of ischaemic damage to the intestinal epithelium. Elevated I-FABP plasma levels have been demonstrated in various setting and degrees of intestinal ischaemia, Including intense exercise in healthy adults (Edinburgh et al., 2018; Karhu et al., 2017), major non-abdominal surgery (Derikx et al., 2008; Habes et al., 2017; Zou et al., 2018), trauma (de Haan et al., 2009; Timmermans et al., 2015), acute mesenteric ischaemia (Cronk et al., 2006; Kanda et al., 2011; Vermeulen Windsant et al., 2012), cardiac arrest (Grimaldi et al., 2013; Piton et al., 2015) and a variety of other conditions.

I-FABP appears in the circulation rapidly, within 30 minutes after onset of small bowel ischaemia (Schellekens et al., 2014), and disappears within 120 minutes of reperfusion (Schellekens et al., 2017). However, in critically ill patients, the symptoms of bowel ischaemia may go unnoticed for a while due to analgesia and sedation. In a pragmatic study involving critically ill patients, the suspicion of bowel ischaemia arose and samples were collected hours after a potential triggering event, and I-FABP plasma values did not differ between those who developed small bowel ischaemia vs those who did not (Ludewig et al., 2017). It was argued that irreversible ischaemia causing no wash-out of I-FABP may explain the lack of I-FABP increase in patients with bowel ischaemia (Ludewig et al., 2017).

A relationship with elevated plasma I-FABP values and poor outcomes has been demonstrated. In studies by Piton et al. involving critically ill patients, admission I-FABP values greater than 355 pg/mL (Piton et al., 2013) and 524 pg/mL (Piton, Cypriani, et al., 2015) were independently associated with higher mortality at 28 days. In patients resuscitated from cardiac arrest, admission I-FABP value greater than 260 pg/mL was independently associated with a poor neurological outcome (OR 13.6, 95% CI 1.4–129) (Piton, Belin, et al., 2015). Additionally, post-resuscitation admission values of I-FABP were positively correlated with endotoxin levels, signalling gut barrier failure due to ischaemia (Grimaldi et al., 2013).

Renal failure delays clearance of I-FABP from the plasma (Kittaka et al., 2014), with a twofold increase seen in patients with end-stage renal failure and normalization of plasma levels after haemodialysis (Okada et al., 2018).

An important consideration when comparing the studies is the measurement technique used for I-FABP and its reference values. Commonly enzyme-linked immunosorbent assay (ELISA) is used. Several kits are available that demonstrate greater than 100-fold inter-assay differences in I-FABP values both in controls as well as in patients with acute mesenteric ischaemia (Treskes et al., 2017). Therefore, values between studies using different measurement techniques are not interchangeable and dynamics rather than absolute values can be compared.

In summary, evidence from settings outside intensive care support the use of citrulline and I-FABP as markers of enterocyte function and damage, respectively. Several confounding factors complicate the interpretation of the values of the biomarkers. Associations of low citrulline and high I-FABP values with outcome of critically ill patients are well described, however, the role of the biomarkers in assessing the functioning of the GI tract and guiding of nutrition is less clear.

In this dissertation we explore whether citrulline and I-FABP could be used in assessment of GI dysfunction as a part of multiple organ dysfunction and in guiding decision-making in enteral nutrition. In study IV, the contribution of the biomarkers towards a score quantifying gastrointestinal dysfunction is assessed. In study V, the dynamics of citrulline and I-FABP are investigated in relation to the application and success of early enteral nutrition during the first week of intensive care.

## 2.5 Gastrointestinal dysfunction and failure

The GI tract has several functions, including digestion and absorption of nutrients and water, barrier, endocrine and immune functions, while adequate perfusion, secretion, motility and coordinated gut-microbiome interactions are necessary for normal functioning (Reintam Blaser et al., 2012). However, it is not easy to identify normal GI function in the critically ill. Some aspects of the adaptation of the GI tract to critical illness have been described above, including loss of appetite, anorexia and decreased motility. Even though no unified definition of normal functioning of the GI tract in critical illness exists, the recognition and diagnosing of abnormal function is necessary for both clinical and research use to assess and manage gastrointestinal problems in intensive care patients.

Clinical assessment has remained the main method to monitor GI function in the critically ill. No imaging strategy, biomarker nor method to assess absorption or barrier function has been sufficiently validated or is available for clinical use. Consequently, previous attempts at quantifying GI dysfunction in intensive care patients have mostly centred around clinical assessment of gastrointestinal or abdominal signs and symptoms. Previous attempts at defining GI dysfunction or failure, notably varying, are shown in Table 2 (adapted from (Reintam Blaser et al., 2016). There is also significant inconsistency in the terminology of such attempts, with the terms “dysfunction” and “failure” both having been used to represent a continuum of abnormal functioning, but also a yes/no-phenomenon. In our opinion, the term “dysfunction” would be appropriate to describe the continuum of changes, while “failure” would be a dichotomous characteristic of the severity of condition.

**Table 2.** Different approaches to define gastrointestinal dysfunction/failure in ICU patients (adapted from (Reintam Blaser et al., 2016).

| Name/acronym | Components/rationale | Gradation | Research-derived | External validation* | Problems |
|---|---|---|---|---|---|
| **GI failure** (Goris et al., 1985) | Specific diseases (cholecystitis, stress ulcer etc) | Yes, 2 grades | Yes | Yes | Initially included in MOF score |
| **GI dysfunction** (Chang et al., 1987) | FI defined through 4 abdominal/GI symptoms | None | Yes | No | Poorly defined and subjective GI features. |
| **GI dysfunction** (Mayr et al., 2006) | Prolonged ileus or GI bleeding | None | Yes | No | GI failure in 2.6% of patients, not a predictor of mortality |
| **GI failure** (Reintam et al., 2006) | FI, GI bleeding, ileus | None | Yes | No | FI and ileus poorly defined. |
| **GIF score** (Reintam et al., 2008a) | Amount of EN, FI, IAH, ACS | Yes, 4 grades | Yes | Yes | Poor continuity |
| **LIFE score** (Berger et al., 2008) | IAP, lactic acidosis, progression of enteral feeding, GI symptoms | Yes, 5 grades | No | No | Never tested/validated. |
| **Acute GI Injury** (Reintam Blaser et al., 2012) | Descriptive grading, rationale:<br>1. risk/self-limiting condition<br>2.GI dysfunction<br>3. GI failure<br>4. life-threatening GI failure | Yes, 4 grades | No | Yes | Developed with consensus. FI poorly defined. Other organ dysfunctions play an important role |
| **GI failure** (Reintam Blaser et al., 2013) | ≥3 coincident GI symptoms | None | Yes | Yes | Poorly defined and subjective GI features. |
| **Intestinal failure** (Pironi, Arends, et al., 2015) | Descriptive categorization, rationale:<br>1. Acute, short-term condition<br>2. Prolonged acute condition<br>3. Chronic condition | No | No | Partial | Based on duration = not well applicable at any time point |

| Name/acronym | Components/rationale | Gradation | Research-derived | External validation* | Problems |
|---|---|---|---|---|---|
| **Gut failure** (Piton et al., 2013; Piton & Capellier, 2016) | Plasma citrulline and I-FABP | No | Yes | No | Relation to clinical features and EN not included |
| **Modified GIF score** (Aperstein et al., 2019) | 0–4 points for each category: daily energy balance, gastric residual volumes and vomiting, stool passage | Yes, 0–12 points | Yes | No | Retrospective; link between GI dysfunction and energy balance not certain |

** The score has been tested (for prediction of outcome) in a general adult ICU population other than the development cohort.*

*Legend: GI – gastrointestinal; MOF – multiple organ failure; FI – feeding intolerance; GIF – Gastrointestinal Failure (score); EN – enteral nutrition; IAH – intra-abdominal hypertension; ACS – abdominal compartment syndrome; LIFE – Lausanne Intestinal Failure Estimation; IAP – intra-abdominal pressure; MODS – Multiple Organ Dysfunction Score; I-FABP – intestinal fatty acid binding protein.*

Below, a few approaches laying the groundwork to the research in the present dissertation are described in more detail.

In 2008, the GIF score was created on the basis of feeding intolerance and intra-abdominal hypertension (Reintam et al., 2008a). FI was defined as the need to discontinue EN due to repeated or profuse vomiting, high GRV, ileus, severe diarrhoea, abdominal pain or distension. FI was not considered present if feeding was not undertaken during the first 3 days after abdominal surgery. Among 264 mechanically ventilated patients admitted consecutively to a single study centre, with an ICU length of stay of at least one day, FI developed in 58% and IAH in 27% of patients. A clinical score with 4 grades of severity was created, with the following gradation: 0 – normal gastrointestinal function; 1 – enteral feeding possible, but achieving <50% of calculated needs or no feeding during 3 days after abdominal surgery; 2 – FI or IAH; 3 – FI and IAH; 4 – abdominal compartment syndrome. The average GIF score during the first 3 days of ICU appeared as an independent risk factor for ICU mortality and slightly improved the ability to predict mortality of the Sequential Organ Failure Assessment (SOFA) score. Nevertheless, while the GIF score can be easily assessed using readily available clinical data, major limitations include the subjective nature of determining FI and the fact that the score does not reflect a continuum of function.

In a subsequent attempt to create a GI dysfunction score able to predict outcome, 377 mechanically ventilated adult patients from 40 ICUs were included in a prospective study collecting data on prespecified GI symptoms (absent bowel sounds, vomiting/regurgitation, GRV, diarrhoea, bowel distension, GI bleeding), feeding and IAH (Reintam Blaser et al., 2013). Based on daily comparisons between survivors and nonsurvivors with different number of GI symptoms, a cut-off for GI failure was identified at the presence of 3 concomitant symptoms in one day. GIF diagnosed by the presence of 3 symptoms occurred in 6.4% of patients and if present on admission day, was associated with a threefold independent increase in mortality. In creating a GI failure score, neither feeding-related variables nor IAH improved the predictive ability of the score. Accordingly, a score, named similarly the GIF score, was proposed based on 6 aforementioned GI symptoms, where the severity gradation was as follows: 0 – no GI symptoms; 1 – 1 symptom; 2 – 2 symptoms; 3 – 3 symptoms; 4 – ≥4 symptoms. Even though an increasing GIF score was associated with a higher mortality rate, the score was not able to add any value to the SOFA score in terms of mortality prediction. It was argued that this may be explained with GIF occurring secondary to other organ failures, already included in the SOFA score, and not as a primary organ failure.

In 2012, the Working Group on Abdominal Problems of the ESICM produced a consensus document unifying the terminology and definitions of acute GI failure and GI symptoms (Reintam Blaser et al., 2012). A conceptual model of gastrointestinal dysfunction was proposed in the form of the Acute Gastrointestinal Injury (AGI) grading, which included five degrees of severity, with AGI 0 corresponding to normal functioning of the GI tract; AGI 1 – risk;

AGI 2 – GI dysfunction; AGI 3 – GI failure; AGI 4 – life-threatening condition due AGI causing distant organ failure (Table 3).

**Table 3.** Acute Gastrointestinal Injury grades (Reintam Blaser et al., 2012).

| | |
|---|---|
| AGI 0 | Definition: GI system appears to function normally, no signs of GI dysfunction |
| AGI I | Definition: GI symptoms related to a known cause and perceived as transient.<br>Rationale: Condition is clinically seen as occurrence of GI symptoms after an insult, which expectedly has temporary and self-limiting nature.<br>Examples:<br>- Postoperative nausea or vomiting during the first days after abdominal surgery<br>- Postoperative absence of bowel sounds<br>- Diminished bowel motility in the early phase of shock |
| AGI II | Definition: GI symptoms requiring therapeutic interventions for achievement of nutrient and fluid requirements.<br>Rationale: This condition occurs without previous GI interventions or is more severe than might be expected in relation to the course of preceding abdominal procedures. No changes in general condition of the patient related to GI problems.<br>Examples:<br>- Gastroparesis with high gastric residuals or reflux<br>- Paralysis of the lower GI tract<br>- Diarrhoea<br>- Intra-abdominal hypertension (IAH) grade I (intra-abdominal pressure (IAP) 12–15 mmHg)<br>- Visible blood in gastric content or stool |
| AGI III | Definition: restoration of GI function is not achieved despite interventions and the general condition is not improving.<br>Rationale: sustained intolerance to enteral feeding without improvement after treatment (e.g., erythromycin, postpyloric tube placement), leading to persistence or worsening of multiple organ dysfunction syndrome.<br>Examples:<br>- Despite treatment, feeding intolerance is persisting possibly associated with persistence or worsening of multiple organ dysfunction syndrome:<br>- High gastric residuals<br>- Persisting GI paralysis<br>- Occurrence or worsening of bowel dilatation<br>- Progression of IAH to grade II (IAP 15–20 mmHg)<br>- Low abdominal perfusion pressure (APP) together with IAH (below 60 mmHg) |
| AGI IV | Definition: AGI has progressed to become directly and immediately life-threatening, with worsening of multiple organ dysfunction syndrome and shock.<br>Rationale: AGI has led to an acute critical deterioration of the general condition of the patient with distant organ dysfunction(s).<br>Examples:<br>- Bowel ischaemia with necrosis<br>- GI bleeding leading to haemorrhagic shock<br>- Ogilvie's syndrome<br>- Abdominal compartment syndrome (ACS) |

*GI – gastrointestinal; IAH – intra-abdominal hypertension; IAP – intra-abdominal pressure; APP – abdominal perfusion pressure; ACS – abdominal compartment syndrome.*

Proposed for both clinical and research purposes, the AGI grading was initially developed based on expert opinion with no research directly backing its constitution. The AGI grading has later been externally validated regarding mortality in several studies (Hu et al., 2017; Zhang et al., 2018; Loudet et al., 2020; Ding et al., 2020). Although performing well in clinical practice, important limitations of the AGI grading include inability to apply it retrospectively, subjectivity and likely effect from other organ dysfunctions, elaborated further in the discussion section of this dissertation.

Currently, no existing clinical score of GI dysfunction is perfect for both clinical and research use. The main objective of the iSOFA project (study IV) was to create a new score to quantify GI dysfunction, based on a combination of GI symptoms, IAP and biomarkers.

