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ANNIKA REINTAM

Gastrointestinal failure in intensive care patients

TARTU UNIVERSITY
PRESS

Clinic of Anaesthesiology and Intensive Care, University of Tartu

Dissertation is accepted for the commencement of the degree of Doctor of Philosophy in Medicine on May 21, 2008 by the Council for the Commencement of Doctoral Degree in Medicine

Supervisors:

Joel Starkopf, MD, PhD, Professor of Anaesthesiology and Intensive Care, University of Tartu, Estonia
Hartmut Kern, MD, PhD, Visiting Professor of Anaesthesiology and Intensive Care, University of Tartu, Estonia; Clinic of Anaesthesiology, Intensive Care and Pain, DRK Kliniken Berlin, Germany

Reviewers:

Heidi-Ingrid Maaroos, MD, PhD, Professor of Policlinic and Family Medicine, University of Tartu, Estonia
Ants Peetsalu, MD, PhD, Professor of Surgery, University of Tartu, Estonia

Opponent:

Manu Ludovic Nelly Guido Malbrain, MD, PhD, Director of ICU, ZiekenhuisNetwerk Antwerpen Campus Stuivenberg, Antwerp, Belgium

Commencement: September 5, 2008

Publication of this dissertation is granted by the University of Tartu

ISSN 1024–395X
ISBN 978–9949–11–924–0 (trükis)
ISBN 978–9949–11–925–7 (PDF)

Tartu Ülikooli Kirjastus
www.tyk.ee
Tellimus nr. 271

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LIST OF ORIGINAL PUBLICATIONS

I. Reintam A, Parm P, Redlich U, Tooding LM, Starkopf J, Köhler F, Spies C, Kern H. Gastrointestinal failure in intensive care: a retrospective clinical study in three different intensive care units in Germany and Estonia. *BMC Gastroenterology* 2006, 22; 6:19

II. Reintam A, Parm P, Kitus R, Kern H, Starkopf J. Primary and secondary intra-abdominal hypertension – different impact on ICU outcome. *Intensive Care Med* 2008 (in press)

III. Reintam A, Parm P, Kitus R, Tamme K, Starkopf J. Intra-abdominaalse hüpertensiooni esinemissagedus intensiivravihaigetel ja mõju ravitulemustele. *Eesti Arst* 2008; 87(3):191–197

IV. Reintam A, Parm P, Kitus R, Kern H, Starkopf J. Gastrointestinal symptoms in intensive care patients (submitted to *Intensive Care Med*)

V. Reintam A, Parm P, Kitus R, Starkopf J, Kern H. Gastrointestinal Failure Score in critically ill patients: a prospective observational study (submitted to *Crit Care*)

VI. Reintam A, Kern H, Starkopf J. Defining Gastrointestinal Failure. *Acta Clin Belg* 2007, 62(Suppl 1):168–172

Contributions by Annika Reintam
In all papers Annika Reintam participated in study design, performed the data analysis and wrote the first draft of the manuscript.

ABBREVIATIONS

ACS	– abdominal compartment syndrome
ANOVA	– Analysis of variance
APACHE	– Acute Physiology and Chronic Health Evaluation
AUROC	– area under the receiver operator characteristic curve
BMI	– body mass index
CVP	– central venous pressure
FI	– food intolerance
GIF	– gastrointestinal failure
ICU	– intensive care unit
IAH	– intra-abdominal hypertension
IAP	– intra-abdominal pressure
MAP	– mean arterial pressure
MODS	– Multiple Organ Dysfunction Score
MOF	– multiple organ failure
MPM	– Mortality Probability Model
PEEP	– positive end-expiratory pressure
OR	– odds ratio
PIP	– peak inspiratory pressure
ROC	– Receiver Operator Characteristic
SAPS	– Simplified Acute Physiology Score
SOFA	– Sequential Organ Failure Assessment
95% CI	– 95% confidence interval

1. INTRODUCTION

Multiple organ failure (MOF) is a major cause of morbidity and mortality in critically ill patients. In modern intensive care, failure of a single organ rarely leads to patient death, but the higher the number of organ systems in failure, the higher the expected mortality. Gastrointestinal (GI) problems occur frequently and are associated with adverse outcome in critically ill patients. Yet, in routine clinical practice there is no consensus for precise assessment of the gastrointestinal function. For a complex evaluation of all vital organs, several scoring systems for MOF have developed. The GI system is not included in any of the scores widely used today and there are no universally accepted diagnostic criteria for gastrointestinal failure (GIF) in critically ill patients. Present dissertation investigates practical aspects of GI function in intensive care patients, immunological and endocrine function of the gut are not specifically assessed. The occurrence of gastrointestinal problems in adult critically ill patients and their impact on intensive care outcome is described and the terminology and definitions in this area are discussed. A new disease severity score – the Gastrointestinal Failure Score – is proposed and tested in a prospective, single-centre study.

2. REVIEW OF THE LITERATURE

2.1. Evaluation of gastrointestinal function

The well-established and validated tool for measurement of gastrointestinal function is absent and the research in the area is rather limited. Below the strengths and weaknesses of both the methods of objective measurement and the assessment of clinical symptoms in evaluation of GI function are briefly discussed.

2.1.1. Objective measurement of GI function

Motor function of GI tract

Delayed gastric emptying is common in ICU patients, occurring in approximately 50% of mechanically ventilated patients (Montejo 1999; Ritz et al. 2001; Deane et al. 2007). Measurements of lower oesophageal sphincter pressure (Nind et al. 2005) and antro-pyloro-duodenal manometry (Bosscha et al. 1998; Chapman et al. 2005) have revealed severe impairment of oesophageal and gastric motor function in critically ill patients. Other tests for measuring motor function of the GI tract include scintigraphy by use of radiolabelled feed (Batchelor et al. 2002) and ^{13}C-octanoic acid breath test (Toumadre et al. 2001). Some authors assessed gastric motility function by measuring plasma concentrations of previously enterally given acetaminophen (Cohen et al. 2000; Landzinski et al. 2008).

A number of studies demonstrate that critical illness is associated with slower gastric emptying (Ritz et al. 2001; Nind et al. 2005; Landzinski et al. 2008; Chapman et al. 2008), fewer antegrade and more retrograde waves and shorter wave propagation (Chapman et al. 2008). The organization of antro-duodenal pressure waves in critically ill patients is abnormal and associated with slow gastric emptying (Chapman et al. 2008). There appears to be virtual absence of gastric phase III motility during the fasting state, even though the phase III activity persists in the duodenum (Dive et al. 1994, Deane et al. 2007) possibly with abnormal organization (Deane et al. 2007; Chapman et al. 2008). When the small bowel is exposed to even low levels of nutrients, delayed fundal relaxation, reduced antral motility and increased isolated pyloric activity occur with potentially delayed gastric emptying (Dive et al. 1994, Chapman et al. 2005, Deane et al. 2007). Small intestinal motor waves may be detected immediately after major abdominal surgery, but migration of these waves is often abnormal (Toumadre et al. 2001).

In conclusion, remarkable gastrointestinal motor dysfunction occurs frequently in critical illness and it is an important cause of unsuccessful enteral

feeding. The aetiology of this dysfunction is unclear, but is probably multifactorial (Deane et al. 2007).

Routine measurement of motor function of the GI tract is not available for most ICUs and gastric emptying is rarely directly measured for other than research purposes (Deane et al. 2007).

Gastrointestinal perfusion

Impairment of gastrointestinal mucosal perfusion is associated with gut injury and a decrease in gut barrier function, possibly causing an augmentation of systemic inflammation and a distant organ dysfunction. A range of techniques have been developed and used for assessment of gastrointestinal perfusion, including tonometry, laser Doppler flowmetry, reflectance spectrophotometry, near-infrared spectroscopy, orthogonal polarisation spectral imaging, indocyanine green clearance and hepatic vein catheterisation (van Haren et al. 2007). Each of these techniques measures different elements of gastrointestinal perfusion. Despite all recent advances, the usefulness of gastrointestinal perfusion parameters in clinical decision-making is still limited and the results of the measurement are not interchangeable (van Haren et al. 2007).

Gastrointestinal permeability

Intestinal barrier loss in critically ill patients is assumed to result in increased intestinal permeability. Intestinal permeability has been estimated by monitoring the urinary excretion of enterally administered agents, most often carbohydrates (Harris et al. 1992; Doig et al. 1998; Poeze et al. 2002).

However, reliability of these methods is questionable since non-permeability related factors act as confounders (Oudemans van Straaten et al. 2002), and the tests are seldom used in clinical routine.

The interactions between motor function, splanchnic perfusion and intestinal permeability are not clear as well as the role and order of them in the pathophysiological complex of gastrointestinal failure in critically ill patients.

In summary, despite of extensive technical progress, majority of methods developed for objective measurement of different aspects of GI function have shortages that have impeded the routine use of these techniques.

2.1.2. Gastrointestinal symptoms

In everyday practice, the GI function is rather assessed by clinical symptoms than objective measurements described above. “Due to the lack of objective, uniform definitions, monitoring of gut function must be based on indirect indicators” is the suggestion of round table conference ten years ago (Rombeau et al. 1997). However, there exists a wide variability also in definitions of gastrointestinal symptoms. Still, it is demonstrated that GI complications (decreased bowel sounds, high gastric residual volumes, food intolerance and diarrhoea) occur in up to 50 % of mechanically ventilated patients (Montejo et al. 1999; Mutlu et al. 2001). Intolerance to gastric feeding due to delayed gastric emptying is frequent in critically ill patients and has adverse impact on outcome (Dive et al 1994; Nguyen et al. 2007).

Gastric residual volume (GRV)

Gastric emptying, assessed by measurement of gastric aspirate volumes, is often impaired in critical illness (Mentec et al. 2001; Heyland et al. 2001). Most of the feeding protocols accept regular measurement of gastric residual volume during the enteral nutrition as a surrogate to indicate gastric emptying, success of feeding and potential risk of aspiration (Deane et al. 2007). In the literature contradictory data about acceptable (“normal”) GRV level are available. Most authors regard residual aspirate volume below 150 ml as safe for continuing intragastric feeding and volume above 250 ml as high (MacLaren L 2000; van Haren et al. 2002; Kattelmann et al 2006; Nguyen et al. 2007; Landzinski et al. 2008). Mentec et al., in contrast, suggested upper digestive tract intolerance to be diagnosed, if patients had gastric aspirate volumes between 150 and 500 ml in two consecutive measurements; or >500 ml in one measurement, or when vomiting occurred (Mentec et al. 2001). A recent publication recommends to continue enteral feeding at residual volumes up to 500 ml (Montejo et al. 2007).

The accuracy of GRV in assessment of gastric function, however, is questionable – high residual volumes weakly correlate with gastric emptying (Ritz et al. 2001; Batchelor et al. 2002; Chapman et al. 2004; Deane et al. 2007).

High residual volume is believed to be associated with increased risk of tracheal aspiration of gastric contents. However, recent studies demonstrate that this measurement has limited sensitivity (Mizock 2007). No difference in incidence of aspiration was detected whether 150 or 400 ml was used as acceptable GRV (McClave et al. 2005).

The occurrence of large GRVs is probably less than 10% in patients receiving postpyloric feeding (Montejo 2002; Metheny et al. 2005).

In summary, GRV seems to be an unreliable parameter of GI function. Dependence of GRV on a number of factors (tube characteristics, vomiting, interval of measurements etc.) has led to the lack of consensus on an acceptable value for GRV during enteral feeding (Deane et al. 2007).

Food intolerance

The nutritional goals are met by enteral feeding only in about 25% of ICU patients (de Beaux 2001). By this route of feeding usually no more than 50% of targeted calories (de Beaux 2001; Rubinson et al. 2004; Deane et al. 2007) are delivered. The higher amounts cannot be achieved due to cessation of feeding, commonly because of delayed gastric emptying (Deane et al. 2007). Surprising variability exists in definitions of food intolerance (e.g. feed intolerance – FI). While most authors define it based on high gastric residuals or vomiting (Mentec et al. 2001; Elpern et al. 2004; Deane et al. 2007; Nguyen et al. 2007), others include also abdominal pain or distension, and diarrhoea as reasons to stop feeding and declare FI to be present (O'Leary-Kelley et al. 2005). Some authors use the term "intolerance of enteral feedings" in case if diarrhoea is provoked by enteral nutrition (Martin 2007).

Although no consensus exists on definition, we believe that food intolerance would be the best clinical entity to describe gastrointestinal failure. As also stated by the experts: despite obvious limitations to the definition of intolerance to enteral feeding, it provides a functional assessment with some clinical relevance (Rombeau et al. 1997). Unavoidable disruption of enteral feeding (for whatever reason – high GAV, diarrhea, etc.), reflects most likely the disturbed function of GI tract. Therefore we included food intolerance into the proposed gastrointestinal failure score, tested in Paper V of present dissertation. Our ideas are supported by other studies demonstrating the impact of food intolerance on ICU outcome (Mentec et al. 2001; Montejo et al. 2002; Nguyen et al. 2007).

GI bleeding

Bleeding from GI tract was commonly seen in ICU patients treated in 70ies and 80ies of last century (Durham et al. 1991). The studies from that period therefore included the GI bleeding as a main sign of gastrointestinal failure into severity of disease scoring systems (Goris et al. 1985). Later, however, the authors concluded that GI failure should not at all be considered in multiple organ failure score due to problems in definition and reliability (Lefering et al. 2002).

The era of routine prophylaxis of stress ulceration has apparently reduced the incidence of major GI bleeding in intensive care patients (Durham et al. 1991; Harty et al. 2006). Clinically significant GI bleeding occurs in 2–4% of mechanically ventilated patients (Mutlu et al. 2001; Mayr et al.2006), even though clinically evident bleeding may be seen in 5–25%, and asymptomatic, endoscopically evident damage even in 74–100% of cases (Mutlu et al. 2001). Whether decreased incidence of GI bleeding is related to a reduced mortality is not so obviously clear (Harty et al. 2006; Klebl et al. 2007). The negative side-effect of stress ulceration prophylaxis is bacterial overgrowth due to suppressed acidity, which may increase the risk of nosocomial pneumonia (Steinberg 2002). Use of sucralfate instead of antacids may carry a smaller risk of

pneumonia (Cook et al. 1996; Steinberg 2002), but seems to be less effective in prevention of bleeding (Klebl et al. 2007). Data indicate that not all critically ill patients should receive prophylaxis for stress-induced GI haemorrhage (Klebl et al. 2007).

To overcome the variability in terminology, the term stress-related mucosal disease (SRMD) for description of non-variceal bleeding might be suggested (Peura 1986; Sesler 2007). SRMD may be related to increased morbidity and mortality of critically ill patients (Cook et al. 1994; Steinberg 2002; Yang et al. 2003), but the incidence depends on the definition of bleeding (Sesler 2007).

In summary, the incidence of major GI bleeding remains nowadays below 5%, and the data about its impact on mortality are controversial. Different terms and definitions are used. GI bleeding is not suitable for monitoring of GI dysfunction due to its variable characteristics (Rombeau et al. 1997).

Diarrhoea

Diarrhoea is one of the most unpleasant complications from nursing perspective and is often handled by reducing the rate of enteral feeding (Mutlu et al. 2001; O'Leary-Kelley et al. 2005; Martin 2007). 15 to 50% of patients suffer from diarrhoea during their ICU stay (Dark et al. 1989; Ringel et al. 1995; Montejo 1999; Mutlu et al. 2001; Nguyen et al 2008). The aetiology is multifactorial – different drugs, Clostridium difficile infection and different enteral feeding substrates are just some of the most common reasons for diarrhoea in critical illness (Ringel et al. 1995). Only few studies have investigated the impact of diarrhoea on ICU outcome. Bunnapradist et al. recently demonstrated that diarrhoea doubles the hazard of graft loss and patient death after kidney transplantation (Bunnapradist et al. 2008).

The evidence how to avoid and how to handle the diarrhoea is also very limited.

Continuous instead of intermittent enteral feeding may be associated with less diarrhoea (Wiesen et al. 2006). The prokinetic agents may facilitate diarrhoea, and therefore their prescription should always be considered carefully (Nguyen et al. 2008). At which stage of diarrhoea the enteral feeding should be stopped is not known. Chan et al. suggested that enteral feeding should be discontinued if the amount of fecal output exceeds 1000 mL/day (Chan et al. 1999).

Such poor evidence and described controversies have recently led the researchers to emphasize the need for concise definitions of diarrhoea (Wiesen et al. 2006).

Decreased bowel sounds

The bowel sounds are often decreased or absent in critically ill patients. The symptom may be observed in half of all mechanically ventilated patients (Dark et al. 1989; Mutlu et al. 2001). For a long time, decreased bowel sounds have

been used as an important symptom in diagnosis of acute abdominal pathology in surgical emergency patients. Its importance in ICU patients, however, has not been systematically analyzed. The symptom is obviously very subjective by nature. Furthermore, there are several different reasons for decreased bowel sounds in critical illness.

Vomiting

The vomiting in ICU patients is assessed only in few studies, describing its prevalence from 6 to 12 per cent (Elpern et al. 2004; O'Leary-Kelley et al. 2005; Montejo 1999). According to the expert opinion, nausea and vomiting are commonly seen in postoperative patients (Steele et al. 2007). The incidence of vomiting is expectedly variable, since it is not uniformly defined, and is influenced by several factors such as enteral feeding, nasogastric aspiration, patient's position etc. Vomiting is seldom the cause for intensive care admission, but it may complicate and extend the length of stay as well as the patient's feelings about his or her hospitalization (Garrett et al. 2003; Steele et al. 2007).

Constipation

Similar to other GI symptoms, the constipation is not uniformly defined and not widely studied in critically ill patients. In one of the few studies, constipation, defined as "failure of the bowel to open for three consecutive days", was observed in 83% of mechanically ventilated patients treated in ICU for at least three days (Mostafa et al. 2003). The patients with constipation exhibited significantly lower rate of success of weaning from mechanical ventilation. In another study, roughly one third of the patients, treated in ICU for more than three days, had constipation (van der Spoel et al. 2007). In a Spanish multi-centre study constipation was observed in 16% of 400 study patients (Montejo 1999). Constipation is one possible problem that prevents discharge of critically ill patients from ICU (Asai 2007).

