MONITORING GASTROINTESTINAL MUCOSAL PERFUSION BY TISSUE CAPNOMETRY IN ANAESTHESIOLOGY AND INTENSIVE THERAPY

PhD Thesis

Péter Palágyi MD

Szeged

2016

MONITORING GASTROINTESTINAL MUCOSAL PERFUSION BY TISSUE CAPNOMETRY IN ANAESTHESIOLOGY AND INTENSIVE THERAPY

PhD Thesis

Péter Palágyi MD

Tutors:

Zsolt Molnár MD, PhD

József Kaszaki PhD

Department of Anaesthesiology and Intensive Therapy

& Institute of Surgical research

University of Szeged

Graduate School of Multidisciplinar Medical Sciences

Szeged

2016

Original papers directly related to the thesis:

I. Palágyi P, Vimláti L, Boda K, Tálosi G, Boda D. Practical experiences and in vitro and in vivo validation studies with a new gastric tonometric probe in human adult patients. J Crit Care. 2010; 25(3):541.e9-15 **IF: 2.077**

II. Palágyi P, Kaszaki J, Rostás A, Érces D, Németh M, Boros M, Molnár Z. Monitoring Microcirculatory Blood Flow with a New Sublingual Tonometer in a Porcine Model of Hemorrhagic Shock. Biomed Res Int. 2015; 2015:847152 **IF: 1.579**

III. Palágyi P, Barna S, Csábi P, Lorencz P, László I, Molnár Z. Recent Advances Of Mucosal Capnometry And The Perspectives Of Gastrointestinal Monitoring In The Critically Ill. A Pilot Study. The Journal of Critical Care Medicine 2016; 2(1):30-37

Table of Contents

Abbreviations

ANOVA	analysis of variance
ASA	American Society of Anesthesiology
BMI	body mass index
CO_2	carbon dioxide
CPR	capillary perfusion rate
CVP	central venous pressure
Ea	actual daily energy provided enterally
Et	daily total energy requirement
H^+	hydrogen ion, proton
HCO_3^-	bicarbonate ion
H_2CO_3	carbonic acid
ICU	intensive care unit
MAP	mean arterial pressure
MOF	multi-organ failure
O_2ER	oxygen extraction rate
PCO_2	partial pressure of CO_2
P_aCO_2	arterial partial pressure of CO_2
$P_{cva}CO_2$	central venous to arterial PCO_2 gap
$P_{ET}CO_2$	end-tidal partial pressure of CO_2
P_gCO_2	gastric partial pressure of CO_2
$P_{ga}CO_2$	gastric to arterial PCO_2 gap
$P_{gcath}CO_2$	P_gCO_2 measured by the conventional catheteter
$P_{gprobe}CO_2$	P_gCO_2 measured by the new probe
PiCCO	pulse contour continuous cardiac output
$P_{SL}CO_2$	sublingual partial pressure of CO_2
$P_{SL}CO_2$ gap	sublingual mucosal to arterial PCO_2 difference
P_tCO_2	tissue partial pressure of CO_2
$P_{ta}CO_2$	tissue to arterial PCO_2 gap

pHi	gastric intramucosal pH
pKa	dissociation constant
RBCV	red blood cell velocity
RGV	residual gastric volume
SaO_2	arterial oxygen saturation
$ScvO_2$	central venous oxygen saturation
seLac	serum lactate concentration
VMI	videomicroscopic imaging

1. INTRODUCTION

There is growing body of evidence that monitoring regional perfusion and microcirculation is necessary in the critically ill, as normal parameters of global oxygen delivery do not exclude tissue hypoperfusion. Sustained tissue hypoperfusion is associated with cellular hypoxia and metabolic dysfunction in each patient groups, and eventually leads to organ failure and death [1,2]. Inadequate regional perfusion may also have serious consequences in high-risk patients undergoing major surgery, so rapid correction of such derangements is important in order to reduce the occurence of postoperative complications. In case of haemodynamic instability the redistribution of circulation directs blood flow away from the splanchnic area to vital organs, which process may result in the normalization of the macro-haemodynamic variables. This is the so called compensated shock phase, in which different neurohumeral processes serve the survival of the organism at the expense of decreased perfusion to peripheral tissues. However, while systemic haemodynamic parameters remain within normal limits, ischaemia may remain undiagnosed and persists exerting its deleterious effects [2-5]. In order to minimize organ injury, decreased regional oxygen delivery should be diagnosed and treated as soon as possible.

The significance of monitoring gastrointestinal mucosal perfusion in the clinical practice is based on specific features. The gastrointestinal tract is highly susceptible to the sympathetic and endocrin responses associated with shock, so in haemodynamic stress situations its blood supply decreases early, providing possibility for the prompt diagnosis of shock. On the other hand, the ischaemic injuries related to compensatory vasoconstriction contribute to the development of multiple organ failure [6-8]. In addition, owing to anatomical characteristics, the oral cavity, the stomach or in special cases the gut offer easily accesible sites for monitoring the high risk patients.

Tissue capnometry provides an opportunity for the indirect evaluation of regional blood flow. This method is based on the principle that tissue hypercarbia is a general phenomenon during hypoperfusion. Mucosal capnometry is a term referring to the localisation of the applied sensors or probes used for monitoring the partial pressure of carbon dioxide (PCO_2) in

mucous membranes. Carbon-dioxide is an important end-product of cellular respiration, generated mainly by oxidative metabolism in the tricarboxylic acid (Krebs) cycle. Under aerobic circumstances the CO_2 molecule is produced in large amounts in the mitochondria. The magnitude of CO_2 production depends not only on the energy content but on the respiratory quotient of the metabolized substrates. In hypoxic conditions, when oxygen delivery decreases below a critical level, tissue CO_2 content may also rise. In this case of anaerobic CO_2 generation intracellular H^+-ions will be accumulated and subsequently buffered by bicarbonate:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow \mathbf{CO_2} + H_2O.$$

The consequential intracellular acidosis increases CO_2 formation [9]. Undoubtedly, the disturbance of regional oxygen delivery results in tissue hypercapnia, but according to several investigations the predominant process is ischaemia not dysoxia which eventually leads to tissue PCO_2 elevations [10-15]. It means that tissue capnometric monitoring is a feasible technique for the assessment of regional perfusion. As CO_2 diffuses easily both in tissues and through biological membranes, the CO_2 content of the capillaries equilibrate quickly with the overlying mucosal or the luminal CO_2. Thus the PCO_2 measured by a sensor positioned next to a mucosal surface of an organ or in the lumen of a hollow viscus reflects primarily the PCO_2 in the examined tissue. Because acute changes in the PCO_2 of the arterial blood (P_aCO_2) result in comparable changes of tissue PCO_2 (P_tCO_2), it should be interpreted in relation to P_aCO_2 [16]. By subtracting P_aCO_2 from P_tCO_2 special gap values can be calculated, which are more sensitive and accurate indicators of hypoperfusion than the mucosal PCO_2 alone, as they are independent of concurrent changes in P_aCO_2:

$$P_tCO_2\text{-}P_aCO_2 = P_{ta}CO_2 \text{ gap}.$$

$P_{ta}CO_2$ gap: tissue to arterial PCO_2 gap

Different sites of the gastrointestinal tract are available for tissue capnometry and the assessment of the adequacy of mucosal blood flow. Gastric tonometry is based upon the monitoring of gastric mucosal PCO_2 level (P_gCO_2), sublingual and buccal capnometry measure mucosal PCO_2 of the proximal gastrointestinal tract [17-19].

The method of gastric tonometry is long established, has good prognostic value and is capable of the objective assessment of the patients condition [7,20,21]. According to a recently published meta-analysis it can also be used in guiding therapy of the critically ill [22]. Still, for about a decade the method has practically disappeared from clinical monitoring and the devices from the market, which can be explained by several technical problems encountered during the history of gastric tonometry [23]. In the first decades after the introduction of gastric tonometry [24,25] intramucosal pH (pHi) was calculated via the Henderson-Hasselbalch equation:

$$pHi = 6,1 + \log HCO_3^-/pCO_2 \times \alpha \times F_{(SS)} .$$

6,1: pKa of CO_2

HCO_3^-: arterial bicarbonate concentration

PCO_2: gastric intraluminal PCO_2

α: constant representing the solubility of CO_2 in the plasma (= 0,03)

$F_{(SS)}$: correction factor proportional to the equilibrium time

Unfortunately the pHi calculation was based on a flawed assumption that gastric intramucosal HCO_3^- concentration equals that of the arterial blood, which was measured and substituted in the equation. This assumption can cause errors in the determination of pHi [26,27], thus the estimation of pHi has been gradually abandoned in favour of the calculation of PCO_2 gap values. The next main problem with gastric tonometry was the long equilibrium time resulting in significant latency in the measurements. Thus researchers applied correction factors in order to get quicker results, and calculated the PCO_2 value corresponding to the actual intramucosal PCO_2. This was the so called „steady state adjusted PCO_2". The longer equilibration was used the smaller was the correction factor required, and the risk of error was also smaller. However, steady state is uncommon in our patient groups, the balance between oxygen delivery and cosumption is challeneged in many ways. Therefore this feature was obviously unfavourable in case of this monitoring modality designed for use in areas of perioperative medicine, intensive therapy or emergency medicine etc., where acute deterioration of the patients' condition can be anticipated. These drawbacks of gastric

tonometry were partly solved by the switch from liquid to gas tonometry, and by the automatization of the method [28,29]. Still there are other factors like catheter dead space, patient dyscomfort, high costs, the interference of gastric acid and enteral feeding, which made the classical method cumbersome and impractical [23,30,31]. The new, quick equilibrating, silicone rubber gastric tonometer invented in our university was designed to exploit the advantages and eliminate the drawbacks of the conventional method. This simple, balloon-free U-shaped tube has already been investigated in experimental animals, but human application was restricted to critically ill or anaesthetized children [32-35].

In parallel with the „retirement" of gastric tonometry researchers have found alternative sites for mucosal capnometry. The sublingual or buccal mucosa offer easily accessible locations for tissue capnography. Although these regions strictly are not part of the splanchnic area, PCO_2 values measured in the oral and gastric mucosa proved to be interchangeable according to several studies, and parallel changes of sublingual or buccal PCO_2 were detected with decreasing blood flow [18,36-38]. According to experimental data even the severity of shock can be estimated by these methods [39-41], and sublingual PCO_2 measurement in bleeding trauma patients gave similar results [42]. The prognostic value of tissue PCO_2 monitoring is confirmed in case of sublingual capnometry, too [43-45].

Although the different versions of mucosal capnometry are promising techniques in the diagnosis and management of circulatory failure, more information is required to define their role during anaesthesia, and in the monitoring and management of the critically ill. The lack of availibility of feasible bedside monitors may contribute to the shortage of clinical data, so the improvement of appropriate, minimally invasive and cost-effective methods should be encouraged to gain more clinical evidence in this field.

2. AIMS

The main goal of our investigations was to acquire clinical and experimental data by mucosal capnometric monitoring of the gastrointestinal perfusion. During our investigations we used specially designed capillary tonometric probes developed for tissue PCO_2 measurements.

Study I provides practical experiences with a new, simple, balloon-free gastric tonometric probe, and reports the results of simultaneous in vitro and in vivo measurements with the conventional, ballooned gastric air tonometer and the new device. This is the first clinical study about the use of the new gastric tonometric method in adults. In Study II a new sublingual mucosal capnometric probe was tested in an animal model of haemorrhagic shock. This is one of the leading causes of hypovolemia in clinical practice. The main goal of these investigations was to evaluate the results of sublingual capnometry during shock, and correlate these results with direct microcirculatory measurements gained by videomicroscopic imaging (VMI). Another aim was to investigate how the capnometry-derived values relate to global indicators of haemodynamic changes during haemorrhage and resuscitation. Study III is a prospective clinical investigation examining the relationship between gastric emptying, indirectly assessed gastric mucosal perfusion and systemic oxygenation parameters in critically ill patients receiveing early enteral nutrition.

The investigations related to the thesis were performed in order to:

I. Measure the CO_2 uptake of a new gastric tonometric probe and the reference method simultaneously *in vitro* and *in vivo*, in volunteers and in anaesthetised patients undergoing surgery.

II. Monitor the changes in sublingual PCO_2 measured by a new sublingual capnometric probe in haemorrhage of different severity, and investigate the correlation of capnometry with microcirculatory and global oxygenation parameters in an experimental setting.

III. Determine the influence of mucosal perfusion abnormalities on gastric emptying during early enteral feeding in critically ill patients.

IV. Examine the influence of mucosal perfusion abnormalities detected by our new device on the efficiency of tube feeding during early enteral nutrition in critically ill patients.

3. MATERIALS AND METHODS

3.1. Study I: a new gastric tonometric method

3.1.1. Technique for the paired in vitro measurements with the new capillary tonometric probe (probe) and the conventional, ballooned air tonometric device (catheter)

The new balloonless gastric tonometric probes applied in our investigations is entirely made of silicone rubber, which is highly permeable of gases. It has already been introduced in an animal study and the former human investigations carried out exclusively in infants and children [32-35]. The probes used in adults were 65 cm in length with a lumen diameter of 2 mm and a wall thickness of 0.25 mm in case of the larger diameter tube, and with a lumen diameter of 0.8 mm and a wall thickness of 0.2 mm in case of the smaller diameter tube. For the comparison of the in vitro uptake of CO_2 by the probe and the catheter (TRIP, NGS catheter; Tonometrics, Helsinki, Finland) a glass container was used as an equilibrium chamber. The part of the new probe up to the fastening ring and the balloon part of the catheter were inserted simultaneously into the chamber, which was then sealed in an airtight manner. For the measurement of different PCO_2 levels, appropriate quantities of nitrogen and carbon dioxide were mixed with a precision gas blender to reach the desired CO_2 partial pressure inside the equilibration chamber. The mixtures were filling the chamber at a flow rate of 10 L/min. During the tonometric measurements, the PCO_2 level of the gas mixture inside the chamber was determined by the microcapnograph (Sidestream Microcap Handheld Capnograph; Oridion Medical Ltd, Jerusalem, Israel) by measuring the CO_2 content of the gas flowing from the container. Figure 1. shows the schematic drawing of the new gastric tonometric probe and the capnograph. During the study, the equilibration chamber was submerged in water thermostated at 37°C.

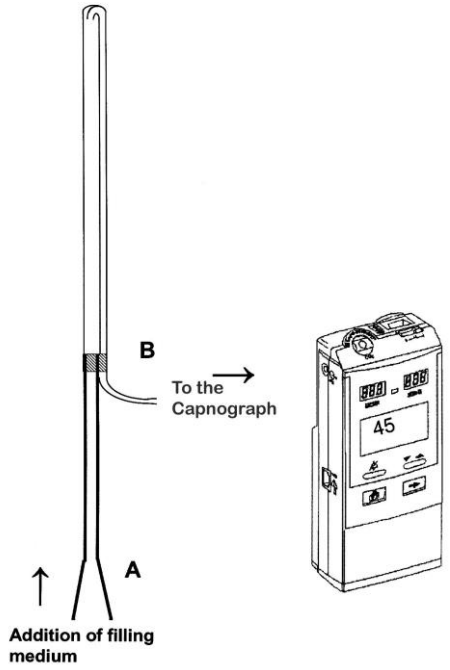

Figure 1. The U-shaped balloonless silicone gastric tonometric probe and the microcapnograph.

3.1.2. Study population and measurement technique during the first adult in vivo application of the new gastric tonometric method

The first experiences on the insertion and measurement with the probe were obtained from 10 healthy volunteers. In their cases no special premedication was applied except for a light spray of lidocaine into the throat to facilitate the insertion process. In this pilot study both fasting and 3-hour postprandial tonometric measurements were performed on 2 consecutive days, inserting a new probe each day. In this study group, only the gastric tonometric measurements were recorded. In the clinical part of the examinations 50 adult patients scheduled for neurologic, orthopedic, trauma, and cardiac surgery were enrolled (Table 1). The exclusion criteria were nonfasting state, pregnancy, a contraindication to nasogastric tube insertion, erosive gastritis or esophagitis and gastric or duodenal ulcer. The individuals who met the eligibility criteria were fully informed during the preoperative visit about the purpose of the study and the insertion of the catheters, and their written consent was obtained. In the case of 2 critically ill, ASA V patients the written consent was obtained from the escorting first-grade relatives.

Group of patients	No.	Sex (M/F)	Age, mean (min.-max.)
Healthy volunteers	10	6/4	31 (21-84)
Coronary surgery	23	15/8	68 (52-81)
Aortic surgery	3	2/1	62 (55-68)
Neurosurgery	8	4/4	53 (17-79)
Orthopedic surgery	7	3/4	52 (15-81)
Trauma surgery	9	2/7	70 (21-86)

M indicates male; F, female.

Table 1. Characteristics of the patients involved in Study I.