## 2.6. Summary of the review of the literature

The importance of problems related to the GI tract in critically ill patients is increasingly recognised. The research in the field has greatly advanced in the last decades, allowing for development of wide-scoping societal guidelines in the areas of nutrition and intra-abdominal hypertension. Still, large areas of uncertainty remain. Optimal targets of nutrition as well as the timing and mode to achieve them are a matter of debate. Unlike other organ systems, assessment of the functioning of the GI tract in everyday practice currently remains based on an unstructured evaluation of abdominal and GI symptoms, with only a few numerical values available. Further, while the importance of these symptoms is recognised, it is generally not clear whether, when and with which methods should they be attempted to be treated to achieve better outcomes for critically ill patients.

# 3. AIMS OF THE RESEARCH

The studies in this dissertation were focused on the prescription and management of enteral nutrition, the diagnosis and outcome of gastrointestinal dysfunction and the use of biomarkers to aid in the previous fields as well as the management of the closely related intra-abdominal hypertension and abdominal compartment syndrome.

The specific aims were the following:

1. To evaluate the effect of an enteral feeding protocol on nutritional provision, gastrointestinal symptoms and outcome in long-staying ICU patients (study I).
2. To describe the prevalence and outcome of gastrointestinal failure, defined through the simultaneous occurrence of several GI symptoms, and to characterise GIF according to its aetiology (study II).
3. To evaluate the effectiveness and safety of deepening of sedation, a recommended treatment option of IAH, among mechanically ventilated intensive care patients (study III).
4. To create an objective and reproducible score for gastrointestinal dysfunction based on gastrointestinal and abdominal signs and symptoms as well as the biomarkers citrulline and I-FABP, and evaluate its ability to predict treatment outcome (study IV).
5. To evaluate the associations of the biomarkers citrulline and I-FABP with enteral nutrition (study V).

# 4. MATERIALS AND METHODS

This dissertation is based on 5 original studies, including over 4500 ICU patients in total, the main characteristics of which are shown in Table 4.

**Table 4.** Characteristics of studies and reviews.

| Abbreviated study name | Study no. | Years | Type | Patients | Aim |
|---|---|---|---|---|---|
| Enteral feeding protocol study | I | 2011–2015 | Retrospective single centre | 480 long-staying ICU patients | To evaluate the effect of an enteral feeding protocol on nutritional practices, complications and outcomes |
| Gastrointestinal failure study | II | 2004–2015 | Retrospective single centre | 3959 ICU patients | To describe the prevalence and outcome of GIF, compare GIF according to its aetiology |
| Intra-abdominal pressure and sedation study | III | 2016–2020 | Interventional single centre | 37 mechanically ventilated ICU patients with IAH | To evaluate the effect of deepening of sedation on IAP and other physiologic parameters |
| iSOFA study | IV | 2015–2018 | Prospective observational multicentre | 540 consecutive ICU patients | To create a score quantifying gastrointestinal dysfunction and evaluate its effect in predicting outcome |
| Enteral nutrition and biomarkers study | V | 2015–2018 | Prospective observational multicentre (substudy of IV) | 224 consecutive ICU patients | To describe the dynamics of citrulline and I-FABP and their association with nutrition during the first week of ICU |

*ICU – intensive care unit; GIF – gastrointestinal failure; IAH – intra-abdominal hypertension; IAP – intra-abdominal hypertension; iSOFA – intestinal-specific organ failure assessment; I-FABP – intestinal fatty acid-binding protein; ACS – abdominal compartment syndrome.*

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## 4.1. Ethics

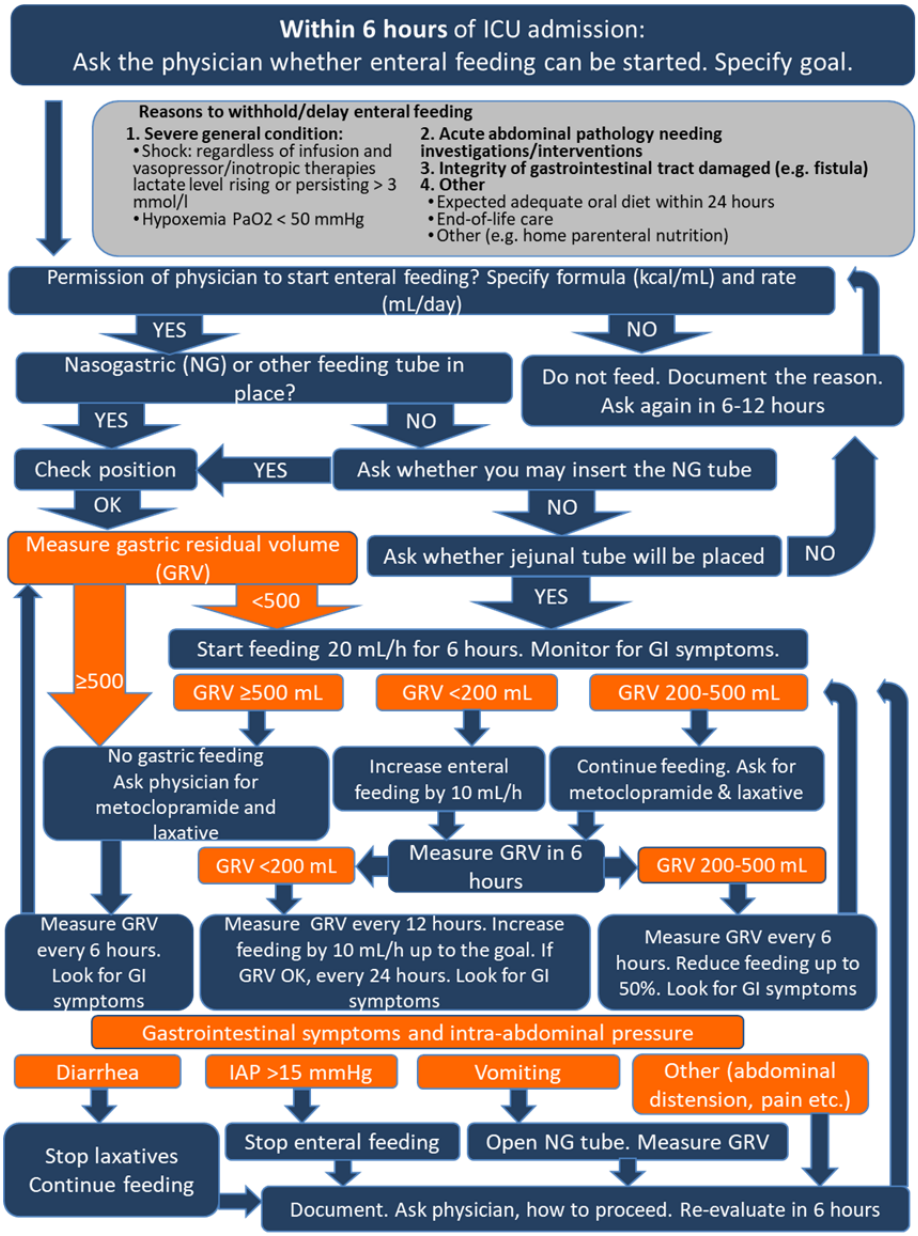
The Research Ethics Committee of the University of Tartu approved the studies I (approval no. 258/T-6) and II (approval no. 264/T-4) with waived informed consent. Study III was approved by the Research Ethics Committee of the University of Tartu (approval nos. 260/T-8 and 289/T-27). Delayed informed consent was obtained from the patient or the next of kin and in case of refusal to participate in the study, collected data were discarded. The study is registered at ClinicalTrials.gov (NCT02944292).

The iSOFA study (studies IV and V) was approved by the Research Ethics Committee of the University of Tartu (approval 265/M-28). Approval from the local ethics committee was obtained at each study site. The study is registered at ClinicalTrials.gov (NCT02613000).

## 4.2. Patients and study design

### 4.2.1 Enteral feeding protocol study (I)

The study population consists of adult patients (≥18 years) who were treated for at least 7 consecutive days in the 1st ICU of the Tartu University Hospital, excluding readmissions. In a retrospective before-and-after study, the effects of implementing a nurse-driven enteral feeding protocol were evaluated. In 2013, a feeding protocol, constructed based on examples found in the literature, was implemented in the study unit (Figure 1). The Before group consists of eligible patients admitted to the ICU in years 2011 and 2012, while the After group includes patients admitted in years 2014 and 2015. The year 2013 was considered a period of adaptation to the feeding protocol. Nutrition of patients in the Before group was handled by intensive care physicians in a non-protocolised manner and nurses were responsible for the delivery of nutrients, while in years 2014 and 2015 the enteral feeding protocol was in everyday use. Adherence to the protocol was not assessed in the current study. Clinical characteristics, nutritional and outcome data were compared between patients in the Before and the After group.




*ICU – intensive care unit; PaO2 – partial pressure of oxygen in arterial blood; NG – nasogastric; GRV – gastric residual volume; GI – gastrointestinal; IAP – intra-abdominal pressure.*

**Figure 1.** Enteral feeding protocol (developed in the 1st ICU of Tartu University Hospital).

The feeding protocol draws attention to the possibility of enteral nutrition early after admission to ICU, also specifying situations where EN is to be delayed. The progression of feeding rate relies on the regularly measured GRV and GI symptoms, with a reduction or cessation of feeding in case of GI problems. If GRV is low and GI symptoms absent, a target rate of 70–80 ml/h is achieved by 72–96 hours from the start of feeding.

### 4.2.2. Gastrointestinal failure study (II)

All adult patients, including readmissions, that were admitted to the 1st ICU of the Tartu University Hospital in years 2004–2015 were included in this study. GIF was defined as the simultaneous presence (during one day) of 3 or more gastrointestinal symptoms. According to its aetiology, GIF was divided into primary (GIF occurring in a patient with a GI pathology, including oesophageal, gastric, hepatic, pancreatic, biliary, small and large intestine sites of illness, trauma or surgery) and secondary (due to some other pathology). Clinical characteristics and treatment outcomes were compared between patients with and without GIF, and primary and secondary GIF.

### 4.2.3. Intra-abdominal pressure and sedation study (III)

Mechanically ventilated intensive care patients with intra-abdominal hypertension, treated in adult ICUs of the Tartu University Hospital, were eligible for inclusion in this study. Exact inclusion and exclusion criteria are shown in Table 5. The effect of deepening of sedation on intra-abdominal pressure, haemodynamic and respiratory parameters was evaluated.

**Table 5.** Inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| - Age ≥18 years | - Contraindication to propofol |
| - Use of invasive mechanical ventilation | - Contraindication to measuring IAP in the supine position |
| - Intra-abdominal pressure 12–20 mmHg in at least 2 consecutive measurements within 12 hours | - Ongoing high dose infusion of propofol (>4 mg/kg/h actual body weight) |
| - Spontaneous respiratory rate ≥6 breaths per minute | - Other intervention planned to reduce IAP during anticipated study period |
| - RASS 0…-4 points | |

*RASS – Richmond Agitation-Sedation Scale; IAP – intra-abdominal hypertension.*

Study layout is illustrated in Figure 2.

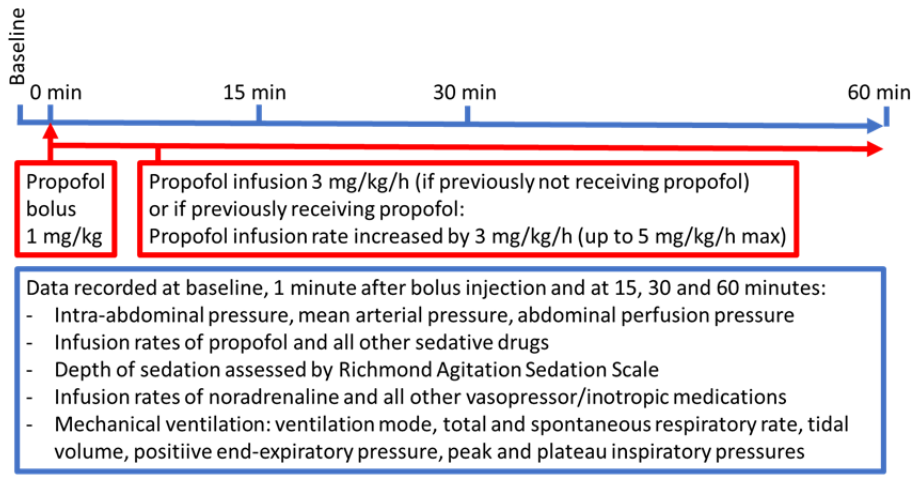



**Figure 2.** Study layout.

To counteract the possible hypotension related to the intervention, a haemodynamic management algorithm was in place with prompt administration of vasoactive therapy upon development of hypotension. Briefly, the general hypotension trigger was MAP of 60 mmHg. In some patients, a higher threshold had been individually specified where clinically indicated (e.g., hypertension) outside of the study intervention. In these cases, the MAP goal was used as the hypotension trigger. If a patient developing hypotension was previously receiving noradrenaline, the infusion rate was increased in order to preserve MAP at >60 mmHg or above individual target. If a patient developing hypotension had not previously been receiving noradrenaline, intravenous boluses of noradrenaline were given. If more than 3 boluses were needed, a continuous infusion of noradrenaline was started to preserve the MAP above the target level. MAP was assessed throughout the study (not only at pre-specified time points) and if hypotension occurred, it was managed immediately. The dose of propofol was reduced by steps of 1 mg/kg/h if more than 0.2 mcg/kg/min (or an increase of more than that amount) of noradrenaline was needed to counteract hypotension. If used, infusion rates of other vasoactive or inotropic drugs were left unchanged throughout the study intervention. The primary study outcome was IAP at 30 minutes of propofol infusion, secondary outcomes included changes in haemodynamic and respiratory parameters during the study.

### 4.2.4. iSOFA study (IV) and Enteral nutrition and biomarkers study (V)

In the multicentre prospective observational study, consecutive adult patients admitted to the 11 participating ICUs in nine countries were included, excluding those with limitation of care present on ICU admission. Patients with no informed consent and those readmitted after previously completing the observation period were also excluded.

Part A of the study, comprising of clinical data collection, was conducted in all 11 study centres, while part B, where plasma citrulline and I-FABP were measured in addition, was carried out in 6 centres. Between 2015 and 2018, each study centre aimed to enrol at least 25 patients during a period of 2–4 consecutive weeks. The observation time for each patient was 7 days or until ICU discharge, whichever occurred earlier. Standard care was continued at all study sites.

