BALLOON-FREE GASTRIC TONOMETRY COMBINED WITH THE EVALUATION OF THE GASTRIC-TO-END-TIDAL CO₂ GAP IN CHILDREN

Ph.D. Thesis

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List of publications

Original papers directly related to the thesis

I. Király Á, Boda D, Tálosi Gy, Boda K. Intraoperative gastric tonometric examinations in children and infants with a new probe, combined with measurement of the endtidal PCO_2. *Pediatric Anesthesia* 2008; 18:501-507. [IF: 1.469]

II. Szakál O, Király Á, Szűcs D, Katona M, Boda D, Tálosi Gy. Measurement of gastric-to-end-tidal carbon dioxide difference in neonates requiring intensive care. *The Journal of Maternal-Fetal and Neonatal Medicine* 2012; 25(9): 1791-1795 [IF: 2.071]

Original papers not related to the thesis

Ökrös Zs, Endreffy E, Novák Z, Maróti Z, Monostori P, Varga I, Király Á, Túri S. Changes in NADPH oxidase mRNA level can be detected in blood at inhaled corticosteroid treated asthmatic children. *Life Sciences* 2012; 91:907-911 [IF: 2.529]

Abbreviations

ADP	adenosine diphosphate
ANOVA	analysis of variance
ATP	adenosine triphosphate
BE	base excess
CAVC	complete atrioventricular canal
CO_2	carbon dioxide
CRIB	clinical risk index for babies
$ctCO_2$	total concentration of CO_2 in the plasma
H^+	hydrogen ion, proton
Hb	haemoglobin
HCO_3^-	bicarbonate ion
H_2CO_3	carbonic acid
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
$-NH_2$	non-ionized terminal amino group of molecules
N_2O	nitrous oxide
O_2	oxygen
P_aCO_2	arterial partial pressure of CO_2
PCO_2	partial pressure of CO_2
PCO_2 gap	difference between two different partial pressures of CO_2
$P_{ET}CO_2$	end-tidal partial pressure of CO_2
P_gCO_2	gastric partial pressure of CO_2
$P_{g-a}CO_2$ gap	difference of gastric and arterial partial pressures of CO_2
$P_{g-ET}CO_2$ gap	difference of gastric and end-tidal partial pressures of CO_2
pHi	gastric intramucosal pH
PO_2	partial pressure of O_2
Ptx	pneumothorax
RDS	respiratory distress syndrome
SD	standard deviation

1. INTRODUCTION

1.1. Physiological characteristics of infancy and small childhood

Because of their wide-ranging immaturity, prematures, term neonates and infants may undoubtedly be considered the most vulnerable population of patients. This period of life can be characterized by overall unsteadiness, with sudden and unusual reactions to different stimuli. Their reduced reserves and limited compensatory mechanisms, accompanied by their increased and altered reflex activity, predispose them to undergo rapid changes in their condition. This physiologically unstable state may be coupled with various diseases and/or special age-related diseases, such as congenital defects, necrotizing enterocolitis (NEC), the respiratory distress syndrome (RDS) or neonatal sepsis. In certain cases, they cannot be treated by conservative therapy, and surgical interventions may be required. The younger the patient, the higher is the risk of cardiovascular complications during anaesthesia and surgery (1, 2).

In spite of its immaturity at birth and the dynamic changes that occur throughout the further development of the patient, the cardiovascular system (in close conjunction with the respiratory system) forms a dynamic to-and-fro metabolic passage between the cells and the environment. A blood supply deterioration caused by hypovolaemia, sepsis or shock results in an early rearrangement of the circulation, diverting the blood flow from the splanchnic region towards organs of vital importance. During the recovery period, the splanchnic circulation is the last to be restored (3, 4).

In view of the possible very rapid changes in the condition of these patients, there is a need for a reliable, not very expensive, complication-free, non-invasive and reproducible monitoring method with which to be able to follow the changes in their status and to predict the outcome of the disease. Monitoring should be started as early as possible and should be continued as long as required.

Apart from the discrepancies caused by the different sizes of the patients and tonometric probes currently available, gastrotonometry or gastric tonometry could meet these requirements (5, 6). Boda et al. recently developed a balloon-free new generation of gastric tonometric sampling probes which can be applied even in the smallest population of patients (7). Gastric tonometry has proved to be a simple, sensitive, organ-specific and early detector of the condition of the splanchnic circulation and the oxygenation of the gastrointestinal organs. Deterioration of the gastrointestinal blood flow can be the first sign

of an insufficiency of the systemic circulation. Splanchnic vasoconstriction is part of the redistribution process of the systemic circulation in response to generalized stress stimuli. In consequence of a reduction of tissue oxygenation, cellular anaerobic metabolism results in the excessive production of carbon dioxide (CO_2) in the gastrointestinal mucosa. Measurement of the intragastric partial pressure of CO_2 (P_gCO_2) and calculation of its difference from the arterial partial pressure of CO_2 (P_aCO_2) may provide valuable information concerning the metabolic and circulatory conditions of the stomach and the splanchnic region.

In our studies, we set out to examine the feasibility and reliability of the new neonatal probes under paediatric surgical conditions and on critically ill, ventilated patients in the neonatal intensive care unit (NICU). Furthermore, we compared the $P_{g-a}CO_2$ gap (the difference of P_gCO_2 and P_aCO_2) with the $P_{g-ET}CO_2$ gap (the difference of P_gCO_2 and $P_{ET}CO_2$, the end-tidal partial pressure of CO_2), as an alternative, and investigated the relationship between increased $P_{g-ET}CO_2$ gap values and an unfavourable outcome.

## 1.2. Characteristics of CO_2 in the human body

1.2.1. Metabolism and role of CO_2 in the human body

CO_2 is a final product of great importance in the cellular metabolism. During the aerobic metabolism, the mitochondria consume oxygen (O_2) and produce CO_2. CO_2 diffuses from the mitochondria into the cellular cytoplasm, crosses the cell membrane and travels into the blood flow.

There are four types of CO_2 transport in the blood (8):

- That of the amount of physically dissolved CO_2 (5%), which can be calculated via Henry's law, and accounts for the partial pressure of CO_2 in the blood (PCO_2). Its level increases linearly with increases in PCO_2. Changes in temperature can modify the solubility of CO_2 in the blood and hence PCO_2.

- Nearly 5% of the blood CO_2 is transported in the form of carbamino compounds, as CO_2 binds reversibly to the non-ionized terminal amino ($-NH_2$) groups of blood-borne proteins and haemoglobin (Hb). Following a concentration gradient into the red cells, a small fraction remains dissolved in the cytoplasm and some is loosely bound to $-NH_2$ groups of reduced Hb forming carbamino-Hb.

- Some of the dissolved CO_2 reacts with water, and rapidly undergo hydration to form carbonic acid (H_2CO_3) through the action of the enzyme carbonic anhydrase. H_2CO_3 immediately dissociates to the bicarbonate ion (HCO_3^-) and a hydrogen ion (H^+).

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^-$$
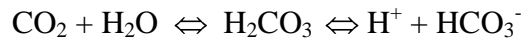
  This reaction is slow in the plasma, but more than 10 000 times faster in the erythrocytes. HCO_3^- diffuses out of the erythrocytes into the plasma according to the law of mass action. Nearly 90% of the total CO_2 content is transported in the form of HCO_3^- : 65% by the plasma, and the remaining 25% by red cells.

- A negligible amount (less than 0.1%) of CO_2 is transported as $H_2CO_3^-$.

Three parameters of the blood CO_2 content can be determined in routine practice by blood gas analysis: PCO_2, the plasma concentration of HCO_3^- and the total concentration of CO_2 in the plasma ($ctCO_2$).

Of these, only PCO_2 is actually measured during blood gas analysis; the other two parameters are calculated from the blood pH and PCO_2. HCO_3^- , PCO_2 and pH are the main determinants of the acid-base status.

The blood pH and $ctCO_2$ in the plasma or serum can be measured by chemical methods.

CO_2 has multiple roles of in the human body:
- It is regulator of breathing.
- It is a relaxant of the vascular smooth muscles and a regulator of vascular resistance (and hence the blood flow of the organs).
- It plays an important role in the acid-base balance.
- It is a regulator of the O_2 affinity of haemoglobin via the Bohr - effect.
- CO_2 is presumed to act as a signalling molecule in various physiological processes, such as the control of blood flow, breathing, hearing and reproduction (9).

The redundant CO_2 is exhaled by the lungs and the gastric mucosa or excreted with the urine and stools in the form of HCO_3^- . The theory of gastric ventilation (10) postulates that, with regard to the common embryological origin, the anatomical-functional similarities (large internalized surface areas and direct communication with the external environment of the body) and the shared and communicating innervation of the respiratory and gastrointestinal systems, the stomach plays a supplementary ventilation-like role in the

process of CO_2 elimination. The importance of gastric ventilation has been proved during digestion in the normocapnic state, in non-deglutitive respiratory acidosis and in non-deglutitive metabolic acidosis (10).

1.2.2. Formation of CO_2 in the gastric lumen

As a result of the accumulation of CO_2 in the bloodstream, hypercapnic acidosis develops and the nucleus tractus solitarius receives input from the central chemoreceptors (such as the retrotrapezoid nucleus, ventrolateral medulla, rostroventrolateral medulla, medullary raphe, locus coeruleus, fastigial nucleus and lateral hypothalamus), from the peripheral chemo- and baroreceptors and from a variety of airway receptors. The caudal solitary complex maintains several ventilatory-cardiovascular and gastrointestinal functions under integrative control and finally, as a vagus-mediated reflex mechanism, it enhances the development of changes in the respiratory rhythmogenesis and ventilatory pattern formation and in the cardiovascular output, and gives rise to an increased gastric mucosal blood flow and the increased production of gastric juice and HCO_3^- (10).

Arterialized blood rich in CO_2 supplies the stomach and, according to the law of mass action, CO_2 from the blood crosses the basolateral membrane by diffusion to the gastric epithelium. This process is enhanced by an increased gastric blood flow. Inside the epithelial cells, CO_2 reacts with water to form H_2CO_3. A certain amount of H_2CO_3 quickly dissociates into H^+ and HCO_3^-, generating a steady-state condition. Some of the intracellularly formed HCO_3^- then returns to the gastric circulation in exchange for Cl^- in order to decrease respiratory acidosis, and the remaining HCO_3^- crosses the apical membrane and enters the gastric lumen to neutralize the intraluminal H^+ in the canaliculi and gastric mucosa, resulting in the regeneration of CO_2. In contrast with its passage into the gastric lumen, the gastric mucosa is impermeable to CO_2, preventing its diffusion back from the intragastric space, especially during gastric acid secretion (10, 11).

In the case of an acid-base balance and in the absence of food stimuli, the production of CO_2 and gastric acid is minimal, but a significant amount of CO_2 is generated after meals or in the event of an acid-base imbalance (10, 11).

The CO_2 required for the production of gastric acid, and hence the intragastric mucosal CO_2, is mostly supplied by the blood, transported largely as HCO_3^- and to a lesser extent as carbamino compounds, but the volume of physically dissolved CO_2 (which sets P_aCO_2) is also noteworthy. The results of gastric tonometric studies demonstrate a close correlation

between P_aCO_2 and the gastric mucosal tissue PCO_2 during alveolar hyperventilation and hypoventilation in humans (12 - 14).

1.3. Measurement of gastric CO_2

1.3.1. Basic considerations of gastric tonometry

Gastrointestinal luminal PCO_2 tonometry is a method of measuring the mucosal PCO_2 and thereby the adequacy of the local tissue oxygenation in the hollow organs of the gastrointestinal tract. During its long history, tonometry has been performed in different parts of the gut, such as the sublingual region, the oesophagus, the stomach, the bowel and the sigma. Of these, gastric tonometry proved to be the easiest and most practical way of gaining reliable and sensitive information about the adequacy of oxygenation in the stomach mucosa and hence the condition of the systemic and splanchnic circulations. The theory that fluid inside a hollow organ approximates the gas tension in the surrounding tissues was first proposed by Dawson and his colleagues, but the publications relating to the method of gastrotonometry in the late 1950s are strongly linked with the name of the paediatrician Boda and his research fellow Murányi (12), and Boda and his colleagues subsequently made a number of significant contributions (6, 7, 15 - 21). In 1995, Fiddian - Green and his colleagues revised the concept of gastrotonometry (22). During recent decades, both the tools and the method have undergone a number of changes and the procedure is generally referred to in the literature under the name gastric tonometry.

In a state of adequate oxygenation, mitochondrial oxidative phosphorylation is able to produce sufficient adenosine triphosphate (ATP) for the metabolism of the cells. During hypoxia, the only possibility for energy production is the unsatisfactory anaerobic glycolysis. A pathological condition develops, irreversible ATP hydrolysis, when the hydrolysis of ATP exceeds the rate of ATP synthesis.

$$2\ ATP \rightarrow 2\ ADP + 2\ H^+ + Pi + energy$$
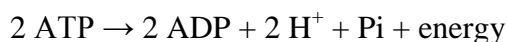
where ADP = adenosine diphosphate and Pi = phosphate ion.

As an end-product of the process, H^+ accumulates and provokes acidosis. The H^+ formed is buffered by tissue HCO_3^- resulting in excessive gastric CO_2 production.

Because of the lack of other compensatory blood vessels, this mechanism can be detected the earliest in the intestinal villi supplied with blood by only one end-artery. Intestinal mucosa lies over the end-point of this arteriola where the partial pressure of O_2 (PO_2) and

the O_2 gradient are the smallest, and the intestinal mucosa can therefore be considered the most sensitive indicator of tissue hypoxia.

In shock conditions, as part of the redistribution of the circulation, early selective vasoconstriction of the splanchnic area in order to enhance the blood supply of the most important organs can be observed. The oesophagus and the sublingual regions are not supplied by the splanchnic blood vessels, and unlike the stomach or the bowels, cannot be thought of as sensitive early indicators of deterioration of the systemic circulation.