In each clinical case H_2-receptor blocker medication was administered preoperatively. The anaesthesia method was not standardized. In most cases, intravenous induction with a combination of benzodiazepines, opioids, and propofol was followed either by inhalational maintenance with isoflurane/sevoflurane in nitrous oxide and oxygen with additional opioid boluses, or total intravenous anesthesia using the combination of sufentanyl and propofol. After induction the tonometric probes were inserted nasogastrically or orogastrically into each anaesthetized patient, which was followed by endotracheal intubation. The minute ventilation was adjusted to maintain arterial carbon dioxide partial pressure (P_aCO_2) at 35 to 45 mm Hg. Each patient received a 20G arterial catheter into the radial artery (Arterial Cannula with Floswitch, BD, Swindon, UK). P_aCO_2 values were determined with a Stat Profile pHOx Plus blood gas analyzer (Nova Biomedical, Waltham, MA. U.S.A.) at 37°C and were corrected for the patient's actual body temperature. Samples for the end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) measurements in the operating room were obtained from the sampling line of the anesthesia machine (Dräger Zeus or Primus; Dräger Inc, DrägerwerkAG Lübeck, Germany), whereas $P_{ET}CO_2$ values in the intensive care unit were measured with the microcapnograph. The data obtained were recorded in parallel with the measurements of PCO_2 values obtained by the probe ($P_{gprobe}CO_2$). The room air, which initially fills the probe, equilibrates with the environmental PCO_2 throughout the full length of the probe within 10 minutes. After the equilibration period of 10 minutes, the microcapnograph, which aspirates the gas content of the probe at a flow rate of 60 mL/min, was used for the periodic measurement of $P_{gprobe}CO_2$. Between two measurements the capnograph was turned off. After

the transfer of the equilibrated filling medium, the probe refills automatically with fresh room air, becoming ready for equilibration for the next measurement.

3.1.3. Technique for the in vivo paired tonometric measurements with the new probe and the catheter

The subgroup of patients involved in this part of the study belong to the clinical cases described in the previous section, thus enrollment and exclusion criteria are the same. In these 12 patients 101 parallel measurements were performed after inserting both the catheter and the probe. The TRIP-catheters were used as reference during the simultaneous in vivo measurements, similarly to the in vitro experiments. The PCO_2 levels obtained with the catheter ($P_{gcath}CO_2$) were analyzed automatically in 10-minute cycling times by a Tonocap monitor (Datex-Ohmeda, Helsinki, Finland). Under general anaesthesia the probe was inserted first (nasogastrically or orogastrically), and it was followed by the nasogastric insertion of a catheter. The insertion of the tonometric tools was immediately followed by orotracheal intubation. The correct position of the catheter was verified by auscultation over the epigastrium, while the position of the probe could be verified radiologically. In general, the inappropriate positioning of the probe (eg. kinking or rolling-up in the esophagus) is indicated by a flexible resistance encountered during the insertion, or by an abnormal CO_2 pattern on the capnogram resulting from the partial or complete obstruction of the lumen.

3.1.4. Statistical analysis. In order to compare the $P_{gprobe}CO_2$, P_aCO_2 and $P_{gprobe\text{-}a}CO_2$ means, the ASA groups were combined as follows: ASA I + II, ASA III, and ASA IV + V. To compare the means of $P_{gprobe}CO_2$, P_aCO_2 and $P_{gprobe\text{-}a}CO_2$ in the 3 ASA groups, a mixed model repeated-measurements analysis of variance method was used, where not only the group differences but also the individual within-subject variation in time can be modeled as well. Group means were compared based on estimated marginal means with Sidak adjustment for multiple comparisons. Means of in vitro measurements were compared by Student's paired t test. *P*-values < 0.05 were considered statistically significant. To examine the agreement between the two simultaneous measurements for the in vivo tonometric study Bland-Altman analysis was performed on the multiple measurement results per individual. Bias, defined as the mean difference between values; precision, defined as the SD of the bias; and limits of agreement, defined as bias ± 1.96 SD were determined. SPSS 15.0 for Windows (SPSS, Chicago, Ill) was used for statistical calculations.

3.2. Study II: sublingual tonometry in haemorrhagic shock

3.2.1. Animals and instrumentation

The experiments were performed on the EU Directive 2010/63/EU on the protection of animals used for experimental and other scientific purposes and carried out in strict adherence to the NIH guidelines for the use of experimental animals. The study was approved by the National Scientific Ethical Committee on Animal Experimentation (National Competent Authority), with the license number: V./142/2013. The study was conducted in the research laboratory of the Institute of Surgical Research in a manner that does not inflict unnecessary pain or discomfort upon the animals. Thirty six Vietnamese mini-pigs of both genders, weighing 16-25 kg underwent a 24-hr fasting preoperatively with free access to water; the animals were randomly allocated into control (sham operated; n=9) and hemorrhagic shock groups (shock; n=27). Anesthesia was induced by an intramuscular injection with a mixture of ketamine (20 mg/kg) and xylazine (2 mg/kg) and maintained with a continuous infusion of propofol (50 μg/kg/min iv; 3 mg/kg/hr). After endotracheal intubation, the animals were mechanically ventilated with room air (Harvard Apparatus, South Natick, MA, U.S.A.). The tidal volume was set at 9±2 ml/kg, and the respiratory rate was adjusted to maintain the P_aCO_2 in the range of 35-45 Torr (4.7-6.0 Pa). The depth of anesthesia was assessed by monitoring the jaw tone regularly. The animals were placed in supine position on a heating pad for maintenance of the body temperature between 36 and 37 ^oC. For measurement of the sublingual PCO_2 ($P_{SL}CO_2$) the new sublingual capillary tonometer (see below) was placed under the tongue, and a specially designed latex face mask was used to close the oral cavity. Capnography was performed with a Microcap® handheld capnograph (Oridion Medical Ltd, Jerusalem, Israel). The sublingual mucosal-to-arterial PCO_2 difference ($P_{SL}CO_2$ gap) was calculated by subtracting $P_{SL}CO_2$ from the simultaneously taken P_aCO_2 values. For central venous access the left jugular vein was catheterized. A three lumen central venous catheter (7 F; Edwards Lifesciences LLC, Irvine, U.S.A) was introduced for blood sampling and fluid administration using aseptic surgical technique. The central venous pressure (CVP) was monitored continuously with a computerized data-acquisition system (SPELL Haemosys; Experimetria Ltd., Budapest, Hungary). For hemodynamic measurements a special thermodilution catheter (Pulsiocath, PULSION Medical Systems AG, Munich, Germany) was placed into the left femoral artery. The cardiac output was monitored by transpulmonary thermodilution and continuous pulse contour analysis (PiCCO method). The right carotid

artery was also catheterised for bleeding (7F; PE, Access Technologies, Illinois, USA). The blood gas measurements were carried out by taking arterial and central venous blood samples simultaneously according to the study protocol, which were then analyzed by co-oximetry with a blood-gas analyzer (Cobas b221, Roche, Austria). Simplified oxygen extraction rate (O_2ER) was calculated according to the standard formula from arterial (SaO_2) and central venous oxygen saturations ($ScvO_2$): $O_2ER = (SaO_2\text{-}S_{cv}O_2)/SaO_2$. From the central venous and arterial blood gas values the central venous-to-arterial PCO_2 gap ($PcvaCO_2$) was also determined.

For direct evaluation and noninvasive visualization of the sublingual microcirculation the intravital OPS imaging technique (Cytoscan A/R, Cytometrics, Philadelphia, PA, USA) was used. A 10x objective was placed onto the sublingual mucosa, and microscopic images were recorded with an S-VHS video recorder (Panasonic AG-TL 700, Matsushita Electric Ind. Co. Ltd, Osaka, Japan). Quantitative assessment of the microcirculatory parameters was performed off-line by frame-to-frame analysis of the videotaped images. Red blood cell velocity (RBCV; μm/s) changes in the postcapillary venules were determined in three separate fields by means of a computer-assisted image analysis system (IVM Pictron, Budapest, Hungary) [46]. Capillary perfusion rate (CPR; 1/1) was determined as the length of continuously perfused microvessels per the total length of capillaries in the observational area. During quantitative assessment of CPR we used a diameter limitation for determination of the microvascular network. Exclusively those vessels were selected for analysis, whose diameters were less than 20 μm. All microcirculatory evaluations were performed by the same investigator.

3.2.2. Description of the new sublingual capnometric probe

The new sublingual capillary tonometer (Mediszintech Ltd, Budapest, Hungary) is a specially coiled silicone rubber tube (ID: 1.5 mm, OD: 2.0 mm, length: 640 mm) with high permeability for gases, which is formed into a multiple V-shape by using a mould and is glued along five lines (Fig. 2). To prevent the soft-walled tube from flattening, a polyamid fiber of 0.3 mm thickness is inserted along its full length. Thereby after folding the tube a sufficient gap remains ensuring the free transport of the filling medium. The afferent and deferent parts of the tube are fixed together at their branching. The end of the deferent tube is equipped with a Luer connector. The filling material is room air, which equilibrates quickly

with the PCO_2 content of the capillaries in the sublingual mucosa. After the required equilibration time it can be aspirated and measured by capnometry.

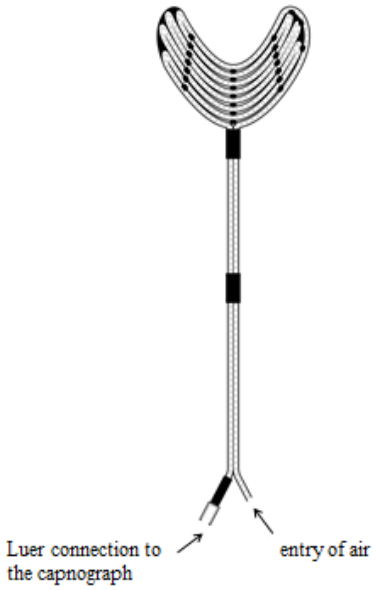

Figure 2. Depiction of the new sublingual tonometric device.

The duration of the full equilibration of the sublingual probe is about 15 minutes. The PCO_2 of the aspirated gas is measured by infrared spectrophotometry. The results are immediately displayed in units of mmHg.

3.2.3. Experimental protocol

The preparation period was followed by a 30 min resting period. After baseline measurements at 0 min (T_0) in the shock group, hemorrhagic shock was induced by bleeding the animals through the right carotid arterial catheter into a heparin (100 IU/ml) containing reservoir. The target mean arterial pressure (MAP) of approx. 40 mm Hg was reached in 10-15 min, and was kept by repeated bleeding periods until the 60th min of the experiment (T_2). The amount of shed blood was precisely monitored. The average blood loss was about 25 mL/kg 15 min after the onset of hemorrhage, which increased to an average of around 40 mL/kg by the end of bleeding at T_2. This was about 50% of the animals' circulating blood volume. At 60 min (T_2) volume resuscitation with colloid solution (hydroxyethyl starch 130 kDa/0.4, 6% Voluven®, Fresenius, Germany) was started. 75% of the starting MAP was reached in 10-15 min. In case of decreasing blood pressure further colloid infusion was given, but the total amount of

colloid infusion was maximized in 25 mL/kg. This means that the pigs were partially resuscitated and remained hypovolemic in the following period between 60 and 180 min (T_2 and T_6). The reason for choosing this protocol was to enable us to investigate the alterations of different macro- and microcirculatory parameters in two well separated periods: severe shock and moderate hypovolemia. Hemodynamic-, arterial- and central venous blood-gas measurements and tissue capnometry were repeated and recorded every 30 min for duration of 3 hr (T_0-T_6). Videomicroscopic imaging was performed at baseline *(T_0)*, at 60 (T_2) and 180 min (T_6). Animals in the control group were not submitted to bleeding. They underwent the same operation procedure, and received the same instrumentation and monitoring. In this group 0.9% sodium chloride was infused at a rate of 10 mL/kg/h during the experiment. Hemodynamics, blood gas analysis and microcirculatory measurements were performed at the same time points (Fig. 3.).

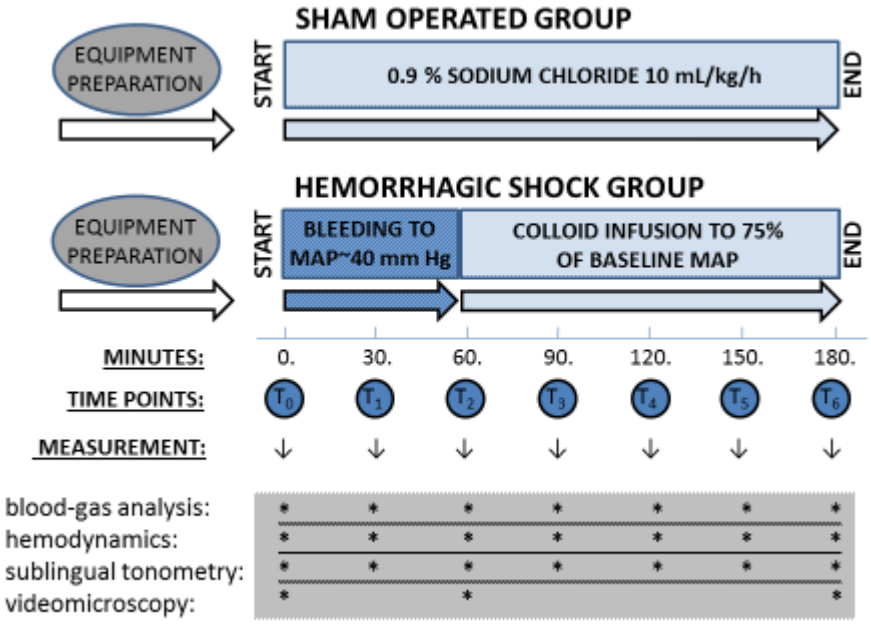

Figure 3. Flow diagram representing the experimental protocol in both groups of animals. MAP: mean arterial pressure, T_0-T_6: seven time points of measurements *: indicates the implementation of different types of measurements

3.2.4. Statistical analysis. The statistical software package SigmaStat for Windows (Jandel Scientific, Erkrath, Germany) was applied for data analysis. After testing for normality parametric methods were used. Two-way repeated measures analysis of variance (ANOVA) was applied for statistical analysis. For the analysis of differences between the sham operated and the hemorrhagic shock groups, the time dependent differences from the baseline (T_0) for each group were assessed by Holm-Sidak post hoc test. When we examined the effect of partial resuscitation starting at 60 minutes (T_2), we performed multiple pairwise comparisons of T_3–T_6 results versus T_2 data serving as control. The pairwise comparison of different variables was made with Pearson-correlation. *P*-values < 0.05 were considered statistically significant. The numeric data in the text and values on the figures are given as mean and standard deviations.

3.3. Study III: gastric tonometry during early enteral nutrition

3.3.1. Patients receiving early enteral feeding

Critically ill, mechanically ventilated patients were included in this prospective observational study. The study was approved by the Regional Human Biomedical Research Ethics Committee of the University of Szeged. All patients' next-of-kin were informed of the procedures and gave written consent. In the first 24 hours of treatment a conventional nasogastric tube was introduced into the stomach to provide enteral feeding, and a silicon gastrotonometric device was inserted through the other nostril, for gastric mucosal PCO_2 measurements.

3.3.2. Feeding and sampling protocols

The patients were given proton-pump inhibitors twice a day in order to reduce the interference of gastric acid. After early cardiopulmonary stabilization 1 kcal/ml standard enteral formula (Nutrison Standard, Nutricia) was started via the feeding tube. The caloric requirements were defined as 20-25 kcal/kg, for obese patients with a BMI > 30 kg/m^2 it was calculated for BMI of 30. In case of delayed gastric emptying with high residual gastric volume (RGV), the algorithm depicted on Figure 4. was used for dose adjustments.

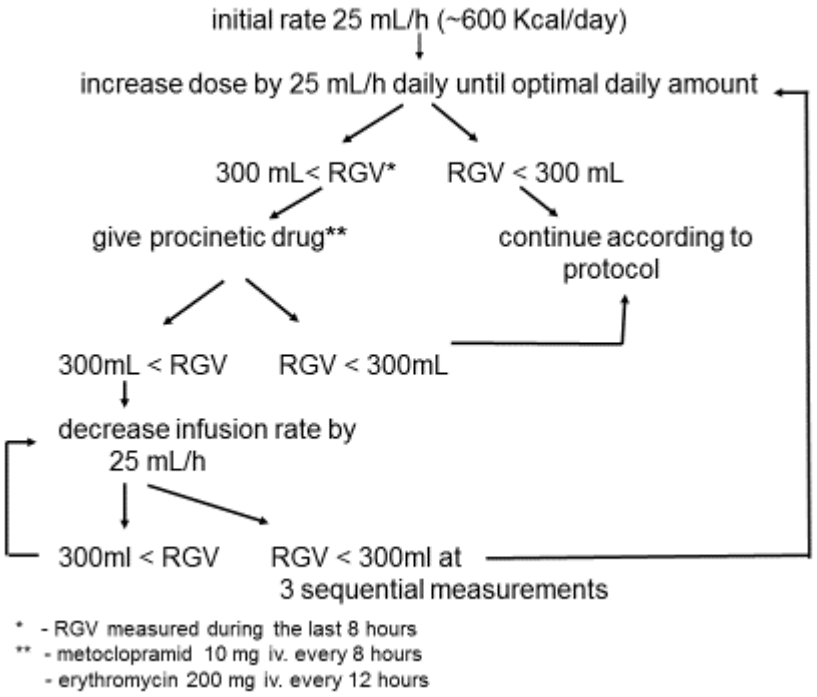

Figure 4. Feeding protocol in Study III and the algorythm for dose adjustments

In order to minimize the confounding effects of nutrition tube feeding was stopped two hours before tonometric measurements. At the end of these feeding pauses overall arterial and central venous blood-gas analysis and gastric tonometric measurements were performed twice a day (Fig. 5).