Bowel distension

Bowel distension may be diagnosed radiologically or clinically, but there are no consensus criteria for either of them. Spanish survey reports abdominal distension in 13% of all studied patients (Montejo 1999), while almost half of the patients with acute respiratory failure presented this symptom in earlier study (Dark et al. 1989). Other authors observed abdominal distension/pain less frequently – only in 5% of the patients (O'Leary-Kelley et al. 2005). Bowel distension may occur often in patients with constipation and may carry a potential risk for bowel perforation (Mostafa et al. 2003).

Summarized, there is very limited evidence about the incidence of GI symptoms and their impact on outcome in intensive care patients. Wide variability exists in terminology and definitions, and the approach to GI symptoms is rather unsystematic.

The decisions made in everyday practice of intensive care, are mostly based on opinions, rather than on scientific evidence. It is not clear to which extent the described symptoms reflect the actual function of GI tract. In present dissertation, we have assessed the incidence of various GI symptoms in a mixed surgical-medical ICU population and investigated their impact on outcome.

2.1.3. Indirect measures in estimation of GI function

Intra-abdominal pressure
Intra-abdominal pressure (IAP) has recently deserved increasing attention influencing the function of vital organs in critically ill patients (see Chapter 2.2). The measurement of IAP is easy to perform, and it is well reproducible. The role of IAP in context of GI function, however, is poorly understood. So far, the impact of IAP on GI function and vice versa is not fully clear.

Radiology
The usefulness of radiological studies in assessment of GI function is limited due to absence of precise criteria and, mainly, by restricted possibility to repeat the examinations. For example, bowel dilatation and intestinal pneumatosis are suggested as characteristic signs of impaired GI function (Delgado-Aros et al. 2003; Lin et al. 2006). However, there is no clear definition for radiological evaluation of bowel dilatation. Although intestinal pneumatosis is included in diagnostic criteria for necrotic enterocolitis in neonates, the value of this symptom in adult patients is not known. The right-sided colonic pneumatosis may occur in 0.1% in routine CT colonography examinations and should not be confused with symptomatic perforation (Pickhardt et al. 2008).

Summing up, in lights of extremely sophisticated technologies applied in modern ICUs for monitoring of other organs, the evaluation of gastrointestinal function is by contrast rather primitive and not systematized. Delayed gastric emptying, an important sign in ICU patients, may today be evaluated by measuring the motoric activity, absorption of the agent (Cohen et al. 2000), residuals in stomach or occurrence of vomiting. How absorption (with increased permeability in critical illness) is influenced by motoric activity and which factors confound the GRV and incidence of vomiting, is still a matter of discussion. Important is, that if the patients cannot be fed enterally they have increased incidence of infections and longer hospitalization (Marik PE et al. 2001; Rubinson et al. 2004) and possibly higher mortality. In analysis of single detailed parameters it seems to be often forgotten that the main practical function of GI tract is to digest food and fluids in sufficient amount to keep the person alive. Clearly, there is need for easy and reproducible definition of gastrointestinal failure.

2.2. Intra-abdominal pressure

2.2.1. Definitions and measurement

Intra-abdominal pressure (IAP) is defined as stable pressure in intra-abdominal cavity (Table 1). The raise in IAP affects the organs inside the abdominal cavity, but also in retroperitoneal and thoracic compartment.

Table 1. Consensus definitions list (*ACS* abdominal compartment syndrome, *APP* abdominal perfusion pressure, *FG* filtration gradient, *GFP* glomerular filtration pressure, *IAH* intra-abdominal hypertension, *IAP* intra-abdominal pressure, *MAP* mean arterial pressure, *PTP* proximal tubular pressure). (Malbrain et al. 2006)

Definition 1	IAP is the steady-state pressure concealed within the abdominal cavity.
Definition 2	APP = MAP − IAP.
Definition 3	FG = GFP − PTP = MAP − 2×IAP.
Definition 4	IAP should be expressed in mmHg and measured at end-expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the midaxillary line.
Definition 5	The reference standard for intermittent IAP measurement is via the bladder with a maximal instillation volume of 25 ml sterile saline.
Definition 6	Normal IAP is approx. 5–7 mmHg in critically ill adults.
Definition 7	IAH is defined by a sustained or repeated pathological elevation in IAP ≥ 12 mmHg.
Definition 8	IAH is graded as follows: grade I, IAP 12–15 mmHg; grade II, IAP 16–20 mmHg; grade III, IAP 21–25 mmHg, grade IV, IAP > 25 mmHg.
Definition 9	ACS is defined as a sustained IAP > 20 mmHg (with or without an APP < 60 mmHg) that is associated with new organ dysfunction/failure.
Definition 10	Primary ACS is a condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or interventional radiological intervention.
Definition 11	Secondary ACS refers to conditions that do not originate from the abdominopelvic region.
Definition 12	Recurrent ACS refers to the condition in which ACS redevelops following previous surgical or medical treatment of primary or secondary ACS.

There is evidence that empirical methods as observation and palpation of the abdomen, also the measurement of the abdominal perimeter, are incorrect to estimate the possible level of IAP (Sugrue et al. 2002). The only way to estimate IAP is to measure it.

Braune of Germany (1865) is thought to be the first to measure IAP through the rectum, Schatz of Germany (1872) measured pressure within the gravid uterus, Oderbrecht of Germany (1875) within the urinary bladder (Emerson 1911). Even though the relevance of IAP was understood by Emerson almost hundred years ago, the topic was forgotten for a long time (Schein 2006). A "benchmark" in a clinical perception of IAH is the paper by Kron and co-authors published in 1984, which also described the method for measurement of IAP, the basis for most of the recent methodologies (Kron et al. 1984; Kron 1989). This Original Open System Single Measurement Technique involves disconnecting the patient's Foley catheter, instilling 50 to 100 ml of saline into the urinary bladder and connecting the manometer to a clamped system with a needle for each individual measurement. The concerns of this technology towards aseptic technique lead to development of closed loop measurement techniques allowing the measurements without disconnection of the system every time. The Closed System Repeated Measurement Technique introduced by Cheatham and Safcsak (Cheatham et al. 1998) and revised by Malbrain and Sugrue (Malbrain 2004) is presented on Figure 1.

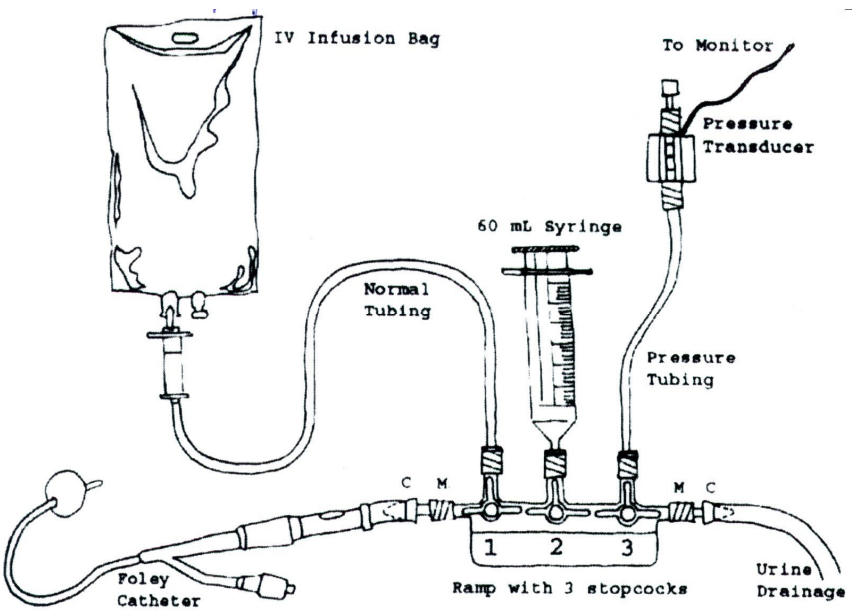

Figure 1. The Revised Closed System Repeated Measurement Technique (Malbrain 2004)

The disadvantage of the IAP measurements via bladder is the potential risk of infections, especially in patients with anuric renal failure.

Collee and co-authors introduced The Classic Intermittent Technique of IAP measurement via stomach (Collee et al. 1993). Basic of this technique is similar to the bladder measurement, but all the air needs to be aspirated from the stomach before the saline injection and pressure reading. This technology may be biased due to enteral feeding (Malbrain 2004).

A few industrial monitors for intermittent and continuous measurement of IAP via bladder and stomach are available today.

The uterine and rectal measurements are less reliable due to several confounders and have no clinical implications in the ICU setting (Malbrain 2004). The inferior vena cava pressure measurement has limited implications due to its invasiveness (Malbrain 2004). Direct measurement by cannulation of the peritoneal cavity is a gold standard, but the use of it is limited within the patients on peritoneal dialysis or undergoing the laparoscopic procedures (Malbrain 2004).

The remarkable progress has recently made in validation the methods for IAP measurements resulting in release of the Consensus Definitions (Malbrain 2004; Malbrain et al. 2005; Malbrain et al. 2006).

The instillation volume suggested for IAP measurement via bladder by Kron was 100 ml (Kron et al. 1984), by other authors even up to 250 ml (Iberty et al.1989). During the last years the proposed instillation volume has constantly decreased (Fusco et al. 2001; De Waele et al. 2007; De laet et al. 2008).

However, the "best" volume for instillation is still not very strongly supported by the studies (Gudmundsson et al. 2006; Chiumello et al. 2007).

2.2.2. Incidence of intra-abdominal hypertension

The incidence of IAH in literature is variable depending on the definition of IAH. Malbrain and colleagues used the maximum value of IAP ≥ 12 mmHg as a criteria for IAH, and showed the incidence as high as 50% of all ICU patients. (Malbrain et al.2004). While using not the maximum, but the mean IAP ≥ 12 as criteria for IAH, the incidence was twice less. In the earlier study Hong used higher threshold and reported the incidence of IAH only 2% (Hong et al. 2002). Most studies on IAH epidemiology, however, include only selected groups of patients. Thus, extremely high incidence of IAH and ACS has been described (85% and 25%, respectively) in medical ICU patients who received large volume replacement (Daugherty et al. 2007). The prevalence of intra-abdominal hypertension (IAH) in severe acute pancreatitis is reported to be about 40%, manifesting in ACS in about 10% of the patients (Leppäniemi et al. 2007). High incidence of IAH and ACS is also reported in patients with ruptured abdominal aortic aneurysms (Djavani et al. 2006).

So far Malbrain and colleagues published the only larger study addressing IAH incidence in whole ICU population in 2004. According to present Consensus definitions they reported the incidence of IAH 23.7 % in mixed ICU

population (Malbrain et al. 2004). In our preliminary study we observed similar results (Reintam et al. 2007).

2.2.3. Pathophysiology

Remarkably elevated IAP may lead to failure of almost all organs of the body. The most exposed organs in abdominal and retroperitoneal compartment are the kidneys and gastrointestinal tract. It is also shown that elevated IAP may be the reason for respiratory failure or shock. The pathophysiological reason for impaired organ function is above all the reduced blood flow. The difference between the mean arterial pressure (MAP) and IAP – perfusion pressure for abdominal organs – becomes therefore important. In this setting the MAP value, which usually would be considered as sufficient for adequate organ perfusion, may appear insufficient in the presence of IAH. This is one of the main reasons to consider the value of IAP while setting the goals for treatment of certain critically ill patient. The IAP and intra-thoracic pressure are known to influence each other (Valenza et al. 2007). Already in 19th century Marey of Paris wrote that the "effects that respiration produces on the thorax are the inverse of those present in the abdomen" (Emerson 1911). This leads to relative usefulness of filling pressures (central venous pressure – CVP; pulmonary artery occlusion pressure – PAOP) in management of patients with IAH. High CVP, which in usual circumstances can be considered as sign of hypervolaemia, may result from elevated IAP in an actually hypovolaemic patient. The interpretation of IAP together with other parameters is therefore crucial to make the correct decision to develop a treatment strategy in these patients.

2.2.4. Impact of IAH on outcome

Historically, the detrimental effects of intra-abdominal hypertension are described already in the middle of last century (Bradley et al. 1947). In modern era, Malbrain and co-authors have performed a series of pioneering works on the field. Thus, in a study of 265 consecutive critically ill patients of a mixed population they report that not the presence of IAH at the day one, but the development of IAH during the ICU period is an independent risk factor for death (Malbrain et al. 2005). Other authors have also shown that intra-abdominal pressure does not have prognostic value at admission, but may predict adverse outcome if it develops later during the ICU stay (Lonardo et al. 2007).

In smaller, selected groups, worse outcome of patients with IAH vs. no IAH is described (Busani et al. 2006, Rosas et al. 2007).

The development of ACS in patients with severe acute pancreatitis is associated with increased mortality (Leppäniemi et al 2007). Our own observa-

tions suggest that IAH has an adverse impact on ICU outcome, but this impact may be different between medical and surgical patients (Reintam et al. 2005).

2.2.5. Primary and secondary IAH

The World Society on Abdominal Compartment Syndrome has defined primary and secondary abdominal compartment syndrome (ACS) according to the origin of the syndrome (Malbrain et al. 2006). Data about clinical differences between primary and secondary ACS, however, are scarce.

It has been demonstrated that medical patients with secondary ACS may have longer times to decompression and worse outcome in comparison to surgical patients with secondary ACS (Cothren et al. 2007).

Kirkpatrick and co-authors concluded in their review about secondary and recurrent ACS that there have been remarkably little specific studies of these entities outside of specific groups such as those injured by thermal or traumatic injury. The epidemiology, risk factors for, treatment of and most importantly, strategies for prevention all remain scientifically unknown and therefore based on opinion (Kirkpatrick et al. 2007).

Discrepancies between primary and secondary IAH are studied even less. Different effects of primary and secondary IAH on mesenteric lymph flow are only described in an experimental study on dogs (Moore-Olufemi et al. 2005).

In summary, only limited data are available about the incidence of IAH in whole ICU population. The impact of IAH on outcome is not very widely investigated, and it is not known, whether there are any discrepancies between primary and secondary IAH. These issues are addressed in Papers II and III of the present dissertation.

2.3. Definition of gastrointestinal failure

2.3.1. Terminology

A huge variability in terminology describing the gastrointestinal dysfunction exists. Gastrointestinal complications (Montejo 1999; Mutlu et al. 2001), gastrointestinal haemorrhage (Goris et al. 1985; Mayr et al. 2002), non-haemorrhagic gastrointestinal complications (Dark et al. 1989), gastrointestinal disturbances (Deane et al. 2007), intestinal failure (Goulet et al. 2004), gut dysfunction (Batchelor 2002), upper digestive intolerance (Mentec et al. 2001), stress-related mucosal damage (Peura et al. 1986), impaired gastroduodenal motility (Dive et al. 1994), increased intestinal permeability (Harris et al. 1992) and inability to achieve an enteral feeding target (Deane et al. 2007) are just a

few examples in this long list. Clinicians of various specialities are familiar with terms like radiation enteropathy, microscopic colitis, inflammatory bowel disease, necrotizing enterocolitis and others.

There is no consensus to use the term "gastrointestinal failure" (GIF).

2.3.2. Definition

Goulet et al. nicely defined intestinal failure as the reduction of functional gut mass below the minimal amount necessary for digestion and absorption adequate to satisfy the nutrient and fluid requirements for maintenance in adults or growth in children. However, short bowel syndrome, congenital diseases of enterocyte development and severe motility disorders (total or subtotal aganglionosis or chronic intestinal pseudo-obstruction) were listed as causes of severe intestinal failure (Goulet et al. 2004). The gastrointestinal failure in critically ill patients is rather an acute syndrome occurring together with other organ failures, not any of those chronic conditions listed by Goulet. Gastrointestinal failure as a part of multiple organ failure in critically ill has not been clearly defined.

2.3.3. Diagnosis

During the conceptual development of multiple organ failure (MOF) syndrome, several different approaches to GIF were introduced. One of the first scoring systems – the multiple organ failure (MOF) score, developed by Goris et al., evaluated seven organ systems: pulmonary, renal, hepatic, haematological, cardiovascular, gastrointestinal and the central nervous system. In this system, two grades of severity were used: dysfunction and failure (Goris et al.1985). GIF was defined as cholecystitis, stress ulcer, GI haemorrhage, necrotic enterocolitis or pancreatitis and/or spontaneous perforation of gallbladder. However, a revision of the score 15 years later concluded that GI failure should not be considered for assessment of the MOF in the future due to problems in definition and reliability (Lefering et al.2002).

Recently, Mayr et al. introduced a modification of Goris' original MOF score, defining GI dysfunction as ileus > 7 days or GI bleeding requiring less than six blood products per 24 hours, and GI failure as GI bleeding requiring more than six blood products per 24 hours (Mayr at al. 2006). The authors reported low incidence of GIF and no contribution to mortality (Mayr at al. 2006).

Other authors have defined gastrointestinal failure as a presence of mesenteric ischemia, diverticulitis, pancreatitis, peptic ulcer disease or cholecystitis, and

described its impact on morbidity and mortality (D'Ancona et al. 2003; Mangi et al. 2005).

Neonatal intensivists are used to the diagnosis of necrotizing enterocolitis (NEC) to substantiate gastrointestinal problems of the patient. As defined quite uniformly, stage 1 NEC is characterized by mild intestinal signs (gastric residuals and/or mild abdominal distension radiologically seen by dilated bowel loops, intestinal dilatation); the diagnosis of stage 2 NEC is based on intestinal pneumatosis or portal venous air; while clinical symptoms of peritonitis with or without evidence of bowel perforation are mandatory for stage 3 NEC (Hall et al. 2004; Lin et al. 2006).

The diagnostic criteria to assess gastrointestinal problems in adult ICU-s are not set uniformly, and different units use different diagnostic approaches. GIF is not included in any of widely used multiple organ failure scores.