The method of gastric tonometry is based on the fact that the CO_2 content in the superficial layers of the mucosa equilibrates with the CO_2 in the lumen of the gut, which can therefore be deduced from it. A gastric catheter combined with a silicone tonometric balloon permeable to CO_2 is inserted into the lumen of the gut in the same way as a standard nasogastric probe. The balloon is then filled with air (23). After a certain equilibration time, the content of the balloon is sucked out and its PCO_2 (which reflects the PCO_2 of the mucosa) can be determined (23). Normal saline, gastric acid or buffered solutions injected anaerobically can be applied to fill the balloon instead of air (24, 25) (see Fig. 1).
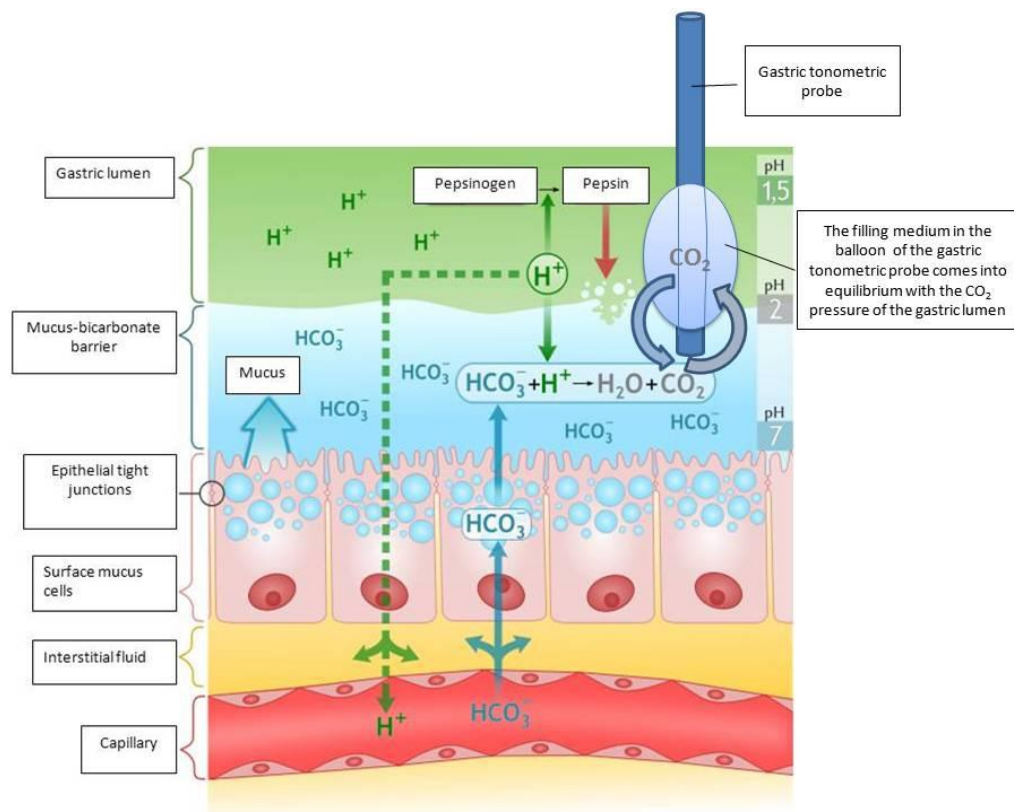

Figure 1 Principles of PCO_2 and HCO_3^- diffusion in gastric tonometry

(Original picture: Stomach mucosal layer labeled.svg. *Commons.wikimedia*.

http://commons.wikimedia.org/wiki/File:Stomach_mucosal_layer_labeled.svg)

1.3.2. Evaluation of gastric tonometric variables

From the measured intragastric PCO_2, the gastric intramucosal pH (pHi) can be calculated via the Henderson – Hasselbalch - equation, with the assumption that the HCO_3^- concentration of the gastric mucosa is equals to the systemic arterial HCO_3^- level, which holds true except for pathologic states involving partial or total gastric ischaemia.

$$pHi = 6.1 + \log \frac{[HCO_3^-]}{PCO_2 \text{ x } \alpha \text{ x } F_{(SS)}}$$

where pHi is gastric intramucosal pH,

6.1 is the pKa of CO_2 ,

HCO_3^- is the gastric intramucosal HCO_3^- concentration ($\approx$ arterial HCO_3^- concentration),

PCO_2 is the gastric intraluminal PCO_2 measured by gastric tonometry,

α is a constant representing the solubility of CO_2 in the plasma (= 0.03), and

$F_{(SS)}$ is a corrective factor proportional to the equilibrium time (26, 27).

Since pHi is affected by both the splanchnic O_2 supply and the systemic acid-base conditions, pHi can be regarded as a sensitive and early predictor of the patient outcome.

In order to avoid possible bias caused by the use of arterial HCO_3^- (for the calculation of mucosal pH, Fiddian - Green recommends the introduction of the use of a standard pH and the pH gap (22). In this manner, the effects of changes in the acid-base balance on the mucosal pH can be eliminated.

Local hypoxia can be differentiated from generalized acidosis through use of a standard pHi instead of the actually determined pHi:

$$\text{Standard pHi} = 7.4 - \frac{\text{tonometer } PCO_2}{P_aCO_2} \quad \text{(normally} = 7.4 \pm 0.04\text{) (28)}$$

In order to be able to make further distinctions between local hypoxia and generalized acidosis on the basis of the results of gastric tonometry, another parameter, the PCO_2 gap, i.e. the difference between the tonometric and arterial PCO_2, can be introduced. Studies on normal volunteers suggest that its acceptable value is 1 kPa. On the assumption that the P_aCO_2 – alveolar PCO_2 difference is constant (normally 4 mmHg = 0.5 kPa), the $P_{g-ET}CO_2$ gap, a minimally invasive marker of gastric perfusion (normal values up to 1.5 kPa) can also be applied during evaluation of the tonometric findings (29). Use of the $P_{g-ET}CO_2$ gap instead of $P_{g-a}CO_2$ gap makes arterial blood gas analyses unnecessary. Widening of the

$P_{g-ET}CO_2$ gap is indicative of an increasing ventilation/perfusion imbalance. Normal values of CO_2 gaps do not necessarily mean healthy states. In the follow-up of the patients' conditions, the changes in their trends can be much more valuable than the actual numerical values. Furthermore, CO_2 gaps should always be considered in conjunction with other clinical findings. Negative CO_2 gaps can be caused either by equipment failure or by the presence of surplus gastric air.

Numerous studies have supported the reliable application of gastric tonometry in different fields of medicine:

- Intensive care (sepsis, shock, multiple organ failure, weaning from a ventilator) (26, 27, 30 - 33)
- Anaesthesiology (34, 35)
- Traumatology (36, 37)
- Neurology (38)
- Nephrology (39)
- Cardiology, cardiac surgery (40 - 42)
- Liver transplantation (43, 44)
- Vascular surgery (29)
- Abdominal surgery (45)
- Abdominal compartment syndrome (46)
- Gastroenterology (29, 47 - 48)
- Clinical investigations on the pharmacological effects of drugs (27, 29, 49)
- Paediatrics and neonatology (50 - 52)
- Major burns (53)

Benefits of gastric tonometry:

- It is a simple and a relatively non-invasive / semi-invasive method.
- It is free from local tissue artifacts caused by electrode insertion.
- It does not require sensors that can suffer drift or need *in vivo* recalibration.
- It provides an organ-specific measure of hypoxia.
- Detection of local tissue hypoxia is possible within minutes.
- It provides predictive information concerning complications and the outcome of the patient's condition.

- It provides a possibility for early, more appropriate and more effective interventional measures, the control of their effectiveness and a valuable end-point for resuscitation.
- It eliminates the need for more expensive forms of monitoring.
- It shortens the length of the hospital stay (54).
- It reduces the costs of intensive care (54).

Possible sources of bias during gastric tonometry:

- Incorrect positioning (the catheter is not in the stomach or it is positioned too close to the pylorus).
- The influence of the traditionally administered H_2-receptor antagonists on the reliability of the measurement is controversial (10, 11, 55).
- The swallowing of air, and the entry of air into the stomach, mostly in spontaneously ventilating, non-intubated patients or those undergoing nasogastric suction may result in a transient lowering of the gastric PCO_2 (11).
- An adequate equilibration time must be ensured. Adoption of a corrective factor proportional to the equilibration time (based on experimental data) during the evaluation of gastric tonometric variables allows the use of shorter equilibration times (27).
- The catheter dead-space should be taken into account. With the help of appropriately prolonged dwell times, the diluting effect of a larger deadpace can be nearly eliminated (56).
- The evaluation is based on the assumption that the HCO_3^- concentration in the gastric mucosa is equal to the systemic arterial HCO_3^- concentration, though this may not be valid in shock (57, 58).
- $PaCO_2$ must be corrected for body temperature.
- A pressure correction can eliminate the influence of the atmospheric pressure and the pressure exerted by the adjacent anatomical structures on PCO_2 in the gaseous phase.
- The molecular weight of Nitrous oxide (N_2O) is equal to that of CO_2, and simultaneous direct measurement of both gases should therefore be performed.
- Technical errors may appear if examination samples are not handled with the necessary care.

1.3.3. Gastric tonometry in childhood

There is an extensive literature on the applications of gastric tonometry in adults, but the number of studies on children is appreciably less. This can mostly be explained by the technical limitations caused by the different sizes of the patients and the tools available. Nevertheless, trials of the method in critically ill children (51), anaesthetized paediatric cases during and after surgery (52), neonates (59) and even very low birth weight infants (50) have been published. The limited data available in this field support the predictive value and clinical usefulness of gastric tonometry in a heterogeneous paediatric population. In order to evaluate the gastric tonometric data obtained in paediatric patients, reference values in children are necessary. Reinoso − Barbero et al. found that the normal range of the pHi in normoventilated and haemodynamically stable children in the age range 6 months to 12 years, who had not been previously treated with ranitidine under minor reconstructive surgery, was 7.35 ± 0.06 (60).

Authors of studies on paediatric tonometry share the unanimous opinion that pHi is a reliable, highly specific and sensitive early predictor of haemodynamic complications and early mortality in the paediatric population. The relative safety, simplicity and semi-invasive character of the method make it especially suitable for routine use in the critically ill paediatric age group, more invasive and complicated methods being reserved for use with special indications. In order to be able to detect the deterioration of splanchnic tissue oxygenation as early as possible, regular measurements on a 4 h basis are advised, unless continuous measurement is available (51, 52). The use of tonometric catheters is generally free of any major complications (epistaxis may sometimes occur).

Several studies support the applicability of blood samples obtained either from veins or capillaries for the determination of the systemic acid-base status, involving the pH, PCO_2, HCO_3^- and base excess (BE) in paediatric patients of different ages. These results correlate well even in patients in poor condition. Venous or arterialized capillary blood gas analyses can therefore be useful alternatives of painful and sometimes complicated arterial blood sampling for arterial blood gas measurements in children (61).

Many authors dealing with gastric tonometry highlight the importance of the method in paediatric care (50, 59). The new Boda's gastric tonometric probe was developed to meet the demand for a tonometric catheter with rapid equilibration and ready applicability in patients of all ages, including very low birth weight neonates (16).

2. AIMS AND QUESTIONS OF THE STUDIES

The usefulness of the novel gastric tonometric probe in paediatric patients has already been proven by earlier studies (7, 15 - 19). We designed two prospective clinical investigations in order to support the applicability and reliability of the new neonatal gastric tonometric tool in extended fields: in the paediatric population under intraoperative conditions (study 1), and in low birth weight NICU patients in critical states (study 2).

We were the first to apply the novel gastric tonometric probe in this age group during surgical procedures. We wished to exploit the known benefits of the method: to assess the adequacy of ventilation and the splanchnic perfusion of the patients and to acquire information as to the severity of the disease.

We investigated the possibility of gaining therapeutic information in a semi-invasive manner, bypassing the risk of infection and vasoconstriction caused by the painful and often difficult blood sampling, and the considerable anaemia and haemodynamic changes that can occur in these small patients due to the significant blood loss caused by repeated blood samplings. In order to reduce the need for repeated blood sampling, we set out to examine and the possible usefulness of the $P_{g\text{-}ET}CO_2$ gap by using capnometric $P_{ET}CO_2$ values instead of P_aCO_2. We are not aware of previous studies of the diagnostic value of the $P_{g\text{-}ET}CO_2$ gap in this age group.

Both studies were approved by the Human Investigation Review Board of the University of Szeged. In every case, informed consent was obtained from the parents.

The main questions studied were the following:

Question I

Can the novel gastric tonometric probe developed for paediatric patients of all ages be used safely and reliably during paediatric surgical procedures (study 1) and in the population of smallest paediatric patients in the NICU (study 2)?

Question II

Is there any difference between the groups in terms of the $P_{ET}CO_2$ values during surgery (study 1) and in NICU patients (study 2)?

Question III

Is there any correlation between the P_aCO_2 and $P_{ET}CO_2$ values in the examined patients during surgery (study 1) and in NICU patients (study 2)?

Question IV

Does the respiratory dead-space of the patients exert any effect on the $P_{g-ET}CO_2$ gap?

Question V

Is there any difference between the groups in terms of the P_gCO_2 values during surgery (study 1) and in NICU patients (study 2)?

Question VI

Is there any difference between the groups in terms of the $P_{g-a}CO_2$ gap values during surgery (study 1) and in NICU patients (study 2)?

Question VII

Is there any difference between the groups in terms of the $P_{g-ET}CO_2$ gap values during surgery (study 1) and in NICU patients (study 2)?

Question VIII

Is there any correlation between the $P_{g-a}CO_2$ and $P_{g-ET}CO_2$ gaps during surgery (study 1) and in NICU patients (study 2)?

Question IX

Does the $P_{g-ET}CO_2$ gap relate to the severity of the disease?

3. STUDY 1

Study no. 1 was a prospective randomized study of the therapeutic value of the $P_{g-ET}CO_2$ gap beyond the already proven clinical reliability of the Boda probe under intraoperative circumstances in paediatric patients.

3.1. Patients

The prospective study enrolled a total of 25 anaesthetized surgical patients: 19 elective and 6 acute cases. The 19 elective surgical patients were assigned to one or other of two groups according to their ages (group I and group II). Group III consisted of the acute surgical patients, independently of their ages. The patient characteristics, the diagnoses and the compositions of the groups are presented in Table 1.

Table 1   Characteristics of the three groups of cases involved in the study

Parameters	Group I (elective surgery group < 2 years old, n = 10)	Group II (elective surgery group > 2 years old, n = 9)	Group III (acute surgery group, n = 6)
Age (months) **Median and Range**	11.2 0.1 - 24	97.7 29 - 261	98 15 - 204
Weight (kg) **Median and Range**	7.3 3.0 - 15	26.6 25 - 261	27.4 28 - 193
Diagnosis	Hydronephrosis (4) Hypospadia Ovarial cyst Duodenal atresia Nephrectomy Port-a-cath insertion	Hypospadiasis (5) Appendicitis Ureter reimplantation Colon resection Port-a-cath insertion	Tenkhoff-catheter insertion Hirschprung's disease Appendicitis (2) Pancreatitis Peritoneal adhesions
Ventilation (V_T ml/kg) **Median and Range**	8.2 6.4 - 9.9	8.9 5.5 - 12.2	8.9 5.5 - 12.2

3.2. Methods

Each patient in the study underwent general anaesthesia during the surgical intervention. Anaesthesia was induced with intravenously administered midazolam, fentanyl and ketamine or propofol. In order to establish optimum conditions for the endotracheal intubation, muscle relaxants (rocuronium or cisatracurium) were applied, and the level of muscle relaxation was monitored by an accelerometer throughout the procedure.