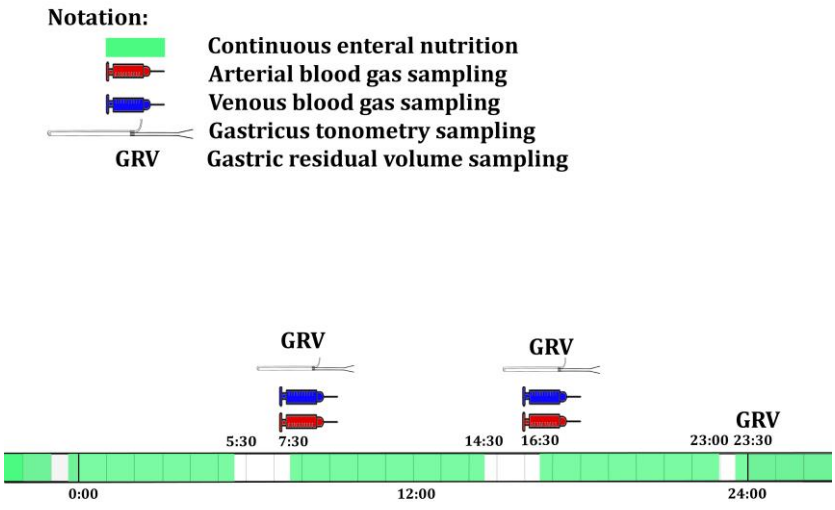

Figure 5. Sampling protocol during early enteral nutrition

The main clinical end-points were the average amount of RGV measured in the eight-hour periods, and the enteral caloric intake of the last 24 hours (actual energy=Ea) divided by the previously calculated optimal daily caloric intake (total energy=Et). The Ea/Et ratio was calculated each day in each individuals, and reflected the daily status of enteral feeding compared to total caloric needs. We examined the frequency of elevated $P_{ga}CO_2$ (20 mmHg <) and pathological seLac, $ScvO_2$ and $PcvaCO_2$ values. The occurrence of feeding intolerance and complications eg. aspiration, regurgitation, vomitus, bowel distention, and diarrhea were also recorded. Subgroups were created in a post hoc fashion according to the median $P_{ga}CO_2$ value and divided into "low" (LG) and "high" (HG) $P_{ga}CO_2$ groups. The main outcome parameters were the differences in RGV and Ea/Et ratios. The numeric data in the text and values on the figures are given as median and 25th and 75th percentiles.

3.3.3. Statistical analysis. The Bartlett test was used to verify if samples were from populations with equal variances and the Kolmogorov-Smirnov test used to determine normal distribution. Individual groups were compared by Mann-Whitney test. Data analysis was done using the statistical software package SigmaStat for Windows (Jandel Scientific, Erkrath, Germany). The level of statistical significance was set at $p < 0.05$.

4. RESULTS

4.1. Results of the in vitro and in vivo validation studies

Sixty in vitro paired measurements were recorded with the new, capillary tonometric probe (probe) and the conventional, ballooned air tonometric device (catheter). The results of the in vitro paired tonometric measurements in the equilibrium chamber at 3 different CO_2 concentrations (PCO_2 of 35, 55, and 80 mmHg) are given in Table 2. The equilibration with the catheter was complete only in 16, 6, and 4 cases at the respective concentrations, whereas complete equilibration was detected in 18, 11, and 15 cases when using the probe. Although the means of the measurements with the two different tonometric devices were significantly different at 55 and 80 mmHg PCO_2 indicating higher accuracy of the probe, these differences were fairly small in case of both methods.

Actual P_{CO_2} in the equilibrium chamber	35	55	80
No. of paired measurements	20	20	20
Difference from the P_{CO_2} measured by the catheter	−0.25 (0.44)	−1.10 (1.25)	−1.05 (0.68)
Difference from the P_{CO_2} measured by the probe	−0.15 (0.30)	−0.20 (0.95)	−0.10 (0.39)

Measurements were made at 10-minute intervals after an initial 20-minute equilibration period, at 37°C. Values are expressed as mean (SD) in mm Hg.

Table 2. Results of the in vitro parallel measurements with the new probe and the catheter: the differences of the PCO_2 values measured by the catheter and by the probe from the actual PCO_2 values in the equilibrium chamber

The probe is, in general, easily applicable in clinical practice. Its use is well tolerated by the patients and does not cause more inconveniences than does the simple insertion of a feeding tube. The complaints and technical difficulties that occurred during the insertion are the same as those during any nasogastric tube placement. During the 20 insertions into the 10 healthy volunteers retching was observed in 6 cases and vomitus in 1 case. When performing tonometric measurements with the probe in the 50 surgical cases, the following technical problems were encountered: temporary obstruction (6 times), permanent obstruction (once), displacement of the instrument (3 times) and failed insertion (once). Nevertheless, we consider most of these difficulties as the results of inexperience, because they occurred mainly in the initial phase of the study. Epistaxis, a common complication of gastric tubing, did not occur. The results of the measurements with the probe in healthy volunteers and in the patients of the different ASA groups are shown in Table 3.

Study group	No. of cases	$\mathbf{P_{gprobe}CO_2}$	$\mathbf{P_aCO_2}$	$\mathbf{P_{gprobe\text{-}a}CO_2}$
healthy volunteers (fasting)	10	10 **55.3** (3.63)		
healthy volunteers (postprandial)	10	10 **56.2** (3.51)		
patients with ASA score I+II	10	144 **44.9** (4.46)	14 **39.2** (4.23)	14 **6.2** (6.98)
patients with ASA score III	30	248 **45.5** (7.62)	117 **35.7** (5.51)	117 **8.8** (7.99)
patients with ASA score IV+V	9	128 **55.4** (17.83)	99 **34.1** (5.75)	99 **22.2** (20.86)

Table 3. Number of the measurements, mean values (SD) of the $P_{gprobe}CO_2$, P_aCO_2, and $P_{gprobe\text{-}a}CO_2$ in the study population. Values are expressed as mean (SD) in mmHg.

The results of the 20 P_gCO_2 measurements performed in healthy volunteers and those of the 520 measurements in the surgical cases correspond to the literary data obtained by conventional balloon tonometry. The statistical analysis of the intraoperative cases revealed that the means of $P_{gprobe}CO_2$ in the ASA I + II and ASA III groups were significantly lower than those in the ASA IV + V category ($P = 0.002$ and $P = 0.012$, respectively). Mean P_aCO_2 values of the ASA I + II group were significantly different from those of the ASA IV + V group ($P = 0.011$). Mean $P_{gprobe\text{-}a}CO_2$ values of the ASA I + II and the ASA III groups are significantly lower than the corresponding values of the ASA IV + V group ($P = 0.016$ and $P = 0.024$, respectively).

The results of the 101 in vivo paired tonometric measurements performed with the catheter and the probe are presented on Figure 6. These results were identical in only 11 measurements. In 13 cases, the PCO_2 values measured using the catheter were higher than those detected by the probe. On the other hand, in 77 cases, higher PCO_2 values were obtained with the probe. The Bland-Altman analysis gave a mean difference of 3.64 mmHg between the parallel measurements, with a precision (SD) of 4.068 mmHg, indicating that the probe gives higher values than the catheter.

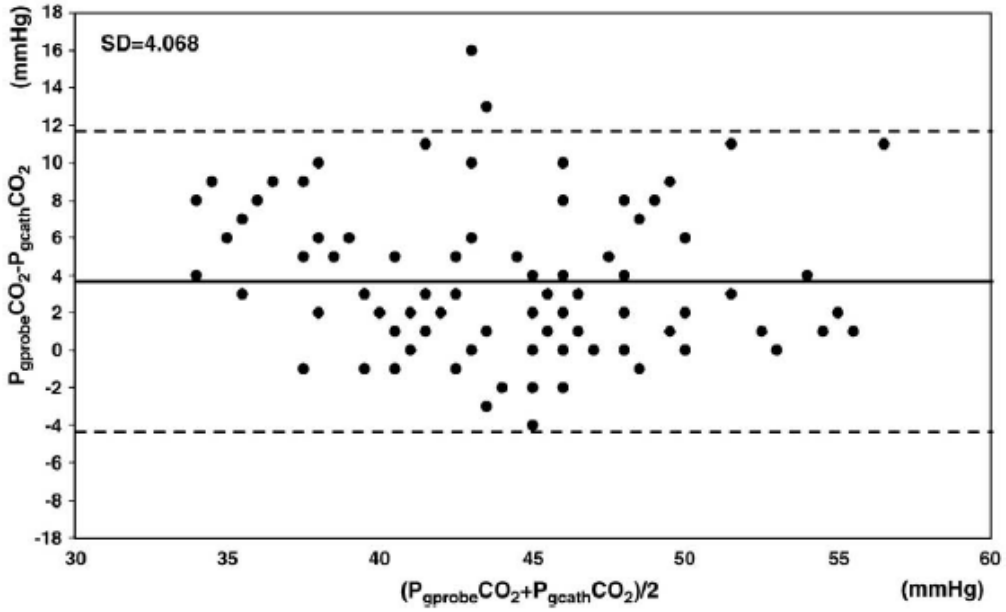

Figure 6. Bias and precision data obtained by Bland-Altman analysis of the 101 paired in vivo measurements of the $P_{gprobe}CO_2$ and of the $P_{gcath}CO_2$ during anesthesia. Bias (mean difference of parallel measurements): 3.64 mmHg. Precision (SD of differences): 4.068 mm Hg. Limits of agreements (bias ± 1.96 SD): −4.33 and 11.62 mmHg.

4.2. Sublingual PCO_2 monitoring with a new capillary tonometric probe in haemorrhage of different severity

During the haemorrhagic shock model in Study II we performed complex macro-haemodynamic monitoring and microcirculatory assessment during severe bleeding and moderate hypovolaemia. In order to illustrate the macro- haemodynamic condition of the animals MAP, HR, CI and GEDVI changes are demonstrated on Figure 7.

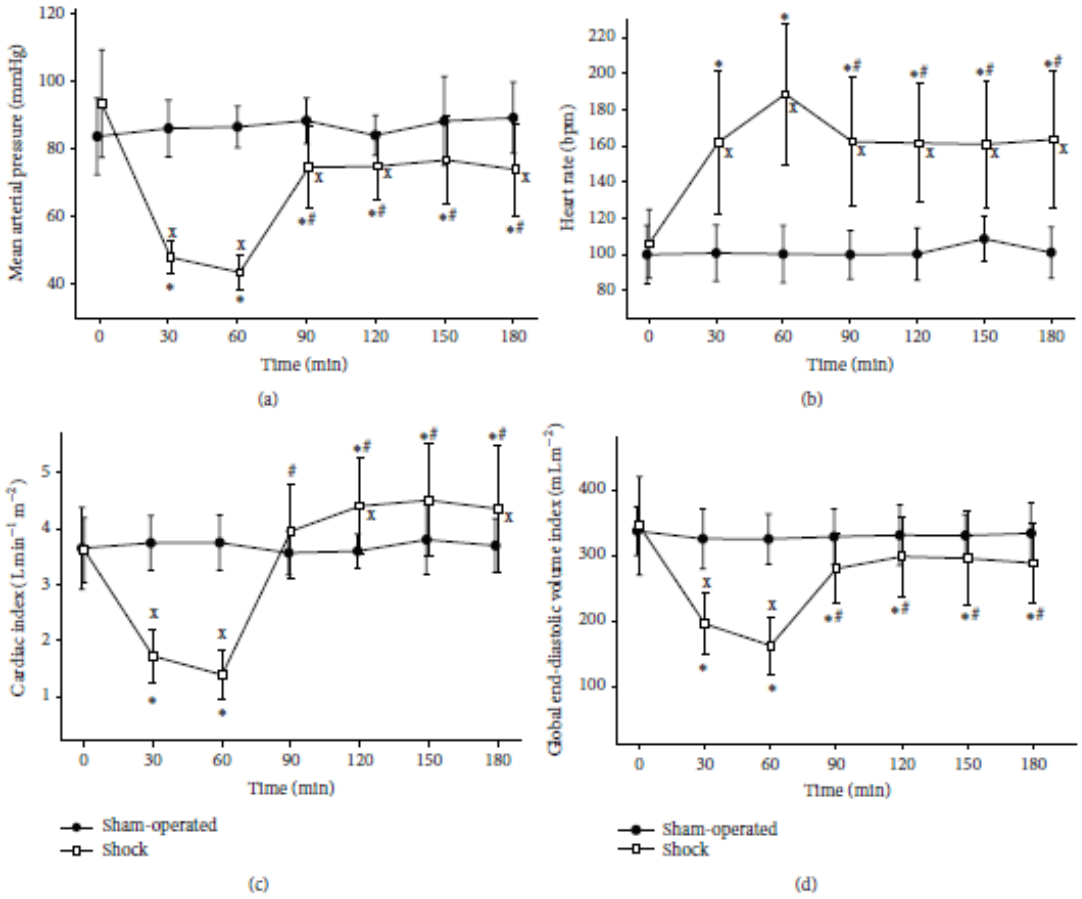

Figure 7. Changes of macro-haemodynamic parameters: mean arterial pressure (a), heart rate (b), cardiac index (c), and global end-diastolic volume index (d). $* p < 0.05$ as compared to 0 min (T_0), $\#p < 0.05$ as compared to 60 min (T_2), and x $p < 0.05$ shock group versus sham-operated group.

The sublingual postcapillary red blood cell velocity ($RBCV_{SL}$) and the sublingual capillary perfusion rate (CPR_{SL}) determined by videomicroscopy decreased significantly in severe shock. During partial resuscitation (T_2 to T_6) both $RBCV_{SL}$ and CPR_{SL} increased in the shock group compared to T_2, but still they remained decreased compared to the baseline values. At 180min (T_6), there was no difference in $RBCV_{SL}$ between shock and sham operated groups, while CPR_{SL} in the shock group remained significantly lower than in the sham operated group (Fig. 8 a,b).

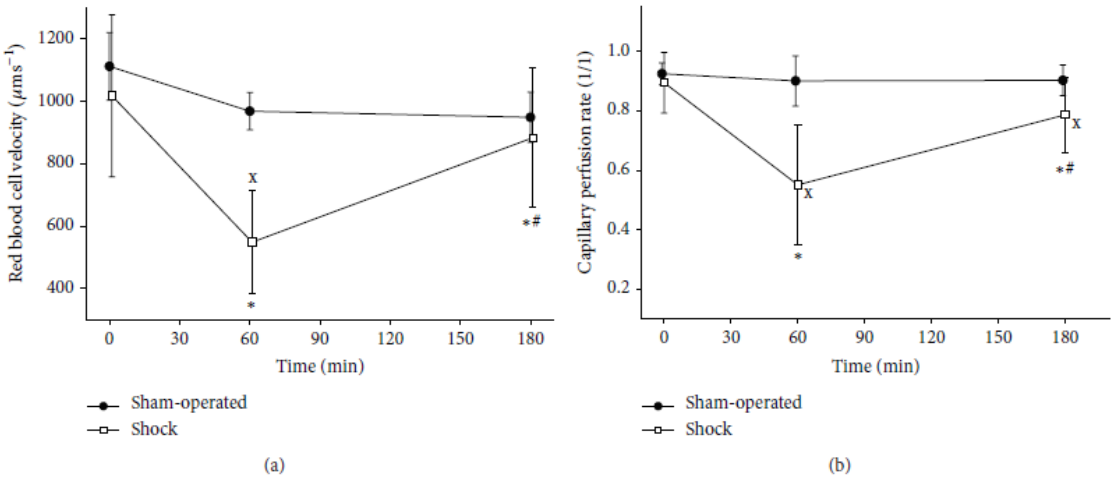

Figure 8. Microcirculatory parameters measured by OPS: red blood cell velocity in postcapillary venules (a) and capillary perfusion rate (b). $* \ p < 0.05$ as compared to 0 min (T_0), # $p < 0.05$ as compared to 60 min (T_2), and x $p < 0.05$ shock group versus sham-operated group.

The central venous blood derived variables showed characteristic alterations too. Corresponding to the significant increase of the oxygen extraction rate the $ScvO_2$ decreased during bleeding, while the $PcvaCO_2$ increased (Fig. 9 a,b,c). These changes at 60 minutes were significant compared to the baseline values and differed significantly from the corresponding values of the sham-operated animals. Fluid resuscitation resulted in a significant decrease of the $PcvaCO_2$ at T_3–T_6 as compared to T_2, but $PcvaCO_2$ changes within the shock group were significant at T_3 compared to T_0. $ScvO_2$ showed a statistically significant elevation after resuscitation as compared to T_2 but remained significantly lower as compared to the baseline value at T_0 and to the sham-operated group. In case of the oxygen extraction rate significant differences were observed between the sham and shock groups at T_4–T_6.