More than 10 years ago the summary of round table conference in gut dysfunction in critical illness concluded that intestinal function is an important determinant in the outcome of critically ill patients; there is no objective, clinically relevant definition of intestinal dysfunction in critical illness; and the definition developed in the future should grade the severity of the dysfunction (Rombeau et al. 1997). Today the conclusions drawn from the literature review are exactly the same.

It is clear, that diagnosis-based approach did not justify itself during the past decades. We have been waiting for methodology to emerge the GI function might be measured with (Rombeau et al. 1997). However, it seems to take longer as expected. Meanwhile the lack of systemized approach is restricting the studies assessing epidemiology, time course, risk factors, treatment etc. In lights of recent studies and our own observations, we hypothesized that concomitant occurrence of food intolerance and intra-abdominal hypertension could give a relevant, easily applicable and reproducible definition of GI failure for intensivists. This hypothesis is tested in Paper V of the present dissertation.

2.4. Prediction of outcome in ICU patients

Intensive care doctors face often the difficulties in prognostication the outcome of critically ill patients. The decisions whether to continue or stop the intensive therapy are necessary to make. It is clear that maximum therapy should be withheld only if it definitely does not improve the outcome. On the other hand, the resources should be kept in mind avoiding the treatment of patients with no perspective in account of the treatable patients on long waiting lists. Even though the final decision is never based only on the scoring systems, these tools are designed to assist doctors in difficult end-of-life decisions.

The other very important aspect of scoring systems is benchmarking, allowing the comparison between different units and hospitals, but also the

stratification of patients in clinical studies. The complexity of critical illness excludes the possibility to compare outcomes according to the diagnosis. Therefore the scoring systems are designed to assess the severity of illness by physiological signs appointing on failure of organ function. Two main kind of scoring systems are used to assess risks of death in the critically ill patients:

1. the scores based on admission parameters for the first maximum 24 hours after ICU admission (APACHE, SAPS, MPM)
2. daily assessed organ failure scores to monitor the dynamics of different organ failures (MOF, MODS, SOFA)

2.4.1. Acute Physiology and Chronic Health Evaluation (APACHE) score

Knaus et al. originally described the APACHE system designed for patients in the intensive care unit setting (Knaus et al. 1981). Initially, 34 physiological variables, which were thought to have an effect on outcome, were selected.

Modifications of APACHE score (APACHE II and APACHE III) are probably the most widely used scoring systems to predict hospital mortality. The original 34 variables were reduced to 12 more commonly measured variables for the APACHE II scoring system published in 1985 (Knaus et al. 1985). Up to four points are assigned to each physiological variable according to its most abnormal value during first 24 hours in intensive care. Points are also assigned for age, history of severe clinical conditions, and surgical status. The system is originally validated for hospital mortality (Knaus et al. 1985).

In 1991, APACHE III was developed by the same authors, mainly because of disparities observed in prediction of outcome of multiple trauma patients without significant head injury (Knaus et al. 1991). The regression formula of that model was published quite recently, and therefore the system is used less widely.

APACHE II is mostly used admission score in Estonian ICU-s.

2.4.2. Multiple Organ Failure (MOF) score

One of the first attempts to quantify multiple organ failure was made by Goris and colleagues in 1985 by proposal of MOF score (Goris et al. 1985). Original MOF score evaluated presence of dysfunction or failure in seven organ systems: pulmonary, renal, hepatic, haematological, cardiovascular, gastrointestinal and the central nervous system. Fifteen years later a revision of the score excluded GI failure from this system (Lefering et al.2002).

2.4.3. Multiple Organ Dysfunction score (MODS)

In 1995, Marshall and colleagues developed MODS system (Marshall et al. 1995), evaluating six organ systems (respiratory, cardiovascular, renal, hepatic, hematologic and central nervous) in scale from 0 to 4. The authors concluded that simple physiologic measures of dysfunction in six organ systems, mirror organ dysfunction as the intensivist sees it and correlates strongly with the ultimate risk of ICU mortality and hospital mortality (Marshall et al. 1995).

2.4.4. Sequential Organ Failure Assessment (SOFA) score

In 1996, a working group of European Society of Intensive Care Medicine published a consensus scoring system very similar to MODS – Sequential (Formerly Sepsis-related) Organ Failure Assessment (SOFA) Score (Vincent et al. 1996) There are several studies that have examined the utility and accuracy of the SOFA score (Ball et al. 2002). All have found that maximum SOFA score and increasing SOFA score are highly prognostic (Janssens et al. 2000; Junger et al. 2002).

Daily assessed organ failure scores are often used in prediction of outcome as mean or maximum values for total ICU stay, not only the first day value as in case of admission scores. Some authors use the different time points or change in score as predicting parameters (Janssens et al 2000; Junger et al. 2002; Peres Bota et al. 2002; Ho 2007). The organ systems can be assessed separately by using the sub-scores as predictors (Peres Bota et al. 2002).

In a study with 949 critically ill patients (with total mortality of 29%) SOFA and MODS scores at admission and at 48 hrs were similar predictors (Peres Bota et al. 2002). Using the scores' cardiovascular components (CV), outcome prediction was better for the SOFA score at all time intervals. There were no significant differences in outcome prediction for the other five organ systems. Authors concluded that both MODS and SOFA are reliable outcome predictors, even though cardiovascular dysfunction is better related to outcome with the SOFA (Peres Bota et al. 2002).

The combination of APACHE II and SOFA in prediction of hospital survival was recently studied in 1311 patients (Ho 2007). APACHE II, Admission SOFA, Delta SOFA and maximum SOFA score were all related to hospital survival in the univariate analyses.

Today the scoring systems enable comparative audit and evaluative research of intensive care, but many questions concerning the practical validity of the scores still need to be answered (Kramer 2005; Sinuff et al. 2006). Of note, none of the common scoring systems include the assessment of gastrointestinal function in the grading of severity of illness similarly to other organ functions. Therefore, we investigated if assessment of GI function adds predictive power to the SOFA score (Papers IV and V).

3. AIMS OF THE STUDY

The general aim of the present study was to create a systematic approach for gastrointestinal failure in critically ill patients.

We hypothesized that the gastrointestinal symptoms and IAH reflect relevant clinical problems accompanied with increased mortality and ICU stay. For diagnosis of gastrointestinal failure the evaluation of clinical symptoms is mandatory. Measurement of intra-abdominal pressure alone is not sufficient for the complex assessment of GI function, as it may leave some of high-risk patients out of attention. Assessment of the gastrointestinal failure by GIF score adds predictive power to SOFA score in estimations of ICU survival.

Specific aims were the following:

3.1. to demonstrate the importance of gastrointestinal problems in ICU. Therefore, the incidence as well as the impact on outcome of GI symptoms and IAH was investigated both retro – and prospectively (Paper I, II, III, and IV).

3.2. to analyze the different approaches to definition of gastrointestinal failure and to assessment of gastrointestinal function. For that purpose the review of scientific literature was performed (Paper VI).

3.3. to develop the scoring system for gastrointestinal failure, which has high prognostic value, is easy to use, and is well reproducible for everyday clinical use (Paper V).

4. MATERIALS AND METHODS

4.1. Patients

The basis for data collection is the electronic database for all patients treated in General ICU of Tartu University Clinics. The database is in use in prospective manner since 1st of January 2004. The data of patients from year 2002 were entered into a similar database retrospectively. The Ethics Committee of the University of Tartu has approved the studies, for the first study ethical approval was also obtained at the Charité – University Medicine Berlin. Patients' groups in different studies are partly overlapping. None of the studies include specific treatment interventions. In overall, data from 3900 intensive care patients are analyzed in present dissertation.

Chronologically, the patients for particular studies were selected as follows:

4.1.1. Gastrointestinal failure in intensive care units in Tartu and Berlin (Study I)

A retrospective analysis of the data of all adult patients admitted to three different ICUs (two 11-bed ICUs at the Charité – University Medicine Berlin, Germany and one 10-bed ICU at Tartu University Hospital, Estonia) during the year 2002 was performed.

4.1.2. Primary and secondary intra-abdominal hypertension (Study II)

All patients admitted to the General ICU of Tartu University Hospital from June 2004 to June 2006 were prospectively screened for the risk factors of IAH. Patients with presumable risk for development of IAH demonstrating two or more risk factors were included into the study group for repeated measurements of IAP. Mechanically ventilated patients who presented at least one of the following: admission due to multiple trauma, abdominal surgery, pancreatitis or post-CPR status and/or fluid resuscitation above 5 litres/24h, vasoactive or inotropic support or renal replacement therapy; were studied.

4.1.3. Intra-abdominal hypertension (Study III)

All consequent patients treated for at least 24 hours in General ICU of Tartu University Hospital between June 2004 and September 2007.

Measurement of intra-abdominal pressure is a routine procedure performed in all risk patients since June 2004 and in all mechanically ventilated patients since September 2006 in General ICU of Tartu University Hospital.

4.1.4. Gastrointestinal symptoms (Study IV)

All patients consequently hospitalized to General ICU of Tartu University Hospital between January 1st 2004 and December 31st 2007 were prospectively studied.

4.1.5. Gastrointestinal Failure score (Study V)

All mechanically ventilated patients consequently admitted to General ICU of Tartu University Hospital from September 2006 to September 2007 were screened for the prospective study. The patients treated for at least 24 hours were included into further analysis.

4.2. Data documentation

Since 1st of January 2004, for every admitted patient the following data were documented into electronic database:

Admission parameters
Age, gender, body mass index (BMI), readmission, diabetes, APACHE II score, surgical profile, resuscitation before ICU admission, laparatomy immediately before ICU admission or during the first 24 hrs.

Daily parameters
SOFA score, mean arterial pressure (MAP), central venous pressure (CVP), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), lactate, glucose, urea, C-reactive protein, fluid gain, use of mechanical ventilation, vasopressor/inotrope and sedation.

Gastrointestinal symptoms – occurrence of vomiting, absence of peristaltics/ abnormal peristaltics, diarrhea, GI hemorrhage, suspected/confirmed bowel distention and nasogastric aspirate volume – were also documented on daily basis, together with amount and route of enteral feeding.

Definitions

A patient was considered of surgical profile if he/she was being operated on at least once during current hospitalization and of medical profile if he was not operated on (except with a tracheostomy).

Vomiting was defined as any regurgitation despite the amount.

Absence of peristaltics/abnormal peristaltics was documented according to the doctors' subjective decision made by auscultation, when bowel sounds were not heard, were extremely infrequent or weak or "high".

Bowel dilatation was documented when confirmed by radiologists subjective decision or highly suspected in clinical evaluation.

Diarrhoea was documented when not formed stools occurred at least three times per day.

GI bleeding was defined as a macroscopically estimated presence of blood in vomited fluids, nasogastric aspirate or stool.

Nasogastric volume equal or higher than 500 ml/day was considered as high.

4.3. Measurement of intra-abdominal pressure

Intra-abdominal pressure was measured in selected patients (presumable risk population) from June 2004 to August 2006 (Study II and III), and in all mechanically ventilated patients treated in ICU for 24 hours or longer from September 2006 to August 2007 (Study III and V).

IAP was measured intermittently at least every 6 hours in patients with an IAP $\geq$12mmHg or at least every 12 hours in patients with an IAP <12mmHg. IAP was measured in supine position, via bladder, using the revised closed system repeated measurement technique.

Instillation volume was 50 mL (Malbrain 2004) from June 2004 and 25 mL (Malbrain et al. 2006) from September 2006.

IAH was defined as sustained or repeated IAP≥12 mmHg (Malbrain et al. 2006).

Primary IAH was defined as IAH associated with injury or disease in the abdomino-pelvic region, while secondary IAH accounted for development of IAH without primary disease in the abdomino-pelvic region (Malbrain et al. 2006).

Abdominal compartment syndrome was defined as a sustained IAP > 20 mmHg with an onset of a new organ failure.

4.4. Outcome parameters

ICU mortality, duration of ICU stay and mechanical ventilation were used as outcome parameters in all studies. Additionally, 28- and 90-day mortality were used in Studies II and V. Follow-up for 90-day survival was performed with assistance of Tartu University Hospital statistics department, using the hospital archive and National Death Register.

4.5. Specific methods in particular studies

The following analyses were made in particular studies:

4.5.1. Gastrointestinal failure in intensive care units in Tartu and Berlin (Study I)

Data recorded in a computerized database were used for the study in Berlin. In Tartu, the data documented in the patients´ charts was retrospectively transferred into a similar database. 47 variables from first ICU day were documented. In this study GIF was defined as the presence of at least one of the following gastrointestinal problems documented in patient data during their ICU stay: food intolerance, gastrointestinal haemorrhage, and ileus.

Food intolerance was defined as the inability to feed the patient via naso-gastric tube due to vomiting or nasogastric aspirate volumes larger than those previously given enterally. Ileus was defined as intestinal obstruction due to inhibition of bowel motility.

Correlations between occurrence of GIF and ICU outcome were studied.

4.5.2. Primary and secondary intra-abdominal hypertension (Study II)

We studied patients treated in ICU for 24 hours or longer.

The mean and maximum values of IAP were recorded daily. Mean ΔIAP was calculated as mean of differences between IAP on 1st (admission day) and 3rd day in ICU.

Comparisons of the groups were performed as follows:

1. no IAH vs. IAH
2. primary IAH vs. secondary IAH
3. survivors vs. non-survivors

Correlations between IAH and outcome were studied.

4.5.3. Intra-abdominal hypertension (Study III)

We studied patients treated in ICU for 24 hours or longer.

Correlations between intra-abdominal pressure and ICU outcome were studied.

4.5.4. Gastrointestinal symptoms (Study IV)

Correlations between occurrence of different GI symptoms and ICU outcome were studied.

4.5.5. Gastrointestinal Failure score (Study V)

We studied patients treated in ICU for 24 hours or longer.

GI function of the patients was daily assessed according to Gastrointestinal Failure Score, described in Table 2.

Table 2. Gastrointestinal Failure Score.

points	clinical symptomatology
0	normal GI function
1	enteral feeding < 50% of calculated needs or no feeding three days after abdominal surgery
2	food intolerance (enteral feeding not applicable due to high gastric aspirate volume, vomiting, bowel distension or severe diarrhea etc.) or IAH
3	food intolerance and IAH
4	abdominal compartment syndrome

Food intolerance (FI) was defined as inability to feed the patient enterally because of any reason, except if the patient was electively not fed first three days after laparatomy.

GIF was considered to be present when IAH and FI occurred simultaneously.

SOFA + GIF was calculated daily by summarizing the SOFA score and the GIF score of the respective day in each patient.

Correlations between GIF score and outcome were studied.

4.6. Statistical methods

Statistical Package for the Social Sciences (Versions 11.5 and 15.0 SPSS Inc., Chicago, Ill, USA) software was used for statistical analysis.

Independent samples t-test or Mann-Whitney U-test for continuous variables, and Chi square test for categorical variables were used for comparisons of two groups.

Analysis of variance (ANOVA) was used for comparison of more than two groups.

Mean scores during first three days were calculated as mean of individual values for three days of every patient.

Univariate analyses of admission parameters were applied to identify the risk factors for ICU mortality. Parameters with $p<0.2$ ($p<0.01$ in Study I) were thereafter entered into the multiple logistic regression model to identify the independent risk factors.

The variables reflecting the total ICU period were used for multiple regression analysis together with admission parameters in Studies I, II and III, and separately in Study V.

In Study V the means of the variables for first three days were added to admission parameters for multiple regression analysis. The first day values of the parameters, included in the scores, were removed from this analysis to exclude the coupling.

In Study V Receiver Operating Characteristic (ROC) curves were used to determine the likelihood ratio of GIF score, SOFA score and SOFA+GIF to predict the ICU mortality.

Kaplan-Meier curves and log-rank tests were used for comparisons of survival of patients:
with vs. without IAH (Study II)
with primary vs. secondary IAH (Study II)
with vs. without Gastrointestinal Failure (Study V)

5. RESULTS

5.1. Gastrointestinal failure in intensive care units in Tartu and Berlin (Study I)

In this retrospective study GIF was detected in 252 patients (9.7%) during their ICU stay. The incidence of GIF among patients with surgical and medical emergencies was significantly higher compared to elective cardiosurgical patients (18.2 % and 19.1 % vs. 5.7% respectively, p<0.001).

On admission only 20% of all GIF cases were seen. 82% of GIF cases were clinically manifested by the end of the first week in ICU.

In logistic regression analysis we identified the independent predictors for development of GIF resulting with the model including: APACHE II (OR 1.05; 95%CI 1.02–1.09); SOFA (OR 1.11; 95%CI 1.02–1.20); patients' emergency profile (OR 3.09; 95%CI 2.11–4.52); use of catecholamines (OR 4.16; 95% CI 2.82–6.15).

Development of GIF during the ICU stay (or its presence on admission) increased the risk of death markedly in the overall study population, but in particular the elective cardiosurgical patients had tremendously greater likelihood to die if they developed GIF during the ICU stay.

In multiple logistic regression analysis APACHE II and SOFA scores at admission and development of GIF during ICU stay were identified as independent risk factors for death.

Table 3. Logistic regression models for prediction of death in whole study population and in different groups according to patients' profile.

	Total	Elective surgical	Emergency surgical	Medical
Predictors	p-value OR (95% CI)	p-value OR (95% CI)	p-value OR (95% CI)	p-value OR (95% CI)
APACHE II	0.020 1.03 (1.01–1.06)	0.031 1.06 (1.01–1.13)	0.730 1.01 (0.97–1.04)	0.259 1.03 (0.98–1.09)
SOFA	<0.001 1.35 (1.27–1.44)	0.013 1.20 (1.04–1.39)	<0.001 1.30 (1.20–1.41)	<0.001 1.36 (1.19–1.55)
GIF	<0.001 7.44 (5.21–10.62)	<0.001 15.42 (7.67–31.04)	<0.001 3.31 (1.97–5.55)	<0.001 7.43 (3.00–18.36)

5.2. Primary and secondary intra-abdominal hypertension (Study II)

In this study, presumable risk population was included for IAP measurement. IAH developed in 95 patients (37.0%), among them primary IAH was observed in 60 and secondary IAH in 35 patients (23.3 and 13.6% of study population, respectively).