## 4.3. Data collection

### 4.3.1. Enteral feeding protocol study (I) and Gastrointestinal failure study (II)

Data were collected from an electronic database, used in 1st ICU of the Tartu University Hospital since January 1st, 2004. Data of all patients admitted to the study unit were entered into the database prospectively. Additional data regarding hospital-acquired infections and mortality were acquired from the hospital's Infection Control Department and the national Population Register, respectively. The following data were collected:

*Admission and outcome parameters*
These included patient age, sex, body mass index (BMI), a surgical or non-surgical diagnostic category, admission after abdominal surgery, APACHE (Acute Physiology and Chronic Health Evaluation) II score, use of vasopressor or inotropic treatment and mechanical ventilation and presence of sepsis, severe sepsis or septic shock on admission to ICU. Outcome data were ICU length of stay and duration of mechanical ventilation, incidence of hospital-acquired infections (ventilator-associated pneumonia, blood stream infection, urinary tract infection, *Clostridioides difficile* infection) and mortality at ICU discharge and at 30, 60, 90 and 120 days.

*Daily data*
Documented gastrointestinal symptoms were the absence of bowel sounds, gastric residual volume, bowel distension, vomiting, GI bleeding, diarrhoea. The number of calories provided via the enteral and parenteral routes and the use of metoclopramide were also documented.

*Definitions*

Absence of bowel sounds – as determined by an intensive care physician on auscultation.

Gastric residual volumes were measured by pausing enteral nutrition for 30 minutes, opening the nasogastric tube and allowing passive drainage for 30 minutes. Frequency of GRV measurements was left at the discretion of the nurse and intensive care physician, but measured at least once a day from 2004 to 2012, and based on the enteral feeding protocol from 2013 to 2015. For study II, a large GRV was considered present when the evacuated amount was >500 mL in one day. Prior to implementing the feeding protocol in 2013, decisions regarding large GRV management were unstandardized, but from 2013 onwards were based on guidance from the feeding protocol (Figure 1).

Bowel distension – radiologically confirmed dilatation of any bowel segment.

Vomiting – Any amount of regurgitated gastric contents.

GI bleeding – Presence of any visible amount of blood in stomach contents or stool.

Diarrhoea – occurrence of liquid stools at least 3 times in one day.

Energy requirement was calculated using a weight-based formula of 25 kcal/kg (adjusted body weight) per day and assessed on day 4 and day 7. Overfeeding was defined as receiving more than 110% of calculated full energy requirement and underfeeding as receiving less than 80% of caloric needs via any route. Dextrose-based maintenance infusions were included in the calculations, whereas the nutrition value of propofol and citrate, used as anticoagulation during renal replacement and plasma exchange therapies, was not considered.

Sepsis was diagnosed according to the Sepsis-2 definitions (Levy et al., 2003) that were in use at the time of conduction of studies I and II. Sepsis was diagnosed in a patient with a confirmed or suspected infection and at least 2 of the following criteria for systemic inflammatory response syndrome: leukopenia <4000/μL or leukocytosis >12000/μL or >10% of immature (band) forms; temperature >38 °C or <36 °C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute, PaCO2 <32 mmHg or mechanical ventilation. Severe sepsis was defined as sepsis with at least 1 organ failure. Septic shock was defined as hypotension related to sepsis, persisting after adequate fluid replacement and requiring vasopressor support.

### 4.3.2. Intra-abdominal pressure and sedation study (III)

Collected data included admission data (age, sex, weight, height, patient profile, principal pathology) and baseline characteristics (SOFA score, cumulative fluid balance, aetiology of IAH). Data documented at pre-specified time points during the intervention were intra-abdominal, mean arterial pressure (MAP) and abdominal perfusion pressure (APP), sedation depth according to Richmond

Agitation-Sedation Scale (RASS), the use and dose of vasoactive/inotropic medication(s), names and doses of sedative drug(s) and respiratory parameters (ventilation mode, spontaneous and total respiratory rate, peak and plateau pressures, tidal volume).

In the study units, intra-abdominal pressure is commonly measured at the discretion of the intensive care physicians and a manometric intravesical technique is used (UnoMeter AbdoPressure, Convatec, United Kingdom). In patients eligible to participate in the study (i.e., sustained intra-abdominal hypertension detected), an AbViser AutoValve IAP monitoring device (Convatec, United Kingdom) was inserted and used to measure IAP during the study. This device was used owing to proven good reproducibility of its results, with an intra-observer variability of 0.57 mmHg (Kimball et al., 2007). IAP was measured with the patients lying supine with no head of bed elevation throughout the intervention. The transducer was positioned at the mid-axillary line and an end-expiratory IAP value was recorded. Each measurement was performed using a 20 mL instillation of 0.9% sodium chloride solution at room temperature. This method is in accordance with the guidelines of the Abdominal Compartment Society (Kirkpatrick et al., 2013).

### 4.3.3. iSOFA study (IV) and Enteral nutrition and biomarkers study (V)

Daily data collection included documentation of gastrointestinal symptoms and abdominal signs, gastric residual volume, intra-abdominal pressure, data on feeding and use of prokinetic drugs and the SOFA sub-scores and evaluation of the Acute Gastrointestinal Injury grade (Reintam Blaser et al., 2012). GRV and IAP were measured only in patients in whom a nasogastric tube and an indwelling bladder catheter were used as a standard practice, respectively.

In sites participating in part B of the study, blood samples were drawn for measurement of the amino acid citrulline and I-FABP immediately upon on admission to the ICU and thereafter daily in the morning for 7 days or until ICU discharge.

Blood samples were collected into standard vacutainers containing EDTA, immediately cooled on ice and centrifuged at 4 °C to separate plasma. Plasma samples were stored at -80 °C at each study site. All samples were analysed at the Bioanalytical Facility of the University of East Anglia, Norwich, United Kingdom. Citrulline was measured using liquid chromatography – mass spectrometry following deproteinization of samples. The reference range for citrulline, obtained from healthy fasted adults, was 17–46 μmol/L. I-FABP was measured using an ELISA kit (R&D Systems, Minneapolis, United States of America).

*List of gastrointestinal symptoms and abdominal signs*

Vomiting/regurgitation, absent bowel sounds, diarrhoea, abdominal distension, GI bleeding, GI paralysis/dynamic ileus were defined according the recommendations of the ESICM Working Group on Abdominal Problems, shown in the Review of the literature section of the dissertation (Reintam Blaser et al., 2012).

Additionally, severe diarrhoea was diagnosed as liquid stools at least 5 times in one day or greater than 1000 mL per day if a stool collector was used.

Gastrointestinal bleeding was further divided according to severity: not needing transfusion; needing transfusion; leading to haemorrhagic shock.

Intra-abdominal hypertension was diagnosed if the mean IAP value of all measurements during one day was ≥12 mmHg.

## 4.4. Statistical methods

Statistical analyses were performed using SPSS Statistics (IBM Corp. IBM SPSS Statistics for Windows, Versions 23.0 and 25.0. Armonk, NY: IBM Corp.) and R (R Foundation for Statistical Computing, Vienna, Austria).

Categorical variables were compared using the $\chi^2$ test for large or Fisher's exact test for small samples. Continuous variables were compared using the Wilcoxon-Mann-Whitney test for non-normally distributed data and the t-test for data with normal distribution.

Univariate analysis was used to identify risk factors for insufficient EN (study I) and IAP decrease in response to deepening of sedation (study III). Variables with $P<0.2$ were entered into multiple logistic regression model to identify independent risk factors for respective outcomes. In study II, SOFA sub-scores and the number of GI symptoms were entered into multiple logistic regression models to comparatively evaluate the variables' ability to predict mortality.

Kaplan-Meier curve and log-rank test were used to compare survival of patients with and without GIF (study II).

Linear mixed models (LMM) were used to describe and compare dynamics of citrulline and I-FABP over time and between patient groups (study V). The biomarkers were used as outcomes, with log-transformation necessary to achieve a normal distribution of residuals. Time, group and interaction between time and group were entered to the models as fixed effects, with various covariance structures tested to achieve an optimal fitness.

In developing the Gastrointestinal Dysfunction Score (GIDS) in the iSOFA study (IV), first the descriptive AGI grading and thereafter single clinical symptoms and biomarkers were tested for 28- and 90-day mortality prediction using time-dependent Cox proportional hazard regression models. The descriptive AGI was able to independently predict mortality, while biomarkers were not. Therefore, the approach to construct the new score using a combination of symptoms to predict the original descriptive AGI grading was chosen. Different types of models were fitted to understand how different GI symptoms

discriminate between different AGI grades. To facilitate categorization, the continuous variables of intra-abdominal pressure and gastric residual volume were dichotomised based on ROC-curve analyses. GI symptoms and conditions identifying a less or more severe condition were identified. Based on evidence that higher AGI grades also corresponded to a greater number of symptoms, the number of symptoms was also considered relevant in creating the score. The most severe category (4) was defined differently from others, based on the rationale that in the descriptive AGI grading, the most severe category is defined as a life-threating condition. Accordingly, three conditions were classified as GIDS 4: GI bleeding causing haemorrhagic shock, mesenteric ischaemia, abdominal compartment syndrome. Each respective case of this highest score was carefully identified from the database through a case-by-case assessment by 3 co-authors independently. Thereafter through the sequential testing of several test-scores against the descriptive AGI grading, the GIDS was developed. After constructing the score with clinical data, addition of biomarkers citrulline and I-FABP to the score was tested using different cut-offs based on the literature and biomarker reference values. The C-statistic was used to describe the predictive capability of the scores and their combinations. To reduce the effect of different study sites, the Cox regression models are reported centre stratified.

### 4.4.1. Sample size calculations

#### 4.4.1.1. Intra-abdominal pressure and sedation study (III)

With the assumption of normally distributed data, the t-test was to be used to test the primary hypothesis that deepening of sedation reduces IAP by 3 mmHg. This effect size was chosen as it was considered to be clinically relevant and achievable. Assuming that 1) standard deviation was 6 mmHg at both time points (baseline and at 30 minutes of propofol infusion), based on a previous study (Reintam A et al., 2008); 2) the between-group correlation is 0.7; 3) the type I error rate is 0.05; then 28 patients would be needed to test the hypothesis. For possible dropouts and later refusal to participate in the study, inclusion of 40 patients was aimed. However, as IAP as well as other continuous variables were non-normally distributed, comparisons between groups were done using the Wilcoxon-Mann-Whitney test. As the worst that the Wilcoxon-Mann-Whitney test could ever perform against the T-test is 0.864 in terms of asymptotic significance, 1/0.864 more patients, i.e. 33, would be needed certainly to achieve the same power (Hollander et al., 2014). Therefore, our sample size of 37 patients was sufficient to test the primary hypothesis (i.e., a 3 mmHg change in IAP in response to the intervention).

#### 4.4.1.2. iSOFA study (IV)

Sample size calculation for part A of the iSOFA study was based on studies (Reintam et al., 2008a; Reintam Blaser et al., 2013) demonstrating a ROC curve of the SOFA score in prediction of 28 day mortality of 0.75 (SD 0.25). A 5% absolute increase in the predictive ability of the SOFA score was aimed with the addition of a GI dysfunction score. A 28-day mortality of 20% was assumed in the study population. Accepting a type I error of 5% and a power of 90%, 450 patients would be needed. To allow for a dropout rate of 10%, at least 500 patients were aimed to be included.

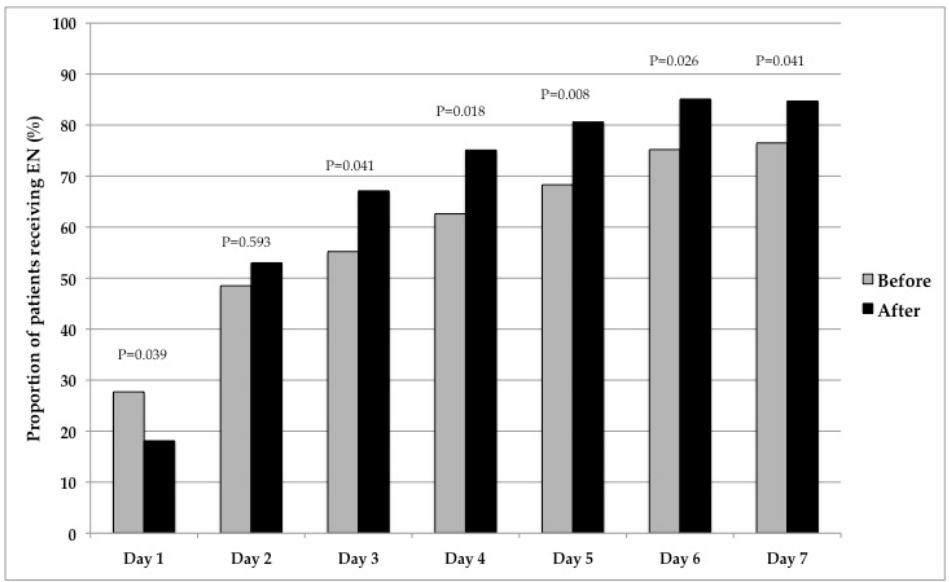
The calculation of the number of patients necessary in part B of the iSOFA study was based on I-FABP measurements in critically ill patients with sepsis (Derikx et al., 2007). With a type I error of 5%, a power of 90% and assuming that the probability of a randomly selected non-survivor having a higher outcome value than a randomly selected survivor is 0.65, the number of patients needed to detect a difference in distribution using a Wilcoxon-Mann-Whitney test is 159. To allow for a 20% dropout and loss to follow-up, at least 199 patients would be needed.

# 5. RESULTS

## 5.1. Enteral feeding protocol study (I)

In total, 665 and 683 patients were admitted to the ICU before and after implementation of the feeding protocol, respectively. 231 patients admitted before and 249 admitted after implementing the enteral feeding protocol fulfilled the inclusion criteria and were studied. There were no differences in patient age, sex, BMI, proportion of nonsurgical vs surgical admission types nor illness severity scores. Mechanical ventilation was slightly more frequent in the Before group (93.1% vs 86.7%, P=0.021). Overall, 53.3% of patients were admitted after surgery, including 29.4% after abdominal surgery. While ICU length of stay, duration of mechanical ventilation and incidence of hospital-acquired infections were similar, long-term mortality rate was higher among patients in the Before group (90-day mortality 37.2% vs 28.5%, P=0.026; 120-day mortality 38.5% vs 30.1%, P=0.033).