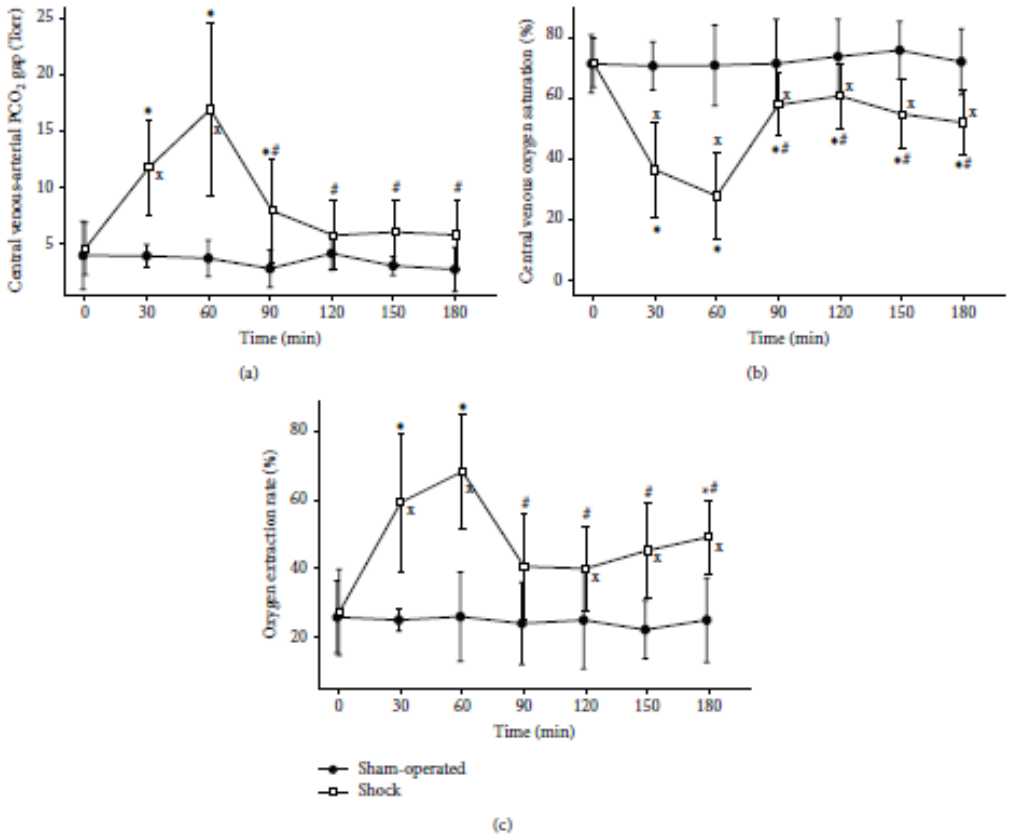

Figure 9. Central venous blood gas derived parameters: central venous-to-arterial PCO_2 gap (a), central venous oxygen saturation (b), and oxygen extraction rate (c). $*$ $p < 0.05$ as compared to 0 min (T_0), # $p < 0.05$ as compared to 60 min (T_2), and x $p < 0.05$ shock group versus sham-operated group.

With respect to the sublingual capnometric data significant increases were detected both in the $P_{SL}CO_2$ and the $P_{SL}CO_2$ gap values during the haemorrhagic shock phase (Fig. 10), while during partial resuscitation a significant improvement of $P_{SL}CO_2$ and $P_{SL}CO_2$ gap was detected, still these values remained elevated as compared to baseline (T_0). Moreover, at T_5 $P_{SL}CO_2$ was significantly higher than in the sham-operated group. Regarding the $P_{SL}CO_2$-gap, it decreased significantly by T_3 as compared to T_2 in the shock group, but it remained significantly higher as compared to T_0 throughout the resuscitation period. The $P_{SL}CO_2$ did not change significantly over time in the sham operated group (Fig. 10 a,b). The results of the correlation analysis are shown on Figure 11 (see text below).

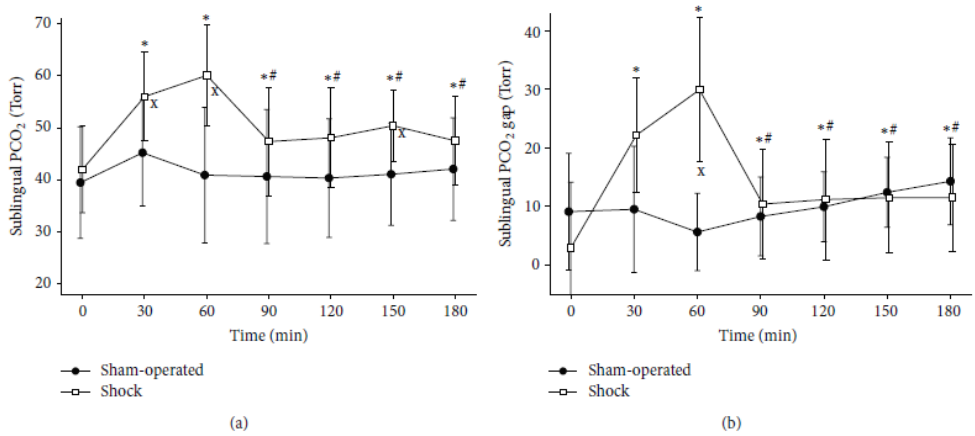

Figure 10. Changes of sublingual tonometric variables measured by the new probe: sublingual PCO_2 (a) and sublingual PCO_2 gap (b). * $p< 0.05$ as compared to 0. min (T_0), # $p< 0.05$ as compared to 60. min (T_2), x $p< 0.05$ shock group vs. sham-operated group.

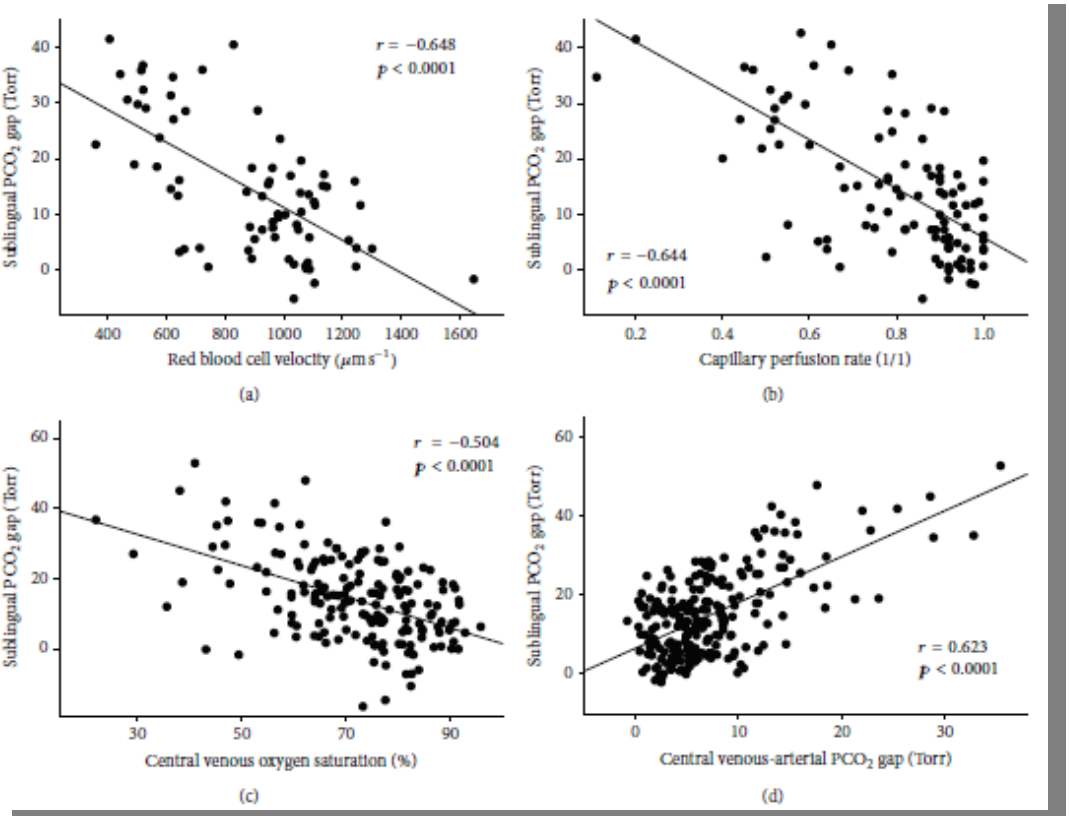

Figure 11. Correlations with sublingual capnometry: relationships between sublingual mucosal to arterial PCO_2 gap and sublingual red blood cell velocity in postcapillary venules (a), sublingual capillary perfusion rate (b), central venous oxygen saturation (c) and central venous-to-arterial carbon-dioxide partial pressure difference (d).

The correlation analysis of the sublingual capnometric and the direct microcirculatory parameters obtained by videomicroscopy revealed a statistically significant correlation between $P_{SL}CO_2$ gap and $RBCV_{SL}$ ($r = -0.648$; $p < 0.0001$) and $P_{SL}CO_2$ gap and CPR_{SL} ($r = -0.644$; $p < 0.0001$). The $P_{SL}CO_2$ gap also correlated with $ScvO_2$ and $PcvaCO_2$ ($r = -0.504$ and $p < 0.0001$; $r = 0.623$ and $p < 0.0001$, respectively) (Fig. 11 a,b,c,d).

4.3. The influence of mucosal perfusion abnormalities on gastric emptying assessed by residual gastric volumes during early enteral feeding.

The clinical characteristics of the examined study population are summarized in Table 4.

Age (years)	**74 (59-87)**
Gender (m/f)	4/4
APACHE II. score	26
Mortality risk (%)	55
Mortality (%)	37
Diagnosis (n)	
intracranial haemorrhage	3
subarachnoid haemorrhage	2
sepsis, MOF	1
cardiogenic shock	2

Data are expressed as mean (min-max), respectively.

Table 4. Characteristics of the patients involved in Study III.

The average APACHE II score of the study patients was 26 points with a calculated mortality risk of about 55%. Elevated $P_{ga}CO_2$ gap was found up to 70% of the measurements, while abnormal seLac, $ScvO_2$ and $PcvaCO_2$ were recorded in 16%, 14% and 39% of all measurements. In 50% of the patients, the average $P_{ga}CO_2$ was lower, while in the other 50% higher than 29 mmHg. This was the median value to develop the low and high $P_{ga}CO_2$ groups (LG and HG). The amount of RGV was found significantly lower in the LG as compared to the HG: 0 (0-50) versus 50 (30-200) ml, $p < 0.001$ (Fig. 12). The comparison of blood-gas derived parameters of LG with HG (patients with low or high mucosal capnometric parameters) showed statistically significant differences regarding $ScvO_2$ and seLac (Table 5).

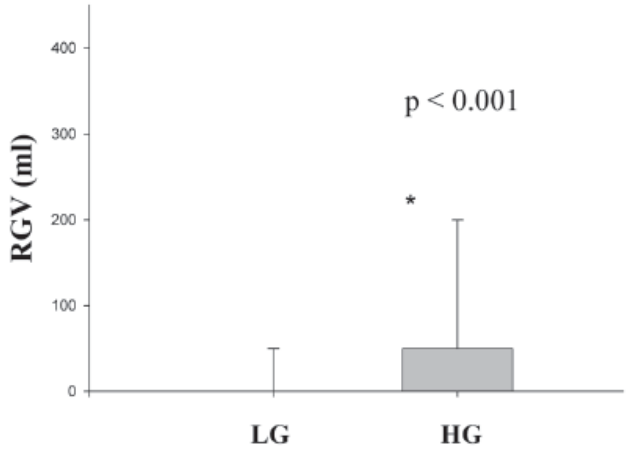

Figure 12. Differences in the average residual gastric volume (RGV) between the two groups. Patients were assigned to low (LG) and high group (HG) based on their average $PgaCO_2$ levels (* $p < 0.001$ Mann-Whitney Rank Sum test.).

The differences in systemic oxygenation parameters of the two groups, reflected by blood gas derived metabolic parameters (such as $ScvO_2$, seLac and $PcvaCO_2$ levels) are summarized in Table 5.

	LG	HG
$PcvaCO_2$ (mmHg)	6.0 (4.6-7.0)	7.0 (5.0-8.0) NS
$ScvO_2$ (%)	80 (77-82)	75 (68-81) *
seLac (mmol/L)	1.1 (0.9-1.2)	1.6 (1.1-3.2) *

Table. 5. Differences in the $PcvaCO_2$, $ScvO_2$ and seLac levels between patients with low (LG) and high (HG) $PgaCO_2$ levels. Values are expressed as median and 75th and 25th percentiles (* $p < 0.05$ Mann-Whitney Rank Sum test).

4.4. The influence of mucosal perfusion parameters monitored by our new device on the efficacy of tube feeding.

In this pilot study there was no statistically significant difference in the rate and escalation of enteral nutrition in the two groups. The average Ea/Et quotient was found similarly 0.47 in both groups. It means that by gradual increase of the pump rate, about 50% of the total caloric requirement could be administered via nasogastric tube feeding by the 3rd to the 5th days of the ICU stay. Complications attributable to early enteral feeding were uncommon, short-term

diarrhea stopped by feeding-pause was reported in two individuals and suspected regurgitation and aspiration in one case.

5. DISCUSSION

The re-establishment of adequate tissue perfusion and oxygenation is the ultimate goal of resuscitation. Because of the relative independency of micro- and macrocirculation, especially in sepsis or in the post-resuscitation phase of critical illness, normal peripheral perfusion is not guaranteed by the optimization of classical haemodynamic targets such as blood pressure, cardiac output, mental status etc. [4,5,47] Unrecognized occult hypoperfusion have a pathogenetic role in the development of postoperative complications in high risk surgery too, which explains the success of extended haemodynamic monitoring and goal-directed therapy in reducing postoperative morbidity [48-50]. These observations have led to the growing interest in the monitoring of regional perfusion and microcirculation in various patient groups. Of all the different monitoring techniques, mucosal capnometry offers a simple, non-invasive or minimal invasive bedside method for the assessment of peripheral circulation.

In Study I we report on the first use of a new gastric tonometric probe in adult humans. As part of its validation process we performed in vitro parallel air tonometric measurements comparing the CO_2 uptake of the new probe and the classical tonometric catheter. Although the in vitro CO_2 uptake of these instruments had been examined previously [32], we used a different protocol and tested the performance of the devices at three different CO_2 concentrations. The paired measurements performed in an equilibrium chamber revealed, that the PCO_2 values measured by the catheter were mostly lower than those obtained by the probe. Complete equilibration was reached more frequently by the new device, and the accuracy of the new probe proved to be superior at higher PCO_2, although these differences are fairly small and probably irrelevant for the clinical practice. During the first clinical experiences in our patient group anaesthetized surgical patients and volunteers were involved, and continuous medical attention was ensured during controlled conditions. The new method is minimally invasive, no injuries to any of the involved individuals were encountered resulting from the use of the probe. The adverse effects can be avoided by using local

anesthesia in awake patients, and the technical problems encountered during the application of the new probe by using proper lubrication before insertion and careful fixation after positioning. According to the human experiences gained so far, the small size and the soft material of these probes is beneficial in general, which makes it easily applicable in any age group including low birth weight neonates. The favorable properties (eg, soft, thin wall) of the new tool, however, were found disadvantageous in certain cases. For the insertion of the soft tube a guide wire is required, and unintentional displacement may happen during the routine nursing procedures. Non-cooperating patients may be able to remove the probe even with their tongues, necessitating replacement of the device. Incorrect fixation to the nose or cheek may result in kinking of the probe outside the body. Our results from 50 patients undergoing major surgery indicate an elevation of both the P_gCO_2 and $P_{ga}CO_2$ gaps parallel with the severity of the general condition of the patients, because higher ASA classification corresponds with higher perioperative morbidity and mortality. The hazards of surgical interventions are clearly based on operative and patient risk, and haemodynamic stabilization plays a key role in postoperative organ function and complications [49-51]. Our observations are in accord with the earlier results demonstrating that unstable haemodynamics with resultant splanchnic vasoconstriction should be avoided or promptly treated. Provided that other investigators in well conducted studies gain further favorable experiences using our method, this type of monitoring during high-risk surgery could be a part of the strategy in decreasing postoperative morbidity. In Study I parallel in vivo air tonometric measurements were performed with the conventional ballooned catheter connected to a Tonocap monitor and with the new balloon-free probe connected to a capnograph, too. The new method and the last generation of gastric tonometers applying automated recirculating air tonometry were compared [52,53]. The results of the in vivo paired measurements revealed that the PCO_2 values measured by the catheter were mostly lower than those obtained by the probe. The observed differences could be explained partly by the underestimation of the values obtained by the catheter, and by the fundamental differences between the two methods. The equilibration time and even more so the response time are rather long in measurements with the catheter. During the initiation period of its use, it requires at least two to three cycles for the complete equilibration of the gas inside its balloon, whereas when using the probe an almost entire equilibrium is reached after 5 minutes [32]. Thus, we suspect that the PCO_2 estimation of the new device may be closer to the actual values. In case of a fairly stable

circulation, the probe may detect higher pressure levels, whereas in case of an improvement in the splanchnic microcirculation, the probe reacts quicker and could show lower P_gCO_2. Another factor can be responsible for the detected differences: the mucosal circulation of the stomach may show minor regional heterogeneity. Because the two tonometers could be placed in different gastric regions, local changes may have resulted in higher in vivo deviations, compared with the in vitro results.