In the selection of the proper size of the intratracheal tubes, we followed the recommendations of internationally accepted guidelines (62). Seventeen of the examined patients were younger than 8 years, and they were therefore intubated with uncuffed tubes. In the case of the 8 patients older than 8 years, cuffed intratracheal tubes that could be passed with ease were inserted, but an important restriction was to have only minimally allowable gas leakage on ventilation.

During the surgical intervention, the patients were ventilated via a paediatric closed breathing circuit by a Dräger Julian ventilator (DrägerwerkAG, Luebeck, Germany) and

for anaesthesia maintenance constant flow of a mixture of O_2, N_2O and sevoflurane was administered.

CO_2 samples for determination of $P_{ET}CO_2$ could be delivered at the gas-sampling port of the endotracheal tube adapter in infants smaller than 4 kg, or at the CO_2 sampling port of the airway filter interconnecting the endotracheal tube and the breathing circuit in patients larger than 4 kg.

Samples for P_gCO_2 measurement were delivered by Boda balloonless gastric tonometric probes after a 10-minute equilibration period (Fig. 2). The examination tools were introduced nasally in every case, because of the need for firm fixation during the surgical procedures. The correct gastric positions of the probes were confirmed by the correct CO_2 curves on the capnograph monitor following the 10-minute equilibration period. For the determination of $P_{ET}CO_2$ and P_gCO_2, the same equipment was used (Sidestream Microcap Handheld Capnograph, Oridion Medical Ltd, Jerusalem, Israel).

In 6 cases, simultaneously with the $P_{ET}CO_2$ and P_gCO_2 measurements, arterialized capillary blood samples were obtained for blood gas analysis. The PCO_2 content of arterialized blood samples was determined with an ABL700 instrument (Radiometer, Copenhagen, Denmark).

Description of the gastric tonometric probes

Figure 2   Boda's original balloonless gastric tonometric probe
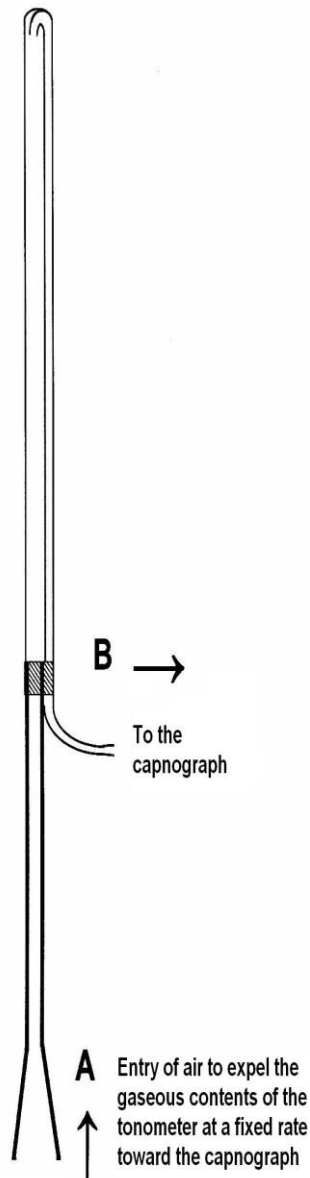
The new tonometric tool is made of silicone, which is highly permeable for CO_2. Two tubes (a thicker and a thinner one) are sealed adjacent to each other over their full length, and are connected to form an uninterrupted tube, free of any kind of balloon. The larger diameter tube (**A**) has a lumen diameter of 2 mm and a wall thickness of 0.25 mm, while the lumen diameter of the thinner tube (**B**) is 0.8 mm and the wall thickness is 0.2 mm. The two tubes can communicate only at the distal end of the probe. At the proximal end of the device, the two tubes are held together with a silicone rubber fastening ring. The probes applied in the studies were 25 or 30 cm in length between the fastening ring and the tip of the device. The well-lubricated probe can be inserted orally or nasally into the stomach in its full length up to the fastening ring with the aid of a similarly lubricated guide wire. For the purpose of lubrication, a symethicon emulsion (Espumisan®, Berlin-Chemie AG, Berlin, Germany) is recommended. The medium initially fillings the probe is usually room air. The room air in the probe equilibrates with the environmental PCO_2 of the body cavity throughout its full length within 10 minutes. After an equilibration period of 10 minutes, the tubing is connected to the microcapnograph for transport of the gaseous examination material and measurement of its PCO_2. Measurements can be performed repeatedly at intervals, as desired. Repeated measurements of the PCO_2 content at stated intervals and storage of the data can also be carried out through use of an automated monitoring device.

Improved types of probes combined with a built-in gastric catheter make another nasogastric catheter unnecessary, which is more convenient for the patients.

Use of the probe in humans was approved by the Ethical Committee of the Hungarian Academy of Sciences and the Human Investigation Review Board of the University of Szeged.

3.3. Statistical analysis

The relationships between the measured $P_{ET}CO_2$ and P_gCO_2 in the study groups were examined by linear regression analysis. Pearson's correlation coefficient and p values were also calculated. To examine the agreement between the measurements, Bland - Altman analysis (63, 64) was performed. The bias (defined as the mean difference between values), the precision (defined as the standard deviation (SD) of the bias) and the limits of agreement (defined as the bias ± 2 SD) were determined for the groups.

Since there were multiple measurement data from each patient for the various PCO_2 values, we used a two-way mixed-model repeated-measurements analysis of variance (ANOVA) with groups as between-subject factor and time as within-subject factor for the comparison of the different groups. This method is a generalization of the two-sample t-test, where both group differences and the individual within-subject variations in time can be modelled.

SPSS 15.0 for Windows (SPSS for Windows Rel. 15.0, SPSS Inc., Chicago, Illinois, USA) was applied for the statistical calculations.

4. STUDY 2

In the second prospective study, 2 groups, 44 ventilated NICU patients in different severities of their disease, were enrolled.

4.1. Patients

The 35 NICU patients in group 1 were in a severe but stable condition, with clinical risk index for babies (CRIB) scores ≤ 10, while group II consisted of 9 patients with severe illness (CRIB scores > 10). Details of these patients and their diagnoses are given in Table 2.

Table 2   Characteristics of the examined NICU patients

Parameters		Group 1 (*CRIB scores ≤ 10, n = 35*)	Group 2 (*CRIB scores > 10, n = 9*)
Age	**Gestational age at birth** [weeks ± SD]	32.1 ± 3.7	30.9 ± 6.9
	Age at the time of examination [days ± SD]	11.9 ± 16.2	12.3 ± 11.14
Weight [g ± SD]		1833 ± 885	1871 ± 1281
Diagnoses	**Prematurity with sepsis**	**5**	**3**
	+ RDS + NEC	2	-
	+ RDS + pulmonary haemorrhage	1	-
	Prematurity with RDS	**11**	**2**
	+ Ptx	1	-
	+ IVH (grade II)	1	-
	+ PDA	3	-
	+ Infant of mother with DM	1	-
	Persistent foetal circulation		
	+ Ptx	1	-
	+ RDS + VSD + Down sy.	1	-
	Meconium aspiration syndrome	**2**	**-**
	Post-cardiac surgery care		
	• VSD (PA banding)	1	-
	• CAVC defect (PA banding)	-	1
	• Coarctation of aortic arch	-	1
	Other anomalies		
	• Biliary atresia	1	-
	• Infection + convulsions	1	-
	• Perinatal hypoxia	3	-
	• Short rib syndrome	-	1
	• Glycogenosis + hypoxia	-	1
CRIB score (mean ± SD)		3.54 ± 2.3	12.25 ± 2.17***

There was significant difference between the two groups (Student's unpaired *t*-test) in terms of their CRIB scores (***$p < 0.001$),
CAVC, complete atrioventricular canal; IVH, intraventricular haemorrhage; PA, pulmonary artery; PDA, persistent ductus arteriosus; Ptx, pneumothorax; VSD, ventricular septal defect.

4.2. Methods

The patients were investigated throughout their full stay in the NICU. Each of them was ventilated and sedated to meet their demands. For the determination of the sizes of the uncuffed tubes to be used for intratracheal intubation, we followed the recommendations of internationally accepted guidelines (62), in accordance with gestational age and body weight, similarly as in study 1.

The observed neonates were ventilated with SLE 2000, SLE 2000 HFO or SLE 5000 ventilators in conventional modes (synchronized intermittent mandatory ventilation and continuous mandatory ventilation) according to the requirements of their conditions. The need for other types of ventilation, such as high-frequency oscillation, was a criterion for exclusion from the study. The patients involved in the study were assigned to one or other of two groups. The 35 neonates (all survivors) with their CRIB scores lower than 10 were delegated to group 1, while group 2 consisted of 9 patients in severe condition with CRIB scores higher than 10 (2 out of 9 survived).

The treatment followed the local protocols, but the routine administration of H_2 receptor blockers was omitted. Three types of PCO_2 measurements were made in each patient, the ventilator setting parameters remaining unchanged.

$P_{ET}CO_2$ was measured on samples obtained from the gas-sampling port of the intratracheal tube adapter. Each measurement lasted for at least 4 minutes and the highest measured value was accepted. $P_{ET}CO_2$ was measured with a Sidestream Microcap Handheld Capnograph (Oridion Medical Ltd, Jerusalem, Israel).

P_gCO_2 levels were examined with the use of Boda's gastric tonometric probes, inserted orally or nasally. To ease the introduction, a flexible guide wire was used in the probe. Both were well lubricated with symethicon. The positions of the probes were considered gastric if correct CO_2 curves were obtained on the capnograph monitor after the 10-minute of equilibration period. Gastric tonometric measurements were performed after the appropriate equilibration interval had passed, and measurements were also made with the Sidestream Microcap Handheld Capnograph.

The acid-base parameters (pH, HCO_3^-, BE, PO_2 and PCO_2) were obtained from the blood gas analysis of umbilical artery blood samples or arteriolized capillary blood samples with an ABL 700 instrument (Radiometer, Copenhagen, Denmark).

Two more data were calculated from the results of the measurements: the $P_{g-a}CO_2$ gap and the $P_{g-ET}CO_2$ gap. The dead-space ventilation fraction was estimated via the equation: dead-space volume / tidal volume = $(P_{a-ET}CO_2) / P_aCO_2$.

4.3. Statistical analysis

As there were multiple measurement data from each patient for the various PCO_2 values, we used a two - way mixed - model repeated - measurements ANOVA for the comparison of the two groups. For the comparison of the PCO_2 gap values in the groups, a three-way mixed-model ANOVA was used, with the groups as between-subject factor, gaps as within-subject factor and time as within-subject factor. The various PCO_2 values and PCO_2 gap values were compared using Bland - Altman analysis for multiple measurements per individual, and the correlation recommended for repeated measurements was used for the comparison of the characteristics of the neonates in the two groups of patients with unpaired Student's t-tests.

5. RESULTS (in the sequence of the main questions studied)

Result I

Study 1. Apart from 2 cases, the gastric tonometric probes could be introduced with ease. In one case, the probe stopped at a certain point of the oesophagus and could not be passed further. In the other case, the probe could not be passed through the pharynx. There were no further technical difficulties during the measurements.

Study 2. The oral or nasal introduction manoeuvres of the tonometric probes proved facile in all cases. There were no difficulties, unintended side-effects or serious complications during the introduction procedure or the repeated measurements.

Result II

Study 1. In spite of the differences between the ages of the group I and II patients, their $P_{ET}CO_2$ levels were nearly identical (mean difference 0.10 mmHg and $p = 0.96$), whereas the result in group III differed significantly from those for the elective surgery cases (mean differences: 1.9 mmHg and 2.0 mmHg, $p = 0.03$ and 0.031, respectively).
When groups I and II were combined, their $P_{ET}CO_2$ levels differed significantly from that for group III (mean difference 1.94, $p = 0.014$) (Table 3).

Table 3 Number of measurements, measured CO_2 levels and calculated $P_{g\text{-}ET}CO_2$ gaps of the three groups in study 1.

	Group I (*elective surgery group < 2 years old, n = 10*)	Group II (*elective surgery group > 2 years old, n = 9*)	Group III (*acute surgery group, n = 6*)
Number of measurements	**42**	**34**	**32**
$P_{ET}CO_2$ **(mmHg) mean ± SD**	34.19 ± 3.95	34.09 ± 2.85	36.09 ± 3.87[*]
P_gCO_2 **(mmHg) mean ± SD**	40.31 ± 4.73	39.46 ± 3.56	48.12 ± 5.93[**]
$P_{g\text{-}ET}CO_2$ **(mmHg) mean ± SD**	6.12 ± 3.9	5.37 ± 2.48	12.03 ± 5.67[**]

Significant differences between the data for group III and the pooled data for groups I + II regarding $P_{ET}CO_2$, P_gCO_2, and $P_{g\text{-}ET}CO_2$ values ([*]$p < 0.05$; and [**]$p < 0.001$).

Study 2. There were no significant differences in $P_{ET}CO_2$ between the groups of NICU patients with conditions of different severity, nor when either group I or group II was compared with the overall group ($p = 0.05$) (Table 4).

Table 4 Comparison of $P_{ET}CO_2$, P_gCO_2, P_aCO_2, $P_{g\text{-}ET}CO_2$ gap and $P_{g\text{-}a}CO_2$ gap values in the different groups of NICU patients in study 2

Parameters	Group 1 (*n = 35*)	Group 2 (*n = 9*)	All patients (*n = 44*)
$P_{ET}CO_2$ **(mean ± SD)**	36.53 ± 6.65	36.41 ± 5.75	36.51 ± 6.47
P_gCO_2 **(mean ± SD)**	46.45 ± 8.13	54.68 ± 13.7*	47.91 ± 9.81
P_aCO_2 **(mean ± SD)**	43.92 ± 8.22	45.97 ± 8.81	44.29 ± 8.33
$P_{g\text{-}ET}CO_2$ **gap (mean ± SD)**	9.92 ± 6.2[a]	18.27 ± 10.49**,[a]	11.4 ± 7.79[a]
$P_{g\text{-}a}CO_2$ **gap (mean ± SD)**	2.53 ± 6.78	8.71 ± 10.89*	3.63 ± 7.98
Number of parallel examinations (median[min–max])	3 (1 – 10)	3 (1 – 4)	3 (1 – 10)

Between-group values were compared with a mixed - model repeated - measurements ANOVA, while the two gap values of the same patients were compared with Student's paired t-tests. Significance was taken as [a] $p < 0.001$ in the case of the paired t-tests and *$p < 0.05$, **$p < 0.01$ in the case of mixed - model repeated - measurements ANOVA tests.