After implementing the feeding protocol, EN was less frequently prescribed on day 1, but more frequently from day 3 onwards (Figure 3). Enteral caloric intake on each day in ICU is shown on Figure 4.




*EN – enteral nutrition.*
**Figure 3.** Proportion of patients receiving enteral nutrition by day in ICU.

| Daily enteral caloric intake | Before | After | P-value |
|---|---|---|---|
| Day 1 | 0 (0–100) | 0 (0–0) | 0.016 |
| Day 2 | 0 (0–480) | 100 (0–480) | 0.409 |
| Day 3 | 160 (0–700) | 370 (0–767) | 0.031 |
| Day 4 | 340 (0–800) | 500 (10–960) | 0.003 |
| Day 5 | 400 (0–1000) | 580 (176–1100) | 0.142 |
| Day 6 | 500 (53–1000) | 695 (240–1138) | 0.003 |
| Day 7 | 500 (108–1000) | 720 (200–1155) | 0.018 |

*Data presented as median (IQR), kcal.*
**Figure 4.** Daily enteral caloric intake.

Median cumulative caloric intake during one week from enteral nutrition increased after implementation of the feeding protocol: Before 2300 (IQR 380–5030) kcal vs After 3210 (IQR 1280–5215) kcal (P=0.049). Simultaneously the provision of parenteral calories decreased: Before median 3977 (IQR 1775–6646) kcal vs After median 2600 (IQR 825–4287) kcal (P<0.001). Accordingly, the overall median number of calories provided to patients during the first week was lower in the After group (7030 (IQR 5667–8970) kcal vs 6000 (4715–7498) kcal, P<0.001) than in the Before group.

The incidence of overfeeding in all analysed days decreased (Before 8.4%, After 4.5%, P<0.001), while underfeeding was more frequent (Before 59.4%, After 76.9%, P<0.001), largely related to less frequent use of PN. The caloric need was calculated for each patient using a weight-based equation and was the same on all study days, although was not targeted during the first days.

Admission day risk factors for not receiving at least 80% of daily caloric needs via the enteral route by day 4 were identified as belonging to the Before group (OR 4.02, 95% CI 1.55–10.40), admission after abdominal surgery (OR 3.97, 95% CI 1.26–12.46), a higher number of gastrointestinal symptoms (OR 6.01, 95% CI 2.55–14.14) and presence of IAH (OR 4.20, 95% CI 1.32–13.34).

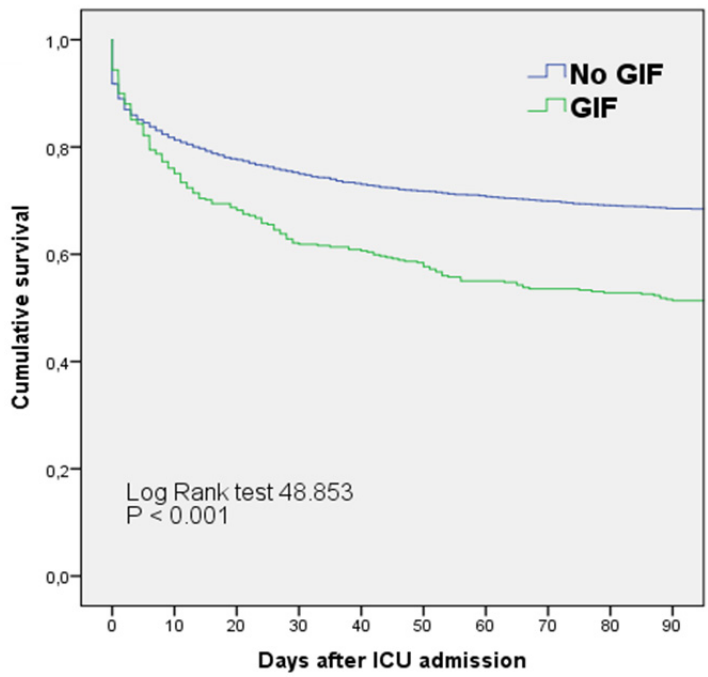
No differences in the daily occurrences of vomiting, radiologically confirmed bowel distension, GI bleeding nor large GRV (>500 mL/d) were detected. Diarrhoea and IAH were more frequent in the After group on only one study day (day 4, diarrhoea: 7.6% vs 2.8%, P=0.022; day 5, IAH: 29.5% vs 20.5%, P=0.043). The prescription of metoclopramide was similar between groups, with less frequent prescription in the After group on day 2 (3.6% vs 9.1%, P=0.011).

## 5.2. Gastrointestinal failure study (II)

Out of the 3959 patients included in the study, 81.7% were mechanically ventilated on admission, sepsis (any severity) was seen in 30.7%, 45.8% were of surgical profile and 16.8% admitted after gastrointestinal surgery. 29% of

patients received enteral feeding on admission day. ICU length of stay was median 4 (IQR 2–10) days, ICU mortality 19.6% and 90-day mortality 33.9%.

GIF, defined as concomitant occurrence of 3 or more GI symptoms, developed in 412 (10.4%) patients at some time during their stay in ICU, being present already on admission in 181 (4.5%). Thereafter, nearly 80% of cases of GIF occurred during the first week of ICU. Patients that developed GIF were older, more severely ill on admission to ICU and more often admitted after surgery, including GI surgery. A significantly smaller proportion of patients with GIF received EN on admission day compared to others (30.7% vs 14.5%, P<0.001). ICU length of stay (median 4 (IQR 2–8) vs 11 (5–25) days), duration of mechanical ventilation (median 2 (1–6) vs 9 (3–21) days) and mortality at ICU discharge (17.8% vs 34.9%, P<0.001), 30 days (26.5% vs 39.6%, P<0.001) and 90 days (32.1% vs 49.6%, P<0.001) were higher in patients with GIF. A Kaplan-Meier curve (Figure 5) illustrates the mortality difference in patients with vs without GIF. In multivariate regression analysis, a higher number of GI symptoms on admission day independently predicted 90-day mortality alongside SOFA sub-scores for other organ failures (Table 6).




*GIF – gastrointestinal failure; ICU – intensive care unit.*
**Figure 5.** Survival of patients with GIF vs no GIF.

**Table 6.** SOFA sub-scores and number of GI symptoms.

| Multiple regression analysis for 90-day mortality | | | | |
|---|---|---|---|---|
| Admission day variables | OR | Lower CI 95% | Upper CI 95% | P-value |
| SOFA respiratory | 1.094 | 1.015 | 1.179 | 0.019 |
| SOFA haematologic | 1.189 | 1.101 | 1.283 | < 0.001 |
| SOFA hepatic | 1.164 | 1.063 | 1.274 | 0.001 |
| SOFA cardiovascular | 1.453 | 1.368 | 1.543 | < 0.001 |
| SOFA neurological | 1.442 | 1.375 | 1.513 | < 0.001 |
| SOFA renal | 1.345 | 1.279 | 1.415 | < 0.001 |
| Number of GI symptoms | 1.331 | 1.214 | 1.460 | < 0.001 |

*OR – odds ratio; CI – confidence interval; SOFA – Sequential Organ Failure Assessment; GI – gastrointestinal.*

GIF was caused by a primary gastrointestinal pathology in 253 (61.3%), while secondary GIF was present in 160 (38.7%). Patients with primary GIF compared to those with secondary GIF were more frequently female, had lower illness severity scores (APACHE II median 14 (IQR 10–19) vs 20 (14–26) points, P<0.001; SOFA median 7 (5–10) vs 9.5 (7–12) points, P<0.001) and lower lactate level on admission to ICU, less fluids administered in the first 24h, but more frequent sepsis on admission. Enteral nutrition was more frequently used on admission day in patients with secondary GIF (25% vs 7.9%, P<0.001). During the first five days and on day 10, patients with primary GIF experienced more GI symptoms compared to those with secondary GIF. Mortality at ICU discharge and at 30 and 90 days was slightly higher in patients with secondary GIF, but these differences were not statistically significant.

Intra-abdominal hypertension was detected in 245 (59.3%) patients with GIF and 635 (17.9%) patients without GIF (P<0.001). IAH occurred in 166 (65.6%) patients with primary and 79 (49.4%) patients with secondary GIF (P=0.001). IAP was not measured in 9.1% of patients with primary and 21.3% of patients with secondary GIF.

## 5.3. Intra-abdominal pressure and sedation study (III)

37 patients were included in the study. 28 (75.7%) were male, median age was 59 (range 29–81) years, BMI 33.0 (29.9–36.7) kg/m$^2$, 24 (64.9%) were admitted to ICU with a nonsurgical diagnosis and the most common pathologies on admission were pancreatitis in 11 (29.7%), pulmonary pathologies in 8 (21.6%) and neurological pathologies in 5 (13.5%) of patients. The severity of IAH at baseline was: grade I (12–15 mmHg) 2 patients (64.9%), grade II (16–20 mmHg) 11 patients (29.7%) and grade III (21–25 mmHg) 2 patients (5.4%).

Results of the intervention are summarised in Table 7.

**Table 7.** Study parameters at all time points.

| | Baseline | After bolus | | 15 minutes | | 30 minutes | | 60 minutes | |
|---|---|---|---|---|---|---|---|---|---|
| Parameter | Value | Value | P | Value | P | Value | P | Value | P |
| IAP, mmHg | 15 (13–16) | 14 (12–15) | 0.021 | 14 (12–15) | 0.077 | 14 (13–16) | 0.076 | 14 (12–15) | 0.040 |
| MAP, mmHg | 89 (82–96) | 77 (69–85) | <0.001 | 82 (71–88) | 0.001 | 81 (74–87) | 0.004 | 80 (74–85) | <0.001 |
| APP, mmHg | 72 (67–83) | 64 (55–71) | 0.003 | 68 (56–75) | 0.008 | 66 (61–74) | 0.012 | 65 (60–71) | 0.003 |
| RASS, points | -4 (-4 to -2) | -5 (-5 to -5) | <0.001 | -5 (-5 to -5) | <0.001 | -5 (-5 to -5) | <0.001 | -5 (-5 to -5) | <0.001 |
| Dose of propofol, mg/kg/h | 1.74 (0–2.64) | 4.74 (3–5) | <0.001 | 4.74 (3–5) | <0.001 | 4.94 (3.59–5) | <0.001 | 4.94 (3.59-5) | <0.001 |
| Patients receiving noradrenaline, N (%) | 22 (59.5%) | 21 (56.8%) | 0.814 | 22 (59.5%) | 1 | 26 (70.3%) | 0.330 | 24 (64.9%) | 0.632 |
| Dose of noradrenaline, µg/kg/min | 0.06 (0.02–0.2) | 0.06 (0.03–0.21) | 0.688 | 0.07 (0.03–0.26) | 0.496 | 0.06 (0.03–0.26) | 0.804 | 0.06 (0.03–0.26) | 0.461 |
| Spontaneous respiratory rate, per minute | 16 (13–21) | 12 (0–19) | 0.018 | 12 (1–20) | 0.053 | 9 (1–19) | 0.014 | 7 (0–19) | 0.008 |

*Wilcoxon-Mann-Whitney test was used to compare median values and the Fisher's exact test was used to compare frequencies between baseline and all time points. IAP – intra-abdominal pressure; MAP – mean arterial pressure; APP – abdominal perfusion pressure; RASS – Richmond Agitation-Sedation Scale. P-values for comparisons of values at respective time point with baseline.*

Protocol-based deepening of sedation was effective in most patients as detected by RASS. Other sedative drugs, used at baseline, were continued throughout the intervention in unchanged doses. Median doses used were: midazolam (N=7) 3 (3–4) mg/h; fentanyl (N=22) 50 (50–100) µg/h; dexmedetomidine (N=4) 88 (68–108) µg/h; clonidine (N=1) 60 µg/h. Median intra-abdominal pressure was 15 (IQR 13–16) mmHg at baseline and decreased by 1 mmHg at all time points (difference significant: after bolus and at 60 minutes of infusion). Any decrease in IAP compared to baseline was seen in 91.9% patients, whereas a decrease of ≥3 mmHg was observed in 9 (24.3%) patients.

MAP and APP was reduced at all time points compared to baseline, with lowest values observed after the bolus dose of propofol. Vasoactive therapy with noradrenaline was used in 22 (59.5%) patients at baseline; in 10 of them the dose of noradrenaline was increased (statistically non-significant) and in 6 additional patients a noradrenaline infusion was started during the intervention as guided by the haemodynamic management algorithm.

Respiratory rate decreased during the intervention, but cessation of spontaneous respiratory efforts occurred in a minority of patients. There were no significant changes in tidal volume nor plateau pressures during the intervention.

In regression analyses to detect baseline characteristics associated with IAP decrease by 30 minutes of propofol infusion, a greater cumulative positive fluid balance (regression coefficient –0.156 (95% CI -0.301 to -0.012, P=0.035) and a lower SOFA score (regression coefficient 0.187 (95% CI 0.027–0.348, P=0.024) were independently associated with greater treatment effect.

## 5.4. iSOFA study (IV)

A total of 540 patients were included across 11 study sites: Bern (N=50), Tallinn (N=50), Tartu (N=61), Vienna (N=49), Stockholm (N=50), Brussels (N=57), Buenos Aires (N=25), Kiel (N=56), Luzern (N=60), Maastricht (N=57), Paris (N=25). Admission and outcome data are presented in Table 8.