Mucosal capnometric monitoring in the sublingual area was carried out by a special device in Study II in one of the most common form of shock. For this purpose another new device was used, which is a further development of the new gastric tonometer. In this study we report on the first in vivo application of the new sublingual capnometric device for perfusion monitoring. The major finding of this experiment is, that this non-invasive PCO_2 monitor accurately reflected the changes in submucosal postcapillary blood flow during haemorrhagic shock and fluid resuscitation. The measured capnometric values showed good correlation both with direct indices of microcirculation as determined by videomicroscopy and with global measures of hypovolemia-caused oxygen debt such as $ScvO_2$ and $PcvaCO_2$. Although the value of sublingual capnometry in the diagnosis of circulatory failure has been reported earlier [18,39], the method is not available for everyday clinical practice. Unlike the highly sophisticated and costly devices containing special PCO_2-electrodes or fiber optic sensors used for this purpose in the prior experimental and clinical studies [31], the device applied in our experiments is a simple, non-invasive silicone probe providing real-time assessment of peripheral circulation at the bedside.

In the animals undergoing severe bleeding there were significant changes in macro-haemodynamic parameters (MAP, HR, CI and GEDVI) during the shock phase and during partial resuscitation. The alterations in mucosal PCO_2 showed a similar pattern. Loss of 50% of the circulating blood volume increased the sublingual PCO_2 by 50%: from T_0=41.6 ± 8.3 to T_2=60.1 ± 9.6 Torr, while sublingual PCO_2 gap increased by 5 fold. Therefore it seems that for this purpose the mucosal to arterial gap values may be more sensitive than sublingual PCO_2 on its own. We did not observe strong, significant differences in the $P_{SL}CO_2$ and the $P_{SL}CO_2$ gap values between the sham-operated and the shock groups in the partial resuscitation phase, but there were significant changes in the shock group reflecting the hemodynamic changes throughout the experiment. Therefore we suggest that it is the kinetics of $P_{SL}CO_2$ rather than the absolute value which deserves attention. This has to be investigated

in the future. According to recently published experimental data sublingual PCO_2 monitoring may be useful in guiding fluid resuscitation and the titration of the volume to replace [54], these results were not confirmed in clinical studies yet. In general it is important to note that $P_{SL}CO_2$ or $P_{SL}CO_2$ gap has different role and interpretation during "rapid" or "massive" and "slow" bleeding. No one needs additional indicators during massive bleeding with severe hypotension to confirm that the patient is in trouble, and neither is there time for these measurements. Therefore the initial objective of haemodynamic stabilization is the restoration of the macro-haemodynamic variables, and sublingual capnometry may prove its merit during slow bleeding, occult hypovolemia or ongoing hypoperfusion of different origin, when macro-haemodynamics are within the normal range. Massive bleeding in our study resulted in severe perfusion abnormalities as indicated by significant deterioration of sublingual CPR and RBCV, which was also reflected by changes of the sublingual $P_{SL}CO_2$ gap. Although the close relationship between the sublingual perfusion and PCO_2 has already been described [38,55], and investigations on mucosal PCO_2 and the microcirculation of the ileum [56,57] have been performed in shock, our experiment was the first to describe the correlation between sublingual capnometry and the directly measured microcirculatory parameters during hemorrhagic shock. With respect to the blood-gas derived parameters in our study, $ScvO_2$, O_2ER and $PcvaCO_2$ showed significant changes during hemorrhagic shock and partial resuscitation. Although in cases of impaired oxygen uptake $ScvO_2$ values can be elevated [58,59], our hemorrhagic shock-resuscitation model gives further support to the theory that low $ScvO_2$ and high $PcvaCO_2$ indicate hypovolemia. The significant correlation of these central venous blood-gas parameters with $P_{SL}CO_2$ gap suggest, that in our bleeding-resuscitation model these variables were similarly indicative of shock.

Mechanically ventillated high-risk ICU patients were enrolled in a pilot study (Study III) investigating the influence of regional gastrointestinal perfusion on gastric motility. During critical illness the provision of enteral feeding is crucially important. Unfortunately, gastrointestinal dysfunction, including dysmotility and malabsorption occurs frequently in the ICU, and hinders nasogastric tube feeding, the more physiologic way of nutrition [60,61]. The severity of the illness is associated with higher incidence of gastrointestinal complications and may lead to insufficient enteral calorie delivery. This vicious circle worsens the clinical outcome and delays recovery. Consequently, barriers to feeding and optimization of gut function are of great significance in high risk patients [62].

The key factors in the maintenance of the healthy bowel system are the intact neurohumeral regulation, intraluminal factors and normal splanchnic blood flow. In our investigation we focused on the latter. Gastric motility was assessed by the interval measurements of gastric residuals (RGVs), which method offers - as opposed to more difficult scintigraphic or absorption tests - a rough estimation of gastric motoric function, but proved to be a practical and useful method for everyday clinical praxis. Splanchnic hypoperfusion reflected by increased $P_{ga}CO_2$ gap was a common finding in the first days of intensive therapy, as detected up to 70% of all measurements. Such abnormalities remain hidden without regional perfusion monitoring, and can contribute to the development of organ dysfunction worsening clinical outcome. 37% of these high risk patients died in the intensive care unit, whose calculated mortality risk exceeded 55%. The main finding of the study is, that patients with elevated $P_{ga}CO_2$ had significantly higher RGVs. Although the prediction of feeding intolerance is rather diffucult, the increased amount of gastric residuals in the patients with compromised gastric tonometric parameters suggest that normalization of perfusion parameters may positively affect the motility of the stomach. The results of other studies also support this assumption. In an examination performed in neonates decreased Doppler sonographic blood flow in the superior mesenteric artery has been linked to intestinal dysmotility and feeding intolerance [63]. In a prospective study of 124 low birth-weight preterm infants prenatal haemodynamic disturbances adversely affected gut motility, and the decrease in regional blood flow posed higher risk for abdominal problems and a delay in tolerating enteral feeding [64]. The close interaction between gastric myoelectrical, secretory activity and mucosal blood flow has been described in different experimental models, and interventions ameliorating mucosal ischaemia simultaneously improved gastric emptying [65,66]. Not surprisingly, in this study abnormal arterial and central venous blood gas parameters occured less frequently in the first days of ICU stay. Pathological values of seLac, $ScvO_2$ and $PcvaCO_2$ were recorded in 16%, 14% and 39% of all measurements, respectively. These results not only demonstrate the relative stability of systemic parameters compared to those of regional perfusion, but reflect their role in decision making in our everyday clinical practice. The comparison of blood-gas derived parameters of LG with HG (patients with low or high mucosal capnometric parameters) showed statistically significant differences regarding $ScvO_2$ and seLac (Table 5.), but these differences were fairly small and not evaluable with respect to clinical practice. In our interpretation - even if the relationship of macro- and microcirculation

is often loose -, regional hypoperfusion occurs more commonly in patient groups with disturbed global oxygenation and haemodynamics. The results of this pilot study, however, do not allow us to draw such conclusions; further investigations are needed to reveal these correlations. The applied early enteral feeding concept was found to be feasible during Study III, adverse effects were rarely encountered. As mentioned above, there was no statistically significant difference in the rate and escalation of enteral feeding between the two groups, the Ea/Et quotient was found similar. The feeding protocol we applied was in accord with contemporary recommendations, in which the threshold RGV values necessitating dose adjustments are significantly higher than the measured RGVs in our patients. Although in case of relatively normal gastric emptying gastric residuals should be close to zero [67], current guidelines suggest RGVs $\geq$ 250-300 ml per 6-8 hours as threshold values to reduce the rate of tube feeding. Data from recent investigations demonstrate, that both mesenteric perfusion abnormalities and slow passage of nutrients into the small intestine may impair nutrient absorption [62,68,69], and even smaller amounts of RGV may have negative impact on clinical outcomes.

6. SUMMARY

The major findings of the thesis are summarized as follows:

I. We have shown for the first time, that mucosal capnometry with the novel balloon-free probe developed in our institute is a valid tool for measuring gastric mucosal PCO_2 in the adult population.

II. In our animal experiment on haemorrhagic shock, sublingual mucosal capnometry derived variables measured by a new sublingual capnometric probe followed microcirculatory changes, and correlated with global parameters describing macro-haemodynamics, too. Hence our results indicate that sublingual capnometry may be a useful complementary tool for assessing hypovolemia and haemorrhagic shock.

III. In a pilot study on critically ill patients on early enteral feeding, we have shown that significant differences in gastric emptying were found in patients with higher mucosal to arterial CO_2 gap as monitored by our newly developed balloon-free air-tonometric probe, tested in our first study. These data suggest that implementing these measurements in a selected ICU population may be worthwhile.

In conclusion I would like to remark, that considering the intensive research of mucosal capnometry, it is necessary to turn these devices into simple, cost-effective and user-friendly instruments for the further progress in technical development. Provided that other investigators in well-conducted studies gain further favorable experiences using these methods, they may be candidates fulfilling these requirements.

References

1. Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med. 1988; 16(11):1117-20.

2. Sakr Y, Dubois MJ, De Backer D et al. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med. 2004; 32(9):1825-31.

3. Goodrich C. Endpoints of resuscitation: what should we be monitoring? AACN Adv Crit Care. 2006 ; 17(3):306-16.

4. Verdant CL, De Backer D, Bruhn A et al. Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis. Crit Care Med. 2009; 37(11):2875-81.

5. Lebuffe G, Decoene C, Pol A et al. Regional capnometry with air-automated tonometry detects circulatory failure earlier than conventional hemodynamics after cardiac surgery. Anesth Analg. 1999; 89(5):1084-90.

6. Pastores SM, Katz DP, Kvetan V. Splanchnic ischemia and gut mucosal injury in sepsis and the multiple organ dysfunction syndrome. Am J Gastroenterol. 1996; 91(9):1697-710.

7. Maynard N, Bihari D, Beale R et al. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. JAMA. 1993; 270(10):1203-10.

8. Mythen MG, Purdy G, Mackie IJ et al. Postoperative multiple organ dysfunction syndrome associated with gut mucosal hypoperfusion, increased neutrophil degranulation and C1-esterase inhibitor depletion. Br J Anaesth. 1993; 71(6):858-63.

9. Lamia B, Monnet X, Teboul JL. Meaning of arterio-venous PCO2 difference in circulatory shock. Minerva Anestesiol. 2006; 72(6):597-604.

10. Waelgaard L, Dahl BM, Kvarstein G et al. Tissue gas tensions and tissue metabolites for detection of organ hypoperfusion and ischemia. Acta Anaesthesiol Scand. 2012; 56(2):200-9.

11. Dubin A, Murias G, Estenssoro E et al. Intramucosal-arterial PCO2 gap fails to reflect intestinal dysoxia in hypoxic hypoxia. Crit Care. 2002; 6(6):514-20.

12. Vallet B, Teboul JL, Cain S et al. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. J Appl Physiol. 2000; 89(4):1317-21.

13. Gutierrez G. A mathematical model of tissue-blood carbon dioxide exchange during hypoxia. Am J Respir Crit Care Med. 2004; 169(4):525-33.

14. Dubin A, Edul VS, Pozo MO et al. Persistent villi hypoperfusion explains intramucosal acidosis in sheep endotoxemia. Crit Care Med. 2008; 36(2):535-42.

15. Dubin A, Murias G, Maskin B et al. Increased blood flow prevents intramucosal acidosis in sheep endotoxemia: a controlled study. Crit Care. 2005; 9(2):66-73.

16. Pernat A, Weil MH, Tang W et al. Effects of hyper- and hypoventilation on gastric and sublingual PCO2. J Appl Physiol. 1999; 87(3):933-937.

17. Heard SO. Gastric tonometry: the hemodynamic monitor of choice. Chest. 2003; 123(5):469S-474.

18. Nakagawa Y, Weil MH, Tang W et al. Sublingual capnometry for diagnosis and quantitation of circulatory shock. Am J Respir Crit Care Med. 1998; 157(6):1838-1843.

19. Cammarata GA, Weil MH, Fries M et al. Buccal capnometry to guide management of massive blood loss. J Appl Physiol. 2006; 100(1):304-6.

20. Levy B, Gawalkiewicz P, Vallet B et al. Gastric capnometry with air automated tonometry predicts outcome in critically ill patients. Crit Care Med. 2003; 31:474-80.

21. Kirton OC, Windsor J, Wedderburn R et al. Failure of splanchnic resuscitation in the acutely injured trauma patient correlates with multiple organ system failure and length of stay in the ICU. Chest. 1998; 113(4):1064-9.

22. Zhang X, Xuan W, Yin P et al. Gastric tonometry guided therapy in critical care patients: a systematic review and meta-analysis. Crit Care. 2015; 27;19:22.

23. Carlesso E, Taccone P, Gattinoni L. Gastric tonometry. Minerva Anestesiol. 2006; 72(6):529-32.

24. Boda D, Murányi L. Gastrotonometry: an aid to the control of ventilation during arteficial respiration. Lancet. 1959; 181-182.

25. Fiddian-Green RG, Pittenger G, Whitehouse WM Jr. Back-diffusion of CO2 and its influence on the intramural pH in gastric mucosa. J Surg Res. 1982; 33(1):39-48.

26. Morgan TJ, Venkatesh B, Endre ZH. Accuracy of intramucosal pH calculated from arterial bicarbonate and the Henderson-Hasselbalch equation: assessment using simulated ischemia. Crit Care Med. 1999; 27(11):2495-9.

27. Schlichtig R, Mehta N, Gayowski TJ. Tissue-arterial PCO2 difference is a better marker of ischemia than intramural pH (pHi) or arterial pH-pHi difference. J Crit Care. 1996; 11(2):51-6.

28. Heinonen PO, Jousela IT, Blomqvist KA et al. Validation of air tonometric measurement of gastric regional concentrations of CO2 in critically ill septic patients. Intensive Care Med. 1997; 23(5):524-9

29. Bennett-Guerrero E, Panah MH, Bodian CA et al. Automated detection of gastric luminal partial pressure of carbon dioxide during cardiovascular surgery using the Tonocap. Anesthesiology. 2000; 92(1):38-45.

30. Kolkman JJ, Otte JA, Groeneveld AB. Gastrointestinal luminal PCO2 tonometry: an update on physiology, methodology and clinical applications. Br J Anaesth. 84(1):74-86, 2000.

31. Maciel AT, Creteur J, Vincent JL. Tissue capnometry: does the answer lie under the tongue? Intensive Care Med. 2004; 30(12):2157-65.

32. Boda D, Kaszaki J, Tálosi G. A new simple tool for tonometric determination of the PCO2 in the gastrointestinal tract: in vitro and in vivo validation studies. Eur J Anaesthesiol. 2006; 23(8):680-5.

33. Király Á, Boda D, Tálosi G et al. Intraoperative gastric tonometric examinations in children and infants with a new probe, combined with measurement of the end-tidal PCO2. Paediatr Anaesth. 2008; 18:501-7.

34. Tálosi G, Boda D. Applicability of a new gastric tonometric probe in infants requiring intensive care. Med Sci Mon. 2008; 14:PI32-7.

35. Szakál O, Király A, Szűcs D et al. Measurement of gastric-to-end-tidal carbon dioxide difference in neonates requiring intensive care. J Matern Fetal Neonatal Med. 2012; 25(9):1791-5.

36. Povoas HP, Weil MH, Tang W et al. Comparisons between sublingual and gastric tonometry during hemorrhagic shock. Chest. 2000; 118(4):1127-1132.

37. Pellis T, Weil MH, Tang W. Increases in both buccal and sublingual partial pressure of carbon dioxide reflect decreases of tissue blood flows in a porcine model during hemorrhagic shock. J Trauma. 2005; 58(4):817-24.

38. Creteur J, De Backer D, Sakr Y et al. Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med. 2006; 32(4):516-523.

39. Weil MH, Nakagawa Y, Tang W et al. Sublingual capnometry: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock. Crit Care Med. 1999; 27(7):1225-9.

40. Cammarata GA, Weil MH, Castillo CJ et al. Buccal capnometry for quantitating the severity of hemorrhagic shock. Shock. 2009; 31(2):207-211.

41. Lu H, Zheng J, Zhao P et al. Buccal partial pressure of carbon dioxide outweighs traditional vital signs in predicting the severity of hemorrhagic shock in a rat model. J Surg Res. 2014; 187(1):262-269.

42. Baron BJ, Sinert R, Zehtabchi S et al. Diagnostic utility of sublingual PCO2 for detecting hemorrhage in penetrating trauma patients. J Trauma. 2004; 57(1):69-74.

43. Marik PE. Sublingual capnography: a clinical validation study. Chest. 2001; 120(3):923-7.

44. Rackow EC, O'Neil P, Astiz ME et al. Sublingual capnometry and indexes of tissue perfusion in patients with circulatory failure. Chest. 2001; 120(5):1633-8.