Result III

Study 1. Arterialized capillary blood samples were taken simultaneously with the $P_{ET}CO_2$ and P_gCO_2 measurements under intraoperative circumstances in only 6 cases. In these cases, the average $\pm$ SD of the differences between the arterialized blood and end-tidal CO_2 value was 2.38 ± 2.23 mmHg. The difference between the two parameters was statistically not significant ($p = 0.35$) (Table 3).

Study 2. In each group of examined NICU patients, $P_{ET}CO_2$ proved to be lower than P_aCO_2. There was a significant correlation ($p < 0.001$) between each pair of P_aCO_2 and $P_{ET}CO_2$ ($r = 0.631$). This correlation did not reveal a closer connection than that found between the gastric and systemic PCO_2 levels. The various PCO_2 and gap values are detailed in Table 4.

Result IV

Study 1. The fraction of dead-space ventilation was not calculated during this study. In the 6 intraoperative cases where simultaneous arterialized capillary PCO_2 measurements were performed, the average $\pm$ SD of the differences between $P_{ET}CO_2$ and P_aCO_2 was 2.38 ± 2.23 mmHg (not statistically significant: $p = 0.35$).

Study 2. In the low body weight NICU patients, a dead-space of 0.176 ± 0.223 was observed. The dead-space was significantly higher in group 2 (0.236 ± 0.098 versus 0.155 ± 0.143, $p = 0.022$). We also compared the smaller (weight < 1500 g, $n = 13$) and larger (weight > 2500 g, $n = 15$) patients. In this comparison, the dead-space was higher in the case of the low birth weight neonates (0.194 ± 0.115 versus 0.146 ± 0.141), but the difference was non-significant ($p = 0.069$). In each NICU patient group, the $P_{ET}CO_2$ was significantly lower than P_aCO_2, and as a consequence the $P_{g\text{-}ET}CO_2$ gap was significantly higher than the $P_{g\text{-}a}CO_2$ gap. In the cases of P_gCO_2 and both gaps, there was a significant difference between groups 1 and 2.

Result V

Study 1. We obtained nearly identical P_gCO_2 values in groups I and II (mean difference 0.85 mmHg, $p = 0.45$), but the corresponding result in group III of acute patients differed significantly from those for the elective surgery cases (mean differences 7.8 mmHg and 8.66 mmHg, $p < 0.001$ and $p < 0.001$, respectively). When groups I and II were combined, their P_gCO_2 level differed significantly from that for group III (mean difference 8.81, $p < 0.001$ (Table 3).

Study 2. P_gCO_2 was significantly higher in group 2 of severely ill NICU patients than in group 1, consisting of children in a better health state ($p < 0.05$). The data are detailed in Table 4.

Result VI

Study 1. In the course of the study simultaneous arterialized capillary PCO_2 sampling could be performed in only 6 of the total of 25 cases. The differences between the $P_{g-a}CO_2$ values of the investigated groups could not be evaluated because of the low number of data.

Study 2. $P_{g-a}CO_2$ was significantly higher in group 2 (NICU patients in a more severe condition) than in group 1 (NICU patients with a better disease status) ($p < 0.05$) (Table 4).

Result VII

Study 1. Although $P_{ET}CO_2$ was higher in group III, $P_{g-ET}CO_2$ was still greater in the group of acute patients than in groups I and II. This difference proved to be significant ($p < 0.001$) (Table 3).

As the data for the two elective surgery groups did not differ significantly, Bland - Altman analysis was performed on the combined data for groups I and II, while the acute surgery cases were analysed separately (Fig. 3A and 3B).

Figure 3A   Bland - Altman analysis of the data on elective surgery cases (groups I + II).
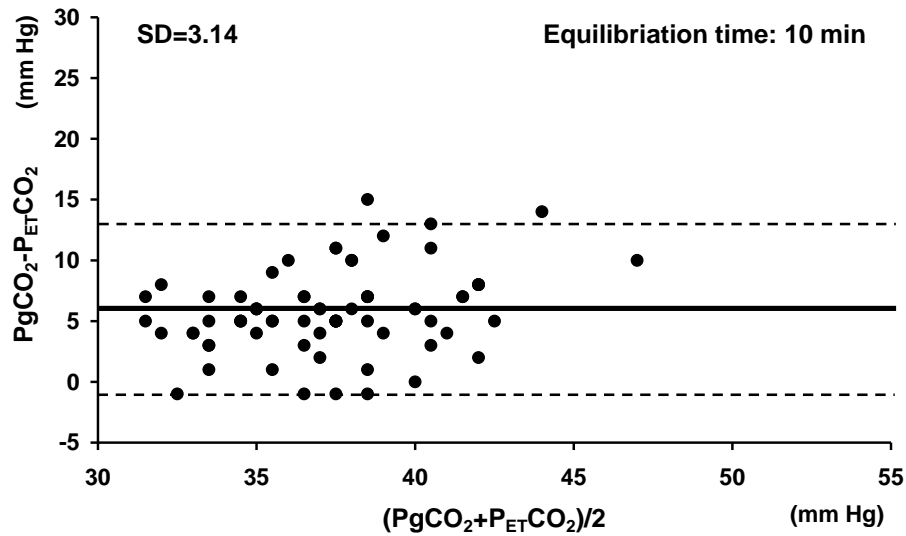
Bias = 5.79, precision = 3.14, limits of agreement -1.04 to 12.62.

Figure 3B   Bland - Altman analysis of the data on acute surgery cases (Group III)
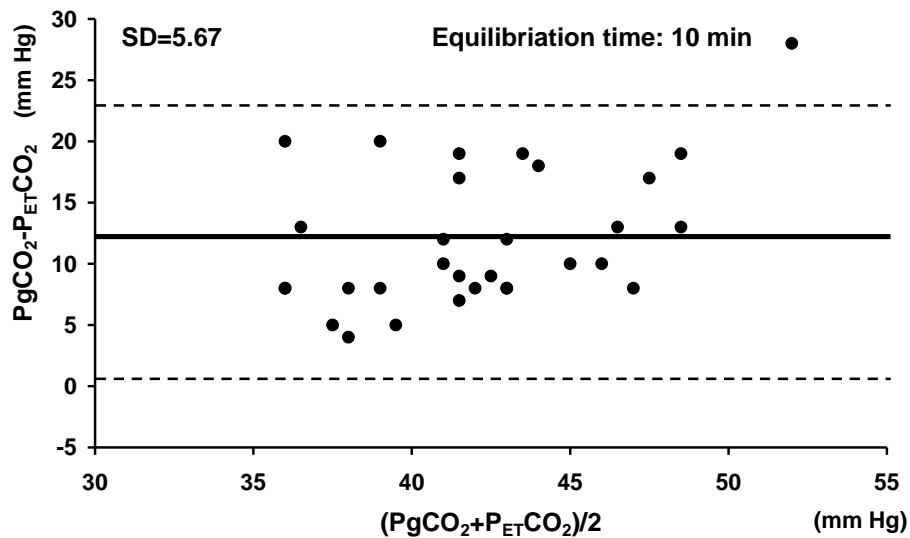
Bias = 12.03, precision = 5.67, limits of agreement 0.68 to 23.37.

The comparison of the bias values between the elective surgical groups and the acute surgical group (i.e. the $P_{g\text{-}ET}CO_2$) revealed a significant difference ($p < 0.001$). Significant correlations were found between P_gCO_2 and $P_{ET}CO_2$ in each group (group I: $r = 0.59$, $p < 0.001$; group II: $r = 0.71$, $p < 0.001$; group III: $r = 0.39$, $p < 0.029$).

Study 2. In each NICU patient group, $P_{ET}CO_2$ was significantly lower than P_aCO_2, and as a consequence, the $P_{g-ET}CO_2$ gap was significantly higher than the $P_{g-a}CO_2$ gap. P_gCO_2 and the $P_{g-ET}CO_2$ gaps were significantly higher in group 2 ($p < 0.01$). The various PCO_2 gap values are reported in Table 4.

Result VIII

Study 1. Since the $P_{g-a}CO_2$ gap could not be calculated as a result of the inappropriate number of arterialized capillary blood samplings, the correlations between the $P_{g-a}CO_2$ gap and $P_{g-ET}CO_2$ gap for the various groups could not be established.

Study 2. There was a significant correlation ($p < 0.001$) between the $P_{g-a}CO_2$ gap and the $P_{g-ET}CO_2$ gap ($r = 0.635$). During the examination of the relation of the two PCO_2 gaps, Bland - Altman analysis (Fig. 4A and 4B) revealed an acceptable correspondence between the two methods (7.78 ± 6.34 mmHg, bias and precision).

Figure 4A   Correlation (calculated with a method recommended for repeated measurements) of the $P_{g-a}CO_2$ gap and the $P_{g-ET}CO2$ gap in neonates.
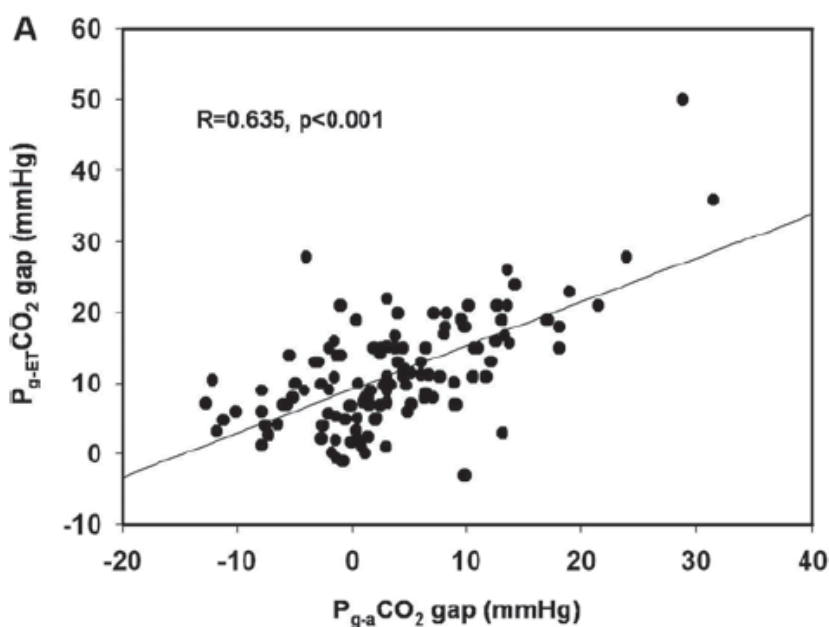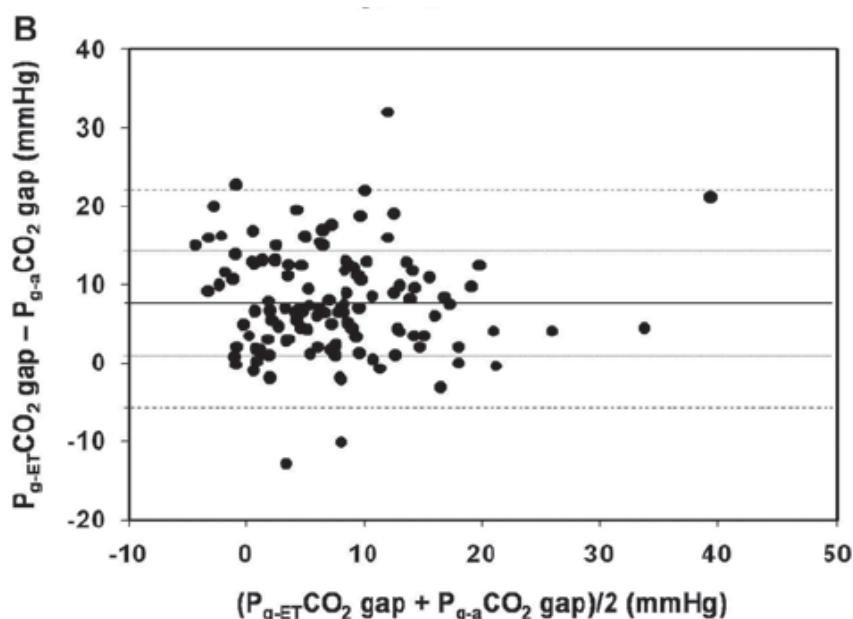
Figure 4B   Bland - Altman analysis of the $P_{g-a}CO_2$ gap and the $P_{g-ET}CO_2$ gap values in neonates

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Result IX

Study 1.   The $P_{g-ET}CO_2$ gap in group I of elective surgical patients younger than 2 years was 6.12 ± 3.9, and in group II, the elective surgical cases older than 2 years, was 5.37 ± 2.48. The $P_{g-ET}CO_2$ gap was significantly higher (12.03 ± 5.87) in group III of acute surgical patients.

Study 2.   The $P_{g-ET}CO_2$ gap for group 2, NICU patients with a worse health status, significantly exceeded that for group 1, NICU patients in a better condition (8.71 ± 10.89 and 2.53 ± 6.78, respectively).

6.   DISCUSSION

CO_2 is a very important and measurable end-product of the cellular metabolism. The measurement and continuous monitoring of the blood PCO_2 content and $P_{ET}CO_2$ in the exhaled gas are considered standard monitoring techniques providing important information about the global circulatory, respiratory and metabolic conditions of patients. Nevertheless, circulation disturbances caused by diseases, sepsis or shock can be hidden in

the early stage of onset if the overall CO_2 production is monitored alone. Early redistribution of the circulation in order to maintain the functions of the vital organs causes a reduction of gut perfusion with a concomitant increase in local CO_2 production in the splanchnic area. Gastric tonometric measurement of the gut tissue PCO_2 has been widely used for the detection of a deterioration of the splanchnic blood supply as an early sign of shock and multiorgan failure, either in intensive care or in the perioperative period of surgery (29, 65).

However, technical difficulties emerged with gastric tonometric measurements in children and infants. Up to the start of our studies, there had been only a few reports in the literature concerning trials of gastric tonometric measurements in small paediatric populations (50 - 52, 59, 66, 67). The most vulnerable point of paediatric tonometry was the limitation of applicability in the population of small patients, caused by the thickness of the adult tube and the relatively large size of the inflatable balloon. There have been studies in children when, in the lack of gastric tonometric probes of appropriate size, small-bore adult gastric tonometric probes, or adult-type sigmoid tonometric tools were applied. Sigmoid tonometers used to measure sigmoid mucosal pHi in adults are much smaller than adult gastric tonometers. In spite of the favourable experiences with the use of adult sigmoid tonometers in paediatric gastric tonometric investigations, it has been emphasized that a much smaller device would be needed for neonates and prematures (51, 52).