ACS developed in 12 patients (4.7% of study population), among them nine were primary and three secondary ACS.

Sixty patients (63.2% of total IAH patients) demonstrated IAH on admission, 39 primary and 21 secondary. ACS was present at the first day in eight cases, one patient developed ACS on the second, two patients on the third and one patient on the seventh day. Even though IAP on admission did not differ significantly between primary and secondary IAH, the time course of IAP was different. The dynamics of IAP in survivors and non-survivors during the first week of treatment did not exactly parallel the changes in mean SOFA score.

The patients with IAH demonstrated a significantly higher ICU- (37.9 vs. 19.1%; p=0.001), 28-day (48.4 vs. 27.8 %, p=0.001), and 90-day mortality (53.7 vs. 35.8%, p=0.004) compared to the patients without the syndrome (Figure 2). The 90-days cumulative survival also differed significantly between primary and secondary IAH (Figure 3).

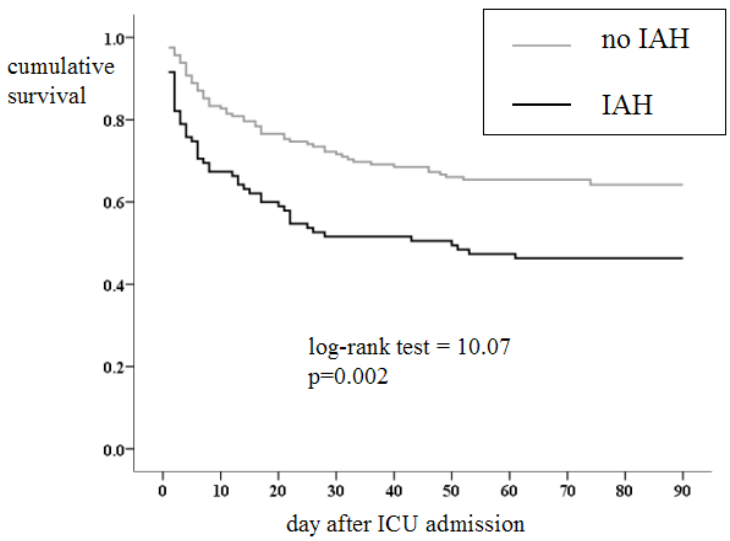

Figure 2. 90-day survival in IAH vs. no-IAH patients

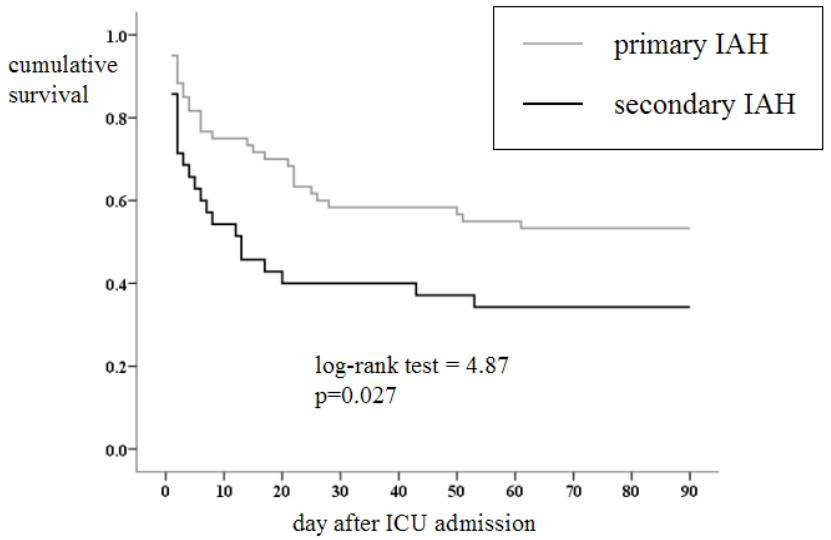

Figure 3. 90-day survival in primary vs. secondary IAH

In stepwise multiple logistic regression analysis APACHE II was identified as the most powerful predictor of ICU mortality of all admission characteristics (Table 4). Lactate level on admission and the development of IAH (independently if primary or secondary) during the patients' ICU stay were also identified as independent risk factors for mortality.

Table 4. Results of regression analysis for prediction of ICU survival with admission parameters with p<0.2 in univariate analysis, and development of IAH.

	p-value	Odds Ratio	95.0% C.I. for OR	
			lower	upper
IAH	0.033	2.50	1.08	5.78
vasopressor/inotrope	0.262	1.96	0.61	6.32
sedation	0.839	1.38	0.06	29.46
APACHE II	<0.001	1.11	1.05	1.17
lactate	0.034	1.10	1.01	1.19
SOFA	0.376	1.07	0.92	1.25
PEEP	0.316	1.05	0.96	1.15
fluid gain	0.449	1.00	1.00	1.00
surgical profile	0.579	0.76	0.29	1.99

5.3. Intra-abdominal hypertension (Study III)

The first study period (period I) describes in Estonian language the observations from the Study II – data from IAP measurements only in population at presumable risk.

In second study period (period II), IAP was measured in all consequent patients, who were mechanically ventilated and were treated for at least 24 hours in ICU.

In this study period, 72 patients developed IAH (27.3%) and 5 had ACS (1.9%).

The ICU and mechanical ventilation periods were not different between IAH and no-IAH patients in first study period. IAH patients of the second study period, in contrast, had significantly longer ICU and mechanical ventilation periods compared to no-IAH patients, (17.5 (19.0) vs. 5,6 (7.3) days, $p<0.001$ and 15.5 (18.0) vs. 4.3 (6.1) days, $p<0.001$; respectively).

The ICU mortality of IAH patients was 25.0% compared to 10.9% in no-IAH patients ($p=0.005$) in second study period. Nine of twelve ACS patients died (75%) in first and four of five in second study period (80%).

In regression analysis the independent predictors of mortality in the first study period were APACHE II (OR 1.13; 95% CI 1.09–1.18) and serum lactate on admission (OR 1.08; 95% CI 1.01–1.16) and development of IAH during patients' ICU stay (OR 2.52; 95% CI 1.23–5.14).

In the second study period APACHE II (OR 1.09; 95% CI 1.01–1.19) and SOFA score (OR 1.27; 95% CI 1.08–1.48) at admission were identified as independent predictors of ICU mortality. Development of IAH during ICU stay was not an independent predictor any more, but mean IAP in the first three days in ICU was (OR 2,57; 95% CI 1,05–6,3).

The IAH patients were older and had higher severity scores at admission compared to no-IAH patients.

5.4. Gastrointestinal symptoms (Study IV)

All together 1374 patients were hospitalized during study period, 62 of them were excluded due to missing data.

The total prevalence of GI symptoms per patient is presented on Figure 4. The prevalence of GI symptoms of total study population and in comparison of survivors and non-survivors are presented in Table 5.

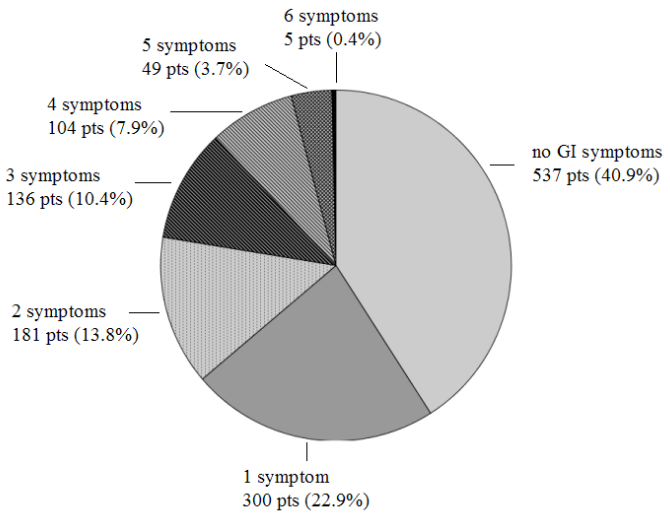

Figure 4. Prevalence of GI symptoms by occurrence per patient whenever during the patients' ICU stay.

Table 5. Prevalence of GI symptoms in total and in comparison in survivors and non-survivors

	total	survivors	nonsurvivors	p-value
absence of bowel sounds	542 (41.3)	300 (30.3)	241 (75.3)	<0.001
vomiting	501 (38.2)	370 (37.3)	131 (40.9)	0.139
ng aspirate >500 ml /day	298 (22.7)	210 (21.2)	88 (27.5)	0.013
diarrhoea	184 (14.0)	135 (13.6)	49 (15.3)	0.251
bowel distension	139 (10.6)	77 (7.8)	62 (19.4)	<0.001
GI bleeding	97 (7.4)	53 (5.3)	44 (13.8)	<0.001

ICU mortality of the patients who had normal bowel sounds at admission was 16.5%, compared to 29.1% in patients with abnormal bowel sounds on admission day and 39.0% in patients in whom bowel sounds were not heard.

The regression model with three most important GI symptoms and mean SOFA score during the whole ICU stay is presented in Table 6. The mean SOFA score alone was able to predict the outcome in 87.5%; by adding GI symptoms the rate of correct prediction was 88.2%.

Table 6. Mean SOFA during the ICU stay and GI symptoms in prediction of mortality

	p-value	OR	95% CI
mean SOFA	<0.001	1.49	1.41–1.56
absence of bowel sounds	<0.001	3.16	2.08–4.80
GI bleeding	0.016	1.94	1.13–3.32
bowel distention	0.097	1.54	0.93–2.56

5.5. Gastrointestinal Failure score (Study V)

373 patients were treated in the General ICU of Tartu University Hospital during the study period. 264 patients were on mechanical ventilation at admission and stayed in ICU for at least 24 hours, and were thereby included into further analysis.

Food intolerance was observed in 154 patients (58.3%), and it developed dominantly during first three days of admission (144/154; 93.5%).

72 patients (27.3%) developed IAH, 5 of them (6.9% of IAH patients) suffered from abdominal compartment syndrome. 87.5% of IAH patients (63/72) developed the syndrome during their first three days in ICU.

GIF (FI+IAH) developed in 60 patients (22.7%), in 36 of them GIF was documented already on the first day.

The GIF score was documented overall in 2348 patient days. GIF score 0 was observed in 52.0%, 1 in 12.2%, 2 in 27.8%, 3 in 7.7%, and 4 in 0.3% of days.

The length of ICU stay and mechanical ventilation, ICU and 90-day mortality were significantly different between IAH and no-IAH patients, as well as FI and no-FI patients.

High values of the mean GIF score during the first three days of ICU stay were related to high mortality (Figure 5).

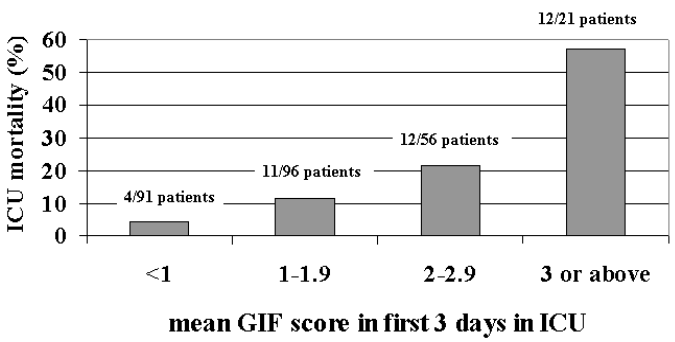

Figure 5. ICU mortality of patients according to their mean GIF score.

The patients with gastrointestinal failure (simultaneous occurrence of IAH and FI) suffered from an ICU mortality of 28.1% compared to 10.8% in patients without this syndrome (p=0.001).

The 90-day cumulative survival of patients with GIF was significantly impaired in comparison to patients without GIF (Figure 6).

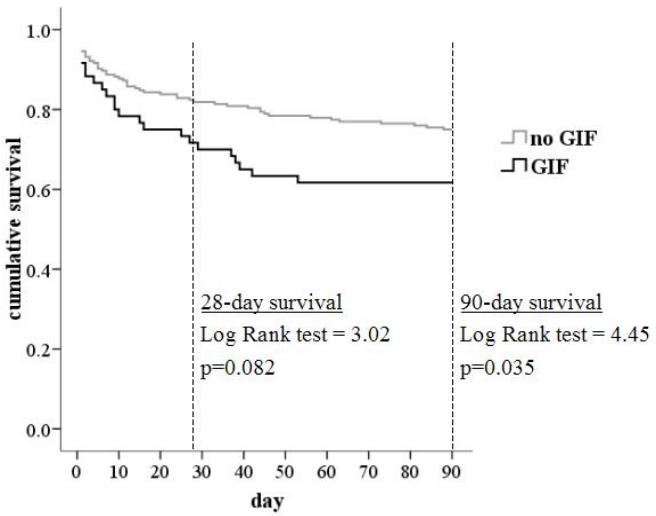

Figure 6. Cumulative survival of patients without GIF (maximum GIF score during ICU stay 2 or less) vs. patients with GIF (maximum GIF score during ICU stay 3 or 4).

In multiple regression analysis only two admission parameters (SOFA and fluid balance during first 24 hours) were identified as independent predictors of ICU mortality of study population.

The mean SOFA score of first three days showed expectedly better prediction than its value at the first day (OR 1.82; 95% CI 1.26–2.63; p=0.002 vs. OR 1.36; 95% CI 1.02–1.82; p=0.037).

The mean GIF score of the first three days was identified as an independent risk factor for ICU mortality (OR 7.09; 95% CI 1.60–31.48; p=0.010).

The mean SOFA+GIF score of the first three days demonstrated slightly better prediction of ICU mortality than the SOFA score alone (OR 2.16; 95% CI 1.39–3.37; p=0.001).

The combination of mean SOFA and GIF score during the first 3 days demonstrated the highest AUROC (0.895) in comparison to mean SOFA (0.840) and mean GIF (0.753) alone.

While combining the mean SOFA sub-scores with mean GIF score of the first three days in the regression analysis for the prediction of ICU mortality

(see also Table 7), the GIF score had the second highest OR (OR 2.20; 96% CI 1.28–3.78; p=0.004) after the cardiovascular SOFA sub-score (OR 5.91; CI 2.83–12.33; p< 0.001).

Table 7. SOFA sub-scores and GIF score in regression analysis for prediction of ICU mortality

	p-value	OR	95% CI
cardiovascular SOFA	<0.001	5.91	2.83–12.33
GIF score	0.004	2.20	1.28–3.78
hepatic SOFA	0.024	1.75	1.075–2.86
renal SOFA	0.087	1.39	0.95–2.04
central nervous system SOFA	0.159	1.23	0.92–1.65
hematological SOFA	0.712	0.92	0.57–1.47
respiratory SOFA	0.518	0.84	0.48–1.44

6. DISCUSSION

This work was undertaken to demonstrate the importance of GIF and to systemize the data in regards of terminology and evaluation of the GI function in critically ill patients.

6.1. Importance of gastrointestinal problems

6.1.1. Gastrointestinal symptoms

In our first, retrospective study, gastrointestinal symptoms were observed less frequently in patients following elective cardiac surgery. Indeed, patients admitted for surgical or medical emergencies developed gastrointestinal problems much more frequently and often presented with these symptoms on admission. However, regardless of ICU location or patient profile, the analysis consistently revealed that development of GIF, defined as presence of at least one GI symptom, during patients' ICU treatment resulted in a significant increase in the duration of mechanical ventilation, length of stay and, most importantly, of ICU mortality. The overall mortality (GIF and non-GIF) in elective cardiosurgical patients summed up to 2.5%, while in patients without GIF it was very low – only 1.1%. Accordingly, the influence of GIF development on mortality was tremendous: the risk of death showed a twenty-three-fold increase. The importance of gastrointestinal function in cardiosurgical patients has been addressed in other recent studies. Hessel demonstrated, that gastrointestinal complications occur in about 2.5% of patients undergoing cardiac surgery (Hessel 2004). Higher mortality associated with gastrointestinal complications is reported in few studies (Hessel 2004, Ishikawa et al. 2004).

In our Study I, the risk of death was significantly increased also among emergency surgical and medical patients with GIF.

In Study IV we demonstrate the high prevalence of different GI symptoms in a mixed ICU population with an important impact on outcome. Our data are in accordance with few earlier reports demonstrating that GI symptoms occur often, some of them in up to 50% of mechanically ventilated patients (Montejo 1999; Mutlu et al. 2001).

The obvious problems of research in this area are the absence of uniform definitions and high degree of subjectivity in assessment of symptoms.The last is the most likely the reason why only few studies assessed the presence of bowel sounds by auscultation as an important finding in intensive care patient. In emergency medicine, in contrast, the absent or abnormal bowel sounds is considered as an important symptom to suspect the acute abdominal pathology. Our results confirm the finding of few studies performed in intensive care suggesting

that bowel sounds may be decreased or absent in half of all mechanically ventilated patients (Dark et al. 1989; Mutlu et al. 2001). Even more, somewhat unexpectedly we found absence of bowel sound, if occurred at least in one day during the patient stay, to be a very good predictor of mortality. Nevertheless, considering the reproducibility of auscultation of the bowel sounds, this symptom alone can hardly be suggested as a marker of GI failure in critically ill.

Measurement of GRV is probably most common assessment of GI function, even if not proven to be an accurate measure (Deane et al. 2007). The lack of consensus on an acceptable value for GRV during enteral feeding is a problem and our approach to GAV is again different, while daily amount is considered instead of single measurements, making the comparisons with previous results rather difficult.

Vomiting is commonly defined as an objective event that results in the forceful evacuation of gastric contents from the stomach, up and out of the mouth (Steele et al. 2007). Even though, vomiting is probably frequent in critically ill patient, it may not always be a very obvious event in sedated and ventilated patients, being difficult to differentiate from regurgitation, which probably occurs in the majority of mechanically ventilated patients (Nind et al. 2005). In our study, vomiting occurred more often as described in previous studies (Montejo 1999; Elpern 2004; O'Leary-Kelley 2005), explained by the fact that also the cases of regurgitation were counted in. Among the patients in whom vomiting occurred, 24.8% died, among patients who did not have vomiting during their ICU stay 24.0% died. Interestingly, in regression analysis with only GI symptoms, occurrence of vomiting reduced the risk of death. However, vomiting appears to be not a good symptom to assess GI function due to its' dependency of several factors as nasogastric aspiration, enteral feeding, patients position etc.