45. Marik PE, Bankov A. Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. Crit Care Med. 2003; 31(3):818-22.

46. Szabó A, Suki B, Csonka E et al. Flow motion in the intestinal villi during hemorrhagic shock: a new method to characterize themicrocirculatory changes. Shock. 2004; 21(4):320–328.

47. Trzeciak S, McCoy JV, Phillip Dellinger R et al. Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med. 2008; 34(12):2210-7.

48. Mythen MG. Postoperative gastrointestinal tract dysfunction: an overview of causes and management strategies. Cleve Clin J Med. 2009; 76(Suppl 4):S66-71.

49. Kirov MY, Kuzkov VV, Molnar Z. Perioperative haemodynamic therapy. Curr Opin Crit Care. 2010; 16(4):384-92.

50. Giglio MT, Marucci M, Testini M et al. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Br J Anaesth. 2009; 103(5):637-46.

51. Lebuffe G, Vallet B, Takala J et al. A european, multicenter, observational study to assess the value of gastric-to-end tidal PCO2 difference in predicting postoperative complications. Anesth Analg. 2004; 99(1):166-72.

52. Taylor DE, Gutierrez G, Clark C et al. Measurement of gastric mucosal carbon dioxide tension by saline and air tonometry. J Crit Care. 1997; 12(4):208-13.

53. Bennett-Guerrero E, Panah MH, Bodian CA et al. Automated detection of gastric luminal partial pressure of carbon dioxide during cardiovascular surgery using the Tonocap. Anesthesiology. 2000; 92(1):38-45.

54. Xu J, Ma L, Sun S et al. Fluid resuscitation guided by sublingual partial pressure of carbon dioxide during hemorrhagic shock in a porcine model. Shock. 2013; 39(4):361-5.

55. Jin X, Weil MH, Sun S et al. Decreases in organ blood flows associated with increases in sublingual PCO2 during hemorrhagic shock. J Appl Physiol. 1998; 85(6):2360-4.

56. Dubin A, Pozo MO, Ferrara G et al. Systemic and microcirculatory responses to progressive hemorrhage. Intensive Care Med. 2009; 35(3):556-64.

57. Tugtekin IF, Radermacher P, Theisen M et al. Increased ileal-mucosal-arterial PCO2 gap is associated with impaired villus microcirculation in endotoxic pigs. Intensive Care Med. 2001; 27(4):757-66.

58. De Backer D, Ospina-Tascon G, Salgado D et al. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. Intensive Care Med. 2010; 36(11):1813-25.

59. Krafft P, Steltzer H, Hiesmayr M et al. Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events. Chest. 1993; 103(3):900-6.

60. Gungabissoon U, Hacquoil K, Bains C et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. JPEN J Parenter Enteral Nutr. 2015; 39(4):441-8.

61. Chapman MJ, Deane AM. Gastrointestinal dysfunction relating to the provision of nutrition in the critically ill. Curr Opin Clin Nutr Metab Care. 2015; 18(2):207-12.

62. Chapman MJ, Nguyen NQ, Deane AM et al. Gastrointestinal dysmotility: evidence and clinical management. Curr Opin Clin Nutr Metab Care. 2013; 16(2):209-16.

63. Robel-Tillig E, Knüpfer M, Pulzer F et al. Blood flow parameters of the superior mesenteric artery as an early predictor of intestinal dysmotility in preterm infants. Pediatr Radiol. 2004; 34(12):958-62.

64. Robel-Tillig E, Vogtmann C, Bennek J. Prenatal hemodynamic disturbances -- pathophysiological background of intestinal motility disturbances in small for gestational age infants. Eur J Pediatr Surg. 2002; 12(3):175-9.

65. Mizuguchi S, Ohno T, Hattori Y et al. Roles of prostaglandin E2-EP1 receptor signaling in regulation of gastric motor activity and emptying. Am J Physiol Gastrointest Liver Physiol. 2010; 299(5):G1078-86.

66. Zhao ZK, Hu S, Zhang LJ et al. Electroacupuncture at Zusanli (ST36) promotes gastric emptying and mucosal blood flow during oral resuscitation of scalded rats with a pyruvate-enriched ORS. Burns. 2015; 41(3):575-81.

67. Chapman MJ, Besanko LK, Burgstad CM et al. Gastric emptying of a liquid nutrient meal in the critically ill: relationship between scintigraphic and carbon breath test measurement. Gut. 2011; 60(10):1336-43.

68. Sim JA, Horowitz M, Summers MJ et al. Mesenteric blood flow, glucose absorption and blood pressure responses to small intestinal glucose in critically ill patients older than 65 years. Intensive Care Med. 2013; 39(2):258-66.

69. Chapman MJ, Fraser RJ, Matthews G et al. Glucose absorption and gastric emptying in critical illness. Crit Care. 2009; 13(4):R140.

Acknowledgements

I would like to express my deep gratitude to my tutor, Professor Zsolt Molnár, who provides high-quality clinical research in his institute. He not only allowed but embraced our investigations, and gave tremendous support in the publication process. I thank him for his encouraging attitude, continuous guidance, support and invaluable advices to this work.

I am very grateful to Professor Tibor Wittmann, who endeared experimental work to me, and selflessly supported me in the early years as a medical student.

I owe very much Professor Domokos Boda (┼), who involved me to the research of tonometry and introduced me to the principles and practice of mucosal capnometric methods. I learned very much from him as a scientist, teacher, physician and a great man. With his tiredless interest, work and help he motivated me throughout the examinations, and was always there for me in time of need. He is a role model.

I am especially thankful to József Kaszaki, my teacher, tutor and co-author in one, who instructed and guided the team throughout the animal experiments. I would also like to thank to Professor Mihály Boros for giving the opportunity for the experimental studies.

I am really grateful to Krisztina Boda for her crucial help in the statistical analysis.

I would like to take the opportunity to express my special gratitude to all of my colleagues at the Department of Anaesthesiology and Intensive Therapy for their professional support.

Finally, I would like to dedicate this work to my family, to Klári, Márió and Kíra. They know why…

Appendix

I

Journal of Critical Care (2010) 25, 541.e9–541.e15

ELSEVIER

Journal of Critical Care

Practical experiences and in vitro and in vivo validation studies with a new gastric tonometric probe in human adult patients☆,☆☆

Péter Palágyi MD[a], László Vimláti MD, PhD[a], Krisztina Boda PhD[b], Gyula Tálosi MD, PhD[c], Domokos Boda MD, MSci[c,*]

[a]*Department of Anesthesiology, University of Szeged, 6720, Hungary*
[b]*Department of Medical Informatics, University of Szeged, 6720, Hungary*
[c]*Department of Pediatrics University of Szeged, 6720, Hungary*

Keywords:
Gastrointestinal tonometry;
Carbon dioxide;
Partial pressure;
Measurement technique;
Validation

Abstract

Purpose: This study provides practical experiences with a new, simple, balloon-free gastric tonometric probe (probe) and reports the results of simultaneous in vitro and in vivo measurements with a conventional, ballooned gastric air tonometer (catheter) and the new device.

Materials and Methods: Ten healthy volunteers and 50 anesthetized surgical patients with different American Society of Anesthesiologists (ASA) scores, scheduled for neurologic, orthopedic, trauma, and cardiac operations, were enrolled in the study. The values of 60 in vitro and, in 12 surgical patients, 101 in vivo paired P_{CO_2} measurements—performed simultaneously with the new tonometric probe and the catheter that was connected to a Tonocap monitor—were compared. The tolerability of the measurement with the new probe was examined, and the results of gastric tonometry and, in surgical cases, the gastric tonometric, end-expiratory, and arterial P_{CO_2} values were registered. The results were evaluated by analysis of variance test. The data of the in vivo paired measurements were evaluated by Bland-Altman analysis.

Results: The use of the probe proved to be well tolerated and easily applicable in the studied cases. The results of 20 measurements obtained in healthy volunteers and those of 520 measurements in the surgical cases correspond to the data obtained with the classical methods published in the medical literature. During in vitro paired measurements, there was a good agreement between the data obtained with the 2 methods; however, in the in vivo studies, the results of measurements performed with the probe were mostly higher.

Conclusions: The differences between the results obtained with the 2 methods might have been caused by the quicker equilibration property of the probe and by the fundamental differences between the 2 methods. The new probe seems to be applicable for routine human measurements.

☆ This study forms part of a project funded by the European Union and the Hungarian Ministry of Economic Affairs (GVOP-3.3.1-05/.-2005-0153/3.0) and of the innovation program at the University of Szeged.

☆☆ Abstract presented at the World Congress of the Society of Intravenous Anaesthesia, 2009, Berlin.

* Corresponding author. Tel.: +36 62545330; fax: +36 62545329.
E-mail address: dboda@pedia.szote.u-szeged.hu (D. Boda).

0883-9441/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcrc.2009.12.002

1. Introduction

Following the first description of gastric tonometry [1] for measurement of the partial pressure of carbon dioxide in the gastrointestinal tract (P_gCO_2) and the demonstration of its adequacy in determining splanchnic perfusion failure [2], the method became extensively used in clinical practice, mainly to monitor the condition of critically ill patients [3-6]. Further progress was achieved with the development of an automated gas tonometer, which eliminated the potential errors of the previous saline method and provided easier measurement facilities [7-11].

Nevertheless, despite the huge amount of published studies demonstrating its utility, gastric tonometry so far has not been generally used in everyday clinical practice.

Recently, we have described a new, simple, balloon-free probe consisting of silicone rubber tubes, which seems to be an easily applicable, reliable instrument for gastric tonometry in patients of all ages and has certain advantages over the traditional method [12]. Both in vitro and in vivo validation studies of the method were performed comparing the results obtained with the probe to those acquired using the conventional balloon tonometer. These studies, however, were carried out using a nonautomated, manual technique, and in vivo experiments were performed only on animals.

The publications on the clinical experiences with the new tonometric technique and its utility in clinical practice have only reported studies carried out on children and infants (including neonates) [13,14].

In the present study,

1. we intend to summarize our practical observations on the new probe used in healthy volunteers and in anesthetized adult patients;
2. furthermore, we would like to present the results of both the in vitro and the in vivo human validation measurements with simultaneously inserted probe and catheter (TRIP, NGS catheter; Tonometrics, Helsinki, Finland).

2. Methods

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.

2.1. Technique and materials for the paired in vitro measurements with the catheter and the probe

For the measurement of the in vitro uptake of CO_2 by the probe and the catheter, a glass container, as an equilibration chamber, was used. The part of the probe up to the fastening ring and the balloon part of the catheter were inserted simultaneously into the chamber, which was then sealed in an airtight manner. For the measurement of different P_{CO_2} levels, appropriate quantities of nitrogen and carbon dioxide were mixed with a precision gas blender to reach the desired CO_2 partial pressure inside the equilibration chamber. The mixtures were filling the chamber at a flow rate of 10 L/min. During the tonometric measurements, the P_{CO_2} level of the gas mixture inside the chamber was determined by the microcapnograph (Sidestream Microcap Handheld Capnograph; Oridion Medical Ltd, Jerusalem, Israel) by measuring the CO_2 content of the gas flowing from the container. During the study, the equilibration chamber was submerged in water thermostated at 37°C.

2.2. Patients

Before the in vivo investigations, the individuals who met the eligibility criteria were fully informed during the preoperative visit about the purpose of the study and the insertion of the catheters, and their written consent was obtained. In the case of 2 critically ill, ASA V patients—because of their altered mental status —the written consent was obtained from the escorting first-grade relatives.

The first experiences on the insertion of and measurement with the probe were gathered in 10 healthy volunteers. In their cases, no special premedication was applied except for a light spray of lidocaine into the throat to facilitate the insertion process. In this pilot study, both fasting and 3-hour postprandial tonometric measurements were performed on 2 consecutive days, inserting a new probe each day. In this study group, only the gastric tonometric measurements were recorded. For ethical reasons, the H_2-blocker medication was not applied in their cases.

In the clinical part of the examinations, 50 adult patients, scheduled for neurologic, orthopedic, trauma, and cardiac surgery, were enrolled. The exclusion criteria were nonfasting state, pregnancy, a contraindication to nasogastric tube insertion (eg, any kind of nasal atresia or obstruction), erosive gastritis or esophagitis, and gastric or duodenal ulcer.

The characteristics of the healthy volunteers and the surgical population are shown in Table 1.

The numbers of patients classified to the different ASA categories are given in Table 2.

In each clinical case, preoperative H_2-receptor blocker medication was administered either orally (150 mg ranitidine

Table 1 Clinical characteristics of the study population

Group of patients	No.	Sex (M/F)	Age, mean (min.-max.)
Healthy volunteers	10	6/4	31 (21-84)
Coronary surgery	23	15/8	68 (52-81)
Aortic surgery	3	2/1	62 (55-68)
Neurosurgery	8	4/4	53 (17-79)
Orthopedic surgery	7	3/4	52 (15-81)
Trauma surgery	9	2/7	70 (21-86)

M indicates male; F, female.

Table 2 Number of the measurements, mean (SD) of the $P_{gprobe}CO_2$, $P_{IT}CO_2$, P_aCO_2, $P_{gprobe-IT}CO_2$, and $P_{gprobe-a}CO_2$ values in the study population

Study group	No. of cases	$P_{gprobe}CO_2$	$P_{IT}CO_2$	P_aCO_2	$P_{gprobe-IT}CO_2$	$P_{gprobe-a}CO_2$
Healthy volunteers, fasting	10	10				
		55.3				
		(3.63)				
Postprandial	10	10				
		56.2				
		(3.51)				
Patients with ASA score I + II	10	144	144	14	144	14
		44.9	33.0	39.2	11.8	6.2
		(4.46)	(3.00)	(4.23)	(4.52)	(6.98)
Patients with ASA score III	30	248	192	117	194	117
		45.5	30.6	35.7	16.3	8.8
		(7.62)	(3.45)	(5.51)	(7.69)	(7.99)
Patients with ASA score IV + V	9	128	33	99	33	99
		55.4	29.1	34.1	18.0	22.2
		(17.83)	(5.05)	(5.75)	(6.75)	(20.86)

Values are expressed as mean (SD) in mm Hg.

the night before surgery and ≤2 hours before surgery) or intravenously (50 mg ≤2 hours preoperatively). In case of longer application, this medication was repeated intravenously every 8 hours.

The anesthesia method was not standardized. In most cases, intravenous induction with a combination of benzodiazepines, opioids, and propofol was followed either by inhalational maintenance with isoflurane/sevoflurane in nitrous oxide and oxygen with additional opioid boluses, or total intravenous anesthesia using the combination of sufentanyl and propofol.

After 5 minutes of preoxygenation, the anesthesia was induced intravenously, and the patients were paralyzed with various nondepolarizing muscle relaxants. A probe was inserted nasogastrically or orogastrically into each anesthetized patient, and it was followed by endotracheal intubation. The minute ventilation was adjusted to maintain arterial carbon dioxide partial pressure (P_aCO_2) at 35 to 45 mm Hg.

Each patient received a 20G arterial catheter into the radial artery (Arterial Cannula with Floswitch, BD, Swindon, UK). P_aCO_2 values were determined with a Stat Profile pHOx Plus blood gas analyzer (Nova Biomedical, Waltham, MA. U.S.A.) at 37°C and were corrected for the patient's actual body temperature.

In 12 clinical patients, 101 in vivo parallel measurements were performed after inserting a catheter and the probe simultaneously

Samples for the end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) measurements in the operating room were obtained from the sampling line of the anesthesia machine (Dräger Zeus or Primus; Dräger Inc, DrägerwerkAG Lübeck, Germany), whereas $P_{ET}CO_2$ values in the intensive care unit were measured with the microcapnograph. The data obtained were recorded in parallel with the measurements of P_{CO_2} values obtained by the probe ($P_{gprobe}CO_2$).

Noninvasive blood pressure and respiratory parameters were determined at regular intervals. Every effort was made to maintain normotension and normovolemia according to traditional clinical parameters, although short periods of hypotension could be detected.

2.3. Description and technique of the use of the probe

The probe was described earlier [12]. Briefly, it consists of a larger and a smaller diameter silicone rubber tube (highly permeable to gases) sealed together so as to communicate with each other only at the distal end of the device. At the proximal end, they are held together by a silicone rubber fastening ring. The larger diameter tube is connected to a polyethylene tube, which serves for the transfer of the filling medium (in the present study, room air) following the equilibrium from the probe into the measuring device.

The probes used in the present experiments were 65 cm in length (the distance between the fastening ring and the tip of the probe), with a lumen diameter of 2 mm and a wall thickness of 0.25 mm in case of the larger diameter tube, and with a lumen diameter of 0.8 mm and a wall thickness of 0.2 mm in case of the smaller diameter tube.

For the in vivo measurements, the probes were inserted into the stomach orogastrically or nasogastrically up to the fastening ring with the aid of a guide wire. It must be emphasized that for the facile insertion, both the probe and the guide wire needed thorough lubrication with simethicone emulsion (Espumisan Berlin-Chemie AG, Berlin, Germany).

The room air, which initially fills the probe, equilibrates with the environmental P_{CO_2} throughout the full length of the probe within 10 minutes. After the equilibration period of 10 minutes, the microcapnograph, which aspirates the

gas content of the probe at a flow rate of 60 mL/min, is used for the periodic measurement of $P_{gprobe}CO_2$. Between the 2 measurements, the capnograph is switched off. After the transfer of the equilibrated filling medium, the probe refills automatically with fresh room air, becoming ready for equilibration for the next measurement.