The problem could be solved by the development of a new, balloon-free type of tonometric probes for paediatric patients of any age. The suitability of Boda's gastric tonometric probe in both adults and the paediatric population has already been extensively studied and proven (15 - 20).

As a step in the validation studies, we demonstrated the feasibility of the procedure with the new tool in children undergoing surgery in study 1. Furthermore, we wished to extend its use to the intraoperative control of anaesthetized children through utilization of the $P_{g\text{-}ET}CO_2$ gap. As far as we know, before the start of our study there had been only one report on an examination of the reliability of the intraoperative P_gCO_2 - $P_{ET}CO_2$ difference in children (68). In study 2, we examined the new probe in very small patients in a severely ill condition and assessed the importance of the $P_{g\text{-}ET}CO_2$ gap in neonates, since we are not aware of any other report on this question in the literature.

From a technical point of view, the Boda probes proved to be well applicable both in intensive care and under intraoperative circumstances. In study 1, the well-lubricated

tonometric probes could be introduced with ease in all but 2 cases. In one case, the probe stopped at a certain point of the oesophagus and could not be passed further. This probe had to be removed, but could easily be replaced by another one. In the second case, the probe could not be passed through the pharynx, probably for anatomical reasons, and the help of Magill forceps was needed. There were no further complications or technical difficulties during the measurements. The minimally invasive probe can be introduced orally or intranasally. In anaesthetized patients, intranasal insertion proved to be more useful because the limited approach in the small patients during surgical interventions required firm fixation of the probe. The facile insertion of the tool could be further enhanced by the use of a thin and flexible guide-wire; both should be thoroughly lubricated with a symethicon (Espumisan®) emulsion. In the NICU patients in study 2 the probes could be inserted orally or nasally into the stomach in a problem-free way. There were no difficulties, unintended side-effects, or serious complications during the introduction procedures or the repeated measurements.

After the short equilibration time, the performance of the measurements was simple. Since the initial studies, the problems of automated measurement, the analysis of P_gCO_2, storage of the measured data and the technical errors caused by either interoperator variability or handling of the gas samples have been solved and the monitoring apparatus is available. Further studies by Boda (publication in preparation) demonstrate that the otherwise short time needed for equilibration of the gases in the probe can be appreciably decreased by using higher concentrations of CO_2 in air as filling medium. Accordingly, extended use of the balloonless gastric tonometric probes in general clinical practice, and particularly in paediatrics, may be highly recommended.

The patients examined in the two studies did not receive antacid medication or H_2-receptor antagonists on a routine basis. The gastric CO_2 generated by the neutralization of gastric acid by duodenal HCO_3^- may disturb the measurement of the gastric pH. The use of H_2-receptor antagonists to reduce the production of gastric acid before tonometric measurement appears reasonable, though it has been debated in small children. The literature on the development of the gastrointestinal tract of premature neonates underlines the various degrees of immaturity of the stomach. The intragastric pH in very low birth weight neonates within the first 48 hours of life is about 5.5-7.0. Campbell and Costeloe found lower pHi values (pHi = 7.27 ± 0.078) in very low birth weight neonates than the values previously reported in children (50). Gastric emptying also proved to be slower in

premature neonates than in term infants. Furthermore, many patients are not fed by enteral food for several days, with a resultant high gastric pH, and H_2-receptor antagonists are often administered in order to decrease gastric acid secretion. The lower gastric capacity of H^+ production of prematures is one of the weak points of the defence against ingested pathogens and toxins. Further reduction of the already low gastric juice production by the use of H_2-receptor antagonists is associated with a higher incidence of greater bacterial translocation, nosocomial sepsis and gastrointestinal diseases such as NEC (69). Since neutralization of the otherwise lower amount of gastric acid in prematures can be harmful, while Calvet and his colleagues found that the administration of ranitidine does not affect the variables of pHi in critically ill patients (70), the routine administration of H_2-receptor antagonists in gastric tonometric measurements would raise ethical questions, and it is not recommended in this age group.

Thre parameters $P_{ET}CO_2$, P_aCO_2 and P_gCO_2 were measured in our studies; the $P_{g-a}CO_2$ and $P_{g-ET}CO_2$ were then calculated and compared.

Capnometry is a routine, non-invasive monitoring method for the continuous evaluation of $P_{ET}CO_2$ in patients, including those in paediatric care. Nevertheless, the acquisition of reliable $P_{ET}CO_2$ values in small patients may encounter difficulties. The higher respiratory rate of small tidal volumes, the considerable air leakage on ventilation, the relatively long distance between the site of gas exchange and the sampling port and the sometimes enlarged respiratory dead-space may result in an apparent reduction of $P_{ET}CO_2$. In our small patients, we srived to minimize the bias in the $P_{ET}CO_2$ measurements through the application of endotracheal tubes of the correct size, the control of air leakage, the nearest position of the sampling port to the patient and the slower than normal speed of gas sampling (71).

In the event of correct monitoring, the level of exhaled PCO_2 is determined by the overall circulatory, respiratory and metabolic factors, the satisfactory functions of the compensatory buffering systems and the eliminating mechanisms. In anaesthetized and ventilated patients, the main determinant of $P_{ET}CO_2$ is the efficiency of ventilation. The parameters of the ventilation in our patients were not determined in advance; they were ventilated according to their requirements in order to keep them within the limits of normocarbia. During the evaluation of the results of the two studies, the increase in $P_{ET}CO_2$ (experienced only in the group of acute surgical patients) can be explained mostly by the position of the patients and the site of the surgery. All of these relaxed patients were

operated on in the supine position, and the increased intrathoracic pressure caused by the transmission of the elevation of the abdominal pressure due to the surgical manipulation decreased the efficiency of the pressure-controlled ventilation. Some of the elective surgical patients were in a lateral position during the surgery, and the sites of the operations were usually more distant from the diaphragm.

$P_{ET}CO_2$ values and the extent of reflecting P_aCO_2 (mostly in small patients) depend considerably on several factors, such as the site and the type of gas sampling (main-stream or side-stream capnography), the speed of gas sample suction (71), the seal of the endotracheal tube and the extent of dead-space ventilation caused by an increased ventilation/perfusion mismatch. Higher dead-space ventilation can be caused by either a decreased cardiac output or a higher pulmonary pressure with right-to-left shunts. Decreased membrane diffusion states (RDS or *Streptococcus agalactiae* infection) may also lead to a greater difference between the P_aCO_2 and $P_{ET}CO_2$ levels. In these cases, $P_{ET}CO_2$ may underestimate P_aCO_2. The results of study 2 demonstrated this phenomenon well, when $P_{ET}CO_2$ was significantly lower than P_aCO_2 in all groups of NICU patients; the lower $P_{ET}CO_2$ may arise from the high proportion of respiratory dead-space caused by the small weight and small tidal volumes. Higher pulmonary arterial pressure may cause right-to-left shunts (through the foramen ovale and patent duct) and may further increase the functional dead-space. We presume that the difference between P_gCO_2 and $P_{ET}CO_2$ reflects the difference between P_gCO_2 and P_aCO_2.

Several studies have emphasized the good correlation at a given patient status between P_aCO_2 and $P_{ET}CO_2,$ not only in adults (72), but also in children and neonates (73 - 75). In study 2, we also found highly significant, acceptable correlations between the two systemic PCO_2 levels, and consequently between the two systemic-gastric PCO_2 gaps.

Numerous studies and reviews have revealed that an elevation in P_gCO_2 may be an early indicator of an impairment of the splanchnic circulation and hence a worsening condition of the patient (11). Similarly, we found a significantly higher P_gCO_2 in the group of acute surgical patients than in the two groups of elective surgical patients in study 1. In study 2, P_aCO_2 and P_gCO_2 in the group of severely ill NICU patients (group 2) were also in excess of the corresponding data in group 1 (NICU patients in better condition).

In order to allow further distinctions between local hypoxia and generalized acidosis on the basis of the results of gastric tonometry, monitoring of the PCO_2 gap (the difference between the tonometric and arterial PCO_2) is recommended. On the assumption that the

P_aCO_2 – alveolar PCO_2 difference is constant (normally 4 mmHg = 0.5 kPa), the $P_{g\text{-}ET}CO_2$ gap, a minimally invasive marker of gastric perfusion, can also be applied during evaluation of the tonometric findings (30). Only very limited data are available on simultaneous intraoperative measurements of $P_{ET}CO_2$ and P_gCO_2 in children (68), and we are not aware of studies that have evaluated the $P_{g\text{-}ET}CO_2$ gap in neonates. We found that, imilarly as in adults, both intraoperative and intensive care monitoring of $P_{ET}CO_2$ and P_gCO_2 can be performed in children and in neonates, and even in prematures. The great advantage of $P_{g\text{-}ET}CO_2$ gap is that it may reflect the adequacy of gastric mucosal perfusion. If it is monitored, perfusion abnormalities, and hence changes or redistribution of the circulation, may be noticed promptly (even in an early phase of shock, often when the systemic haemodynamics is stable). Our study under paediatric surgical circumstances revealed significantly increase of $P_{g\text{-}ET}CO_2$ gap values in group of acute surgical patients, and in study 2 the $P_{g\text{-}ET}CO_2$ gap (similarly to the $P_{g\text{-}a}CO_2$ gap) proved to be significantly higher in severely ill neonates. We also found that in low body weight NICU patients the $P_{g\text{-}ET}CO_2$ gap overestimated the $P_{g\text{-}a}CO_2$ gap. This disagreement between the two gaps may result from the difference between the simultaneously obtained P_aCO_2 and $P_{ET}CO_2$ values, explained above. Our results on neonates did not indicate any larger SD (precision) between the two gap values, as reported by Uusaro et al. in the case of adults (76). Although this SD is not negligible, we consider that the agreement between the two methods is acceptable and allows use of the $P_{g\text{-}ET}CO_2$ gap in clinical practice as a semicontinuous indicator of the adequacy of the splanchnic circulation.

The use of the $P_{g\text{-}ET}CO_2$ gap instead of the $P_{g\text{-}a}CO_2$ gap makes arterial blood gas analyses unnecessary, which is of particular importance in the case of the paediatric population. Measurement of the $P_{g\text{-}ET}CO_2$ gap is convenient: it does not require a laboratory background, and the problems caused by sample handling can be eliminated.

Conventional gastric tonometric parameters are well applicable for prediction of the outcome in paediatrics (65). Krafte-Jacobs et al. reported pHi = 7.32 ± 0.18 in non-surviving and pHi = 7.48 ± 0.07 in surviving seriously septic children treated in an intensive care unit (66). The $P_{g\text{-}ET}CO_2$ gap is also considered a prompt and sensitive indicator of the adequacy of the splanchnic circulation, even in an early phase. A multicentre study has revealed that a higher value of $P_{g\text{-}ET}CO_2$ obtained intraoperatively may serve as a predictor of a postoperative functional recovery delay (34). Our observation of study 2 that children in more severe condition gave higher $P_{g\text{-}ET}CO_2$ gap data may

indicate that the splanchnic perfusion was partially impaired. Although there may be disagreement between the conventional PCO_2 gap and the $P_{g\text{-}ET}CO_2$, this has been suggested not to be important clinically, and the $P_{g\text{-}ET}CO_2$ gap may be regarded as a suitable parameter for the continuous estimation of splanchnic perfusion (76).

However, our studies involve several limitations. In spite of the low number and heterogeneous group of patients without randomization, study 1 demonstrated that this method is suitable for routine intraoperative monitoring in children, infants and neonates, but further randomized studies are needed on a larger population of patients. Furthermore, arterial samples for P_aCO_2 determination may have been necessary, but for ethical and technical reasons indwelling arterial catheters could not be inserted, and in the given circumstances, the data from the measurements with the arterialized capillary technique did not correspond to strict criteria. It is an obvious problem with the $P_{g\text{-}ET}CO_2$ gap that in neonates with impaired gas exchange, $P_{ET}CO_2$ does not represent P_aCO_2 ($P_{ET}CO_2$ may underestimate P_aCO_2). However, there are at least three reasons why the potential overestimation of the gastric-systemic PCO_2 difference is not a major clinical problem. First, if there is a wide $P_{g\text{-}ET}CO_2$ gap, the $P_{a\text{-}ET}CO_2$ gap may be measured and used to interpret the $P_{g\text{-}ET}CO_2$ gap. Secondly, an overestimate of a gastric-systemic PCO_2 difference means that truly increased PCO_2 differences will not be left undetected. Thirdly, if the gastric-systemic PCO_2 differences in each neonate are compared with their own gaps, the widening of the gap values will be noticed and therapeutic interventions can be performed earlier.

As a summary, with some limitations, monitoring of the $P_{g\text{-}ET}CO_2$ gap via application of the balloonless paediatric gastric tonometric probes can almost certainly be recommended in paediatric care, even for the smallest patients and in wide-ranging fields. However, further examinations should be performed, and randomized clinical studies are needed to assess the predictive role of the method.

7. CONCLUSIONS (in the sequence of the main questions studied)

Conclusion I

Boda's novel gastric tonometric probe is a useful tool in the care of the smallest patients. It can reform gastric tonometric monitoring, and enhances the safety of paediatric and neonatal care under a broad range of circumstances. For these reasons, introduction of the device in everyday paediatric and neonatal monitoring practice is strongly recommended.

Conclusion II

Changes in end-tidal CO_2 levels did not seem to be dependent on age or the severity of the condition in our ventilated patients. In spite of the individully set ventilatory strategy, an elevation in $P_{ET}CO_2$ was found only in the acute surgical group of patients. The phenomenon could be explained only by external physical effects on the patients. Nonetheless, all ventilated patients should be monitored by continuous capnometry, and particulary those who are most susceptible to undergo rapid changes in their condition, or who are exposed to external stimuli. $P_{ET}CO_2$ monitoring indicates the effectiveness of ventilation, providing prompt warning sign of abrupt changes in the condition of the patient and furnishing the opportunity for other monitoring techniques, leading to more specific information on the patients' condition.

Conclusion III

In each group of examined NICU patients, $P_{ET}CO_2$ proved to be lower than P_aCO_2, though P_aCO_2 and $P_{ET}CO_2$ correlated significantly in the examined ventilated NICU patients. With the excepcion of certain circumstances, there is a good correlation between the concomitant P_aCO_2 and $P_{ET}CO_2$ values in paediatric patients. In these cases, $P_{ET}CO_2$ monitoring is a pain-free, blood-sparing and non-invasive way to estimate P_aCO_2. However, blood gas sampling can not be omitted. Rapid and excessive changes or an irregular tendency of $P_{ET}CO_2$ are indications of the need for P_aCO_2 control.