The incidence of GI bleeding is higher in our study compared to most of recent data in literature, explained by the fact that also minor bleeding was documented. The data regarding the impact of GI bleeding on outcome are controversial, probably partly due to different definitions. Our results support the idea that even less severe bleeding may be important predictor of outcome of critically ill patients.

The development of diarrhoea in our patients is comparable to the previous studies, where it has been reported to occur in 15 to 50% of patients (Dark et al. 1989; Montejo 1999; Mutlu et al. 2001).

Bowel distension was in our study observed in 10.6% of patients, and it occurred more often in non-survivors, the results are in accordance to the previous studies (Dark et al. 1989; Montejo 1999; O'Leary-Kelley 2005). Even though, the diagnosis of bowel distension remains questionable due to lacking criteria.

In summary, our results from both retro- and prospective studies substantiate the importance of GI complications in ICU patients. The main limiting factor for the research in this area is clearly the lack of consensus definitions. There is an emerging need for easy and reproducible scoring system for GI tract assessment.

6.1.2. Intra-abdominal hypertension

Raising popularity of IAP monitoring in ICU-s gives us at least one real number to assess the intra-abdominal compartment.

In Studies II and III we confirm the data of literature in terms of IAH being a frequent pathology in intensive care patients with adverse impact on outcome.

According to the results of Study III we may speculate that the presumable risk population was not identifying all the patients with IAH. The IAH occurred in approximately 1/8 of all the patients treated during the first study period, when IAP was measured only in presumable risk patients. During the second study period the IAP was measured in all mechanically ventilated patients and IAH was observed approximately in 1/5 of all the patients. The risk patients in first study period were selected according to the expert opinion in literature (Ertel et al. 2000; Hunter et al. 2004; Moore et al. 2004). Recent consensus definitions list in general similar risk factors (Malbrain et al. 2006). Somewhat surprisingly there is no larger study to identify the risk factors for IAH. According to our results, measuring the IAP only in suggested risk patients we may miss a remarkable part of the IAH patients.

In Study III the measurement methodology is different between first and second study period in regards of instillation volume. Even though, according to the literature the larger instillation volume should result in more IAH diagnoses, which was not the case in our study.

Previous studies have shown that development of IAH during patients ICU stay is an independent risk factor for mortality (Malbrain et al. 2005; Reintam et al. 2007). Our observations in Study II and first period of Study III with the same patient population confirm this result. During the second study period in Study III not the development of IAH during the ICU period, but the mean IAP in the first three days in ICU was an independent risk factor for mortality. This result is probably even more important, giving a reason to assume that the less elevated values of IAP may play an important role.

The combination of parameters reflecting the longer period (the first three days, the first week, the whole ICU stay) with the admission parameters is somewhat artificial. However, it is quite expectable that the single value of IAP on admission is not very informative and only the further dynamics may determine the outcome and reflect the treatment effects.

In Study II we observed significant differences between the incidence, time course and mortality of primary and secondary IAH. The mortality among the patients with secondary IAH was higher than among the patients with primary IAH. Primary IAH occurred mostly in surgical patients, while secondary IAH developed in patients with different profiles. Patients with secondary IAH were more severely ill (higher APACHE II and SOFA score on admission), and therefore expectedly, had a higher mortality. Interestingly, IAP on admission was similar in patients with primary and secondary IAH, even though primary IAH might be expected to

develop earlier compared to secondary IAH. During the further treatment course, however, different dynamics were observed – IAP started to decline from the second day in ICU in patients with primary IAH, while it remained elevated for the next five days in secondary IAH. Malbrain et al. have observed significantly elevated IAP during the first week of treatment among non-survivors (Malbrain et al. 2005). Accordingly, in our study, the persistence of higher IAP in the patients with secondary IAH was associated with worse outcome.

The explanations why the prognosis is poor in case of secondary IAH could be only speculative. The dynamics of SOFA score and higher APACHE II on admission suggest that these patients had prolonged and more severely impaired systemic circulation. This triggers a vicious cycle of splanchnic hypoperfusion, bowel oedema, fluid sequestration, need for continuing positive fluid balance, and may result in elevated IAP. The more aggressive fluid resuscitation in trauma patients is associated with significantly higher incidence of IAH and ACS (Balogh et al. 2003; Balogh et al. 2007). Similar to earlier reports we observed excessive fluid gain in patients with IAH. However, differences between primary and secondary origin of the syndrome appeared to be not significant, even though the patients with secondary IAH had a tendency for higher cumulative fluid balance. Thus, according to these results worse outcome of secondary IAH may not exclusively be explained by more aggressive fluid loading. Another explanation for the worse outcome of secondary IAH might be a different time course with prolonged more severe elevation of IAP in these secondary IAH patients. In our opinion, the main factor determining different outcome, is the fact that patients with primary IAH were almost exclusively of surgical profile, and they were operated due to abdominal pathology. We can assume that in most cases the surgery appeared effective in prevention of further progression of the underlying disease and subsequent development of multiple organ failure. In contrast, the underlying pathophysiology responsible for the development of secondary IAH can seldom be resolved as effectively. Some reluctance for surgical decompression even in confirmed ACS patients without primary disease in abdominal cavity is probably still common. According to our results, we cannot distinguish whether the origin of the syndrome, primary or secondary IAH, is the most important factor influencing the outcome. We only may speculate that if the IAH cannot be controlled effectively within the first three days of treatment, a poor outcome is expected.

According to available data at the beginning of the study II and III, 50 mL instillation volume was used for transvesical measurements of IAP (Malbrain 2004; Malbrain et al. 2005). The latest Consensus Definitions of WSACS suggests 25 mL instillation volume for IAP measurement (Malbrain et al. 2006; Cheatham et al. 2007) since higher volumes (50–100 ml) have been demonstrated to falsely elevate IAP (De Waele et al. 2007). Our results from the second period of Study III do not let us suspect that the number of IAH patients in this study might be higher due to the measurement methodology.

IAP on intensive care admission had no prognostic value in our studies. The further course of IAH, however, had a significant impact on mortality in our studies, similar to the findings reported by previous investigators (Malbrain et al. 2005; Busani et al. 2006).

IAH may be just one of the symptoms reflecting the severity of critical illness, lacking a specific value in clinical practice. However, the fact that the development of IAH or the mean IAP in the first three days was identified as an independent risk factor for mortality in multivariate analysis together with important admission parameters is the strongest argument against this theory. The discrepancy between the dynamics of daily SOFA score and IAP in Study II, especially among the patients with secondary IAH, further suggests that the presence of IAH is not an epiphenomenon but rather a sign of separate "organ dysfunction", requiring specific attention.

Based on obtained results, we suggest that monitoring of IAP should be a part of a routine monitoring in critically ill patients.

6.2. Definition of gastrointestinal failure

The review of the literature was performed to present the available data on definitions of GIF in a systematic way (Paper VI).

The review of the literature revealed that there is no consensus on definition of GIF. While the terms "acute respiratory failure" and "acute renal failure" have reached their deserved position, GIF is not a routine term in ICU-s. In a few of the attempts to include the gastrointestinal failure to the scoring systems for MOF, it was defined as a diagnosis of GI haemorrhage, acalculous cholecystitis or ileus - evaluation criteria which are significantly different from those used for other organ systems. This diagnosis-based approach is one of the likely reasons for the lack of assessment of gastrointestinal failure. For example, defining acute respiratory failure as pneumonia, pleuritis or dyspnoe, instead of using oxygenation parameters, could confound the results in incidence and also in prediction of mortality of critically ill patients. In scoring of other organ systems, evaluation is made with the help of either variables for function or treatment used to compensate the dysfunction.

The difficulties in evaluating the function of the GI system and the lack of treatment possibilities are probably the reasons why none of the widely used scoring systems of organ dysfunction and severity of illness takes the function of the gastrointestinal tract into account.

Unfortunately, varying definitions and the lack of an objective evaluation system also hinder the development of treatment strategies. In parallel to rapid progress in treating shock, respiratory and renal failure, no novel strategy for treatment of gastrointestinal problems has been introduced in recent time. It

must be acknowledged that no therapeutic strategy arising from gut hypothesis has yet demonstrated a beneficial effect on general ICU mortality.

The definition of GIF by presence or absence of one GI symptom as in our Study I is probably not ideal. It is obvious that organ failure is not an all-or-nothing phenomenon, but a progression of alterations from normal organ function to organ failure (Ferreira et al. 2001).

Despite of different approaches, the data suggest the impact of GIF on ICU mortality (Chang et al. 1987; Kolkman et al. 2000; Mentec et al. 2001; Malbrain et al. 2005; Reintam et al. 2005).

The use of term "gastrointestinal failure" seems to be reasonable to describe the part of this organ system in MOF approach in critically ill patients to fit together with the terms used for other organ failures.

6.3. Scoring system for gastrointestinal failure

We have shown that IAH and gastrointestinal symptoms both have impact on patients' outcome. In a previous preliminary analysis we observed that occurrence of IAH together with gastrointestinal symptoms is a risk factor for death (Reintam et al. 2005).

The GIF score introduced in this study – a combined assessment of food tolerance and intra-abdominal pressure – was developed based on previous studies to allow dynamic assessment of GI tract at bedside. The mean GIF score of the first three days was identified as an independent risk factor for ICU mortality. Further, the score may add predictive power to the SOFA score in outcome prediction.

Gastrointestinal function has been demonstrated to influence the ICU outcome in previous studies. However, the absence of a scaled assessment system of GI function has been a major limiting factor in these studies.

About half of the patients of present study developed food intolerance during the first three days in ICU. These patients were significantly older and more severely ill (higher APACHE and SOFA scores). They stayed longer in ICU and suffered from a higher mortality than patients with a normal GI function. The prevalence of food intolerance has been described in a similar range in literature and has been shown to influence the outcome (Mutlu et al. 2001; Mentec et al. 2001; Montejo et al. 2002; Nguyen et al. 2007). At first glance, it seems reasonable to use more specific GI symptoms, such as bleeding, high gastric residual etc., for assessment of GI function. However different problems limit their use in this setting: GI bleeding occurs rarely (Mayr et al. 2006), the absence of bowel sounds is not reproducible, the incidence of vomiting is influenced by nasogastric aspiration, a high gastric residual volume is not defined uniformly and has only a week correlation with gastric emptying (Deane et al. 2007). Even though food intolerance is a rather subjective

variable, it is, in our opinion, the most universally used clinical characteristic of GI failure, covering probably the entire spectrum of different GI symptoms.

Intra-abdominal hypertension did not occur in our patients as frequently as food intolerance – it developed only in one third of them. These data are in accordance with earlier observations from Malbrain and colleagues (Malbrain et al. 2004). Different studies appoint the adverse impact of IAH on ICU outcome (Malbrain et al. 2005; Djavani et al. 2006; Rosas et al. 2007). However, prediction of outcome by events occurring during the whole ICU period is of somewhat limited value. Therefore we assessed only the means of the first three days. Accordingly, the GIF score, but not IAH appeared to be an independent predictor of outcome.

Very little is known about the combination of FI and IAH. Our data clearly demonstrate that the patients suffering from these two symptoms are not fully overlapping – not all the patients with GI problems have IAH and vice versa. 76 % of the patients with IAH on admission experienced also food intolerance, while only 25 % the patients with food intolerance had IAH. Some of the future IAH patients demonstrated FI on admission, while IAH itself was not yet present, and only few future FI patients showed IAH, but not yet FI on their admission day. This, in our opinion, further supports the necessity to combine these two variables into GIF score. The definite strength of IAP measurement in this setting is the objective and reproducible measurable numeric value.

It is hard to estimate in which extent the route of enteral feeding influences the GIF score However, the advantage of post-pyloric versus gastric feeding in regard to outcome has not yet been proven (Ukleja et al. 2007) and thus the current evidence does not support routine use of post-pyloric feeding in critically ill (Drover 2007). The post-pyloric route is probably not the first common choice during the first few days of intensive care, even though Montejo et al. report significantly lower incidence of GI complications in patients with early jejunal nutrition (Montejo et al. 2002). It might be speculative that enteral feeding itself produces an increase in IAP in critically ill patients. However, we did not observe such association in a preliminary study (Tamme et al. 2007). On the other hand, there is evidence, that early enteral pharmaconutrition in septic patients results in faster recovery of organ function (Beale et al. 2008).

The main limitation of Study V is that only the patients with prolonged ICU stay > 24 hours were studied. The patients treated in ICU for less than 24 hours are probably the mixture of the least and most severe patients. This preselection may bias the results, for example as explanation of the low predictive power of the APACHE II score. We considered that in most short-staying patients the IAH and FI are not usually the key issues of the treatment. IAH is seldom measured in patients dying within few hours after ICU admission. Accepting this delay in IAH monitoring it is important to underline that in a few ACS patients prompt IAH measurement might be crucial for correct decision-making process and patients survival.

The observed high predictive value of the mean SOFA score on ICU outcome is in accordance with several previous studies. The predictive power of the mean SOFA score of the first three days is correctly placed between the mean SOFA of the whole ICU period (OR 3.06) and the SOFA at 48 hours (OR 1.45) (Ferreira et al. 2001). Similar predictive value of SOFA sub-scores was observed in cardiac surgical patients (Ceriani et al. 2003). The cardiovascular SOFA appeared to be the most powerful while the respiratory and hematological SOFA the least powerful (Ceriani et al. 2003) also in our study. The excellent performance of GIF score in this setting once more confirms the importance of GI failure among other organ failures. The cumulative survival curves of patients with or without GIF further stress this finding. The fact that the difference in favour of patients without GIF is significant in 90-day survival, but not on day 28, is probably explained by the longer ICU stay with subsequently higher ICU mortality in GIF patients.

The limitation of this study is the single centre design. While the GIF score is probably influenced by a case-mix and treatment strategies, a variation between departments may occur.

The main limitation of the GIF score is the subjectivity of estimation of the presence of FI. There is no consensus on definition of food intolerance available and the variability of definitions in literature is distractive.

Further, the continuity of the variables in the GIF score is improvable. The score is not exactly a continuum of alterations, as suggested for an organ failure score by Ferreira et al. (Ferreira et al. 2001). However, it is fulfilling the other criteria set by the same author: it is based on easily accessible variables (Ferreira et al. 2001). As the mean score of the first three days is not very helpful in everyday ICU practice, we propose a possible interpretation of the daily GIF score in clinical practice with the reverence to the authors of RIFLE score (Abosaif et al. 2005) as follows:

RISK – GIF score 1 for at least 2 days
INJURY – GIF score 2
FAILURE – GIF score 3
END-STAGE – GIF score 4

Further multi-centre studies should confirm the validity of GIF score in assessment of GI function in critically ill patients.

7. CONCLUSIONS

7.1. Both retrospective and prospective studies demonstrated considerably high incidence of GI symptoms in critically ill patients. Development of GI symptoms is associated with increased mortality and prolonged ICU stay. The most remarkable raise in risk of death was observed in elective cardiosurgical patients. Similar to clinical symptoms, the incidence of IAH is high in mixed ICU population. Monitoring the IAP only in presumable risk population may result in missing part of the actual IAH patients. The patients with IAH have higher ICU- and 90-day mortality. Secondary IAH has worse outcome than primary IAH.

7.2. Based on review of the literature there is no consensus on definition of GIF. Most of the definitions are diagnosis-based and the new function-based approaches do not include an easily applicable methodology to measure the function.

7.3. Proposed GIF score proved high prognostic value in prediction of ICU mortality in single centre prospective study. The GIF score is useful for systemizing the information about the GI system. Gastrointestinal failure assessed with GIF score has high importance among other organ failures in ICU.

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9. SUMMARY IN ESTONIAN

Gastrointestinaalne puudulikkus intensiivravihaigetel

Hulgiorganpuudulikkus on tänapäeva intensiivravis igapäevane probleem. Mida suurem on puudulikult funktsioneerivate organite arv, seda suurem on patsientide suremus. Kuigi gastrointestinaaltrakti-poolsed probleemid tekivad intensiivravihaigetel sageli ja on seotud ka halvema prognoosiga, ei ole seni ühtset seisukohta gastrointestinaalse puudulikkuse kui sündroomi osas. Organpuudulikkuste raskust hindavad skooringsüsteemid ei käsitle gastrointestinaalset puudulikkust hulgiorganpuudulikkuse osana. Käesolev uurimus hõlmab gastrointestinaaltrakti probleemide ja intensiivravi lõpptulemuse vahelisi seoseid viies eraldiseisvas uuringus. Lisaks käsitleb uurimus ka probleeme terminoloogias ja definitsioonides ning esitab gastrointestinaalse puudulikkuse hindamissüsteemi intensiivravihaigete monitooringuks.

Uurimistöö eesmärgid

Uurimistöö peamiseks eesmärgiks oli intensiivravihaigetel esinevate gastrointestinaaltrakti probleemide süsteemne käsitlus.

Konkreetsed eesmärgid:

1. näidata gastrointestinaaltrakti probleemide olulisust intensiivravihaigetel
2. analüüsida teaduslikus kirjanduses esitatud võimalusi gastrointestinaaltrakti funktsiooni hindamiseks
3. luua gastrointestinaaltrakti puudulikkuse hindamissüsteem praktiliseks kasutamiseks intensiivravihaigete igapäevases monitooringus

Patsiendid ja metoodika

Andmete kogumise aluseks on elektrooniline andmebaas, kuhu sisestatakse kõikide Tartu Ülikooli Kliinikumi (TÜK) üldintensiivravi osakonnas ravitud patsientide andmed. Prospektiivne andmebaas on kasutusel alates 1. jaanuarist 2004, 2002. aasta patsientide andmed sisestati retrospektiivselt analoogsesse andmebaasi. Kokku on uurimuses analüüsitud 3900 patsiendi andmeid.