2.4. Technique and materials for the in vivo paired tonometric measurements with a catheter and the probe inserted simultaneously

As a reference method, catheters were used for simultaneous measurements. The P_{CO_2} levels obtained with the catheter ($P_{gcathCO_2}$) were analyzed automatically in 10-minute cycling times by a Tonocap monitor (Datex-Ohmeda, Helsinki, Finland).

Under general anesthesia, the probe was inserted first (nasogastrically or orogastrically), and it was followed by the nasogastric insertion of a catheter. The correct position of the latter was verified by auscultation over the epigastrium, while injecting 20 mL of room air into the stomach via the feeding lumen of the catheter. The insertion of the tonometric tools was immediately followed by orotracheal intubation.

The position of the probe can be verified radiologically (as it was done in 5 cases in the present series of study) after the insertion procedure and before the removal of the guide wire. In general, the inappropriate positioning of the probe (eg, kinking or rolling-up in the esophagus) is indicated by a flexible resistance encountered during the insertion, or by an abnormal CO_2 pattern on the capnogram resulting from the partial or complete obstruction of the lumen. In case of correct positioning, a plateau with a length of at least 1 cm can be seen on the capnogram between the steadily ascending and descending slopes of the CO_2 curve (this is also characteristic in the radiologically confirmed cases).

2.5. Measurements

In the clinical part of the examinations of 50 adult patients, besides the P_aCO_2, the $P_{gprobe}CO_2$, the $P_{ET}CO_2$, the gastric-to-arterial P_{CO_2} gap ($P_{gprobe\text{-}a}CO_2$), and the gastric-to-end-tidal P_{CO_2} gap ($P_{gprobe\text{-}ET}CO_2$) were also determined.

In each series of paired measurements, both in vitro and in vivo studies, after an equilibration period of 20 minutes, the P_{CO_2} levels of the samples originating from the catheter were read with 10-minute intervals by the Tonocap monitor, whereas the P_{CO_2} levels of the contents of the probes were measured simultaneously by the microcapnograph (again, with 10-minute intervals). Before the measurements, the 2 capnographs (microcapnograph and Tonocap monitor) were checked against each other and were found to show identical results. Although the measurements with the probe yielded fully equilibrated values rapidly, the data for the initial 20-minute period were discarded in this case as well.

2.6. Statistical analysis

To compare the $P_{gprobe}CO_2$, $P_{ET}CO_2$, P_aCO_2, $P_{gprobe\text{-}ET}CO_2$, and $P_{gprobe\text{-}a}CO_2$ means, the ASA groups were combined as follows: ASA I + II, ASA III, and ASA IV + V. $P_{gprobe}CO_2$, $P_{ET}CO_2$, and $P_{gprobe\text{-}ET}CO_2$ were measured every 10 minutes; therefore, the number of measurements is higher than the number of cases. To compare the means of $P_{gprobe}CO_2$, $P_{ET}CO_2$, $P_{gprobe\text{-}ET}CO_2$, and $P_{gprobe\text{-}a}CO_2$ in the 3 ASA groups, a mixed model repeated-measurements analysis of variance method was used, where not only the group differences but also the individual within-subject variation in time can be modeled as well [15]. Group means were compared based on estimated marginal means with Sidak adjustment for multiple comparisons.

Means of in vitro measurements were compared by Student's paired *t* test.

To examine the agreement between the 2 simultaneous measurements for the in vivo tonometric study, Bland-Altman analysis [16] was performed on the multiple measurement results per individual. Bias, defined as the mean difference between values; precision, defined as the SD of the bias; and limits of agreement, defined as bias ± 1.96 SD were determined.

SPSS 15.0 for Windows (SPSS, Chicago, Ill) was used for statistical calculations.

3. Results

3.1. Results of the in vitro paired tonometric measurements

The results of the in vitro paired tonometric measurements in the equilibrium chamber at 3 different CO_2 concentrations (P_{CO_2} of 35, 55, and 80 mm Hg) are given in Table 3. Sixty in vitro paired measurements were recorded. The equilibration with the catheter was complete only in 16, 6, and 4 cases at

Table 3 Differences of the P_{CO_2} values measured by the catheter and by the probe from the actual P_{CO_2} values in the equilibrium chamber (at 3 different partial pressures)

Actual P_{CO_2} in the equilibrium chamber	35	55	80
No. of paired measurements	20	20	20
Difference from the P_{CO_2} measured by the catheter	−0.25 (0.44)	−1.10 (1.25)	−1.05 (0.68)
Difference from the P_{CO_2} measured by the probe	−0.15 (0.30)	−0.20 (0.95)	−0.10 (0.39)

Measurements were made at 10-minute intervals after an initial 20-minute equilibration period, at 37°C. Values are expressed as mean (SD) in mm Hg.

the respective concentrations, whereas complete equilibration was detected in 18, 11, and 15 cases when using the probe. Although the means of the measurements with the 2 different tonometric devices were significantly different at 55 and 80 mm Hg P_{CO_2}, indicating the higher accuracy of the probe, these differences were fairly small in case of both methods.

3.2. Practical experiences and the results of the measurements in 50 surgical patients using the probe

The probe is, in general, easily applicable in clinical practice. Its use is well tolerated by the patients and does not cause more inconveniences than does the simple insertion of a feeding tube. The complaints and technical difficulties that occurred during the insertion are the same as those during any nasogastric tube placement. During the 20 insertions into the 10 healthy volunteers, the following adverse effects were observed: retching in 6 cases and vomiting in 1 case.

When performing the tonometric measurements with the probe in the 50 surgical cases, the following technical problems were encountered: temporary obstruction (6 times), permanent obstruction (once), displacement of the instrument (3 times), and failed insertion (once). Nevertheless, we consider most of these difficulties as the results of inexperience, because they occurred mainly in the initial phase of the study. Epistaxis, a common complication of gastric tubing, did not occur.

The results of the measurements with the probe in healthy volunteers and in the different ASA groups of surgical cases are shown in Table 2. According to the data, the results of the 20 P_gCO_2 measurements performed in healthy volunteers and those of the 520 measurements in the surgical cases correspond with the large amount of data obtained using conventional balloon tonometry and published in the medical literature. The statistical analysis of the intraoperative cases revealed that the means of $P_{gprobe}CO_2$ in the ASA I + II and ASA III groups are significantly lower than those in the ASA IV + V category ($P = .002$ and $P = .012$, respectively). The mean of $P_{ET}CO_2$ in the ASA I + II group is significantly higher than the means of the ASA III and ASA IV + V groups ($P = .017$ and $P = .025$, respectively). Mean P_aCO_2 values of the ASA I + II group are significantly different from those of the ASA IV + V group ($P = .011$). $P_{gprobe\text{-}ET}CO_2$ values in the ASA I + II group are significantly lower than those in the ASA III group ($P = .006$). Mean $P_{gprobe\text{-}a}CO_2$ values of the ASA I + II and the ASA III groups are significantly lower than the corresponding values of the ASA IV + V group ($P = .016$ and $P = .024$, respectively).

3.3. Results of the in vivo paired tonometric measurements

The results of the 101 in vivo paired tonometric measurements performed with the catheter and the probe are presented in Fig. 1.

These results were identical in only 11 measurements. In 13 cases, the P_{CO_2} values measured using the catheter were higher than those detected by the probe. On the other hand, in 77 cases, higher P_{CO_2} values were obtained with the probe. The Bland-Altman analysis gave a mean difference of

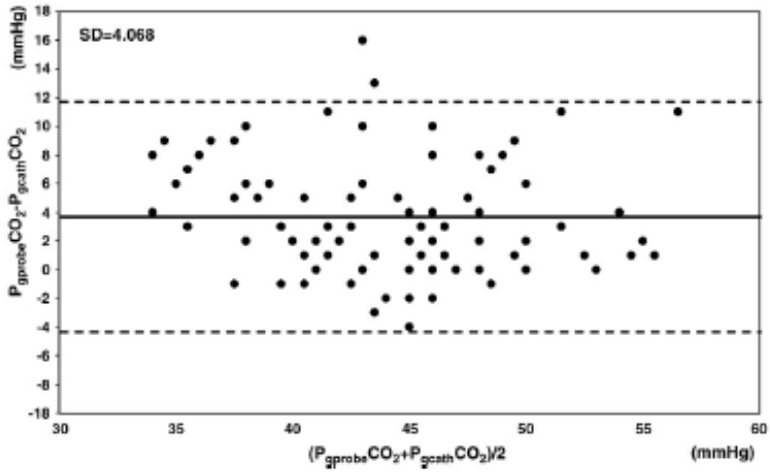

Fig. 1 Bias and precision data obtained by Bland-Altman analysis of the results of in vivo studies involving 101 paired measurements of the $P_{gprobe}CO_2$ and of the $P_{gcath}CO_2$ during anesthesia, in various surgical cases. Bias (mean difference of parallel measurements): 3.64 mm Hg. Precision (SD of differences): 4.068 mm Hg. Limits of agreements (bias ± 1.96 SD): −4.33 and 11.62 mm Hg.

3.64 mm Hg between the parallel measurements, with a precision (SD) of 4.068 mm Hg, indicating that the probe gives higher values than the catheter.

4. Discussion

This is the first study on the use of the probe in adult humans.

During the first clinical experiences in our patient group, only anesthetized surgical patients were involved in the study to guarantee continuous medical attention and to ensure controlled conditions, with special respect to the simultaneous comparative measurements. The adverse effects and technical problems encountered during the application of the new probe can be avoided by using local anesthesia in awake patients, by fixing the probe carefully, and by using proper lubrication before inserting the probe.

According to the human experiences gained so far, including the previous ones in infants [13,14], the method may have certain advantages over the criterion standard balloon tonometry. It is minimally invasive, and no injuries to any of the patients resulted from using the probe in our study.

The simethicone-containing material used for lubrication proved to be favorable without having any pharmacologic or toxic effect.

The measurement is feasible even with the current manual use, but the method can be automated as well.

The favorable properties (eg, soft, thin wall) of the new tool, however, may be found disadvantageous in certain respects. For the insertion of the soft tube, a guide wire is required, and unintentional displacement may happen during the routine nursing procedures. Noncooperating nonintubated patients may be able to remove the probe even with their tongues, necessitating replacement of the device. Incorrect fixation to the nose or cheek may result in kinking of the probe outside the body.

In the present study, parallel in vitro and in vivo air tonometric measurements were performed with the conventional balloon catheter connected to a Tonocap monitor and with the new balloon-free probe. A similar technique was used in earlier studies for the validation of the newly introduced air tonometric method [7-9]. The results of the measurements with the probe correspond with those obtained using the conventional methods. The fact that our results indicate an elevation of both the $P_{g\text{-}ET}CO_2$ and $P_{g\text{-}a}CO_2$ gaps parallel with the severity of the general condition of the patients (because higher ASA classification corresponds to higher perioperative mortality) supports the assumption that the evaluation of these gap values may be useful in predicting postoperative complications. [9,17]. The results of the paired measurements revealed that the P_{CO_2} values measured by the catheter were mostly lower than those obtained by the probe and the degree of the differences varied largely in the measuring periods.

However, it should be borne in mind that, perhaps because of regional differences, a disagreement may occur between paired in vivo measurements (also in normal controls) even when the same type of tonometric device is used [18]. At any rate, these observed differences could be explained partly by the underestimation of the values obtained by the catheter, as reported by other authors as well, and by the fundamental differences between the 2 methods. The equilibration time and even more so the response time are rather long in measurements with the catheter. During the initiation period of its use, it requires at least two to three cycles for the complete equilibration of the gas inside its balloon, whereas when using the probe, an almost entire equilibrium is reached after 5 minutes using room air as filling material, which contains hardly any CO_2 at the start of the measurement [12]. In addition, during our clinical examinations, pathologic alterations may have occurred involving changes in the gastric mucosal perfusion. These changes can be followed only by a device with the property of quick equilibrium. Thus, we suspect that the P_{CO_2} estimation of the new device may be closer to the actual values: in case of a fairly stable circulation, the probe may detect higher pressure levels, whereas in case of an improvement in the splanchnic microcirculation, the probe reacts quicker and shows lower P_gCO_2 levels. Another factor responsible for the differences detected is that the regional circulation of the stomach may show minor alterations. Because the 2 tonometers could be placed in different gastric regions, local changes may have resulted consequently in higher in vivo deviations, compared with the in vitro results.

According to the opinion of some review articles [19-21], there is an increasing evidence of the value of gastric tonometry in clinical practice, although its general use is still far from the desired level at present. This may be the consequence of the existing technical problems of the method and the high cost of the equipment. Therefore, it is necessary to turn the device into a simple, cost-effective, and user-friendly instrument for the further progress in its technical development. Provided that other investigators gain further favorable experiences using our method, it may be a candidate fulfilling these requirements.

5. Conclusions

In conclusion, both the in vitro and the in vivo paired measurements have demonstrated that the P_{CO_2} data obtained with the catheter connected to a Tonocap monitor were in general lower than those measured using the probe. The new, balloon-free probe seems to be applicable for routine human measurements, but further controlled studies should be conducted before its introduction into clinical practice.

References

[1] Boda D, Murányi L. Gastrotonometry: an aid to the control of ventilation during artificial respiration. Lancet 1959;I:181-2.

[2] Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complication after cardiac operations. Comparison with other monitoring. Crit Care Med 1987;15:153-6.

[3] Chapman MV, Mythen MG, Webb AR, et al. Report from the meeting: gastrointestinal tonometry: state of the art. 22nd-23rd May 1998, London, UK. Intensive Care Med 2000;26:613-22.

[4] Knuesel R, Jakob SM, Brander L, et al. Changes in regional blood flow and p_{CO_2} gradients during isolated abdominal aortic blood flow reduction. Intensive Care Med 2003;29:2255-65.

[5] Levy B, Gawaliewicz P, Vallet B, et al. Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. Crit Care Med 2003;31:474-80.

[6] Gutierrez G, Palizas F, Doglio G, et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet 1992;339:195-9.

[7] Oud L, Kruse JA. Poor *in vivo* reproducibility of gastric intramucosal pH determined by saline-filled balloon tonometry. J Crit Care 1996;11:144-50.

[8] Taylor DE, Gutierrez G, Clark C, et al. Measurement of gastric mucosal carbon dioxide tension by saline and air tonometry. J Crit Care 1997;12:208-13.

[9] Uusaro A, Lahtinen P, Parviainen I, Takala J. Gastric mucosal end-tidal P_{CO_2} difference as a continuous indicator of splanchnic perfusion. Br J Anaesth 2000;85:563-9.

[10] Masai T, Taniguchi K, Kuki S, et al. Usefulness of continuous air tonometry for evaluation of splanchnic perfusion during cardiopulmonary bypass. ASAIO J 2003;49:108-11.

[11] Heinonen PO, Jousela IT, Blomqvist KA, et al. Validation of air tonometric measurement of gastric regional concentrations of CO_2 in critically ill septic patients. Intensive Care Med 1997;23:524-9.

[12] Boda D, Kaszaki J, Tálosi G. A new simple tool for tonometric determination of the P_{CO_2} in the gastrointestinal tract: *in vitro* and *in vivo* validation studies. Eur J Anaesthesiol 2006;23:680-5.

[13] Kittly Á, Boda D, Tálosi G, et al. Intraoperative gastric tonometric examinations in children and infants with a new probe, combined with measurement of the end-tidal P_{CO_2}. Paediatr Anaesth 2008;18:501-7.

[14] Tálosi G, Boda D. Applicability of a new gastric tonometric probe in infants requiring intensive care. Med Sci Mon 2008;14:PI32-7.

[15] Brown H, Prescott R. Applied mixed models in medicine. Chichester, UK: John Wiley & Sons; 2001.

[16] Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. J Biopharm Statist 2007;17:571-82.

[17] Lebuffe G, Vallet B, Takala J, et al. European, multicenter, observational study to assess the value of gastric-to-end tidal P_{CO_2} difference in predicting postoperative complications. Anesth Analg 2004;99:166-72.

[18] Roberts PC, Boyle NH, Barber AC, et al. Regional variation in gastric intramucosal pCO_2 may confound tonometric measurement: an evaluation using two tonometers and continuously recirculating gas tonometry. Crit Care 1998;2(Suppl 1):P135.

[19] Carlesso E, Taccone P, Gattinoni E. Gastric tonometry. Minerva Anestesiol 2006;72:529-32.

[20] Černý V, Cvachovec K. Gastric tonometry and intramucosal pH—theoretical principles and clinical application. Physiol Res 2000;49:289-97.

[21] Kolkman JJ, Otte JA, Groeneveld AB. Gastrointestinal luminal P_{CO_2} tonometry: an update on physiology, methodology and clinical applications. Br J Anaesth 2000;84:74-86.