Conclusion IV

Higher dead-space was calculated in the group of NICU patients in a more severe condition, and a non-significantly increased dead-space was found in the low birth weight neonates. Higher dead-space ventilation due to physiological developmental reasons or

diseases leads to a greater difference between P_aCO_2 and $P_{ET}CO_2$, consequently giving rise to a divergence between the $P_{g-a}CO_2$ and $P_{g-ET}CO_2$ gaps.

Conclusion V

Significantly higher P_gCO_2 values were obtained in the acute surgical patients in the first study; similarly, higher P_gCO_2 results were found in group 2 of severely ill NICU patients. An elevation in P_gCO_2 may be a warning sign of a severe condition of paediatric patients or it may suggest an imminent worsening of their health status. In order to acquire more accurate information concerning the condition of the patient, evaluation of either the $P_{g-a}CO_2$ gap or the $P_{g-ET}CO_2$ gap is required.

Conclusion VI

The differences between the P_gCO_2 and P_aCO_2 values of the different groups could be evaluated only in study 2. In terms of the $P_{g-a}CO_2$ gap, there was a significant increase in group 2, comprising NICU patients in a more severe condition, as compared with the patients in better health. This provides support for the finding that widening of the $P_{g-a}CO_2$ gap is a good indicator of the severity of the splanchnic impairment and hence the worsening of the disease.

Conclusion VII

In study 1, the difference between $P_{ET}CO_2$ and P_gCO_2 was significantly greater in the group of acute patients, and in study 2 the $P_{g-ET}CO_2$ gap was significantly higher in group 2 of severely ill patients. We found that monitoring of the $P_{g-ET}CO_2$ gap, similarly to monitoring of the $P_{g-a}CO_2$ gap, provides a useful and sensitive indication of a splanchnic impairment and hence the worsening of the patient's condition. This method is more convenient, and causes no pain and blood loss as compared with monitoring of the $P_{g-a}CO_2$ gap.

Conclusion VIII

The potential correlation between the $P_{g-a}CO_2$ and $P_{g-ET}CO_2$ gaps could not be investigated in study 1. In study 2, we found a significant correlation between the $P_{g-a}CO_2$ gap and the $P_{g-ET}CO_2$ gap, and relation analysis of the data revealed an acceptable correspondence

between the two methods. This result suggests that monitoring of the $P_{g-ET}CO_2$ gap can be an effective alternative to monitoring of the $P_{g-a}CO_2$ gap in neonatal patients.

Conclusion IX

The $P_{g-ET}CO_2$ gap results clearly indicates a significant increase in the acute surgical group in study 1, and in study 2 it also proved to be significantly higher in the group of severely ill patients. Our findings tend to support the assumption that the $P_{g-ET}CO_2$ gap may reflect the severity of the disease.

8. MAJOR FINDINGS OF THE THESIS

I. The clinical utility of Boda balloonless gastric tonometric probes under paediatric intraoperative circumstances was investigated for the first time in our study. It proved to be reliably and easily applicable in patients of different ages and with various surgical diseases, and the measurements provided useful information relating to the severity of the disease.

II. Gastric tonometric investigation of the $P_{g-ET}CO_2$ gap is also a well-applicable method in the course of paediatric surgical interventions and is informative as to the severity of the disease.

III. This was probably the first investigation of the clinical value of the $P_{g-ET}CO_2$ gap as compared with the $P_{g-a}CO_2$ gap in low body weight prematures and neonates. Measurements of the $P_{g-ET}CO_2$ gap with its advantages can be a good alternative to the $P_{g-a}CO_2$ gap investigations in this population of patients, but it can not completely eliminate the need for occasional blood gas samplings.

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Acknowledgements

Appendix I.

Intraoperative gastric tonometric examinations in children and infants with a new probe, combined with measurement of the endtidal PCO$_2$

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Summary

Background: Important progress relating to the early prediction of postoperative complications was recently achieved through the combined use of endtidal PCO$_2$ (P$_{ET}$CO$_2$) and gastric tonometry. The aim of this article was to present results obtained with a new tonometric instrument, proving its feasibility and extending its use to the control of anesthetized infants and children.

Methods: The new tonometric probe, which is balloon free, consists basically of silicone rubber tubing. The room air initially inside the tubes of the probe equilibrates with the PCO$_2$ of the body cavity throughout its full length. The PCO$_2$ content of the gastric cavity (P$_g$CO$_2$) and simultaneously P$_{ET}$CO$_2$ were measured with a micro-capnograph. A total of 108 measurements were performed intraoperatively on 25 infants and young children operated on at the Surgical Unit of the Department of Pediatrics. The patients were divided into elective surgery cases <2 years of age, group I; elective surgery cases >2 years of age, group II; and acute surgery cases, independently of age, group III. To examine the degree of agreement between the measurements, Pearson's correlation coefficients were determined and Bland–Altman analysis was performed. A mixed model repeated measurements ANOVA was used to compare the differences between the groups.

Results: P$_{ET}$CO$_2$ and P$_g$CO$_2$ for groups I and II were nearly identical, and statistically not significantly different (mean difference 0.10 mmHg and 0.85 mmHg, $P = 0.96$ and 0.45, respectively), whereas the corresponding data for group III differed significantly from those for groups I and II ($P = 0.03$ and 0.001, respectively). On Bland–Altman analysis, the bias value for groups proved to be statistically significantly different ($P = 0.001$).

Conclusions: The tested new probe worked very well in small children. The clinical implications of the large gaps found between P$_{ET}$CO$_2$ and P$_g$CO$_2$ values in acutely ill children and children undergoing elective operations must be investigated further.

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Introduction

The measurement of arterial blood gases, and in particular, the continuous follow-up monitoring of the arterial PCO_2 (P_aCO_2), would be the most reliable source of information via which to assess the condition of patients during general anesthesia. As a number of studies have demonstrated strong correlations between the endtidal PCO_2 ($P_{ET}CO_2$) and P_aCO_2 in adults (1,2), in infants and children (3–7) and in newborns (8,9), practical reasons led to the measurement of $P_{ET}CO_2$ as a standard method in operating rooms to monitor the adequacy of patient ventilation. However, the value of this technique may vary widely, depending on many factors (e.g. the age, the type and severity of the illness, the condition of the patient, the sampling site, and the nature of the ventilator used (10).

Accordingly, in special operations, frequent arterial measurement is applied for better control of the patients (11,12). On the other hand, the insertion of an indwelling arterial cannula is an invasive procedure, the correct sampling of the blood can be difficult, especially in children, and the procedure in the operating theater is time consuming.

Important progress was recently achieved in this field when Lebuffe *et al.* (13–15) and Creteur *et al.* (16) combined $P_{ET}CO_2$ measurement with gastric tonometry. The examinations by Lebuffe *et al.* (13–15), which included a multicenter study, revealed that the changes in the gastric mucosal-to-endtidal PCO_2 difference may furnish an opportunity for the early prediction of postoperative complications and mortality. Gastrointestinal tonometry, the only clinically available, minimally invasive technique for the monitoring of hepatosplanchnic perfusion has been widely used in practice for the early detection of shock and multiorgan failure (17,18). The initial methodological drawbacks with saline tonometry have been solved by the development of an automated method (19) in which air tonometry is applied to measure P_gCO_2 semicontinuously, and this has allowed widespread utilization of this procedure in clinical practice.

The knowledge of P_aCO_2 is necessary for calculating the gastric–arterial PCO_2 difference (PCO_2 gap); continuous measurement is advisable (20). Nevertheless, in consequence of the technical difficulties involved in the application of gastric tonometry in children, and especially in newborns (21), the advantages of this type of monitoring have been made use of in only one study (22), so far in patients in this age group.

We recently devised a new instrument for gastric tonometry whereby the examination can be performed with ease in patients of any age, including very low birth weight neonates (23). The aims of this article were to present a brief description of the novel technique and the results obtained with it, proving its feasibility and extending its use to the intraoperative control of anesthetized infants and children.

Patients and methods

Patients

Nineteen elective and six acute surgery patients, i.e. a total of 25 intubated and ventilated cases, were involved in this study. The diagnoses and patient characteristics are presented in Table 1. The elective surgery cases were divided into two groups (group I and group II), depending on the ages of the patients. The acute surgical cases were included in group III, independently of their ages. Anesthesia was induced by the intravenous administration of midazolam, fentanyl and ketamine or propofol. Intratracheal intubation was facilitated with rocuronium or cisatracurium, and the level of muscle relaxation was monitored.

Endotracheal tubes were chosen according to internationally accepted guidelines (24). In children, older than 8 years (eight patients), cuffed tubes were used. Since the addition of an inflatable cuff to the tube is undesirable in younger children, because a tube at least one or two sizes smaller must be used, in the remaining 17 patients uncuffed tubes were introduced. The size of the tracheal tube was chosen

Table 1
Characteristics of the three groups of cases involved in the study

	Group I (elective surgery group <2 years old, n = 10)	Group II (elective surgery group >2 years old, n = 9)	Group III (acute surgery group, n = 6)
Age (months)	11.2	97.7	98
Median and range	0.1–24	29–261	15–204
Weight (kg)	7.3	26.6	27.4
Median and range	3.0–15	29–261	28–193
Diagnosis	Hydronephrosis (4)	Hypospadiasis (5)	Insertion of Tenkhoff catheter
	Hypospadiasis	Appendicitis	Hirschprung's disease
	Ovarial cyst	Ureter reimplantation	Appendicitis (2)
	Duodenal atresia	Resection of colon	Pancreatitis
	Nephrectomy	Insertion of a port-a-cath	Peritoneal adhesions
	Insertion of a port-a-cath		
Ventilation (V_T ml·kg^{-1})	8.2	8.9	7.9
Median and range	6.4–9.9	5.5–12.2	5.3–10.4
Number of measurements	41	32	31
$P_{ET}CO_2$ (mmHg) mean ± SD	34.19 ± 3.95	34.09 ± 2.85	36.09 ± 3.87*
P_gCO_2 (mmHg) mean ± SD	40.31 ± 4.73	39.46 ± 3.56	48.12 ± 5.93**
P_gCO_2–$P_{ET}CO_2$ (mmHg) mean ± SD	6.12 ± 3.9	5.37 ± 2.48	12.03 ± 5.67**

Significant differences between the data of group III and the pooled data of group I + II regarding $P_{ET}CO_2$, P_gCO_2, and P_gCO_2–$P_{ET}CO_2$ values were indicated (*$P < 0.05$ and **$P < 0.001$). There was no significant difference between the groups I and II regarding the same parameters.

so that it passed through the cricoid ring with ease, but allowed no audible gas leak at 30 cm H_2O. Air leakage was also checked after the child was put on the ventilator. If an audible leak was observed or the air leak on the ventilator exceeded 5%, the tracheal tube was replaced with a larger one.

For the maintenance of anesthesia, we applied sevoflurane and nitrous oxide in oxygen, using a pediatric closed breathing circuit. Patients were respirated with constant-flow insufflation, via a Dräger Julian ventilator (Dräger Julian Ventilator, DraegerwerkAG, Luebeck, Germany). Samples for $P_{ET}CO_2$ determination were taken at the CO_2 sampling port of the endotracheal tube adapter in patients under 4 kg, and at the CO_2 sampling port of the airway filter connected to the endotracheal tube adapter in larger children. $P_{ET}CO_2$ and P_gCO_2 monitoring was performed with the Sidestream Microcap Handheld Capnograph (Oridion Medical Ltd, Jerusalem, Israel). The results of the measurements were given in mmHg. In order to be able to compare $P_{ET}CO_2$ and blood P_gCO_2 levels, 'arterialized' capillary blood was sampled simultaneously with the $P_{ET}CO_2$ and P_gCO_2 measurements during the anesthesia in six cases. The blood gases were determined with an ABL700 apparatus (Radiometer, Copenhagen, Denmark).

Description of the tonometric probes

The new tonometer was described earlier (23). Briefly, the new probe is balloon free. It consists of two interconnected silicone rubber tubes, one thicker and one thinner, which are extremely permeable, but only for gases. The two tubes are sealed together with silicone adhesive throughout their whole length, up to the fastening silicone rubber ring (Figure 1). For the measurements, probes of different sizes were applied, one with an external diameter of 2.0 mm and a length (i.e. the distance between the end and the fastening ring) of 25 cm, for infants and toddlers, and another with an external diameter of 2.5 mm and a length of 30 cm (in one special case 65 cm), for older children. The wall thickness of the silicone rubber tubing was 0.25 mm in all cases. For measurements, the probes can be inserted orally or nasally into the stomach up to the fastening ring with the aid of a guide wire. For facile introduction of the probe and extraction of the guide wire after the introduction, both were well lubricated with Espumisan® (Berlin-Chemie AG, (Menarini Group), Berlin, Germany), containing symethicon. The room air initially in the probe equilibrates with the environmental PCO_2 of the body cavity throughout its full length within 10 min. After an equilibration
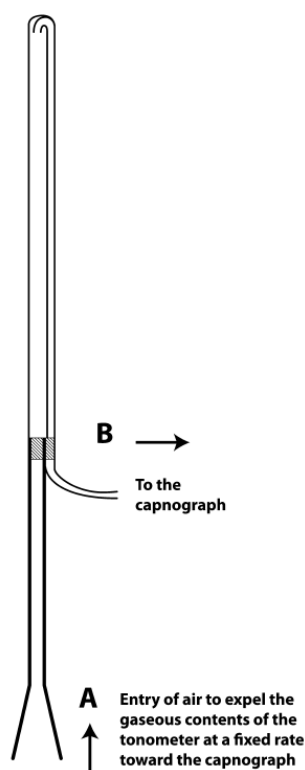
Figure 1
Outline of the new tonometric probe. (a) Thicker section of tube. Length: 25–30 cm. Outer Ø: 2 or 2.5 mm. Wall thickness: 0.25 mm. (b) Thinner section of tube. Outer Ø: 1.2 mm. Wall thickness: 0.2 mm. Arrows indicate the direction of flow of the gaseous contents and the incoming air towards the display unit.

period of 10 min, the tubing is connected to the microcapnograph for transport of the gaseous examination material and measurement of its PCO_2 content. Measurements can be performed repeatedly at intervals of 10 min or more, as desired. The human application of the probe was approved by the Ethical Committee of the Hungarian Academy of Sciences and the examinations were approved by the Human Investigation Review Board of the University of Szeged (1131/2001 O.E.).

Statistical analysis

The relationships between the measured $P_{ET}CO_2$ and P_gCO_2 levels in the three groups were examined by linear regression analysis. Pearson's correlation coefficient and its P values were also calculated. Regression lines were compared by analysis of covariance. To examine the degree of agreement between the measurements, Bland–Altman analysis was performed. The bias (defined as the main difference between values), the precision (defined as the SD of the bias) and the limits of agreement (defined as the bias $\pm 2SD$) were determined for the groups. A mixed model repeated measurements ANOVA was used to compare the differences between the groups. SPSS 15.0 for Windows (SPSS for Windows Rel. 15.0, SPSS Inc., Chicago, Illinois, USA) was applied for the statistical calculations.