**Table 8.** Admission characteristics and outcome data.

| | |
|---|---|
| Male gender | 328 (60.7) |
| Age, years (range) | 65 (18–94) |
| BMI, kg/m$^2$ | 26 (23;29) |
| APACHE II, points | 17 (11;24) |
| Simplified Acute Physiology Score II, points | 38 (26;53) |
| SOFA, points | 6 (3;9) |
| Profile | |
| Nonsurgical | 223 (41.3) |
| Elective surgical | 193 (35.7) |
| Emergency surgical | 124 (23.0) |

| | |
|---|---|
| Main reason for ICU | |
| Postoperative care with mechanical ventilation | 165 (30.6) |
| Postoperative care without mechanical ventilation | 93 (17.2) |
| Respiratory failure | 69 (12.8) |
| Neurological deterioration | 61 (11.3) |
| Shock | 59 (10.9) |
| Cardiac failure | 38 (7.0) |
| Metabolic disorder | 10 (1.9) |
| Other organ failures | 15 (2.8) |
| Multiple organ failure | 9 (1.7) |
| Renal failure | 6 (1.1) |
| Other reason | 30 (5.6) |
| Abdominal surgery | 104 (19.3) |
| of which GI surgery | 62 (11.5) |
| Invasive mechanical ventilation | 305 (56.5) |
| Vasopressor/inotrope | 311 (57.6) |
| **OUTCOME** | |
| ICU length of stay | 3 (1–6) |
| Duration of mechanical ventilation | 1 (0–4) |
| 28-day mortality (N=539) | 79 (14.6) |
| 90-day mortality (N=522) | 102 (18.9) |

*Data are presented as N (%) or median (IQR) if not stated differently. BMI – body mass index; APACHE - Acute Physiology and Chronic Health Evaluation; SOFA – Sequential Organ Failure Assessment; ICU – intensive care unit; GI – gastrointestinal.*

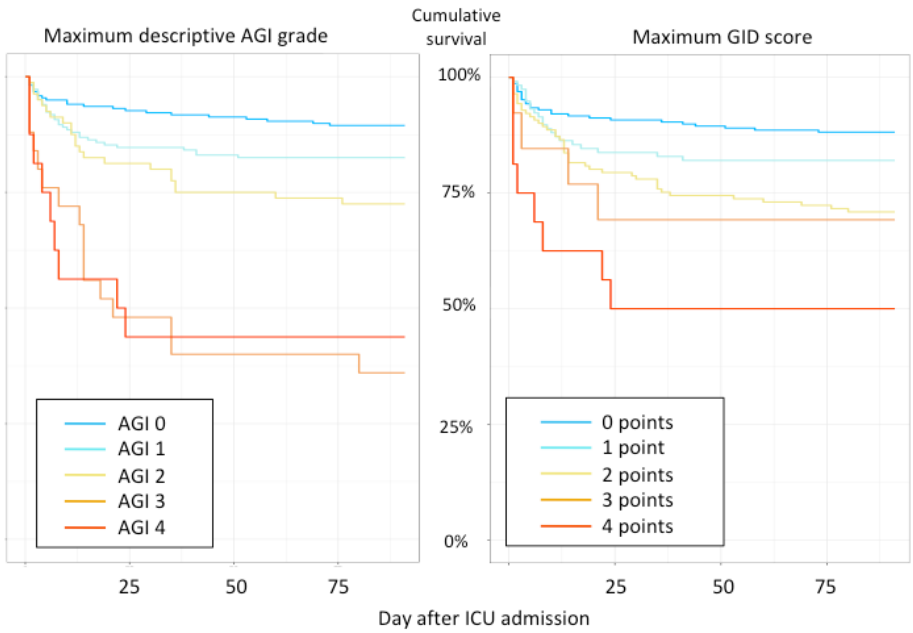
The descriptive AGI grading was independently associated with mortality together with both the SOFA score and its sub-scores separately (data not shown).

Thereafter, a new score was developed based on the rationale of the AGI grading and using single GI symptoms and conditions. As citrulline and I-FABP were not clearly associated with mortality in univariate and multivariate analyses, they were initially omitted in the score development process. Addition of biomarkers to the final version of the new score – GIDS – was tested with no significant improvement in mortality prediction. The newly developed GIDS is shown in Table 9 and Kaplan-Meier curves with the descriptive AGI grading and the GIDS in Figure 6.

**Table 9.** Gastrointestinal Dysfunction Score (GIDS).

| 0 – No risk | 1 – Increased risk | 2 – GI dysfunction | 3 – GI failure | 4 – Life threatening |
|---|---|---|---|---|
| **No symptoms OR one of the following with oral intake** | **Two of the following** | **Three or more symptoms of score 1 OR up to two of the following** | **Three or more of the following** | **One of the following** |
| - Absent bowel sounds<br>- Vomiting<br>- GRV > 200 ml<br>- GI paralysis/ dynamic ileus<br>- Abdominal distension<br>- Diarrhoea (not severe)<br>- GI bleeding without transfusion<br>- IAP 12–20 mmHg | - No oral intake<br>- Absent bowel sounds<br>- Vomiting<br>- GRV >200 ml<br>- GI paralysis/ dynamic ileus<br>- Abdominal distension<br>- Diarrhoea (not severe)<br>- GI bleeding without transfusion<br>- IAP 12–20 mmHg | - Severe diarrhoea<br>- GI bleeding with transfusion<br>- IAP > 20 mmHg | - Prokinetic use<br>- GI paralysis/ dynamic ileus<br>- Abdominal distension<br>- Severe diarrhoea<br>- GI bleeding with transfusion<br>- IAP > 20 mmHg | - GI bleeding leading to haemorrhagic shock<br>- Mesenteric ischaemia<br>- Abdominal compartment syndrome |

*GRV – gastric residual volume; GI – gastrointestinal; IAP – intra-abdominal pressure.*




*Categories from 0 to 4 differed significantly (P<0.0001, Log rank test) in both the original AGI grading and the New AGI score.*
*No. of patients in categories: AGI 0 – 217, AGI 1 – 183, AGI 2 – 81, AGI 3 – 25, AGI 4 – 16; GIDS 0 – 227, GIDS 1 – 119, GIDS 2 – 141, GIDS 3 – 13, GIDS 4 – 16.*
*AGI – Acute Gastrointestinal Injury; GID – Gastrointestinal Dysfunction; ICU – intensive care unit.*

**Figure 6.** Kaplan-Meier survival curves with cumulative 90 days survival based on maximum descriptive AGI grade and maximum GID score.

The performance of the GIDS together with SOFA score and its sub-scores in mortality prediction is shown in Table 10.

**Table 10.** Gastrointestinal Dysfunction Score (GIDS) in prediction of mortality alone and together with SOFA score as time-dependent variables in centre-stratified Cox regression analysis.

| **Unadjusted univariate analyses** | | | | |
|---|---|---|---|---|
| | **Mortality during 28 days** | | **Mortality during 90 days** | |
| **Covariate** | **HR (95% CI)** | **P-value** | **HR (95% CI)** | **P-value** |
| GIDS | 2.15 (1.76–2.63) | $6.39 \cdot 10^{-14}$ | 2.09 (1.72–2.53) | $3.40 \cdot 10^{-14}$ |
| **Multivariate analyses** | | | | |
| | **Mortality during 28 days** | | **Mortality during 90 days** | |
| **Covariates** | **HR (95% CI)** | **P-value** | **HR (95% CI)** | **P-value** |
| **Model 1: SOFA total + GIDS** | | | | |
| SOFA total | 1.23 (1.16–1.30) | $9.53 \cdot 10^{-15}$ | 1.23 (1.16–1.29) | $8.70 \cdot 10^{-16}$ |
| GIDS | 1.40 (1.07–1.84) | 0.014 | 1.40 (1.02–1.79) | 0.005 |
| **Model 2: SOFA subscores + GIDS** | | | | |
| SOFA cardio-vascular | 1.15 (0.95–1.41) | 0.136 | 1.13 (0.95–1.34) | 0.162 |
| SOFA respiratory | 1.20 (0.92–1.56) | 0.167 | 1.25 (1.01–1.54) | 0.036 |
| SOFA haema-tological | 0.88 (0.65–1.20) | 0.422 | 0.89 (0.67–1.18) | 0.425 |
| SOFA renal | 1.48 (1.22–1.80) | $5.54 \cdot 10^{-5}$ | 1.37 (1.14–1.65) | 0.0005 |
| SOFA hepatic | 1.00 (0.72–1.40) | 0.994 | 1.05 (0.77–1.43) | 0.758 |
| SOFA neuro-logical | 1.59 (1.30–1.94) | $4.96 \cdot 10^{-6}$ | 1.58 (1.31–1.89) | $6.90 \cdot 10^{-7}$ |
| GIDS | 1.48 (1.13–1.92) | 0.003 | 1.47 (1.15–1.87) | 0.001 |

*HR – hazard ratio; CI – confidence interval; GIDS – Gastrointestinal Dysfunction Score; SOFA – Sequential Organ Failure Assessment.*

## 5.5. Enteral nutrition and biomarkers study (V)

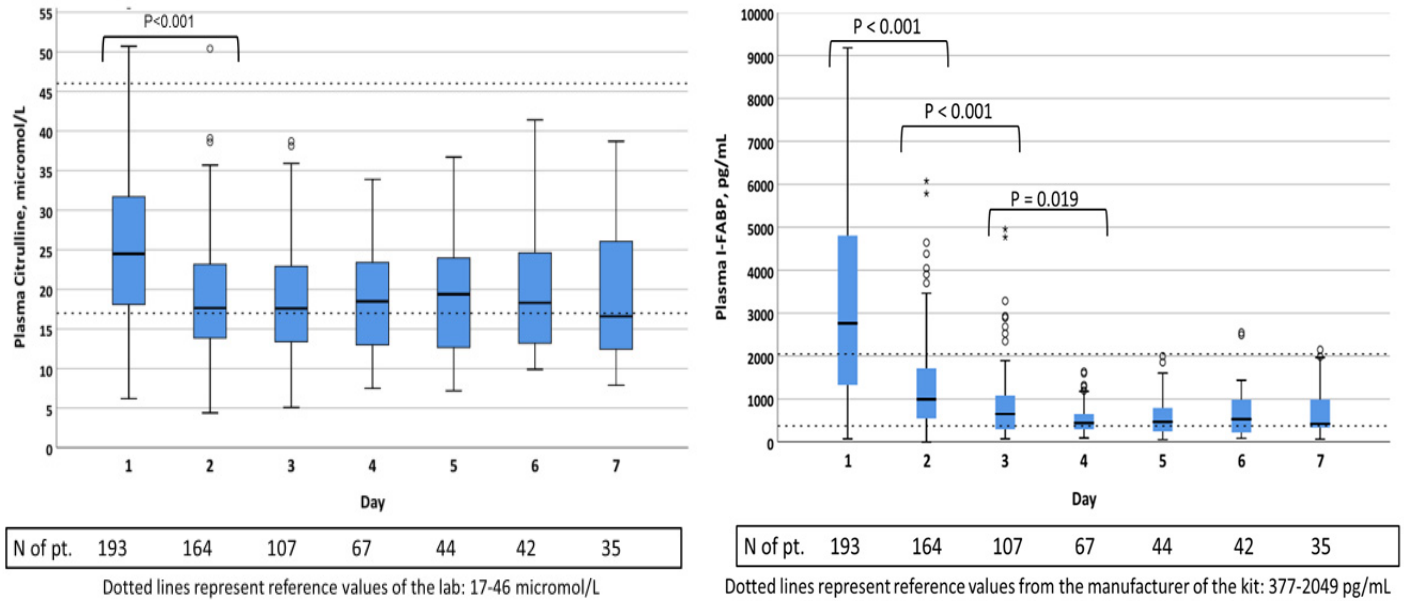
224 patients with 693 measurements of citrulline and 695 measurements of I-FABP were included in this study. Median age was 67 (range 19–94) years and 137 (61.2%) patients were male. Admission categories were elective surgical in 122 (54.5%), nonsurgical in 61 (27.2%) and emergency surgical in 41 (18.3%) patients. 42 (18.8%) patients were admitted after abdominal and 34 (18.8%) after gastrointestinal surgery. Admission day median APACHE II score was 18 (IQR 11–23), median Simplified Acute Physiology Score II score 39 (IQR 26–53) and median SOFA score 6 (IQR 4–9) points.

Median ICU length of stay was 2 (IQR 1–4) days, with 35 (15.6%) patients being long-stayers (≥7 days). Mortality was 7.1% at ICU discharge, 10.3% at 28 days and 14.7% at 90 days.

Median level of citrulline on admission was 24.5 (IQR 18.1–31.7; range 6.2–134.2) μmol/L and that of I-FABP 2763 (IQR 1326–4805; range 73–228328) pg/mL. The dynamics of the biomarkers are shown in Figure 7.

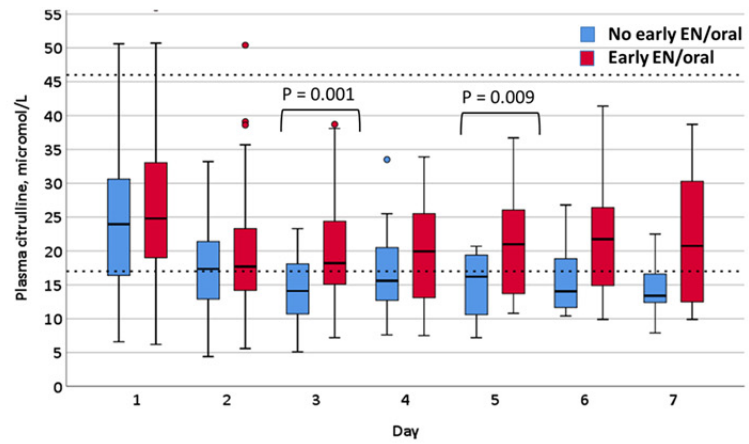
184 (82.1%) patients received enteral or oral nutrition during their ICU stay. Those not receiving any nutrition were mostly short-stayers with a median ICU stay of 1 (IQR 1–2) days. Early enteral or oral nutrition (EEN/ON; started within 2 days of ICU admission) was provided to 164 (73.2%) patients, however only 41 (18.3%) patients received EEN. Out of 164 patients receiving EEN/ON, 60 (36.6%) were in the ICU by day 4 and 39 of them (65%) were successfully fed by day 4 (defined as receiving 80% of the caloric target via EN or oral diet in any amount).

Different dynamics of citrulline over time were seen between patients that received vs did not receive EEN/ON (Figure 8).