Esimeses uuringus uurisime retrospektiivselt gastrointestinaaltraki puudulikkuse (GIP) esinemist kõikidel täiskasvanud patsientidel, kes hospitaliseeriti Charité Ülikooli Haigla kahte ja Tartu Ülikooli Kliinikumi ühte intensiivraviosakonda. GIP oli defineeritud kui vähemalt ühe järgneva probleemi esinemine: toidu talumatus, gastrointestinaalne verejooks, iileus.

Kahes järgnevas uuringus uurisime patsiente, kes viibisid intensiivravil TÜK üldintensiivravi osakonnas üle 24 tunni ja kellel mõõdeti intra-abdominaalset rõhku (IAP). 2004.a. juunist kuni 2006. a. augustini mõõdeti IAP riskirühma patsientidel, alates 2006.a. septembrist kõikidel patsientidel, kes olid aparaadi-

hingamisel. Võrdlesime intra-abdominaalse hüpertensiooni (IAH) esinemissagedust ja mõju ravi lõpptulemusele kahe perioodi võrdluses ja käsitlesime primaarse IAH (põhihaigusega kõhukoopas) ning sekundaarse IAH (põhipatoloogia mujal, mitte kõhukoopas) erinevusi.

Neljandas uuringus uurisime gastrointestinaalsete sümptomite (peristaltika puudumine, oksendamine, diarröa, soolte laienemine, GI trakti veritsus, suur nasogastraalaspiraadi hulk) esinemist ja mõju ravi lõpptulemusele kõikidel patsientidel, kes hospitaliseeriti TÜK üldintensiivravi osakonda 1. jaanuarist 2004 kuni 31. detsembrini 2007.

Viiendas uuringus 2006.a. septembrist kuni 2007.a. septembrini testisime uut GIP hindamissüsteemi patsientidel, kes olid aparaadihingamisel ja viibisid intensiivravil TÜK üldintensiivravi osakonnas üle 24 tunni.

Andmetöötlus teostati *Statistical Package for the Social Sciences* (Versions 11.5 and 15.0 SPSS Inc., Chicago, Ill, USA) programmi abil.

Uurimuse peamised tulemused ja järeldused

1. Nii retrospektiivse kui ka prospektiivse uurimuse põhjal saab väita, et GI sümptomid esinevad intensiivravihaigetel sageli ja on seotud kõrgema suremusega intensiivraviperioodil. Kõige markantsem oli GI probleemidega seotud surmariski suurenemine plaanilistel kardiokirurgilistel patsientidel.

Ka IAH esineb intensiivravihaigetel sageli ja IAH esinemine on seotud kõrgema intensiivraviperioodi- ja ka 90-päeva suremusega. Sekundaarse IAH-ga patsientide prognoos on halvem kui primaarse IAH-ga patsientidel.

2. Kirjanduse analüüsi põhjal saab kokkuvõttes väita, et puudub ühene mõõdik gastrointestinaalrakti funktsiooni hindamiseks intensiivravihaigetel. Puuduvad nii GI sümptomite kui ka GI puudulikkuse konsensusdefinitsioonid.

3. GIP skoor (GI sümptomite käsitlemine enteraalse toidu talumatusena ja kombinatsioonis konkreetselt mõõdetava IAP-ga) on korrelatsioonis ravi lõpptulemusega, võimaldades lihtsalt süstematiseerida kättesaadava informatsiooni GI trakti kohta. GIP hinnatuna GIP skoori abil on oluline võrdluses teiste organpuudulikkustega ja väärib kohta hulgiorganpuudulikkuse hindamissüsteemides.

10. ACKNOWLEDGEMENTS

This work was carried out at the General ICU of Tartu University Hospital and supported by the Estonian Science Foundation grants no 5304 and 6950.

I express my sincere gratitude to:

- all the people working in the General ICU of Tartu University Hospital, especially the nurses, who willingly accepted the introduction of IAP measurements
- Pille and Reet, for filling the database with extreme precision
- all my colleagues in East Tallinn Central Hospital, for their trust
- my supervisors Joel and Hartmut, for being also good friends and colleagues
- the colleagues in Charité Universitätsmedizin Berlin, for cooperation and great help to get my research started
- my mother and father, for total support in all the things I have ever done
- Hannes, for providing the best environment for writing the thesis
- my horses, for joy and pain they gave me

11. PUBLICATIONS

I

Reintam A, Parm P, Redlich U, Tooding LM, Starkopf J, Köhler F, Spies C, Kern H. Gastrointestinal failure in intensive care: a retrospective clinical study in three different intensive care units in Germany and Estonia. *BMC Gastroenterology* 2006, 22; 6: 19

II

Reintam A, Parm P, Kitus R, Kern H, Starkopf J.
Primary and secondary intra-abdominal hypertension – different impact on ICU outcome. *Intensive Care Med* 2008 (in press)

III

Reintam A, Parm P, Kitus R, Tamme K, Starkopf J.
Intra-abdominaalse hüpertensiooni esinemissagedus intensiivravihaigetel ja mõju ravitulemustele. *Eesti Arst* 2008; 87(3): 191–197

IV

Reintam A, Parm P, Kitus R, Kern H, Starkopf J.
Gastrointestinal symptoms in intensive care patients (submitted to *Intensive Care Med*)

Gastrointestinal symptoms in intensive care patients

Annika Reintam[1,2] Pille Parm[3], Reet Kitus[1,3], Hartmut Kern[1,4] , Joel Starkopf[1,3]

[1] Clinic of Anaesthesiology and Intensive Care, University of Tartu, Puusepa 8, Tartu 51014, Estonia
[2] Department of Anaesthesiology and Intensive Care, East Tallinn Central Hospital, Ravi 18, Tallinn 10138, Estonia
[3] Clinic of Anaesthesiology and Intensive Care, Tartu University Hospital, Puusepa 1A, Tartu 51014, Estonia
[4] Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie, DRK Kliniken Berlin Köpenick, Salvador-Allende-Straße 2–8, Berlin 12559, Germany

Key words: intensive care, gastrointestinal symptoms, gastrointestinal failure, epidemiology, outcome

Abstract

Purpose
We aimed to determine the prevalence of different GI symptoms and their impact on the patients' ICU outcome.

Methods
We prospectively studied all patients hospitalized to General ICU of Tartu University Hospital in 2004–2007.

Results
From 1374 patients 62 were excluded due to missing data. 775 (59.1 %) patients had at least one GI symptom at least during one day of their stay, while 475 (36.2%) suffered from more than one symptom.

Absent or abnormal bowel sounds were documented in 542 (41.3%), vomiting/regurgitation in 501 (38.2%), high gastric aspirate volume in 298 (22.7%), diarrhoea in 184 (14.0%), bowel distension in 139 (10.6%) and GI bleeding in 97 (7.4%) patients during their ICU stay.

Absent or abnormal bowel sounds and GI bleeding were associated with significantly higher mortality.

Conclusions
GI symptoms occur frequently in ICU patients. Absence of bowel sounds and gastrointestinal bleeding are associated with impaired outcome.

Introduction

The patients treated in intensive care units (ICU) may suffer from a number of different symptoms during their treatment**.** The majority of the treatment strategies in intensive care are aimed to treat symptoms and syndromes, particularly organ failures. Measurement of organ function is often too complex and seldom available at the bedside; therefore; the clinical symptoms and laboratory markers are often used to estimate the severity of the organ failure, and guide the treatment strategy. As an example, increased creatinine level and reduced urine output are well-known characteristics of renal failure [1,2] and also important indicators to start the renal replacement therapy. Even though the mechanisms of renal failure in critically ill patients are not fully clear and these characteristics are probably not exact measures of renal function, the monitoring of these easily assessable variables enables the evaluation of the treatment effect. Furthermore, several studies have shown the associations between these symptoms and the patients' outcome [3,4,5]. Surprisingly, easily applicable variable(s) for gastrointestinal (GI) system are not available. Experimental data exist about the measurement of absorption of different sugars [6,7], invasive measurements of splanchnic blood flow [7,8] and antro-duodenal motility [9] etc., but none of them is used in everyday clinical practice. Few studies have shown the high prevalence of different gastrointestinal symptoms with adverse impact on outcome [10,11,12]. Some authors outline gastrointestinal hemorrhage as the only specific symptom for GI failure, which at the same time is described to have low incidence and questionable clinical importance [13]. Even though the gut has been called to be the "motor of organ failure" [14,15], this important organ system is today excluded from assessment of multiple organ failure [16] and the data about epidemiology of GI symptoms in ICU are scarce in the literature.

Aim of the study

The aim of our study was to determine the prevalence of different GI symptoms in a mixed ICU population. The secondary aim was to evaluate the impact of these symptoms on the ICU outcome of these patients.

Methods

Ethical approval for this study was obtained from the Ethics Committee of the University of Tartu. All patients consequently hospitalized to General ICU of Tartu University Hospital between January 1st 2004 and December 31st 2007 were prospectively studied.

Following admission parameters were documented on patients' admission day: age, gender, body mass index (BMI), readmission, diabetes, Acute Physiology and Chronic Health Evaluation (APACHE II) score [17], serum protein, urea, C reactive protein, glucose, surgical profile, laparatomy immediately before ICU admission or during the first 24 hrs. Sequential Organ Failure Assessment (SOFA) score [1], central venous pressure (CVP), type of ventilation, peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), lactate, fluid gain, use of vasopressor/inotrope and sedation were registered daily through the patients' ICU period.

GI symptoms as absence or abnormality of bowel sounds, occurrence of vomiting, bowel dilatation, diarrhoea and GI bleeding, as well as a total amount and route of enteral feeding and total nasogastric aspirate volume, were assessed and documented daily by attending physicians.

Definitions

Vomiting was defined as any regurgitation despite the amount.

Absence of or abnormal bowel sounds were documented according to the doctors' subjective decision made by auscultation, when bowel sounds were not heard, were extremely infrequent or weak or "high".

Bowel dilatation was documented when confirmed by radiological examination or highly suspected in clinical evaluation.

Diarrhoea was documented when not formed stools occurred at least three times per day.

GI bleeding was defined as a macroscopically estimated presence of blood in vomited fluids, nasogastric aspirate or stool.

Gastric aspirate volume (GAV) equal or higher than 500 mL per day was considered as high.

Statistics

Statistical Package for the Social Sciences (Version 15.0 SPSS Inc., Chicago, Ill, USA) software was used for statistical analysis.

Data are presented as mean (standard deviation) if not stated otherwise.

T-test for continuous variables and Chi-Square test for categorical variables were used for comparisons of two groups.

Univariate analyses of admission parameters were applied to identify the risk factors for ICU mortality. Parameters with $p<0.2$ were thereafter entered into the multiple logistic regression model to identify the independent risk factors.

The GI symptoms (the incidence of respective symptom any time during the patients ICU stay) were tested for prediction of ICU mortality in separate regression analysis.

The mean SOFA score during the ICU stay and the GI symptoms defined important in separate analysis, were thereafter entered together into the multiple regression model.

Results

All together 1374 patients were hospitalized during the study period, 62 of them were excluded due to missing data and 1312 patients were included to further analysis. Patient mix did not include elective cardio- and neurosurgical patients, 96.2 % of the admissions were by emergency.

Admission parameters and prevalence of GI symptoms of the total study population and in comparison of survivors and non-survivors are presented in Table 1.

The ICU mortality of the whole study population was 24.4% (n=320), mean length of ICU period 7.1 (11.0) days and mechanical ventilation period 5.5 (9.8) days. Mean length of ICU period differed significantly between survivors and non-survivors (7.7±11.0 vs. 5.5±11.0, p=0.002), but differences in mechanical ventilation period were not significant (5.8±9.9 vs. 4.6±9.6, p=0.064, respectively).

GI symptoms

775 (59.1 %) from 1312 patients had one at least one GI symptom at least in one day of their stay, among them 475 (36.2%) patients suffered from more than one of these symptoms. The total prevalence of GI symptoms per patient is presented on Figure 1. The total prevalence of different GI symptoms and a comparison of prevalence in survivors vs. non-survivors are presented in Table 2.

The ICU mortality of the patients who had normal bowel sounds at admission was 16.5% (32/800), compared to 29.1% (34/117) in patients with abnormal bowel sounds on admission day and 39.0% (154/395) in patients in whom bowel sounds were not heard.

Prediction of ICU outcome

Among admission parameters the following three were identified as independent predictors: SOFA (OR 1.23; 95% CI 1.06–1.41); APACHE II (OR 1.08; 95% CI 1.03–1.15) and lactate (OR 1.09; 95% CI 1.00–1.18).

The model of prediction of ICU mortality exclusively with development of GI symptoms is presented in Table 3.

The regression model with three most important GI symptoms and mean SOFA score during the whole ICU stay is presented in Table 4. The mean SOFA score alone was able to predict the outcome in 87.5%; by adding GI symptoms the rate of correct prediction was 88.2%.

Discussion

The present study demonstrated the high prevalence of different GI symptoms in a mixed ICU population resulting in an important impact on outcome.

Our data are in accordance with few earlier reports demonstrating that GI symptoms occur often, some of them in up to 50 % of mechanically ventilated patients [10,11]. The obvious problems of research in this area are the absence of uniform definitions and high degree of subjectivity in the assessment of symptoms.

The last is the likely reason why only few studies have assessed the impact of the absence of the bowel sounds on outcome in intensive care patient. In emergency medicine, in contrast, the absent or abnormal bowel sounds have been used for a long time as an important symptom to suspect the acute abdominal pathology. The few studies performed in intensive care suggest that bowel sounds may be decreased or absent in half of the mechanically ventilated patients [10,18]. The presented results confirm this finding. Even more, somewhat unexpectedly we could demonstrate that the absence of bowel sounds, if occurred at least in one day during the patient stay, would be a very good predictor of mortality. Nevertheless, considering the reproducibility of auscultation of the bowel sounds, this symptom alone can hardly be suggested as a marker of GI failure in critically ill.

Most of the feeding protocols accept regular measurement of gastric residual volume (GRV) during the enteral nutrition as a surrogate to indicate gastric emptying, success of feeding and potential risk of aspiration [19]. Different protocols limit the acceptable GRV between 150–400 ml. A gastric residual volume of below 150 ml is usually considered safe for continuing intragastric feeding [20,21]. The volume above 250 ml is usually considered as high gastric residual volume [22,23,24]. Recent studies recommend to continue the enteral feeding even at residual volumes up to 500 ml [25].

GRV is a convenient clinical tool, however, the utility and significance of this measurement is controversial [19]. It appears to be an inaccurate method for the assessment of gastric emptying [26]. The dependence of GRV on a number of factors (tube characteristics, vomiting, interval of measurements, continuous vs. discontinuous application etc.) has lead to a lack of consensus on an acceptable value for GRV during enteral feeding [19]. Although gastric residual and daily gastric aspirate volumes are tightly interrelated, the presented approach to GAV is different from the studies described above. Therefore, making the comparisons with previous results is rather difficult.

Vomiting is commonly defined as an objective event that results in the forceful evacuation of gastric contents from the stomach, up and out of the mouth [27]. In sedated patients it is difficult to differentiate vomiting and regurgitation, which probably occurs in majority of mechanically ventilated

patients [28]. In a few studies, assessing vomiting in critically ill, the prevalence is 6–12% [11,29,30]. In our study, vomiting occurred more often as described in previous studies. This is most likely explained by the fact that the cases of regurgitation were also counted in. Among the patients in whom vomiting occurred, 24.8% died, among patients who did not have vomiting during their ICU stay 24.0% died. Interestingly, in regression analysis with only GI symptoms, occurrence of vomiting reduced the risk of death. However, vomiting appears to be not a good symptom to assess GI function due to its' dependency of several factors as nasogastric aspiration, enteral feeding, patients position etc.

GI bleeding has been used in early attempts to define gastrointestinal failure in organ failure scoring systems. However, later the authors excluded the GI failure from assessment of the MOF due to problems in definition and reliability [31,32]. Today, the terminology and definitions are variable. Instead of GI bleeding stress-related mucosal disease (SRMD) has been suggested as a correct term to describe non-variceal bleeding. Although SRMD is related to significant morbidity and mortality of critically ill patients [33,34], the incidence and impact of it are very much dependent on the definition of bleeding [35]. Mayr et al. for example introduced recently a modification of Goris' original MOF score, defining GI dysfunction as ileus > 7 days or GI bleeding requiring less than six blood products per 24 hours, and GI failure as GI bleeding requiring more than six blood products per 24 hours [13]. They observed GI failure in 2.6% of 3700 patients without significant impact on outcome [13]. In literature, the incidence of major GI bleeding remains nowadays below 5%, albeit endoscopically visible damage may be seen even in 74–100% of cases [10]. Even though confirmed variceal bleedings were not documented separately, most of the GI bleedings described in this study were obviously manifestations of SRMD.

The data regarding the impact of GI bleeding on mortality are controversial in literature. Our results support the idea that even less severe bleeding may be an important predictor of outcome of critically ill patients.

The development of diarrhoea in our patients is comparable to the previous studies, where it has been reported to occur in 15 to 50% of patients [10,11,18].

The need for concise definitions of diarrhoea was recently re-emphasized [36], until present day there is no consensus.

Bowel distension may be diagnosed radiologically or clinically, but there are no consensus criteria for either of these methods. In our study, bowel distension was observed in 10.6% of patients, and it occurred more often in non-survivors. Abdominal distension was observed in 13% of studied patients by Montejo [11], but in almost half of the patients in an earlier study with acute respiratory failure [18]. Other authors observed abdominal distension/pain as a reason to interrupt enteral feeding in 5% of the patients [30].

In summary, our results further illustrate the importance of GI complications in ICU patients. The main limiting factor for the research in this area is clearly the lack of consensus definitions. Due to the lack of objective, uniform definitions of dysfunction, monitoring of GI function must be based on indirect indicators [37]. However, none of the GI symptoms may be suggested for evaluation of GI function when used alone.

Further studies should evaluate whether some of the clinical symptoms and measurable parameters of GI function could be combined into easy and reproducible scoring system for GI tract assessment [16].

Conclusions

GI symptoms occur frequently in ICU patients. Absence of bowel sounds and occurrence of gastrointestinal bleeding are associated with impaired outcome.