Results

Clinical experience

During the measurements, the tonometric probes were inserted nasally in all cases, generally without any technical difficulties, but with the exception of one case, when the probe stopped in the esophagus. In this case, the probe was replaced with another one. In a further case, Magill forceps had to be used for anatomical reasons. The correct position of the probes in the stomach was checked via a CO_2 curve on the LCD monitor of the capnograph after an equilibration time of 10 min. During the examinations, we did not experience any problems with the measurements.

Measurements

The measurement data are listed in Table 1. In spite of the differences between the ages of the group I and II patients, their $P_{ET}CO_2$ and P_gCO_2 levels were nearly identical (mean differences 0.10 mmHg and 0.85 mmHg, $P = 0.96$ and 0.45, respectively), whereas the corresponding data in group III differed significantly from those for the elective surgery cases (mean differences: 1.9 mmHg and 2.0 mmHg, $P = 0.03$ and 0.031 for $P_{ET}CO_2$; 7.8 mmHg and 8.66 mmHg, $P < 0.001$ and $P < 0.001$ for P_gCO_2, respectively). Combining groups I and II, their $P_{ET}CO_2$ and P_gCO_2 levels differed significantly from those for group III (mean difference 1.94 mmHg and 8.81 mmHg, $P = 0.014$ and $P < 0.001$, respectively). Although the values of $P_{ET}CO_2$ were higher in group III, the difference between the $P_{ET}CO_2$ and P_gCO_2 levels
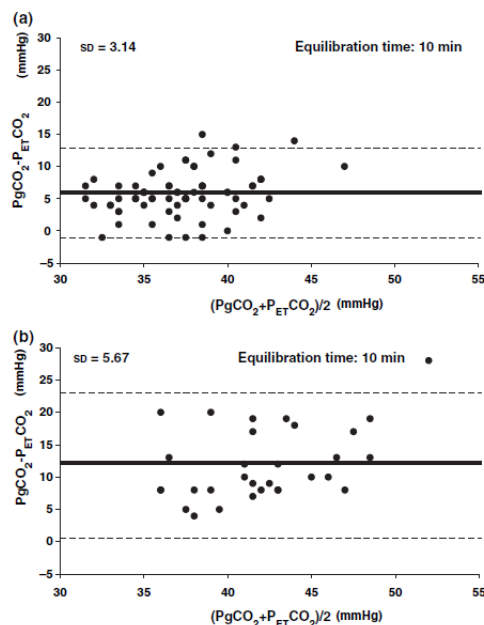
Figure 2
Bland–Altman analysis of the data. (a) Data on elective surgery cases (groups I + II). Bias = 5.79, precision = 3.14, limits of agreement −1.04 to 12.62. (b) Data on acute surgery cases (group III). Bias = 12.03, precision = 5.67, limits of agreement 0.68 to 23.37.

was still greater in the group of acute patients than in groups I and II (Table 1). As the data for the two elective surgery groups did not differ significantly, their Bland–Altman analysis was performed on the combined data for groups I and II, while the acute surgery cases were analyzed separately (Figure 2a,b). The comparison of the bias values between the groups (i.e. the P_gCO_2–$P_{ET}CO_2$ differences) revealed a significant difference ($P < 0.001$). Significant correlations were found between the P_gCO_2 and $P_{ET}CO_2$ levels of each group (group I: r = 0.59, $P < 0.001$; group II: r = 0.71, $P < 0.001$; group III: r = 0.39, $P = 0.029$).

In the cases where simultaneous arterialized capillary PCO_2 sampling was also performed, the average ±SD of the differences between the $P_{ET}CO_2$ and PCO_2 levels was 2.38 ± 2.23 mmHg, the difference between the two parameters are not being statistically significant ($P = 0.35$).

Discussion

Gastric tonometry is a powerful tool for the prediction of circulatory failure, and measurement of the tissue PCO_2 has been widely used for the detection of shock and multiorgan failure, mainly during the perioperative period of anesthesiology (17,18). However, technical difficulties arise in measurements on children and infants (21,25,26). We recently devised a new tool for gastric tonometry whereby the examination can be performed with ease in patients of any age, including very low birth weight neonates (23).

The aim of our present study was to prove the feasibility of this procedure and to extend its use to the perioperative control of anesthetized infants and children with utilization of the P_gCO_2–$P_{ET}CO_2$ difference in pediatric practice. The potential advantages of the novel tonometric tool are obvious. It is minimally invasive, and examinations can be performed with ease, even in small children, including infants and neonates. Accordingly, it appears suitable for extended use in clinical practice in general, and particularly in pediatrics.

Only very limited data are available on simultaneous intraoperative measurements $P_{ET}CO_2$ and P_gCO_2 in children (22). We found that, similarly as in adults, the intraoperative monitoring of $P_{ET}CO_2$ and P_gCO_2 can be performed in children. Utilization of the P_gCO_2–$P_{ET}CO_2$ difference offers a possibility for the online measurement of gastrointestinal CO_2 referenced to the systemic level without the need for arterial blood sampling; a multicenter study has revealed that a higher value obtained intraoperatively may serve as a predictor of a postoperative functional recovery delay (13). However, the control of P_aCO_2 is still important (14). Conventional gastric tonometric parameters are well applicable for prediction of the outcome in pediatrics (27). Although there may be disagreement between the conventional PCO_2 gap and the P_gCO_2–$P_{ET}CO_2$ difference, this has been suggested not to be important clinically and the P_gCO_2–$P_{ET}CO_2$ difference may be regarded as a suitable parameter for the continuous estimation of splanchnic perfusion (20).

Our present study has some limitations. In this study, the 'arterialized' capillary blood PCO_2 levels were measured in only six cases. Arterial PCO_2

samples may have been necessary, similarly as in adult studies. For technical reasons in the given circumstances, the data from the measurements with the arterialized capillary technique did not correspond to strict criteria. The use of indwelling arterial catheters was not possible for ethical reasons. The number of patients was low. The work was undertaken in a heterogenous group of patients without randomization. The degrees of severity of the illnesses in the group of acute cases differed. Nonetheless, the experience gained with this method has demonstrated its suitability for routine intraoperative monitoring in children, infants and newborns. Under standardized conditions, it may yield the same benefit in such patients as already achieved in adults. The observation that children with acute problems had higher P_gCO_2–$P_{ET}CO_2$ differences may indicate that the splanchnic perfusion was partially impaired. Further exploration is necessary in a larger population of high-risk children, to establish the value of the technology for continuous intraoperative monitoring and for the possible prediction of postoperative morbidity.

Conclusions

The tested new tool functioned well technically and indicated increased PCO_2 gaps in acutely ill patients. Further studies are needed to investigate whether the device is capable of indicating a worsening in overall oxygenation during anesthesia or acute care, and of detecting patients at high risk of severe postoperative complications.

Acknowledgment

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Appendix II.

informa
healthcare

Measurement of gastric-to-end-tidal carbon dioxide difference in neonates requiring intensive care

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Objective: Gastric-arterial partial CO_2 pressure gap ($P_{g-a}CO_2$ gap) measured by gastric tonometry may detect the disturbance of splanchnic perfusion. As in the neonatal age it is very difficult to follow up the circulatory condition with frequent acid-base examinations, we wanted to compare the $P_{g-a}CO_2$ gap with an alternative gap of P_gCO_2 – end-tidal carbon dioxide ($P_{g-ET}CO_2$ gap). *Methods*: A prospective study was performed on ventilated neonates requiring intensive therapy ($n = 44$, weight: 1813 ± 977 g). $P_{ET}CO_2$ and P_gCO_2 were measured with a side stream capnograph. We applied a newly developed gastric tonometric probe. Patients were divided into two groups: Group 1 of patients in stable condition ($n = 35$) and Group 2 of patients with severe condition (i.e. Clinical Risk Index for Babies [CRIB] score higher than 10; $n = 9$). For main statistical analysis a mixed model repeated measurements ANOVA, Bland–Altman analysis were applied. *Results*: $P_{g-ET}CO_2$ gap was higher than $P_{g-a}CO_2$ gap (11.40 ± 7.79 versus 3.63 ± 7.98 mmHg, $p < 0.01$). Both gaps were higher in Group 2 (8.71 ± 10.89 and 18.27 ± 10.49 versus 2.53 ± 6.78 and 9.92 ± 6.22 mmHg, $p < 0.01$ and $p < 0.05$). Bland–Altman analysis of the two gaps showed an acceptable correspondence. *Conclusions*: $P_{g-ET}CO_2$ gap may be used as a method for continuous estimation of splanchnic perfusion and a prognostic index also in critically ill neonates. However, the $P_{g-a}CO_2$ gap should not be abandoned.

Keywords: Gastric tonometry, gastrointestinal perfusion, neonate, neonatal intensive care, partial carbon dioxide pressure

Introduction

Gastric tonometry is the sole, clinically available device for monitoring gastrointestinal perfusion. As a deterioration in the splanchnic circulation is one of the first signs of circulatory failure, and is a sensitive predictor of increased morbidity and mortality, the main field of application of gastric tonometry is to monitor the condition of patients in critical states by referencing gastric PCO_2 (P_gCO_2) to arterial PCO_2 (P_aCO_2) as tonometric or gastric-arterial partial CO_2 pressure ($P_{g-a}CO_2$) gap [1,2]. To date, reports in the literature relating to this technique have mainly involved adult patients. Although gastric tonometry is considered to be an important monitoring instrument, it could not be applied in the everyday practice, since in children, and especially in neonates, the procedure demands precision and care at a high degree [3–6], which could be afforded so far only in clinical research studies.

During the last two decades, the measurement of end-tidal PCO_2 ($P_{ET}CO_2$) has become the standard of care in paediatric anaesthesia, paediatric intensive care units and emergency departments [7]. The measurement of $P_{ET}CO_2$ seems to be a useful and reliable tool for assessing the adequacy of ventilation [8] and numerous studies have demonstrated strong correlations between $P_{ET}CO_2$ and P_aCO_2 in adults [9], in infants and children [10,11] and in newborns [12–14].

$P_{ET}CO_2$ may also be considered as a non-invasive monitor of pulmonary blood flow: in a given ventilation, a reduction in the cardiac output (pulmonary blood flow) results in a high ventilation/perfusion ratio and lower $P_{ET}CO_2$ and consequently increased arterial-end-tidal PCO_2 gradient, while an improving pulmonary blood flow results in opposite changes [15]. As in the case of a decrease of cardiac output both the $P_{g-a}CO_2$ gap and the arterial-end-tidal PCO_2 gradient increase, the P_gCO_2-$P_{ET}CO_2$ gap ($P_{g-ET}CO_2$ gap) will rise even more definitely.

In adults, important progress has been achieved in the measurement of gastric mucosal-to-end-tidal PCO_2 difference ($P_{g-ET}CO_2$ gap): several examinations, including a European multicentre study [16,17], have revealed that the changes in it may furnish an opportunity for the early prediction of complications and mortality.

Gastric tonometry, especially in the case of infants, is further limited in its use by the necessity of frequent arterial sampling. Practical considerations thus led to the idea of $P_{g-ET}CO_2$ gap as a non-invasive marker of regional perfusion.

We recently devised a new instrument for gastric tonometry whereby the examination can be performed with ease in patients of any age, including very low birthweight prematures and neonates [18,19]. We also applied $P_{g-ET}CO_2$ gap in an intraoperative study on infants and children at various ages [20]. Conversely, $P_{ET}CO_2$ does not necessarily reflect P_aCO_2 accurately if the proportion of dead space ventilation is increased as in low birthweight prematures or newborns with lung disease [21].

Therefore, the present study was conducted to compare the $P_{g-a}CO_2$ gap with the $P_{g-ET}CO_2$ gap, as an alternative, as well as to investigate the relationship between increased $P_{g-ET}CO_2$ gap values and unfavourable outcome.

Methods

Patients

We performed a prospective study on ventilated neonates requiring intensive care at the neonatal intensive care unit (NICU) of our

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department (n = 44, weight: 1930 ± 1136, gestational week: 30.9 ± 6.9; mean ± standard deviation). This is an 18-bed NICU of a tertiary children's hospital. The neonates were evaluated on admission and throughout their stay. Endotracheal tubes were chosen in line with internationally accepted guidelines, according to gestational age and weight, and cuffed tubes were not used [22].

The patients were intubated, ventilated with SLE 2000, SLE2000HFO and SLE 5000 ventilators in conventional modes (synchronized intermittent mandatory ventilation and continuous mandatory ventilation, as required by their condition) and sedated as clinically appropriate. Infants ventilated in high frequency oscillation mode were excluded from the study. Patients were divided into two groups: Group 1 of patients with Clinical Risk Index for Babies (CRIB) scores lower than 10 (all patients survived, n = 35) and Group 2 of patients in severe perinatal condition (i.e. CRIB score higher than 10 (n = 9; survival rate: 2 out of 9). Survival was taken as the patient remaining alive for at least 28 days after the measurements had been performed. Diagnoses of patients are detailed in Table I.

Their treatment was carried out according to our protocols. As is the general practice in the care of infants [5,23], H_2 receptor antagonists were not given routinely. Acid-base parameters were determined from umbilical artery samples or from arterialized capillary samples, since these results may be considered not to be inferior to acid-base parameters evaluated from arterial samples [24]. The parameters (pH, standard bicarbonate, base excess, PO_2 and PCO_2) were determined with an automatic analyser (ABL 700, Radiometer, Copenhagen, Denmark).

Gastric tonometric examinations were performed with a new, balloon-free tool developed at our department. $P_{ET}CO_2$ was measured with Sidestream Microcap Handheld Capnograph (Oridion Medical Ltd, Jerusalem, Israel, sampling rate: 60 ml/min), through an endotracheal tube adapter (VBM Medizintechnik GmbH), on which a sampling connection ensures the suction of exhaled gas right from the distal end of the endotracheal tube. We measured $P_{ET}CO_2$ at least for 4 min, and the highest value was regarded as appropriate. P_gCO_2 levels were determined with the same Sidestream Microcap Handheld Capnograph. The results of the measurements were given in mmHg. So as to have parallel values of the three various PCO_2 parameters, $P_{ET}CO_2$ was measured when blood samples were taken for blood gas parameters. P_gCO_2 levels were examined some minutes after the other two parameters, allowing the appropriate equilibration of PCO_2, when the other two PCO_2 samples were taken (according to our previous examinations the equilibration time of the new tonometric probes is about 6–7 min, if the equilibration starts from room air) [18]. During the measurement period of the various PCO_2 parameters the respiratory setting was not changed.