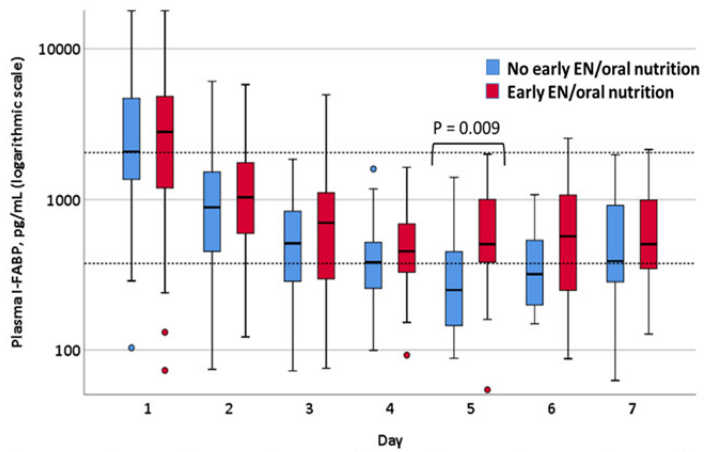



*I-FABP – intestinal fatty acid-binding protein.*

**Figure 7.** Dynamics of citrulline and I-FABP.




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No early EN | 54 | 42 | 26 | 21 | 13 | 12 | 9 |
| Early EN | 139 | 122 | 81 | 46 | 31 | 30 | 26 |




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No early EN | 54 | 42 | 26 | 21 | 13 | 12 | 10 |
| Early EN | 139 | 124 | 81 | 46 | 31 | 30 | 26 |

*EN – enteral nutrition; I-FABP – intestinal fatty acid-binding protein.*
*LMM analysis performed for days 2–7 using log-transformed citrulline. Dynamics over time were different between groups (time x early EN/oral nutrition F = 2.259, P = 0.049). Average values for all days (2–7) were higher in patients with EEN/ON (F = 8.868, P = 0.003).*
*LMM analysis performed for days 2–7 using log-transformed I-FABP. Dynamics over time were similar between groups (time x early EN/oral nutrition F = 1.346, P = 0.245. Average values for all days (2–7) were higher in patients with EEN/ON (F = 8.528, P = 0.004).*

**Figure 8.** Dynamics of citrulline and I-FABP in patients with EEN/ON vs no EEN/ON.

Patients receiving EEN/ON were compared based on increasing (69%) or decreasing (31%) citrulline values from day 2 to day 4. The proportion of patients receiving EEN/ON on day 3 was higher among patients with increasing citrulline (100% vs 79%, P=0.026), but similar and >90% on days 2 and 4. Caloric intake on days 3 and 4 was similar between the groups. In patients with increasing citrulline values, the median AGI grade was lower on day 4 (0 (0–1) vs 1 (1–2), P=0.008) and prokinetics were used less frequently (13 vs 57%, P=0.004). Between patients receiving EEN/ON with increasing vs decreasing citrulline, the prevalence of GI symptoms was similar, as well as the SOFA score, ICU length of stay and 28-day mortality.

Successful EEN/ON (>80% of caloric needs achieved via EN or any amount of oral nutrition) was not associated with different dynamics nor average values of citrulline nor I-FABP over the first week, compared to patients failing to achieve that threshold.

Patients who left ICU before day 7 and therefore had an incomplete dataset (N=189), had higher citrulline values compared to long-stayers on day 1 (25.3 (19.3–32.8) vs 19.7 (15.3–26.0) μmol/L, P=0.011) and day 3 (18.1 (14.8-24.2) vs 15.7 (11.9-19.8), P=0.030). Citrulline values on other days and I-FABP values did not differ between these groups.

On admission to ICU, patients with renal failure (defined as SOFA renal subscore ≥2) had similar citrulline values as those without renal failure. There was an overall weak positive correlation between creatinine and citrulline values, $r(650) = 0.228$, $P < 0.001$, and a very weak negative correlation between 24-hour urine output and citrulline values, $r(650) = -0{,}132$, $P = 0.001$.

Admission day I-FABP values did not differ in patients with renal failure and no correlation with creatinine values was present.

# 6. DISCUSSION

## 6.1. Enteral feeding protocol study (I)

The first study of this dissertation describes the nutritional practices before and after implementing an enteral feeding protocol in the 1st ICU of the Tartu University Hospital. A major finding is that among ICU long-stayers, EN can be enhanced in a safe manner using a feeding protocol.

After implementing the feeding protocol, the median caloric intake from EN during the first week of ICU increased by 40% and the proportion of patients receiving EN was higher on all days from day 3. EN being used more but slightly later may be explained by knowledge on the concepts of autophagy and non-inferiority of early underfeeding becoming incorporated into clinical practice at the time of conduction of the study. This finding is likely also related to adherence to the list of conditions where EN should be delayed, specified in the feeding protocol, as the high admission SOFA score and prevalence of vasopressor and mechanical ventilation use illustrate the high illness severity of the patients included.

In general, our finding of improvement in the provision of EN is in accordance with other studies evaluating the effect of EN protocols. Most of the evidence originates from similar before-and-after studies while some randomised controlled trials have also been performed. A relatively recent review of such studies summarises that, as a whole, protocolised EN therapy leads to optimised nutrition, with a variety of different success measures used across studies, e.g. percentage of achieved nutritional goals, time until initiation and duration of nutrition therapy (Ventura & Waitzberg, 2015).

A simultaneous decrease in the use of PN took place in the After period. The median amount of parenterally provided calories decreased by more than was the increase in enterally given calories and therefore, somewhat unexpectedly, the overall cumulative caloric intake during the first week of ICU decreased from a median of 7000 to 6000 kcal per week. Decisions regarding PN were at the discretion of the intensive care physicians both before and after implementing the feeding protocol. Results from the EPaNIC study (Casaer et al., 2011), demonstrating harm from early initiation of PN causing full or possibly even overfeeding, may have influenced decisions regarding PN predominantly in the After period of the study. A reduction in the use of PN could therefore have been partly unrelated to the use of the feeding protocol. In addition, the more frequent use of and higher caloric provision via EN may have influenced the clinicians' decision to withhold PN altogether in some patients. The use of (full) PN may have been reserved to those in whom EN was not used, less frequent in the After period. Altogether, likely a combination of these interactions led to an important caloric deficit in the first week of long-staying ICU patients. Although the energy utilization of critically ill patients varies considerably, for an average caloric need of 2000 kcal per day and 14 000 kcal per week, a median deficit of around 8000 kcal occurred. Even though according to

current knowledge, full needs should not be attempted to achieve with artificial nutrition in the catabolic phase of critical illness, extensive deficits should still be avoided and cumulative caloric debts of already >4000 kcal have been shown to be associated to an increased risk of complications (Dvir et al., 2006). Bearing in mind that 30% of our patients were admitted after abdominal surgery and subsequently stayed in the ICU for ≥7 days, constituting a nutritionally highly challenging population, a comprehensive strategy also involving the indications and timing of supplemental or full parenteral nutrition would be most helpful in preventing iatrogenic malnutrition.

Overfeeding was infrequent both before and after implementing the feeding protocol. Seemingly trivial but important in the context of overfeeding, are sources of energy outside EN and PN, mainly received in the form of glucose-based maintenance solutions, lipid emulsion of the sedative drug propofol and by metabolizing the anticoagulant citrate used in renal replacement therapy. These non-nutritional calories may account for one third of all given calories in the first days during the start-up of nutrition, and stabilise later at a mean of 6% for glucose and/or propofol and at 18% for citrate anticoagulation (Bousie et al., 2016). In study I, calories from glucose solutions, but not those from propofol and citrate anticoagulation was included in the calculation of parenterally administered calories. It is not clear whether and to which extent the amount of non-nutritional calories influenced the decisions about the nutrition prescribed in the Before and After periods, however the real incidence of overfeeding was probably somewhat greater than demonstrated. Vice versa, the true incidence of underfeeding may have been lower in our patient population.

In some studies, a positive effect of protocolised nutrition has been shown on the incidence of infectious complications and outcomes (Taylor et al., 1999; Martin et al., 2004; Heyland et al., 2013). In our study, the incidence of hospital-acquired infections was similar between the study periods. Lower long-term mortality seen in our study likely reflects changes in other aspects of both ICU and post-ICU management, but some effect of improved EN cannot also be excluded.

Gastrointestinal symptoms are frequent among critically ill patients and associated with complications. Indeed, in study I we demonstrated that development of GI symptoms was independently and out of all factors, most strongly associated to insufficient EN. Therefore, an important finding of study I is that protocolised EN resulting in increased use and dose did not cause harm – daily incidences of GI symptoms and IAH were similar both before and after implementing the feeding protocol, with a few statistically significant differences likely explained by chance. In other studies looking at the rate of complications with protocols where EN is increased incrementally, improvement in EN has similarly been well tolerated, with no increases in the incidences of high GRVs, vomiting or ventilator-associated pneumonia (Arabi et al., 2004; Reignier et al., 2010). A common, important feature of feeding protocols, also in our study, is guidance on how to address intolerance, including reducing the dose of EN. Accordingly, more severe complications e.g., tracheal aspiration of gastric

contents, or mesenteric ischaemia, may be avoided. Another possible explanation for no observed increase in the incidence of GI symptoms or IAH is that the improvement in the provision of EN was modest (a median increase of about 200 kcal or mL per day compared to the Before period), not sufficient to cause signs of intolerance on top of the already low baseline provision of EN.

A recurring theme in the literature is suboptimal adherence to nutrition protocols (Ventura & Waitzberg, 2015). In study I, the compliance of physicians and nurses with the feeding protocol was not specifically assessed and therefore is unknown. Low adherence to a protocol, in general, may be a cause for falsely negative or modest results.

## 6.2. Gastrointestinal failure study (II)

*Gastrointestinal symptoms*

In study II, six GI symptoms were used to define gastrointestinal dysfunction, with simultaneous presence of at least three GI symptoms in one day constituting GI failure. GIF occurred in 10% of patients during their ICU stay. Development of GIF was associated with substantially worse treatment outcomes, including a threefold increase in ICU length of stay and a twofold increase in mortality rate. When the number of GI symptoms experienced on admission day was added to the subscores of the SOFA score, all were independently predictive of 90-day mortality, while addition of GI symptoms slightly improved the predictive capability of the SOFA score.

Findings of this study once more illustrate the importance of gastrointestinal problems in critically ill patients and suggest that GI dysfunction itself can be a cause of poor outcome and not just an epiphenomenon related to a general critical condition. Compared to the original study defining GIF by the presence of ≥3 GI symptoms, GIF was more frequent in our patient population (10.4% vs 6.4%) (Reintam Blaser et al., 2013). In that study, mechanically ventilated ICU patients were monitored during the first 7 days, while we observed the whole ICU stay. At the same time, illness severity and ICU mortality were higher in their study, therefore, the difference in the incidence of GIF could not be explained by GI problems occurring alongside other organ failures. The earlier study also included more surgical, including abdominal surgery patients, in whom more GI symptoms and thus, a higher incidence of GIF, could be expected. This suggests that many cases of GIF develop later in the course of critical illness, after the initial pathology that required ICU admission has subsided. Indeed, in our patients, 20% of cases of GIF occurred beyond the first week.

Nearly two thirds of patients with GIF had a primary disease in the abdominopelvic region, being admitted mostly after surgery, in half of patients performed on the GI tract. These patients experienced a higher number of GI symptoms during the first week of ICU. Contrarily, patients with secondary GIF mostly had a nonsurgical pathology on admission to ICU and a wider list of underlying pathologies. Cases of GIF with a primary cause occurred signi-

ficantly earlier than those with a secondary aetiology. Sepsis, known to be associated with poor outcomes in ICU patients, was more frequent among patients with primary compared to secondary GIF (53.6 vs 42.5%, P = 0.034). Outcomes including length of mechanical ventilation and ICU stay as well as mortality, however, were consistently slightly worse in patients with secondary GIF, although not reaching statistical significance. It can be argued that outcomes are better if an abdominal pathology, including sepsis with an abdominal origin, can be treated promptly and efficiently. In patients with critical illness involving multiple organ systems, GIF occurring secondarily and later during their illness may not be as amenable to treatment.

Although development of GI symptoms was firmly associated with poor outcome, the subjectivity and probably different weight of single symptoms makes a definition based only on symptoms imprecise. Furthermore, considering GI dysfunction as a continuum rather than a yes/no phenomenon (failure) is probably more meaningful. Addition of more objective variables, including IAP and biomarker values, and considering the weight of each symptom together with the evolution of the variables over time would help make a potential score more precise.

*Intra-abdominal pressure*

To detect elevation of IAP, it must be measured. Currently there is no consensus in which patients should IAP measurements be instituted. It would be desirable not to miss many cases of IAH while avoiding unnecessary measurements in patients in whom IAH is unlikely to develop. There are some patient groups in whom IAH is less frequent and omitting IAP monitoring has been suggested. In a single centre observational study with an ICU stay ≥24 hours, these included mechanically ventilated patients with positive end-expiratory pressure (PEEP) <10 cmH2O, pO2/FiO2 >300 mmHg, BMI <30 and none of the following: pancreatitis, liver failure with ascites, GI bleeding, laparotomy and use of vasopressors or inotropes (Reintam Blaser et al., 2011b). Conversely, independent risk factors for development of IAH at any time during ICU stay were recently identified as BMI ≥27 kg/m$^2$, APACHE II score greater than 18, abdominal distension, absence of bowel sounds and PEEP >7 cmH2O, and additionally positive fluid balance for development of IAH beyond day 1 (Reintam Blaser et al., 2019). IAH is twice as prevalent in mechanically ventilated compared to spontaneously breathing patients (Reintam Blaser et al., 2019). However, increasing the proportion of patients with IAP measurements does not necessarily translate into more cases of IAH detected (Reintam Blaser et al., 2014a). The creation of a tool to predict the development of IAH in an individual patient would be most helpful and is underway.

In study II, IAP was measured in 46% of patients during their ICU stay. Importantly, the 3959 patients were admitted during a 12-year period, entailing several practice changes. In patients with GIF (3 simultaneous GI symptoms during1 day), IAP was measured in nearly 90%, while those with GIF due to an extra-abdominal condition received IAP measurements less frequently (79%).

On the other hand, IAH was frequent among patients with GIF, occurring in 60% of them. These results suggest that IAP measurements are more easily started in patients with a primary, intra-abdominal pathology developing GI symptoms.

## 6.3. Intra-abdominal pressure and sedation study (III)

In study III, the effect of protocolised deepening of sedation with propofol on IAP and haemodynamic and respiratory parameters was assessed in mechanically ventilated patients with IAH. Deepening of sedation according to RASS was achieved in most patients. The patient population consisted of mostly male patients with a nonsurgical illness. There was a high prevalence of obesity, IAH was mostly mild (grade I) and the frequencies of primary and secondary IAH were balanced.