Acknowledgements

This work was supported by Estonian Science Foundation grants no. 5304 and 6950.

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Table 1. The admission parameters of total study population and in comparison of survivors vs. non-survivors. Data are presented as mean (SD) if not stated otherwise.

Admission data	total	survivors	non-survivors	p-value
no of patients (%)	1312 (100)	992 (75.6)	320 (24.4)	
age, years	54.4 (19.61)	52.58 (20.24)	60.28 (16.16)	<0.001
male gender, no of pt (%)	819 (62.4)	616 (62.2)	203 (63.4)	0.366
body mass index, kg/m^2	26.03 (6.01)	25.96 (5.92)	26.29 (6.32)	0.453
readmission, no of pt (%)	22 (1.7)	20 (2.0)	2 (0.6)	0.068
diabetes, no of pt (%)	121 (9.2)	93 (11.3)	28 (11.0)	0.498
surgical profile, no of pt (%)	766 (58.4)	605 (61.0)	160 (50.3)	<0.001
laparatomy, no of pt (%)	296 (22.6)	221 (22.3)	75 (23.6)	0.343
resuscitation before admission	108 (8.2)	47 (4.8)	61 (19.2)	<0.001
APACHE II, points	14.95 (9.79)	12.35 (7.99)	25.36 (9.37)	<0.001
SOFA, points	6.53 (4.40)	5.42 (3.73)	11.03 (4.04)	<0.001
mechanical ventilation, no of pt (%)	1085 (82.7)	798 (81.3)	286 (90.2)	<0.001
vasoactive/inotrope, no of pt (%)	914 (69.7)	632 (63.8)	286 (90.2)	<0.001
sedation, no of pt (%)	1005 (76.6)	763 (77.1)	241 (75.3)	0.283
central venous pressure, mmHg	11.91 (5.82)	11.33 (5.47)	13.54 (6.46)	<0.001
peak inspiratory pressure, cmH_2O	24.64 (6.32)	24.02 (6.30)	27.05 (5.82)	<0.001
positive end-expiratory pressure, cmH_2O	9.53 (4.27)	9.06 (4.20)	11.19 (4.10)	<0.001
lactate, mmol/L	4.50 (4.85)	3.19 (3.26)	8.32 (6.45)	<0.001
fluid gain, L/24 hrs	2.87 (4.08)	2.58 (3.56)	3.79 (5.30)	<0.001
serum protein, g/L	59.71 (8.44)	60.35 (8.22)	57.32 (8.88)	<0.001
serum urea, mmol/L	12.03 (9.85)	10.95 (9.53)	16.28 (9.96)	<0.001
C reactive protein,	104.32 (105.97)	98.06 (101.02)	130.28 (120.96)	<0.001
serum glucose, mmol/L	9.04 (4.68)	8.91 (4.58)	9.58 (5.02)	0.051

Table 2. Prevalence of GI symptoms in total and in comparison in survivors and non/survivors.

	total	survivors	nonsurvivors	p-value
absence of bowel sounds	542 (41.3)	300 (30.3)	241 (75.3)	<0.001
vomiting	501 (38.2)	370 (37.3)	131 (40.9)	0.139
ng aspirate 500 ml or more/day	298 (22.7)	210 (21.2)	88 (27.5)	0.013
diarrhoea	184 (14.0)	135 (13.6)	49 (15.3)	0.251
bowel distension	139 (10.6)	77 (7.8)	62 (19.4)	<0.001
GI bleeding	97 (7.4)	53 (5.3)	44 (13.8)	<0.001

Table 3. Different GI symptoms in regression analysis for prediction of ICU moratlity.

	p-value	OR	95% CI
absence of bowel sounds	<0.001	9.49	6.62–13.61
GI bleeding	<0.001	2.88	1.75–4.75
bowel distension	0.025	1.64	1.07–2.53
diarrhoea	0.832	0.95	0.61–1.50
high nasogastric aspirate volume	0.352	0.81	0.51–1.27
vomiting	<0.001	0.44	0.29–0.68

Table 4. Mean SOFA during the ICU stay and GI symptoms in prediction of mortality

	p-value	OR	95% CI
mean SOFA	<0.001	1.49	1.41–1.56
absence of bowel sounds	<0.001	3.16	2.08–4.80
GI bleeding	0.016	1.94	1.13–3.32
bowel distension	0.097	1.54	0.93–2.56

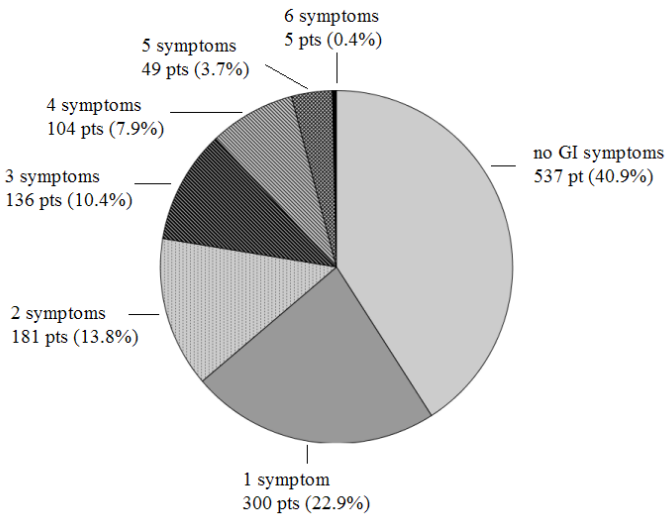

Figure 1. Prevalence of GI symptoms by occurrence per patient whenever during the patients' ICU stay.

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Reintam A, Parm P, Kitus R, Starkopf J, Kern H.
Gastrointestinal Failure Score in critically ill patients: a prospective observational study
(submitted to *Crit Care*)

Gastrointestinal Failure Score in critically ill patients: a prospective observational study

Annika Reintam[1,2], Pille Parm[3], Reet Kitus[1,3], Joel Starkopf[1,3], Hartmut Kern[1,4]

[1] Clinic of Anaesthesiology and Intensive Care, University of Tartu, Puusepa 8, Tartu 51014, Estonia
[2] Department of Anaesthesiology and Intensive Care, East Tallinn Central Hospital, Ravi 18, Tallinn 10138, Estonia
[3] Clinic of Anaesthesiology and Intensive Care, Tartu University Hospital, Puusepa 1A, Tartu 51014, Estonia
[4] Klinik für Anästhesiologie und Intensivmedizin, DRK Kliniken Berlin Köpenick, Salvador-Allende-Straße 2–8, Berlin 12559, Germany

Abstract

Background
There are no universally accepted diagnostic criteria for gastrointestinal failure (GIF) in critically ill patients. In the present study we tested if the occurrence of food intolerance (FI) and intra-abdominal hypertension (IAH), combined into a five grade scoring system for assessment of gastrointestinal function – GIF score – predict correctly mortality. The prognostic value of GIF score alone and in combination with SOFA score is evaluated, and the incidence and outcome of GIF, according to the proposed score, is described.

Methods
264 subsequently hospitalized patients, who were mechanically ventilated on admission and stayed in ICU for more than 24 hours, were prospectively studied. GIF score was documented daily: 0 point – normal GI function; 1 point – enteral feeding < 50% of calculated needs or no feeding three days after abdominal surgery; 2 points – FI or IAH; 3 points – FI and IAH; 4 points – abdominal compartment syndrome. Admission parameters and mean GIF and SOFA scores for the first three days were used for prediction of ICU outcome.

Results
FI developed in 58.3%, IAH in 27.3% and both of them together in 22.7% of all patients. The mean GIF score for the first three days in ICU is an independent risk factor for mortality (OR 7.09; 95% CI 1.60–31.48; p=0.010). The GIF score integrated into the SOFA score allowed a slightly better prediction of ICU mortality as the SOFA score alone and was an independent predictor of mortality (OR 2.16; 95% CI 1.39–3.37; p=0.001).

The development of GIF (FI+IAH) was associated with significantly higher ICU and 90-day mortality (p=0.019).

Conclusions
The GIF score is useful for systemizing the information about GI system. The mean GIF score in the first three days in the ICU demonstrated high prognostic value of ICU mortality. Development of GIF is associated with significantly impaired outcome.

Introduction

Gastrointestinal problems occur frequently and are associated with an adverse outcome in critically ill patients [1,2,3,4]. Yet, in routine clinical practice there is no consensus for precise assessment of the gastrointestinal function. Further on, gastrointestinal (GI) function is not included in any of the widely used scoring systems assessing organ failures in critical illness. The importance of gastrointestinal failure (GIF) in critically ill patients is underestimated starting already with the definition. Different, mostly diagnosis-based definitions have been used by different authors, making comparative interpretation of studies upon GI function rather impossible [5].

Different GI complications (decreased bowel sounds, delayed gastric emptying and diarrhea) may occur in up to 50% of mechanically ventilated patients [1,6]. Intolerance to gastric feeding due to delayed gastric emptying occurs frequently in critically ill patients [1,6,7,8] and has adverse impact on outcome [6,10]. However, a gastric residual volume – a commonly used surrogate for gastric emptying and success of feeding – is not a reliable measure [11].

Monitoring of intra-abdominal pressure (IAP) is gaining more and more popularity in everyday clinical practice. It is easily performable and resulting in a reliable number to interpret. Several studies have demonstrated adverse impact of intra-abdominal hypertension (IAH) on mortality [12,13,14]. Still, IAP has not been proven to be an adjuvant measure of GI function. Some evidence suggests that not all the patients with IAH have gastrointestinal problems and vice versa [15]. Based on this information we hypothesized that combination of IAP with gastrointestinal symptoms might have a good predictive value for ICU outcome.

In the present prospective study we assessed the gastrointestinal function through combination of gastrointestinal symptoms and intra-abdominal pressure into a five-grade scale – the Gastrointestinal Failure Score.

The aim of the study was to test the accuracy of the Gastrointestinal Failure Score in evaluation of gastrointestinal failure as a part of multiple organ failure in mixed ICU patients by evaluating its' prognostic value alone and in

combination with SOFA score. We also aimed to describe the incidence and outcome of Gastrointestinal Failure according to the GIF score.

Materials and methods

All mechanically ventilated patients subsequently admitted to a mixed surgical-medical ICU of Tartu University Hospital from September 2006 to September 2007 were screened for the prospective study. The patients treated for at least 24 hours were included into further analysis. On admission, the following parameters were recorded: age, gender, body mass index (BMI), readmission rate, diabetes, Acute Physiology and Chronic Health Evaluation (APACHE II) score [16], surgical profile, laparatomy immediately before ICU admission or during the first 24 hrs,. Sequential Organ Failure Assessment (SOFA) score [17], mean arterial pressure (MAP), central venous pressure (CVP), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), IAP, lactate, fluid gain, use of vasopressor/inotrope and sedation were recorded on daily basis.

GI function of the patients was daily assessed according to Gastrointestinal Failure Score, described in Table 1.

Food intolerance (FI) was defined as the inability to feed the patient enterally because of any reason, except if the patient was electively not fed during the first three days after laparatomy.

Intra-abdominal pressure (IAP) was measured via bladder, at patients' supine position, using the Closed Loop System Repeated Measurements Technique [18]. The IAP was measured at least twice a day in case of normal values, and at least four times a day if elevated above 12 mmHg. Mean and maximum values of IAP were daily documented. Intra-abdominal hypertension (IAH) was defined as a sustained IAP 12 mmHg or above [19]. Abdominal compartment syndrome was defined as a sustained IAP > 20 mmHg with an onset of a new organ failure.

GIF was considered to be present when IAH and FI occurred simultaneously.

ICU-, 28-day and 90-day mortality, duration of ICU stay and mechanical ventilation were used as primary outcome parameters.

SOFA + GIF was calculated daily by summarizing the SOFA score and the GIF score of the respective day in each patient.

Ethical committee of University of Tartu has approved the study. Written informed consent was considered not necessary for the study, as it is an observation of our usual everyday work. No special interventions were used. All the data were impersonalised before analysis, and no harm could be weighed against benefit.

Statistics

Statistical Package for the Social Sciences (Version 15.0 SPSS Inc., Chicago, Ill, USA) software was used for statistical analysis.

T-test for continuous variables and Chi-Square test for categorical variables were used for comparisons of two groups.

Mean scores during first three days were calculated as mean of individual values for three days of every patient.

Univariate analyses of admission parameters were applied to identify the risk factors of ICU mortality. Parameters with $p<0.2$ were thereafter entered into the multiple logistic regression model to identify the independent risk factors.

The means of the variables for first three days were thereafter added to admission parameters for multiple regression analysis. The first day values of the parameters, included in the scores, were removed from this analysis to exclude the coupling.

Receiver Operating Characteristic (ROC) curves were used to determine the likelihood ratio of GIF score, SOFA score and SOFA+GIF to predict the ICU mortality.

Kaplan-Meier curves and log-rank tests were used for comparison of survival of patients with and without Gastrointestinal Failure.

Data are presented as mean (standard deviation) if not stated otherwise. P value < 0,05 was considered significant.

Results

373 patients were treated in the General ICU of Tartu University Hospital during the study period. 264 patients were on mechanical ventilation at admission and stayed in ICU for at least 24 hours, and were thereby included into further analysis.

93.9% of them were emergency patients. The case-mix does not include cardiac surgical and neurosurgical patients. Most of the surgical patients were admitted due to respiratory failure (43%) or shock (29%). Among medical patients the main causes for admission were coma (30%), shock (21%), post-resuscitation state (20%) and respiratory failure (12%). Admission parameters and outcome data of study patients are presented in Table 2.

Incidence of Food Intolerance and IAH

Food intolerance was observed in 154 patients (58.3%), and it developed dominantly during first three days of admission (144/154; 93.5%).

72 patients (27.3%) developed IAH, 5 of them (6.9% of IAH patients) suffered from abdominal compartment syndrome. 87.5% of IAH patients (63/72) developed the syndrome during their first three days in ICU.

GIF (FI+IAH) developed in 60 patients (22.7%), in 36 of them (13.6% of study population) it was present already on the day of admission (see also Table 2).

GIF score

The GIF score was documented overall in 2348 patient days. GIF score 0 was observed in 52.0%, 1 in 12.2%, 2 in 27.8%, 3 in 7.7%, and 4 in 0.3% of days.

The jejunal feeding was used in 11 % of total patient days, but very rarely (1%) during the first three days.

The patients with GIF score 1 for one day, developed higher GIF scores later in 27.6% of the cases. In patients with GIF score 1 for two or more subsequent days, the progression of the syndrome was more common – 72.3% of them developed higher GIF scores during the following days.

The mean GIF score during first three ICU days was 1.2±0.9 points, being significantly different between survivors and non-survivors (1.1±0.8 vs.2.0±1.0, respectively, $p<0.001$). The mean of the maximum GIF score was 1.6±1.0 in survivors vs. 2.3±1.1 in non-survivors ($p<0.001$).

Outcome

ICU mortality of the study population was 14.8%. 28- and 90-days mortality was 20.5% and 28.4%, respectively.

The length of ICU stay and mechanical ventilation, ICU and 90-day mortality were significantly different between IAH and no-IAH patients, as well as FI and no-FI patients (see also Table 2).

High values of the mean GIF score during the first three days of ICU stay were related to high mortality (Figure 1). The patients with gastrointestinal failure (simultaneous occurrence of IAH and FI) suffered from an ICU mortality of 28.1% compared to 10.8% in patients without this syndrome ($p=0.001$). The mortality was higher also after 90 days (40.0% vs. 25.0%; $p=0.019$), but not after 28-days (28.3% vs. 18.1%; $p=0.065$).

Prediction of outcome

Admission parameters in prediction of ICU mortality

In multiple regression analysis only two admission parameters (SOFA and fluid balance during first 24 hours) were identified as independent predictors of ICU mortality of study population.

Means of the first three days in combination with admission parameters

The mean SOFA score of first three days showed expectedly better prediction than its value at the first day (OR 1.82; 95% CI 1.26–2.63; $p=0.002$ vs. OR 1.36; 95% CI 1.02–1.82; $p=0.037$).

The mean IAP of the first three days was not an independent risk factor for mortality.

The mean GIF score of the first three days (used instead of the mean IAP) was identified as an independent risk factor for ICU mortality (OR 7.09; 95% CI 1.60–31.48; p=0.010).

The mean SOFA + GIF score of the first three days demonstrated slightly better prediction of ICU mortality than the SOFA score alone (OR 2.16; 95% CI 1.39–3.37; p=0.001).

Combination of GIF and SOFA scores

The combination of mean SOFA and GIF score during the first 3 days demonstrated the highest Area under the Curve (0.895) in comparison to mean SOFA (0.840) and mean GIF (0.753) alone (see also Figure 2).

In the regression analysis for the prediction of ICU mortality (see also Table 3), the GIF score of first three days had the second highest OR (OR 2.20; 96% CI 1.28–3.78; p=0.004) after the cardiovascular SOFA sub-score (OR 5.91; CI 2.83–12.33; p< 0.001). The 90-day cumulative survival of patients with GIF was significantly impaired in comparison to patients without GIF (Log Rank test = 4.45; p = 0.035). There was no significant difference in 28-day survival as shown in Figure 3,

Discussion

In the present single-centre pilot study we demonstrate the usefulness of the GIF score – a combined assessment of food tolerance and intra-abdominal pressure – for dynamic assessment of GI function in critically ill patients. Combining the food intolerance with values of intra-abdominal pressure appeared to be a better predictor of outcome than both of the entities alone. The mean GIF score of the first three days is an independent risk factor for ICU mortality. Further, the score may add predictive power to the SOFA score in outcome prediction.

Gastrointestinal function has been demonstrated to influence the ICU outcome in previous studies. However, the absence of a scaled assessment system of GI function has been a major limiting factor in these studies. The role of the GI tract as a motor of multiple organ failure has been stated already more than two decades ago and confirmed more recently by Clark and Coopersmith [20]. However, due to a lack of definition, reliability and incidence [21,22], GI failure has not been included in severity of illness scoring systems used today.