$P_{g-a}CO_2$ gap was calculated by subtracting arterial PCO_2 from gastric PCO_2, while $P_{g-ET}CO_2$ gap was calculated by subtracting end-tidal PCO_2 from gastric PCO_2.

The fraction of dead space ventilation was estimated using the following equation: death space volume (VD)/tidal volume (VT) = (P_aCO_2 − $P_{ET}CO_2$) / P_aCO_2.

Description of the tonometric probes

The new tonometer was described earlier [8]. Briefly, the new probe is balloon-free. It consists of two interconnected silicone rubber tubes, one thicker and one thinner, which are extremely permeable, but only for gases. The two tubes are sealed together with silicone adhesive throughout their whole length, up to the fastening silicone rubber ring. For the measurements, probes of two different sizes were applied: one with an external diameter of 2.0 mm and another with an external diameter of 2.5 mm. Length (i.e. the distance between the end and the fastening ring) was 25 cm in both cases, while the wall thickness of the silicone rubber tubing was 0.25 mm in all cases. For

Table I. Characteristics of the neonates examined.

	Group 1 (n = 35)	Group 2 (n = 9)
Gestational age (weeks ± SD)	32.1 ± 3.7	30.9 ± 6.9
Age at the time of examination (days ± SD)	11.9 ± 16.2	12.3 ± 11.14
Diagnoses		
Prematurity with sepsis	5	3
	+RDS and NEC: 2	
	+RDS + lung haemorrhage: 1	
Prematurity with RDS	11	2
	+Ptx: 1	
	+IVH grade II.: 1	
	+PDA: 3	
	+Infant of diabetic mother: 1	
Persistent foetal circulation	+Ptx: 1	
	+RDS, VSD and Down syndrome:1	
Meconium aspiration syndrome	2	
Postoperative cardiac surgery	VSD (PA banding): 1	CAVC (PA banding): 1
		Coarctation of the aortic arch (correction):1
Other anomalies	Biliary atresia: 1	Short rib syndrome: 1
	Infection and convulsions: 1	Glycogenosis and hypoxia: 1
	Perinatal hypoxia: 3	
Weight (g ± SD)	1833 ± 885	1871 ± 1281
CRIB score (mean ± SD)	3.54 ± 2.3	12.25 ± 2.17***

There was no significant difference between the two groups (Student's unpaired *t*-test), except the CRIB score values (***p < 0.001).
CAVC, canalis atrioventricularis communis; CRIB, Clinical Risk Index for Babies; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; PA, pulmonary artery; PDA, persistent ductus arteriosus; Ptx, pneumothorax; RDS, respiratory distress syndrome; VSD, ventricular septal defect.

measurements, the probes can be inserted orally or nasally into the stomach up to the fastening ring with the aid of a fine, flexible guide wire. For facile introduction of the probe and extraction of the guide wire after the introduction, both were well lubricated with Espumisan®, containing symethicon. The room air initially in the probe equilibrates with the environmental PCO_2 of the body cavity throughout its full length within 10 min. After an equilibration period of 10 min, the tubing is connected to the microcapnograph for transport of the gaseous examination material and measurement of its PCO_2 content. Measurements can be performed repeatedly at intervals of 10 min or more, as desired.

The human application of the probe was approved by the Ethical Committee of the Hungarian Academy of Sciences and the examinations were approved by the Human Investigation Review Board of the University of Szeged (1131/2001 O.E.). In the case of each examination, after giving appropriate information, a written consent was obtained from the parents.

Statistical analysis

As there were multiple measurements from each patient for the various PCO_2 values, we used a two-way mixed model repeated measurements ANOVA for the comparison of the two groups. This method is a generalization of the two sample *t*-test, where not only group differences, but the individual within-subject variation in time can be modelled [25]. For the comparison of the PCO_2 gap values in the two groups, a three-way mixed model ANOVA was used with the groups as between-subject factors, gaps as within-subject factors and time as within subject factor. We compared the various PCO_2 values and PCO_2 gap values using Bland–Altman analysis for multiple measurements per individuals and correlation recommended for repeated measurements [26,27] for the comparison of the characteristics of the neonates if the two groups of patients two-tailed Student's *t*-tests were performed.

Results

The various PCO_2 levels, as well as the gap values are detailed in Table II. $P_{ET}CO_2$ levels were significantly lower than P_aCO_2 levels in all groups and, as a consequence, $P_{g-ET}CO_2$ gaps were significantly higher than $P_{g-a}CO_2$ gaps. In the case of P_gCO_2 and both gaps, there was a significant difference between the two groups of patients.

There were significant correlations ($p < 0.001$ in all cases) between each pair of the three PCO_2 levels (P_aCO_2-$P_{ET}CO_2$: $r = 0.631$; $PaCO_2$-P_gCO_2: $r = 0.624$; $P_{ET}CO_2$-P_gCO_2: $r = 0.610$) and between the gap values ($P_{g-a}CO_2$ gap-$P_{g-ET}CO_2$ gap: $r = 0.635$) (Figure 1A). The correlation between the two systemic PCO_2 levels, P_aCO_2 and $P_{ET}CO_2$ did not show a closer connection than what we found between the gastric and systemic PCO_2 levels. This finding, together with the lower values of $P_{ET}CO_2$, may arise from the high proportion of respiratory dead space in our patients, because of the small weight and small tidal volumes. As right-to-left shunts (foramen ovale and patent duct) are often present with a higher pulmonary pressure, shunts may further increase the functional dead space. In our patients, a dead space of 0.176 ± 0.223 could be detected. The dead space was significantly higher in Group 2 (0.236 ± 0.098 versus 0.155 ± 0.143, $p = 0.022$). We also compared our smaller (weight < 1500 g, $n = 13$) and larger (weight > 2500 g, $n = 15$) patients. In this comparison the dead space was higher in the case of low birthweight neonates (0.194 ± 0.115 versus 0.146 ± 0.141), but the difference was nonsignificant in this case ($p = 0.069$).

Table II. Comparison of partial arterial, end-tidal and partial gastric carbon dioxide pressures, as well as gastric-to-arterial and arterial-to-end-tidal partial carbon dioxide pressure gap values in neonates.

	Group 1 ($n = 35$)	Group 2 ($n = 9$)	All patients ($n = 44$)
$P_{ET}CO_2$	36.53 ± 6.65	36.41 ± 5.75	36.51 ± 6.47
P_gCO_2	46.45 ± 8.13	54.68 ± 13.7[a]	47.91 ± 9.81
P_aCO_2	43.92 ± 8.22	45.97 ± 8.81	44.29 ± 8.33
$P_{g-ET}CO_2$ gap	9.92 ± 6.2[a]	18.27 ± 10.49[**,a]	11.4 ± 7.79[a]
$P_{g-a}CO_2$ gap	2.53 ± 6.78	8.71 ± 10.89[*]	3.63 ± 7.98
Number of parallel examinations (median [min–max])	3 (1–10)	3 (1–4)	3 (1–10)

Values between the groups were compared with a mixed model repeated measurements ANOVA, while the two gap values of the same patients were compared with Student's paired *t*-tests. Significance was given as [a]$p < 0.001$ in the case of the paired *t*-tests and [*]$p < 0.05$, [**]$p < 0.01$ in the case of mixed model repeated measurements ANOVA tests. Values are given as mean ± SD, while the numbers of examinations are shown as median (range).
P_aCO_2, partial arterial/arterialized capillary carbon dioxide pressure; $P_{ET}CO_2$, end-tidal carbon dioxide pressure; P_gCO_2, partial gastric carbon dioxide pressure; $P_{g-a}CO_2$ gap (P_gCO_2-P_aCO_2), gastric-to-arterial partial carbon dioxide pressure gap; $P_{g-ET}CO_2$ gap (P_gCO_2-$P_{ET}CO_2$), gastric-to-end-tidal carbon dioxide pressure gap.
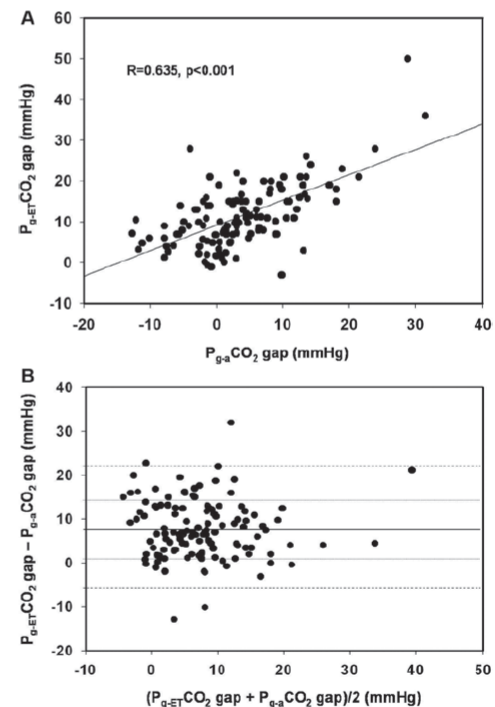

Figure 1. (A) Correlation (calculated with a method recommended for repeated measurements) of the gastric-to-arterial and arterial-to-end-tidal partial carbon dioxide pressure gap values in neonates. (B) Bland–Altman analysis of the gastric-to-arterial and arterial-to-end-tidal partial carbon dioxide pressure gap values in neonates. Gastric-to-arterial partial carbon dioxide pressure gap: $P_{g-a}CO_2$ gap (P_gCO_2-P_aCO_2). Gastric-to-end tidal carbon dioxide pressure gap: $P_{g-ET}CO_2$ gap (P_gCO_2-$P_{ET}CO_2$).

During the examination of the relation of the two PCO_2 gap values, Bland–Altman analysis was also performed (Figure 1B). We found an acceptable correspondence between the two methods (7.78 ± 6.34 mmHg, bias and precision).

Discussion

Gastric tonometry can monitor the stability of splanchnic perfusion and, since the visceral circulation is the first to deteriorate, it may detect hypovolaemia within minutes [17]. With its brief period of equilibration [18], our gastric tonometry method, combined with the $P_{g-ET}CO_2$ gap measurement, allows us to recognize gastric hypoperfusion at an early phase. In our study, similarly to previous observations [11–14], we found highly significant, acceptable correlations between the two systemic PCO_2 levels, and consequently, between the two systemic-gastric PCO_2 gaps.

We are not aware of any studies that have evaluated the $P_{g-ET}CO_2$ gap in neonatology. We found that the difference between gastric mucosal PCO_2 and end-tidal PCO_2 reflects the difference between P_gCO_2 and P_aCO_2. Both gaps were significantly higher in the group of severely ill neonates. We also found that $P_{g-ET}CO_2$ gap systematically overestimated the conventional gap. Our results on neonates found no larger standard deviation (precision) between the two gap values as it was reported by Uusaro et al. [17] in the case of adults. Although the deviation is not negligible, we consider that the agreement between the two methods is acceptable and allows the $P_{g-ET}CO_2$ to be used in clinical practice as a semicontinuous indicator of the adequacy of splanchnic circulation. We could already gain some paediatric experience with the method, in intraoperative conditions [20].

The great advantage of $P_{g-ET}CO_2$ gap is that it may reflect the adequacy of gastric mucosal perfusion. If it is monitored, perfusion abnormalities, thus the change/redistribution of circulation, may be noticed promptly (even in an early phase of shock, often when systemic hemodynamics are stable). In the case of neonates, the practice of drawing and analysing arterial blood samples is even less feasible, than in adult cases. From this point of view, the measurement of $P_{g-ET}CO_2$ difference is more convenient: no laboratory is needed and problems related to sample handling are avoided. A higher $P_{g-a}CO_2$ gap in adults and also in children at various ages may be associated with higher mortality rate or prolonged hospital stay [2,4,5]. Similar observations could be seen if $P_{g-ET}CO_2$ gap was applied [16,20].

In our study, the same side stream capnograph was used to aspirate samples both from the gastric tonometer (P_gCO_2) and the endotracheal tube ($P_{ET}CO_2$). This way, we could exclude any difference between the measurement devices. Recently, mainstream capnography has been applied more frequently than the side stream technique, as it is suspected that fresh gas will entrain into the sampling line in infants with small tidal volumes and rapid respiratory rates. We tried to minimize this effect by using a capnograph with a much lower suction rate (60 ml/min) than usual. This technique was found to be accurate in the measurement of $P_{ET}CO_2$ in neonates [28].

However, the measurement of $P_{g-ET}CO_2$ gap has several limitations. Especially in the case of neonates, there are several factors which may increase the respiratory dead space and so decrease the accuracy of the method. In the very low birthweight group, there is a relatively higher dead space ventilation, although if we compared our patients with the weights >2500 g and <1500 g the difference was not significant. There is an increased ventilation/perfusion mismatch accompanying either a decreased cardiac output or higher pulmonary pressure with right-to-left shunts, which may be present also in mature neonates with higher pulmonary pressure. Decreased membrane diffusion states (respiratory distress syndrome, Streptococcus agalactiae infection) may also lead to a greater difference between the arterial and end-tidal PCO_2 levels. It is an obvious problem with $P_{g-ET}CO_2$ gap that in neonates with impaired gas exchange, end-tidal PCO_2 does not represent arterial PCO_2 ($P_{ET}CO_2$ may underestimate P_aCO_2). However, there are at least three reasons the potential overestimation of gastric-systemic PgCO2 difference is not a major clinical problem. First, if there is a wide $P_{g-ET}CO_2$ gap, P_aCO_2-$P_{ET}CO_2$ difference may be measured and used to interpret the $P_{g-ET}CO_2$ gap. Second, an overestimate of a gastric-systemic P_gCO_2 difference means that truly increased PCO_2 differences will not be left undetected. Third, if gastric-systemic P_gCO_2 differences in each neonate are compared to their own gaps, the widening of the gap values can be noticed and therapeutic interventions may be performed earlier.

As alternatives to gastric tonometric methods, other monitoring devices may also help to satisfy the demand of an indicator of splanchnic perfusion in neonates; recently, abdominal site near infrared spectroscopy was reported [29], as a possible choice, giving a strong correlation with gastric tonometry. Although the method and the detector were primarily developed for the measurement of brain tissue oxygenation, they may be reliable for the detection of abdominal tissues in neonates and infants and may be a possible alternative to gastric tonometry, especially in the case of very low birthweight prematures.

In conclusion, with some limitations, the difference between gastric mucosal and end-tidal PCO_2 is a potentially useful method for a semicontinuous monitoring of splanchnic perfusion, even in neonates. It does not require much additional work from the staff, especially, if automated technique is developed for this purpose, and it does not jeopardize patient care. It may help us to control the circulatory conditions of neonates, instead of using invasive methods. However, further examinations should be performed, and randomized clinical studies are needed to assess the predictive role of the method.

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