IAP decreased in most patients during the intervention, with a median decrease of 1 mmHg from baseline. This change in IAP is comparable to the intra-observer variability – 0.57 mmHg – of the pressure measurement device used (Kimball et al., 2007). Compared to other medical/minimally invasive management options of IAH, used as first line interventions to avoid sustained and worsening IAH, this effect across the overall study population is probably clinically insignificant. For example, a decrease in IAP of 4 mmHg has been shown with the use of neuromuscular blockade (De Laet et al., 2007) and changing the body position from head-of-bed elevation to supine (Cheatham et al., 2009). In some specific instances, percutaneous drainage of large volume ascites may be very effective in reducing IAP and avoiding a surgical approach to resolve ACS (Umgelter et al., 2008; Cheatham & Safcsak, 2011). In patients with abdominal burn injuries suffering from ACS, the use of escharotomy as a method for abdominal decompression can significantly reduce IAP and improve haemodynamics and ventilation without the need to create an open abdomen (Oda et al., 2005). Indeed, the nature and course of the clinical condition together with the effect of IAP on organ function(s) should also be taken into account beside the measured IAP value, when deciding whether and with which method should IAH be treated (De Laet et al., 2020). The same principle likely holds true when deciding whether to apply deep sedation in a patient with IAH. In study III we saw that approximately one quarter of patients demonstrated a decrease in IAP of ≥3 mmHg with deep sedation. Therefore, it would be helpful if we could predict in which patients the intervention will be helpful and in which patients it could be rather harmful and should be avoided in the absence of expected effect and considering side effects. According to regression analysis, patients with a greater previous fluid balance and less severe illness seemed to experience a greater treatment effect with deepening of sedation. The impact of these baseline characteristics was very low and does not help to guide in which patients should sedation be deepened. Therefore, we believe that in the absence of good predictors, a trial of deep sedation is justified if IAH is considered as needing

treatment, bearing in mind possible side effects of prolonged deep sedation, including inhibition of GI motility. If IAP does not change or there is an extensive haemodynamic effect, deep sedation could then be discontinued.

While the effect on IAP was in general small, a noticeable impact on haemodynamics was observed. Prolonged hypotension was avoided with prompt use of a vasopressor drug to counteract the propofol-induced vasodilation. In 40% of patients, noradrenaline was either started during the intervention or its dose increased, while in only 1 patient the dose of propofol needed to be decreased due to an excessive increase in the dose of vasopressor, as specified by the study protocol. Haemodynamic management in the study was guided by MAP goals. Similar to cerebral perfusion pressure (mean arterial pressure minus intracranial pressure), the effective perfusion pressure in the abdomen may be more important in determining the perfusion of abdominal organs. Whether it is a better treatment endpoint than MAP or IAP in patients with IAH, is currently not known, although some authors suggest to consider APP >50–60 mmHg as a treatment end-point (Malbrain & De Waele, 2013) with few data supporting this suggestion (Cheatham et al., 2000; Al-Dorzi et al., 2012). In our study, if APP instead of MAP would have been used to guide fluid and/or vasopressor therapy in patients with IAH, even greater vasopressor doses would have been needed to achieve APP >60 mmHg.

No improvements in respiratory volumes nor decreases in respiratory pressure were seen with the intervention, possibly related to the low overall effect on IAP. PEEP was 10 (8–12) cmH2O, but it was unchanged during the intervention and the effect on IAP at PEEP values <12 cmH2O is likely marginal (De Keulenaer et al., 2009). Respiratory activity ceased completely in only one quarter of patients. Theoretically, abdominal compliance could be improved by reducing the tone in the muscles of the abdominal wall, including the diaphragm, by complete cessation of spontaneous respiration. However, in patients in whom spontaneous breathing stopped with deep sedation, the decrease in IAP was similar compared to others.

Obesity, a known risk factor for IAH, was prevalent in our patient population. As pre-ICU IAP values are not known, it is difficult to distinguish whether an elevated IAP value in an obese patient is acute or chronic and whether it can or should be lowered. In this study, IAP changed similarly in obese and normal-weight patients in response to deepening of sedation.

An important limitation of this study is that the sedation end-point was defined by a drug dose and not a sedation or respiratory parameter. Some patients did not achieve a very deep sedation or complete cessation of spontaneous breathing, possibly diluting the results. Further, with the exclusion of awake and agitated patients we may have omitted those who could benefit the most from deeper sedation in terms of IAP reduction. A long study conduction period and the fact that not all consecutive eligible patients were recruited brings along a possibility of bias.

## 6.4. iSOFA study (IV)

In the iSOFA study, 540 consecutively admitted intensive care patients from 11 centres in 9 countries were observed during their first week of ICU, with daily data collection including predefined abdominal and GI symptoms (Reintam Blaser et al., 2012), AGI grading and biomarkers citrulline and I-FABP. As the original AGI grading performed well in mortality prediction, a new score, named the GIDS, was created based on the logic of AGI grading. Inclusion of biomarkers did not improve the score. When added to the SOFA score, GIDS was independently associated with 28- and 90-day mortality and slightly improved the predictive power of the SOFA score.

Compared to previous attempts at creating a score to quantify gastrointestinal dysfunction in critically ill patients, all consecutive patients were included and prospective data collection used. A complex, stepwise statistical approach allowed to take into account the individual contribution of different symptoms and conditions towards mortality prediction.

The original AGI grading (Reintam Blaser et al., 2012) has been shown to be related to mortality in several studies in the recent years (Hu et al., 2017; Zhang et al., 2018; Loudet et al., 2020; Ding et al., 2020). Likewise, in this study it performed well in prediction of mortality both alone and together with the SOFA score and its subscores. Furthermore, the AGI grading was the best-functioning component of these models. Instead of specific GI symptoms, AGI considers the overall condition of the patient and includes a great deal of subjectivity in determining whether the GI or other organ system(s) may drive a deterioration of a patient's condition. A higher AGI grade may be given in a patient with multiorgan dysfunction compared to a less severely ill patient with exactly the same GI symptoms. Therefore, assessment of other organ dysfunctions may contribute to determining an AGI grade, likely also explaining the best predictive ability out of all organ dysfunction scores. Further, lack of clear definition of feeding intolerance within AGI adds another component of subjectivity.

It could be argued that organ dysfunction can better be described by measuring some specific function(s) of the organ system, rather than by its ability to predict outcome. Firstly, the intricacy of the GI system, critical illness and the intensive care environment precludes an easily applicable method to consider at the same time several different aspects of GI function, including its motor function, perfusion and absorption, as well as permeability and other non-digestive aspects. Secondly, the SOFA score, currently the most widely used in assessing organ dysfunction, but missing a GI component, has also been validated against mortality (Minne et al., 2009). Therefore, a mortality endpoint was chosen. Already more than two decades ago, authors of the SOFA score noted the importance of including the GI system in the score but deemed it too complex (Vincent et al., 1996). The GIDS should undergo further validation to consider including it in a score assessing multiple organ dysfunction.

The score is composed of 4 grades of severity, with 0 points corresponding to a normal functioning of the GI tract in an intensive care patient. The situation

where a patient was able to eat and experienced just one GI symptom or had grade I-II IAH was best categorised as 0 points. Included in this list of symptoms are also abdominal distension and GI paralysis. Even though these symptoms were associated with increased mortality in some of the multivariate analyses exploring associations of single symptoms with outcome, the performance of the score worsened when considering these symptoms individually as being more "severe". Thus, it seems that the concurrent presence of several symptoms is more informative than any single symptom. The score performed best, however, when abdominal distension and GI paralysis were also included in the list of more severe symptoms under GIDS=3.

The ability of an intensive care patient to eat could be considered an important feature of normal GI function. As such and also being beneficial to the performance of the score, it was incorporated in GIDS. However, including oral intake in the score may introduce the effect of other organ systems, as independent eating also requires consciousness, sufficient respiratory function etc. Further, some patients unable to eat due to for example, a swallowing disorder, may be "falsely" classified from GIDS=0 to GIDS=1.

IAH is not a measure of GI function per se, although associations with GI symptoms have been demonstrated as discussed before. Inclusion of IAP may increase the objectivity of the score and likely complements the assessment of GI symptoms. Similar to other less severe GI symptoms, occurrence of isolated grade I-II IAH does not suggest presence of GI dysfunction and anticipated poor outcomes, also supported by research in patients undergoing elective abdominal hernia repair and transient IAH in the postoperative period (Petro et al., 2015).

We chose to define GIDS=4 as certain life-threating conditions arising from the GI tract – bleeding with haemorrhagic shock, mesenteric ischaemia and abdominal compartment syndrome. With this approach, however, the influence from other organ systems likely remains. Defining GIDS=4 as a critical condition is based on the logic of the AGI grading. It was evident from the discriminant analyses of single symptoms that no particular symptom or a number of symptoms could satisfactorily describe such a state.

Although desirable as objective components, addition of citrulline or I-FABP to the score did not improve its performance. Despite not being related to mortality, associations with enteral nutrition and possibly enterocyte function are not excluded and were indeed demonstrated in study V. As there exists no standard to measure the functioning of the GI tract in critically ill patients, choosing the most suitable outcome variable is difficult. Ideally, a clinical score would be able to both accurately identify organ dysfunction as well as predict outcome.

Unfortunately, the biomarkers were measured in only a subset of the whole iSOFA study population due to financial constraints, possibly weakening their effect in the current analysis.

GIDS, being developed on a prospective multicentre population of consecutively admitted ICU patients, deserves further validation studies to consider

using it for clinical and research purposes. Although some of the single symptoms remain subjective, for the time being the available components are the most practical.

## 6.5. Enteral nutrition and biomarkers study (V)

In study V, patients were prospectively observed during the first week of ICU to assess the dynamics of the biomarkers citrulline and I-FABP in response to EEN and its success. The patient population between studies I and V differs considerably. Study V included consecutive patients, including short-stayers admitted after major, mostly cardiac surgery, while abdominal surgery preceded ICU admission less often (29% vs 19%). Consequently, while illness severity according to APACHE II and SOFA scores was rather similar, mortality was lower in patients of study V. Nutrition was given according to local practices, with about 80% receiving enteral or oral nutrition at any time during their ICU stay. 50% of patients received early oral nutrition and 20% received EEN. A stepwise increase in enteral caloric intake was observed with a median of about 1000 kcal per day provided after day 4 in those receiving EN.

On the background of an overall decrease during the first week of ICU in the values of citrulline from normal to low-normal, a few interesting findings emerged related to the application of early enteral or oral nutrition. From day 3 onwards, increasing citrulline levels were observed in patients who had received EEN/ON, unlike in those who did not. It seems that enteral or oral nutrition is associated with recovery of enterocytes, reflected by citrulline plasma concentration. A recent study, part of the NUTRIREA-2 project, comparing the dynamics of citrulline in patients receiving either enteral or parenteral nutrition supports this assumption, demonstrating a greater recovery of citrulline values during the first week in those who received EN vs those who were given exclusively PN (Piton et al., 2019). The direction of the association observed in our study and that by Piton et al, however, is not entirely clear. Whether nutrition increases citrulline by providing glutamine, a precursor for its synthesis, or nutrition itself helps restore the enterocytes, or it is the recovery of enterocytes that makes giving EN possible, remains to be clarified. Citrulline levels failed to increase in about one third of patients receiving EEN/ON. These patients showed signs of feeding intolerance, demonstrated by interruption of nutrition in ~20%, higher AGI grades and more frequent use of prokinetics. Again, this finding of FI being related to non-recovery of citrulline values needs to be explained in further studies. In patients with early ON in any amount or EEN and receiving at least 80% of caloric needs by day 4, citrulline values increased and diverged visually from day 4 onwards from patients receiving <80%, however this trend was not statistically significant, likely affected by small patient numbers.

In general, high values of I-FABP were observed on admission to ICU, with a rapid subsequent decrease into “normal” values, i.e., into the lower part of the

reference range of the laboratory kit used. Patients who received EEN/ON presented similar dynamics, but on average higher values during the first week, compared to their counterparts. A similar dynamic of I-FABP during the week was observed in patients with successful EEN/ON, but a trend towards higher average values was seen compared to those receiving <80% of caloric needs by day 4. These findings allow to hypothesise that enteral nutrition in the early phase of critical illness may be associated with enterocyte damage, caused by an imbalance in the delivery and demand of oxygen. In the study by Piton et al. comparing EN vs PN, EN was given early and in full amount to patients in shock (Piton et al., 2019). Three-to-four-fold greater values of I-FABP were observed in patients receiving EN vs PN during the one-week observation period with no cases of clinically obvious acute mesenteric ischaemia in this population. However, in the total population of the NUTRIREA-2 project, early full enteral nutrition was established to carry a higher risk of acute mesenteric ischaemia than no EN (Reignier et al., 2018). Among patients in study V, one presented with acute mesenteric ischaemia and very high I-FABP (>68000 pg/mL) on admission to ICU. Unfortunately, the absolute values of I-FABP are not comparable between our study and the one by Piton et al, as different ELISA kits were used and their reference values differ greatly. Also, an important consideration when interpreting results of study V is the fact that blood samples for biomarkers measurements were collected immediately after admission to ICU, facilitated by delayed informed consent. This may partly explain the very high I-FABP values seen in our study. Taking into account the rapid kinetics of I-FABP, significantly lower values are expected in trials with a more lengthy inclusion process, as in the NUTRIREA-2 substudy (Piton et al., 2019).

There were no clear associations between the studied biomarkers and renal function. Reduced elimination of citrulline in renal failure could be expected from studies in non-critically ill patients. In critically ill patients, the presence of confounding factors may tend to decrease the values of the biomarker and counteract an increase due to renal failure, as hypothesised by Cynober (Cynober, 2013).

All in all, somewhat conflicting signals of improvement of citrulline levels with EEN/ON and at the same time, possible enterocyte damage related to EEN/ON were seen. EEN and oral nutrition were considered together in study V, while calories provided with oral nutrition were not assessed. This shortcoming may affect the groupwise comparisons of patients with successful vs unsuccessful EEN/ON. Inclusion of short-staying, mostly postoperative patients with an incomplete dataset steered the citrulline values of the whole study population higher on days 1 and 3, while I-FABP was not influenced. A relatively small patient population and substantial overlaps in the values of biomarkers between the compared groups calls for hypothesis-generation but does not invite to use these biomarkers in decision-making regarding nutrition of intensive care patients.