About half of the patients of present study developed food intolerance during the first three days in ICU. These patients were significantly older and more severely ill (higher APACHE and SOFA scores). They stayed longer in ICU and suffered from a higher mortality than patients with a normal GI function. The prevalence of food intolerance has been described in a similar range in literature and has been shown to influence the outcome [1,2,3,23]. At first

glance, it seems reasonable to use more specific GI symptoms, such as bleeding, high gastric residual etc., for assessment of GI function. However different problems limit their use in this setting: GI bleeding occurs rarely [22], the incidence of vomiting is influenced by nasogastric aspiration, a high gastric residual volume is not defined uniformly and has only a weak correlation with gastric emptying [11]. None of these evaluations of GI function take into account for example severe diarrhea, which is often handled with reducing the rate of enteral feeding [1] and has been shown to double the hazard of graft loss and patient death following kidney transplantation [24]. Most of the attempts to define GI dysfunction, described in the literature, have been based on diagnosis rather than function. For example, presences of cholecystitis [25] and GI bleeding [22,25] have been suggested to diagnose GIF. Such approach excludes the possibility for functional assessment of GI tract in its whole complexity. Even though food intolerance is a rather subjective variable, it is, in our opinion, the most universally used clinical characteristic of GI failure, covering probably the entire spectrum of different GI symptoms.

Intra-abdominal hypertension did not occur in our patients as frequently as food intolerance – it developed only in one third of them. These data are in accordance with observations from Malbrain and colleagues [26] who described similar prevalence of IAH in a mixed ICU population. Different studies on selected patients groups appoint the adverse impact of IAP on ICU outcome [14,27]. Malbrain and coauthors demonstrated the development of IAH during the ICU stay, but not IAP on admission, as an independent risk factor of mortality [12]. However, prediction of outcome by events occurring during the whole ICU period is of somewhat limited value. Therefore we assessed only the means of the first three days. Accordingly, the GIF score, but not IAH appeared to be an independent predictor of outcome.

Very little is known about the combination of FI and IAH. Our data clearly demonstrate that the patients suffering from these two symptoms are not fully overlapping – not all the patients with GI problems have IAH and vice versa. 76 % of the patients with IAH on admission experienced also food intolerance, while only 25 % the patients with food intolerance had IAH. Some of the future IAH patients demonstrated FI on admission, while IAH itself was not yet present, and only few future FI patients showed IAH, but not yet FI on their admission day. This, in our opinion, further supports the necessity to combine these two variables into GIF score. The definite strength of IAP measurement in this setting is the objective and reproducible measurable numeric value.

It is hard to estimate in which extent the route of enteral feeding influences the GIF score However, the advantage of post-pyloric versus gastric feeding in regard to outcome has not yet been proven [28] and thus the current evidence does not support routine use of post-pyloric feeding in critically ill [29]. The post-pyloric route is probably not the first common choice during the first few days of intensive care, even though Montejo et al. report the lower incidence of

GI complications in patients with early jejunal nutrition [3]. It might be speculative that enteral feeding itself produces an increase in IAP in critically ill patients. However, we did not observe such association in a preliminary study [30]. On the other hand, there is evidence, that early enteral pharmaconutrition in septic patients results in faster recovery of organ function [31].

The main limitation of the present study is that only the patients with prolonged ICU stay > 24 hours were studied. The patients treated in ICU for less than 24 hours are probably the mixture of the least and most severe patients. This pre-selection may bias the results, for example as explanation of the low predictive power of the APACHE II score. We considered that in most short-staying patients the IAH and FI are not usually the key issues of the treatment. IAH is seldom measured in patients dying within few hours after ICU admission. Accepting this delay in IAH monitoring it is important to underline that in a few ACS patients prompt IAH measurement might be crucial for correct decision-making process and patients survival.

The observed high predictive value of the mean SOFA score on ICU outcome is in accordance with several previous studies. The predictive power of the mean SOFA score of the first three days is correctly placed between the mean SOFA of the whole ICU period (OR 3.06) and the SOFA at 48 hours (OR 1.45) [32].

Similar predictive value of SOFA sub-scores was observed in cardiac surgical patients [33]. The cardiovascular SOFA appeared to be the most powerful while the respiratory and hematological SOFA the least powerful [33]. The excellent performance of GIF score in this setting once more confirms the importance of GI failure among other organ failures. The cumulative survival curves of patients with or without GIF further stress this finding. The fact that the difference in favor of patients without GIF is significant in 90-day survival, but not on day 28, is probably explained by the longer ICU stay with subsequently higher ICU mortality in GIF patients.

The limitation of this study is the single center design. While the GIF score is probably influenced by a case-mix and treatment strategies, a variation between centers may occur.

In our opinion, the major limitation of the GIF score is the subjectivity of estimation of the presence of FI. There is no consensus on definition of food intolerance available and the variability of definitions in literature is distractive.

Secondly, the continuity of the variables in the GIF score is improvable. The score is not exactly a continuum of alterations, as suggested for an organ failure score by Ferreira et al. [32]. However, it is fulfilling the other criteria set by the same author: it is based on easily accessible variables [32]. As the mean score of the first three days is not very helpful in everyday ICU practice, we propose a possible interpretation of the daily GIF score in clinical practice with the reverence to the authors of RIFLE score [34] as follows:

RISK – GIF score 1 for at least 2 days
INJURY – GIF score 2
FAILURE – GIF score 3
END-STAGE – GIF score 4

Conclusions

The mean GIF score in the first three days on ICU demonstrated a high prognostic value in prediction of ICU mortality. The GIF score is useful for systemizing the information about the GI system. Development of gastrointestinal failure during ICU stay is associated with significantly higher ICU- and 90-day mortality. Further multicenter studies should confirm whether GIF score could be advocated as adjuvant sub-score for GI tract assessment in the SOFA score.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AR participated in the design of the study, statistical analysis and drafted the manuscript. PP and RK carried out the data collection and participated in the statistical analysis. JS participated in the design of the study and writing the manuscript. HK participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgements

This work was supported by Estonian Science Foundation grant no. 6950.

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Table 1. Gastrointestinal Failure Score.

Points	**clinical symptomatology**
0	normal GI function
1	enteral feeding < 50% of calculated needs or no feeding three days after abdominal surgery
2	food intolerance (enteral feeding not applicable due to high gastric aspirate volume, vomiting, bowel distension or severe diarrhea etc.) or IAH
3	food intolerance and IAH
4	abdominal compartment syndrome

Table 2. Admission and outcome parameters of study patients. The values are presented as mean (SD), if not stated otherwise.

Admission parameters	total	no IAH	IAH	p-value	no FI	FI	p-value
no of patients (%)	264 (100.0)	192 (72.3)	72 (27.3)		110 (41.7)	154 (58.3)	
male gender, no of pt (%)	166 (62.9)	117 (60.9)	49 (68.1)	0.178	60 (54.5)	106 (68.8)	0.013
age, years	53.8 (20.0)	52.3 (21.0)	57.8 (16.8)	0.047	48.6 (21.0)	57.5 (18.5)	<0.001
diabetes, no of pt (%)	35 (13.3)	26 (13.5)	9 (12.5)	0.502)	11 (10.0)	24 (15.6)	0.128
readmission, no of pt (%)	8 (3.0)	6 (3.1)	2 (2.8)	0.622	2 (1.8)	6 (3.9)	0.287
sedation, no of pt (%)	243 (92.0)	174 (90.6)	69 (95.8)	0.125	98 (89.1)	145 (94.2)	0.103
vasoactive/inotrope, no of pt (%)	200 (75.8)	136 (70.8)	64 (88.9)	0.001	67 (60.9)	133 (86.4)	<0.001
surgical profile, no of pt (%)	175 (66.3)	122 (63.5)	53 (73.7)	0.080	67 (60.9)	108 (70.1)	0.077
laparatomy, no of pt (%)	60 (23.3)	21 (15.6)	31 (43.7)	<0.001	9 (8.4)	51 (34.0)	<0.001
enteral feeding, no of pt (%)	49 (18.6)	42 (21.9)	7 (9.7)	0.015	25 (22.7)	24 (15.6)	0.095
APACHE II, points	14.2 (7.7)	13.5 (7.6)	16.0 (7.7)	0.016	11.8 (7.3)	15.8 (7.6)	<0.001
BMI, kg/m^2	27.6 (13.1)	25.4 (4.6)	33.1 (22.2)	<0.001	25.8 (5.6	28.9 (16.4)	0.080
SOFA, points	7.0 (4.2)	6.3 (4.2)	8.9 (3.6)	<0.001	5.3 (4.2)	8.2 (3.8)	<0.001
fluid gain in first 24 h, L	2.4 (3.6)	2.0 (2.4)	3.6 (5.5)	0.001	1.7 (2.4)	2.9 (4.2)	0.007
MAP, mmHg	81.5 (15.9)	82.1 (16.4)	80.5 (15.0)	0.512	82.1 (15.8)	81.3 (16.1)	0.758
IAP, mmHg	8.5 (4.7)	6.5 (3.8)	12.1 (4.0)	<0.001	6.3 (4.0)	9.5 (4.6)	<0.001
CVP, mmHg	11.6 (5.7)	10.3 (4.9)	14.3 (6.3)	<0.001	10.4 (5.1)	12.2 (5.9)	0.031
PIP, cmH_2O	23.9 (6.2)	22.6 (6.0)	27.2 (5.2)	<0.001	22.5 (6.5)	24.8 (5.7)	0.006
PEEP, cmH_2O	9.2 (4.2)	8.5 (4.1)	11.2 (3.7)	<0.001	7.8 (4.1)	10.2 (3.9)	<0.001
lactate, mmol/L	4.6 (5.4)	4.4 (4.6)	4.9 (6.9)	0.519	4.4 (4.9)	4.7 (5.7)	0.741
food intolerance, no of pt (%)	124 (47.0)	69 (35.9)	55 (76.4)	<0.001	–	–	
IAH, no of pt (%)	42 (15.9)	–	–		3 (2.7)	39 (25.3)	<0.001
GIF (FI+IAH), no of pt (%)	36 (13.6)	–	36 (50.0)		–	36 (23.4)	

Admission parameters	total	no IAH	IAH	p-value	no FI	FI	p-value
outcome parameters							
MV days	7.4 (11.9)	4.3 (6.1)	15.5 (18.0)	<0.001	3.6 (5.9)	10.0 (14.1)	<0.001
ICU days	8.8 (12.8)	5.6 (7.3)	17.5 (19.0)	<0.001	4.8 (6.9)	11.7 (15.1)	<0.001
ICU mortality, no of pt (%)	39 (14.8)	21 (10.9)	18 (25.0)	0.005	7 (6.4)	32 (20.8)	0.001
28-day mortality, no of pt (%)	54 (20.5%)	36 (18.8%)	18 (25.0%)	0.171	13 (11.8%)	41 (26.6%)	<0.001
90-day mortality, no of pt (%)	75 (28.4%)	48 (25.0%)	27 (37.5%)	0.033	17 (15.5%)	58 (37.7%)	0.002

Table 3. SOFA subscores and GIF score in regression analysis for prediction of ICU mortality

	p-value	OR	95% CI
cardiovascular SOFA	<0.001	5.91	2.83–12.33
GIF score	0.004	2.20	1.28–3.78
hepatic SOFA	0.024	1.75	1.075–2.86
renal SOFA	0.087	1.39	0.95–2.04
central nervous system SOFA	0.159	1.23	0.92–1.65
hematological SOFA	0.712	0.92	0.57–1.47
respiratory SOFA	0.518	0.84	0.48–1.44

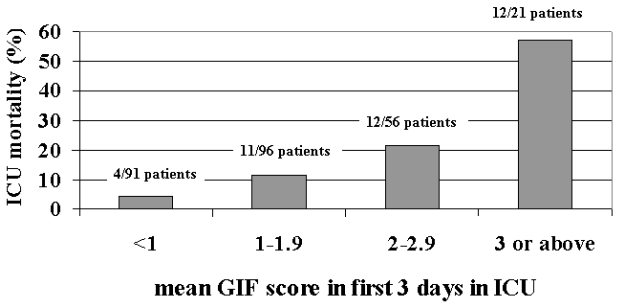

Figure 1. ICU mortality of patients according to their mean GIF score.

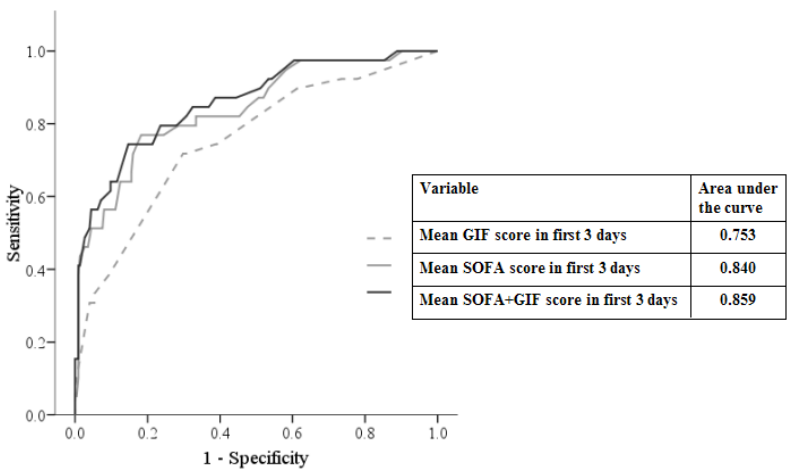

Figure 2. ROC curves with different scores in prediction of ICU mortality.

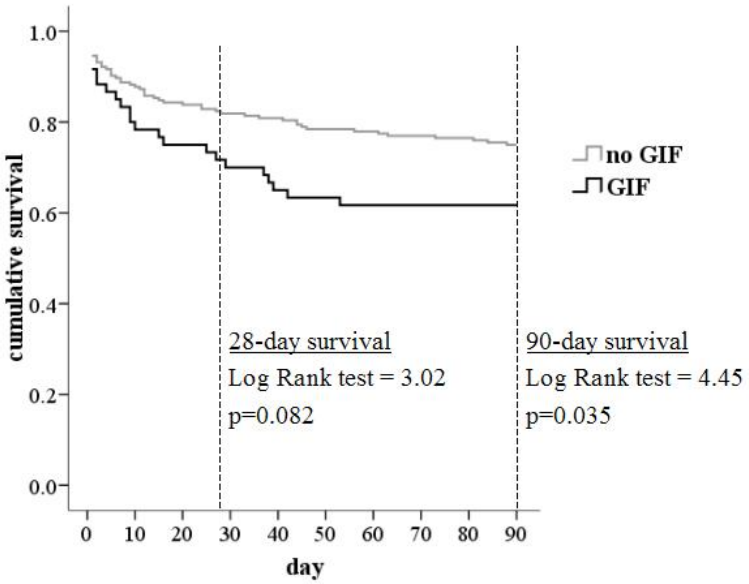

Figure 3. Cumulative survival of patients without GIF (maximum GIF score during ICU stay 2 or less) vs. patients with GIF (maximum GIF score during ICU stay 3 or 4).

VI

Reintam A, Kern H, Starkopf J.
Defining Gastrointestinal Failure.
Acta Clin Belg 2007, 62(Suppl 1): 168–172

CURRICULUM VITAE

ANNIKA REINTAM

Born: October 1, 1971, Tartu, Estonia
Citizenship: Estonia
Address: East Tallinn Central Hospital, Dept. of Anaesthesiology and Intensive Care
Ravi 18, Tallinn 10138, Estonia
Phone: +372 514 2281
Fax: +372 620 7924
E-mail: annika.reintam@itk.ee

Education

1978–1985	A.H. Tammsaare secondary School No 1, Tartu, Estonia
1985–1989	Tallinn Sports College, Tallinn, Estonia
1989–1995	Faculty of Medicine, University of Tartu
1995–1997	Internship in anaesthesiology and intensive care, University of Tartu
2004–2008	PhD student, Clinic of Anaesthesiology and Intensive Care, University of Tartu

Professional employment

1997–1999	Anaesthesiologist, General ICU, Tartu University Hospital, Tartu
2000–2005	Teaching Doctor, General ICU, Tartu University Hospital, Tartu
2005–	Head of Department of Anaesthesiology and Intensive Care, East Tallinn Central Hospital, Tallinn

Scientific work

Research fields: gastrointestinal failure, intra-abdominal hypertension and monitoring of volume status in ICU patients

5 publications, 16 presentations in international congresses

Memberships

Medical Association of Tartu
Estonian Society of Anaesthesiologists
European Society of Intensive Care Medicine

CURRICULUM VITAE

ANNIKA REINTAM

Sünd.	Tartus, 1. oktoobril 1971
Kodakondsus:	eesti
Address:	Ida-Tallinna Keskhaigla, Anestesioloogia ja intensiivravi osakond, Ravi 18, Tallinn 10138, Estonia
Telefon:	+372 514 2281
Faks:	+372 620 7924
E-mail:	annika.reintam@itk.ee

Haridus

1978–1985	A.H. Tammsaare nim. Tartu I keskkool
1985–1989	Tallinna Spordi-internaatkool
1989–1995	Tartu Ülikooli arstiteaduskond
1995–1997	anestesioloogia ja intensiivravi internatuur, Tartu Ülikool
2004–2008	doktoriõpe, Tartu Ülikooli arstiteaduskond

Teenistuskäik

1997–1999	anestesioloog, Tartu Maarjamõisa Haigla üldintensiivravi osakond
2000–2005	arst-õppejõud, Tartu Ülikooli Kliinikumi üldintensiivravi osakond
2005–	osakonna juhataja, Ida-Tallinna Keskhaigla anestesioloogia ja intensiivravi osakond

Teadustegevus

Uurimisvaldkonnad: gastrointestinaalne puudulikkus, intra-abdominaalne hüpertensioon ja voluumeni staatuse monitooring intensiivravis

5 publikatsiooni, 16 ettekannet rahvusvahelistel kongressidel

Kuuluvus erialaseltsidesse

Tartu Arstide Liit, eestseisuse liige 2002–2005
Eesti Anestesioloogide Selts
Euroopa Intensiivravi Selts

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