# 7. CONCLUSIONS

Results of the conducted studies consolidate the understanding of the importance of gastrointestinal problems and indicate areas where their diagnosis and management can be improved.

1. Using a protocol to guide the administration of and troubleshooting related to enteral nutrition improves the delivery of nutrition via the enteral route in long-staying critically ill patients. This improved enteral intake is not related to more frequent gastrointestinal symptoms and intra-abdominal hypertension. With enhanced enteral nutrition, the use of parenteral nutrition decreases and in a nutritionally challenging patient population with frequent underfeeding, use of an enteral feeding protocol alone is not sufficient in avoiding large caloric deficits.
2. Gastrointestinal failure, defined as the simultaneous presence of at least 3 GI symptoms, occurs in one tenth of ICU patients and is associated with poor treatment outcomes. The importance of several concurrent GI symptoms is highlighted by the approach of defining GIF by the presence of multiple symptoms, where a higher number of simultaneous GI symptoms independently predicts long-term mortality similar to other organ dysfunctions, characterised by the SOFA sub-scores. Primary and secondary GIF are both associated with high mortality, while GIF in a patient without a primary abdominopelvic pathology tends to occur in more severely ill patients, later in the course of critical illness, and possibly carry a worse prognosis. The monitoring of intra-abdominal pressure is warranted in patients that experience GIF as the prevalence of IAH is high in this patient group.
3. Management options to treat sustained IAH and avoid its progression to ACS are limited, triggers to initiate treatment not clear and their effectiveness poorly described. Our research underlines the pitfalls of sedation as a measure to reduce IAP. The effect of deepening of sedation on IAP is generally small, whereas many patients require vasopressor therapy to correct the hypotension ensuing from deep sedation. Nevertheless, a possibly clinically important decrease in IAP occurs in some patients and it cannot be excluded before a trial of sedation is undertaken. Therefore, deepening of sedation can be considered if IAH is considered as needing treatment, with careful evaluation of its effect and side effects.
4. The newly developed GID score was created based on different GI symptoms, following the rationale of the AGI grading. The score demonstrated a good mortality prediction ability both individually and in addition to organ dysfunction sub-scores of the SOFA score. The biomarkers citrulline and I-FABP did not contribute to the performance of the score.
5. The biomarkers citrulline and I-FABP do not sufficiently discriminate between patients able to achieve their energy needs with EN from those who do not. Even though citrulline increases in patients receiving early enteral or

oral nutrition, possibly reflecting a recovery of enterocyte function, the direction and reproducibility of this association is not fully clear, and needs to be elucidated in further studies. A wide overlap in the values of citrulline and I-FABP among patients with early vs no early EN and successful vs unsuccessful EN currently does not favour their use in managing nutrition of intensive care patients.

**Future directions**

Acknowledging the importance of avoiding large cumulative energy deficits in long-staying ICU patients, a comprehensive approach to nutrition involving both EN and PN, as appropriate, should be consolidated into an improved nutrition protocol. Further research exploring the effects of different nonsurgical management options to lower IAP are warranted. In the face of likely small effects of each individual measure, a bundle of measures to treat IAH could be developed and tested in a larger population. Even though citrulline and I-FABP did not prove themselves useful in our studies neither in guiding enteral nutrition nor as components of the Gastrointestinal Dysfunction Score, the role of intestinal biomarkers in assessing GI dysfunction and non-occlusive mesenteric ischaemia will need to be elucidated. The Gastrointestinal Dysfunction Score requires validation in future studies.

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# 9. SUMMARY IN ESTONIAN

## Enteraalne toitmisravi, seedetrakti düsfunktsioon ja soole biomarkerid intensiivravipatsientidel

Organpuudulikkuste diagnoosimine ja ravi on üks intensiivravi nurgakividest. Seedetrakti olulisust intensiivravipatsientidel on teadvustatud aastakümnete vältel, kuid ometi on selle organsüsteemi düsfunktsioon ebapiisavalt defineeritud ning ei kuulu erinevalt teistest organpuudulikkustest intensiivravipatsiendi seisundit kirjeldavatesse skooridesse. Seedetrakti düsfunktsiooni ja toitmisprobleemide diagnoosimine põhineb siiani peamiselt subjektiivsel kliinilisel läbivaatusel. Võimalikud ravimeetodid seedetrakti probleemide lahendamiseks intensiivravipatsientidel ning nende tõenduspõhisus on vähesed.

**Uurimistöö eesmärgid**

Käesolev uurimistöö keskendus enteraalse toitmise läbiviimisele ja jälgimisele, seedetrakti düsfunktsiooni ja puudulikkuse diagnoosimisele ja mõju selgitamisele ning intra-abdominaalse hüpertensiooni ravivõimaluste uurimisele intensiivravipatsientidel.

Täpsemad eesmärgid olid järgmised:

1) selgitada enteraalse toitmise protokolli kasutusele võtmise mõju toiduenergia pakkumisele, seedetrakti sümptomite esinemissagedusele ja ravitulemustele pikaajalist intensiivravi vajavatel patsientidel (I uuring);
2) kirjeldada mitme seedetrakti sümptomi samaaegse esinemise kaudu defineeritud seedetrakti puudulikkuse esinemissagedust, mõju ravitulemustele ja iseärasusi sõltuvalt tekkepõhjusest (II uuring);
3) hinnata sedatsiooni süvendamise efektiivsust ja ohutust intra-abdominaalse hüpertensiooni ravis mehaaniliselt ventileeritud intensiivravipatsientidel (III uuring);
4) luua seedetrakti düsfunktsiooni hindamiseks objektiivne skoor, kasutades selleks seedetrakti ja kõhukoopa poolseid sümptomeid, haigustunnuseid ning biomarkereid tsitrulliin ja I-FABP; hinnata skoori võimet ennustada ravitulemusi (IV uuring);
5) selgitada tsitrulliini ja I-FABP-i seoseid enteraalse toitmisraviga intensiivravipatsientidel (V uuring).

**Patsiendid ja metoodika**

I ja II uuring põhinevad prospektiivselt koostatud andmebaasil, kus sisalduvad kõigi alates 2004. aastast Tartu Ülikooli Kliinikumi 1. intensiivravi osakonda hospitaliseeritud patsientide olulisemad kliinilised andmed.

I uuringus hinnati 2013. aastal kasutusele võetud enteraalse toitmise protokolli mõju toitmisravi tulemustele. Selleks võrreldi retrospektiivselt 2011.–2012. ja 2014.–2015. aastal osakonnas vähemalt ühe nädala jooksul ravil olnud patsientide ravitulemusi. Uuringus võrreldi kokku 480 täiskasvanud patsienti.

II uuringus analüüsiti retrospektiivselt 3959 täiskasvanud intensiivravipatsienti, keda raviti aastatel 2004–2015. Seedetrakti puudulikkuse defineerimiseks kasutati meie uurimisgrupi varasemalt kirjeldatud lähenemist – kolme seedetrakti sümptomi esinemine ühe päeva jooksul. Sümptomid olid: sooleperistaltika puudumine, nasogastraalaspiraadi hulk >500 mL päevas, soolte laienemine, oksendamine, seedetrakti verejooks, kõhulahtisus. Seedetrakti puudulikkus oli primaarne, kui arenes kõhukoopa- või vaagnapiirkonna patoloogiaga patsiendil, ning sekundaarne, kui oli seotud mõne muu haigusseisundiga.

III uuring oli prospektiivne sekkumisuuring, mis hõlmas 37 täiskasvanud mehaaniliselt ventileeritud intensiivravipatsienti, kellel esines intra-abdominaalne hüpertensioon. Kõhukoopasisese rõhu vähendamise eesmärgil süvendati patsientidel sedatsiooni propofooliga ning seejärel hinnati ühe tunni jooksul selle mõju intra-abdominaalsele rõhule, vererõhule ja vasoaktiivse ravi vajadusele ning hingamisparameetritele.

IV uuring oli mitmekeskuseline prospektiivne jälgimisuuring 9 riigi 11 intensiivraviosakonnas, hõlmates 540 järjestikkust patsienti. Andmekogumine, mille rõhuasetuseks olid seedetrakti ja kõhukoopa sümptomid ning haigustunnused, vältas ajal, mil patsient viibis intensiivraviosakonnas, ning maksimaalselt 7 päeva. Lisaks määrati osades uuringukeskustes (kokku 224 patsiendil) osakonda saabumisel ja seejärel igapäevaselt vereplasmast biomarkerite tsitrulliini ning I-FABP-i tase. V uuringus kirjeldati biomarkerite dünaamikat neil 224 patsiendil seoses varajase suukaudse või enteraalse toitmisravi ning selle edukusega.

**Peamised tulemused ja järeldused**

1. Toitmisprotokolli kasutuselevõtu järgsel perioodil manustati intensiivravipatsientidele esimese nädala jooksul enteraalse toitmise teel 40% võrra rohkem toiduenergiat kui enne toitmisprotokolli kasutuselevõttu. Sellega seoses ei suurenenud seedetrakti sümptomite ja intra-abdominaalse hüpertensiooni esinemissagedus. Siiski oli see kasv väiksem, kui samaaegne parenteraalse toitmise vähenemisest tingitud toiduenergia defitsiit. Kokkuvõttes vähenes pärast protokolli kasutuselevõttu nädala summaarne manustatud toiduenergia hulk. Parenteraalse toitmise vähesem kasutamine võis olla tingitud asjaolust, et patsiente toideti rohkem enteraalsel teel ning seetõttu pakuti parenteraalset toitmist väiksemale hulgale patsientidele. Välistada ei saa ka sekkumisest sõltumatut mõju, kuna protokolli kasutuselevõtu järgsel perioodil võidi eelistada parenteraalse toitmise hilisemat alustamist tulenevalt tol perioodil ilmnenud uutest teadmistest varajase parenteraalse toitmise kahjulikust mõjust ravitulemustele. Uuring osutas, et ainuüksi enteraalse toitmise protokolli rakendamisest ei piisa, et vältida suuri toiduenergia puudujääke.
2. Kolme seedetrakti poolse sümptomi samaaegse esinemise abil defineeritud seedetrakti puudulikkus esineb 10%-l intensiivravipatsientidest ning on seotud halvemate ravitulemustega. Samaaegselt esinevate sümptomite olulisusele viitab asjaolu, et esimesel intensiivravipäeval esinev suurem seedetrakti sümptomite arv on suremuse sõltumatu riskifaktor. Lisatuna SOFA

skoori alaskooridele parandab seedetrakti sümptomite arv mõnevõrra SOFA skoori võimet suremust ennustada. Nii primaarne, st kõhukoopa- ja vaagnapiirkonna patoloogiaga seotud, kui sekundaarne ehk muu põhjusega seedetrakti puudulikkus on seotud kõrge suremusega. Sekundaarse põhjusega seedetrakti puudulikkuse juhud leiavad sagedamini aset hilisemal intensiivraviperioodil, patsientide seisund on raskem ning ravitulemused võivad olla kehvemad. Seedetrakti puudulikkusega patsientidel on intra-abdominaalse hüpertensiooni esinemissagedus kõrge ning kõhukoopasisese rõhu mõõtmine näidustatud.

3. Intra-abdominaalse hüpertensiooni ravivõtted on piiratud, nende efektiivsus ebapiisavalt tõendatud ning näidustused ravi alustamiseks ebaselged. Käesolev uurimistöö osutab sedatsiooni süvendamise kui ühe intra-abdominaalse hüpertensiooni ravimeetodi vähesele toimele ja võimalikele kõrvaltoimetele. Sedatsiooni süvendamise tulemusena intra-abdominaalne rõhk küll vähesel määral langeb, kuid samal ajal leiab aset arteriaalse vererõhu oluline langus, mis põhjustab kõhukoopa perfusioonirõhu vähenemist ning ligi pooltel patsientidel on vaja alustada või tõhustada vasoaktiivset ravi. Siiski väheneb ligi veerandil patsientidest sedatsiooni süvendamise tulemusena intra-abdominaalne rõhk oluliselt, mistõttu tuleks seda ravivõtet vajaduse korral kaaluda. Sellisel puhul on vaja võimalikke kõrvaltoimeid hoolikalt jälgida ja saadavat kasu analüüsida.
4. Liikumaks edasi seedetrakti puudulikkuse kui dihhotoomse fenomeni kirjeldamisest, töötasime välja seedetrakti sümptomite ja intra-abdominaalse hüpertensiooni raskusastmete kombinatsioonil põhineva kliinilise skoori – GIDS (*GastroIntestinal Dysfunction Score*). Biomarkerid tsitrulliin ja I-FABP skoori toimimist ei parandanud. Loodud skoori võime ennustada suremust oli hea nii iseseisvalt kui lisatuna SOFA skoorile.
5. Tsitrulliini ja I-FABP-i tase vereplasmas ega ka markerite dünaamika ei võimaldanud ennustada toitmisravi edukust enteraalset toitmisravi saavatel intensiivravipatsientidel. Ehkki tsitrulliini tase on kõrgem varajast toitmisravi saavatel patsientidel, viidates seosele enterotsüütide funktsiooni taastumisega, ei ole selle seose olemus selge ning vajab edasist uurimist. Tsitrulliini ja I-FABP-i väärtuste suur kattuvus võrdlusrühmade vahel ei võimalda anda soovitust nende biomarkerite kasutamiseks enteraalse toitmisravi läbiviimisel.

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# 11. PUBLICATIONS

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**Scientific work:**

Research fields: gastrointestinal dysfunction, intra-abdominal hypertension and enteral nutrition in intensive care patients. 8 publications, 5 presentations in international congresses

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Uurimisvaldkonnad: seedetrakti düsfunktsioon, intra-abdominaalne hüpertensioon ja enteraalne toitmine intensiivravis. 8 publikatsiooni, 5 ettekannet erialakongressidel.

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# DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos**. The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
2. **Mihkel Zilmer**. Na-pump in normal and tumorous brain tissues: Structural, functional and tumorigenesis aspects. Tartu, 1991.
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