II

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 847152, 10 pages
http://dx.doi.org/10.1155/2015/847152

Research Article

Monitoring Microcirculatory Blood Flow with a New Sublingual Tonometer in a Porcine Model of Hemorrhagic Shock

Péter Palágyi,[1] József Kaszaki,[2] Andrea Rostás,[2] Dániel Érces,[2] Márton Németh,[1] Mihály Boros,[2] and Zsolt Molnár[1]

[1]*Department of Anesthesiology and Intensive Therapy, University of Szeged, 6 Semmelweis Street, Szeged 6725, Hungary*
[2]*Institute of Surgical Research, University of Szeged, 6 Szőkefalvi-Nagy Béla Street, Szeged 6720, Hungary*

Correspondence should be addressed to Zsolt Molnár; zsoltmolna@gmail.com

Received 21 January 2015; Revised 23 March 2015; Accepted 24 March 2015

Academic Editor: Stephen M. Cohn

Tissue capnometry may be suitable for the indirect evaluation of regional hypoperfusion. We tested the performance of a new sublingual capillary tonometer in experimental hemorrhage. Thirty-six anesthetized, ventilated mini pigs were divided into sham-operated ($n = 9$) and shock groups ($n = 27$). Hemorrhagic shock was induced by reducing mean arterial pressure (MAP) to 40 mmHg for 60 min, after which fluid resuscitation started aiming to increase MAP to 75% of the baseline value (60–180 min). Sublingual carbon-dioxide partial pressure was measured by tonometry, using a specially coiled silicone rubber tube. Mucosal red blood cell velocity (RBCV) and capillary perfusion rate (CPR) were assessed by orthogonal polarization spectral (OPS) imaging. In the 60 min shock phase a significant drop in cardiac index was accompanied by reduction in sublingual RBCV and CPR and significant increase in the sublingual mucosal-to-arterial PCO_2 gap ($P_{SL}CO_2$ gap), which significantly improved during the 120 min resuscitation phase. There was significant correlation between $P_{SL}CO_2$ gap and sublingual RBCV ($r = -0.65$, $p < 0.0001$), CPR ($r = -0.64$, $p < 0.0001$), central venous oxygen saturation ($r = -0.50$, $p < 0.0001$), and central venous-to-arterial PCO_2 difference ($r = 0.62$, $p < 0.0001$). This new sublingual tonometer may be an appropriate tool for the indirect evaluation of circulatory changes in shock.

1. Introduction

Disturbances of the microcirculation are tightly linked to circulatory failure of different origin; thus evaluation of the microcirculatory status has gained increasing importance in the diagnosis and treatment of critically ill patients. It is recognized that in spite of the normal values of global oxygen delivery regional tissue hypoperfusion may exist, which cannot be detected by conventional monitoring tools [1, 2]. Besides, compensatory mechanisms may lead to the normalization of macrohemodynamic parameters in the early phase of circulatory shock, and silently ongoing microcirculatory insufficiencies can cause cellular hypoxia and metabolic dysfunctions, eventually leading to organ failure [3].

The measurement of the partial pressure of carbon dioxide (PCO_2) in tissues is a potentially feasible technique for the indirect evaluation of the microcirculation [4, 5]. This parameter reflects the adequacy of regional microvascular blood flow, as intramucosal PCO_2 is inversely related to the proportion of well perfused capillaries, and is mainly dependent on tissue perfusion [6, 7]. However, acute increases or decreases in the PCO_2 of the arterial blood (P_aCO_2) result in comparable changes in the tissue PCO_2 [8]; thus it should be interpreted in relation to P_aCO_2. By subtracting P_aCO_2 from the tissue PCO_2, special gap values can be calculated which are more accurate than the mucosal PCO_2 alone, as they are independent of concurrent changes in P_aCO_2. Although there is no consensus on the most sensitive hemodynamic and laboratory parameters indicating the onset of shock, the tissue-to-arterial PCO_2 gap may provide an early and important additional signal of perfusion failure [1, 2, 9]. In addition, the tissue-to-arterial PCO_2 gap values also have prognostic importance [1, 10, 11]; therefore the monitoring of tissue levels of CO_2 may be helpful in titrating therapeutic interventions in critical states [12], or in selecting

patients with compromised physiologic reserve who require expanded hemodynamic monitoring.

Different sites of the gastrointestinal tract are available for the purpose of tissue capnometry and the assessment of the adequacy of mucosal blood flow. As PCO_2 results gained from the stomach and the sublingual regions proved to be interchangeable [6, 13], and the latter is free of some limitations of gastric tonometry, such as interference of gastric acid, enteral feeding, and potential pitfalls of pHi calculation [14], sublingual tonometry may be a useful alternative for measuring mucosal PCO_2. Though promising, this technique is still not available at the bedside because of the lack of a suitable monitoring device; hence clinical and experimental evidence on its efficacy is also missing.

It is generally acknowledged that monitoring of the sublingual microcirculation, the only site of intravital microscopy (IVM) available at the point of care for most critically ill patients, is of particular prognostic value [3]. In our institute a special instrument has been designed and manufactured for the measurement of sublingual PCO_2 (Figure 1), which is a further development of a gastric tonometer [15, 16]. The performance of this new probe was recently tested *in vitro* and also in patients with respiratory disease, and the results showed its suitability for sublingual tonometry [17].

The main goal of the current study was to test this new sublingual probe in a porcine model of hemorrhagic shock and compare its performance to direct microcirculatory measurements with IVM using the orthogonal polarization spectral (OPS) imaging technique. Another aim was to investigate how the capnometry-derived values relate to global indicators of hemodynamic changes during hemorrhage and resuscitation. We also hypothesized that if the same diagnostic end points can be reached, sublingual capnometry could offer a technically simpler, alternative method to monitor sublingual microcirculatory changes noninvasively.

2. Materials and Methods

The experiments were carried out in strict adherence to the National Institute of Health guidelines for the use of experimental animals and the study was approved by the Ethics Committee and the Institutional Animal Care and Use Committee at the University of Szeged. The study was conducted in the research laboratory of the Institute of Surgical Research in a manner that does not inflict unnecessary pain or discomfort upon the animals.

2.1. Animals and Instrumentation. Thirty-six Vietnamese mini pigs of both genders, weighing 16–25 kg, underwent a 24 hr fasting preoperatively with free access to water; the animals were randomly allocated into control (sham-operated, $n = 9$) and hemorrhagic shock groups (shock, $n = 27$). Anesthesia was induced by an intramuscular injection with a mixture of ketamine ($20\,mg\,kg^{-1}$) and xylazine ($2\,mg\,kg^{-1}$) and maintained with a continuous infusion of propofol ($50\,\mu g\,min^{-1}\,kg^{-1}$ iv, $3\,mg\,kg^{-1}\,hr^{-1}$). After endotracheal intubation, the animals were mechanically ventilated with room air (Harvard Apparatus, South Natick, MA, USA).

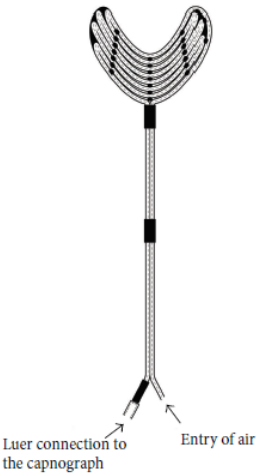

FIGURE 1: The new capillary tonometer. Illustration of the new sublingual tonometer applied during the examinations.

The tidal volume was set at $9 \pm 2\,mL\,kg^{-1}$, and the respiratory rate was adjusted to maintain the end-tidal partial pressure of carbon dioxide ($EtCO_2$) and P_aCO_2 in the range of 35–45 Torr (4.7–6.0 Pa). The depth of anesthesia was assessed by monitoring the jaw tone regularly. The animals were placed in supine position on a heating pad for maintenance of the body temperature between 36 and 37°C.

For measurement of the sublingual PCO_2 ($P_{SL}CO_2$) the new sublingual capillary tonometer (see below) was placed under the tongue, and a specially designed latex face mask was used to close the oral cavity. Capnography was performed with a Microcap handheld capnograph (Oridion Medical Ltd, Jerusalem, Israel). The sublingual mucosal-to-arterial PCO_2 difference ($P_{SL}CO_2$ gap) was calculated by subtracting $P_{SL}CO_2$ from the simultaneously taken P_aCO_2 values.

For central venous access the left jugular vein was catheterized. A three-lumen central venous catheter (7 F, Edwards Lifesciences LLC, Irvine, USA) was introduced for blood sampling and fluid administration using aseptic surgical technique. The central venous pressure (CVP) was monitored continuously with a computerized data-acquisition system (SPELL Haemosys; Experimetria Ltd., Budapest, Hungary). For hemodynamic measurements a special thermodilution catheter (Pulsiocath, PULSION Medical Systems AG, Munich, Germany) was placed into the left femoral artery. The cardiac output was monitored by transpulmonary thermodilution and continuous pulse contour analysis (PiCCO method). The right carotid artery was also catheterised for bleeding (7 F, PE, Access Technologies, Illinois, USA). The blood gas measurements were carried out by taking arterial and central venous blood samples simultaneously according to the study protocol, which were then analyzed by cooximetry with a blood gas analyzer (Cobas b221, Roche, Austria). Simplified oxygen extraction

rate (O_2ER) was calculated according to the standard formula from arterial (SaO_2) and central venous oxygen saturations ($ScvO_2$): $O_2ER = (SaO_2 - ScvO_2)/SaO_2$. From the central venous and arterial blood gas values the central venous-to-arterial PCO_2 gap ($PcvaCO_2$) was also determined.

For direct evaluation and noninvasive visualization of the sublingual microcirculation the intravital OPS imaging technique (Cytoscan A/R, Cytometrics, Philadelphia, PA, USA) was used. A 10x objective was placed onto the sublingual mucosa, and microscopic images were recorded with an S-VHS video recorder (Panasonic AG-TL 700, Matsushita Electric Ind. Co. Ltd, Osaka, Japan). Quantitative assessment of the microcirculatory parameters was performed offline by frame-to-frame analysis of the videotaped images. Red blood cell velocity (RBCV; $\mu m\,s^{-1}$) changes in the postcapillary venules were determined in three separate fields by means of a computer-assisted image analysis system (IVM Pictron, Budapest, Hungary) [18]. Capillary perfusion rate (CPR; 1/1) was determined as the length of continuously perfused microvessels per total length of capillaries in the observational area. During quantitative assessment of CPR we used a diameter limitation for determination of the microvascular network. Exclusively those vessels were selected for analysis, whose diameters were less than 20 μm. All microcirculatory evaluations were performed by the same investigator.

2.2. Description of the New Tonometric Probe. The new sublingual capillary tonometer (Mediszintech Ltd, Budapest, Hungary) is a specially coiled silicone rubber tube (ID: 1.5 mm, OD: 2.0 mm, and length: 640 mm) with high permeability for gases, which is formed into a multiple V-shape by using a mould and is glued along five lines (Figure 1). To prevent the soft-walled tube from flattening, a polyamide fiber of 0.3 mm thickness is inserted along its full length. Thereby after folding the tube a sufficient gap remains ensuring the free transport of the filling medium. The afferent and deferent parts of the tube are fixed together at their branching. The end of the deferent tube is equipped with a Luer connector. The filling material is room air, which equilibrates quickly with the PCO_2 content of the capillaries in the sublingual mucosa. After the required equilibration time it can be aspirated and measured by capnometry. The duration of the full equilibration of the sublingual probe is about 15 minutes. The PCO_2 of the aspirated gas is measured by infrared spectrophotometry. The results are immediately displayed in units of mmHg.

2.3. Experimental Protocol. The preparation period was followed by a 30 min resting period. After baseline measurements at 0 min (T_0) in the shock group, hemorrhagic shock was induced by bleeding the animals through the right carotid arterial catheter into a heparin ($100\,IU\,mL^{-1}$) containing reservoir. The target mean arterial pressure (MAP) of approximately 40 mmHg was reached in 10–15 min and was kept by repeated bleeding periods until the 60th min of the experiment (T_2). The amount of shed blood was precisely monitored. The average blood loss was about $25\,mL\,kg^{-1}$ 15 min after the onset of hemorrhage, which increased to an average of around $40\,mL\,kg^{-1}$ by the end of bleeding at T_2. This was about 50% of the animals' circulating blood volume. At 60 min (T_2) volume resuscitation with colloid solution (hydroxyethyl starch 130 kDa/0.4, 6% Voluven, Fresenius, Germany) was started. 75% of the starting MAP was reached in 10–15 min. In case of decreasing blood pressure further colloid infusion was given, but the total amount of colloid infusion was maximized in $25\,mL\,kg^{-1}$. This means that the pigs were partially resuscitated and remained hypovolemic in the following period between 60 and 180 min (T_2 and T_6). The reason for choosing this protocol was to enable us to investigate the alterations of different macro- and microcirculatory parameters in two well separated periods: severe shock and moderate hypovolemia. Hemodynamic, arterial, and central venous blood gas measurements and tissue capnometry were repeated and recorded every 30 min for duration of 3 hr (T_0–T_6). Intravital video microscopy was performed at baseline, at 60 (T_2), and at 180 min (T_6) (Figure 2).

Animals in the control group were not submitted to bleeding. They underwent the same operation procedure and received the same instrumentation and monitoring. In this group 0.9% sodium chloride was infused at a rate of $10\,mL\,kg^{-1}\,h^{-1}$ during the experiment. Hemodynamic, blood gas analysis and microcirculatory measurements were performed at the same time points.

2.4. Statistical Analysis. The statistical software package SigmaStat for Windows (Jandel Scientific, Erkrath, Germany) was applied for data analysis. After testing for normality parametric methods were used. Two-way repeated measures analysis of variance (ANOVA) was applied for statistical analysis. For the analysis of differences between the sham-operated and the hemorrhagic shock groups, the time dependent differences from the baseline (T_0) for each group were assessed by Holm-Sidak post hoc test. When we examined the effect of partial resuscitation starting at 60 minutes (T_2), we performed multiple pairwise comparisons of T_3–T_6 results versus T_2 data serving as control. The pairwise comparison of different variables was made with Pearson-correlation. p values < 0.05 were considered statistically significant. The numeric data in the text and values on the figures are given as mean and standard deviations.

3. Results

3.1. Hemorrhagic Shock Phase (T_0 to T_2). Severe shock state was achieved in the animals of the shock group as indicated by marked and significant changes in macrohemodynamics during the first 60 minutes: MAP decreased, heart rate (HR) increased, and cardiac index (CI) and global end-diastolic volume index (GEDVI) decreased significantly (Figures 3(a), 3(b), 3(c), and 3(d)). This change in global hemodynamics was accompanied by a significant drop in base excess (BE) in the shock group (T_0: 6.4 ± 2.1 and T_2: $1.1 \pm 2.8\,mmol\,L^{-1}$ $p < 0.05$), while there was no similar change in the sham group (T_0: 5.6 ± 1.8 and T_2: $5.9 \pm 1.9\,mmol\,L^{-1}$). We detected significant increases both in the $P_{SL}CO_2$ and in the $P_{SL}CO_2$ gap

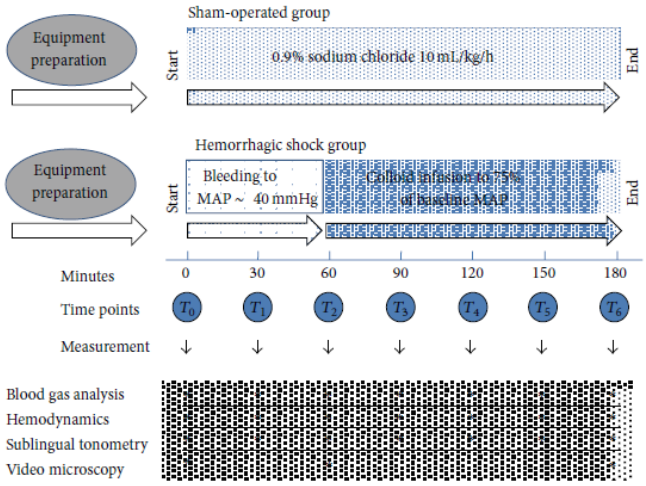

FIGURE 2: Experimental protocol. Flow diagram representing the experimental protocol in both groups of animals. MAP is mean arterial pressure, T_0–T_6 are seven time points of measurements, and ∗ indicates the implementation of different types of measurements.

values (Figures 4(a) and 4(b)). The sublingual postcapillary red blood cell velocity ($RBCV_{SL}$) and the sublingual capillary perfusion rate (CPR_{SL}) decreased significantly (Figures 5(a) and 5(b)). The central venous blood derived variables showed characteristic alterations too: corresponding to the significant increase of the oxygen extraction rate the $ScvO_2$ decreased during bleeding, while the $PcvaCO_2$ increased (Figures 6(a), 6(b), and 6(c)). These changes at 60 minutes were significant compared to the baseline values and differed significantly from the corresponding values of the sham-operated animals.

3.2. Partial Resuscitation Phase (T_2 to T_6). Statistically significant alterations were found regarding MAP, HR, CI, and GEDVI (Figures 3(a), 3(b), 3(c), and 3(d)). The CI increased significantly at T_4, T_5, and T_6 compared to baseline values and at T_4 and T_6 compared to the sham-operated group as well (Figure 3(c)). Improvement in global hemodynamics was also reflected by the significant improvement in BE in the shock group from T_2 to T_6 (1.1 ± 2.8, $3.1 \pm 3.4\,\text{mmol}\,\text{L}^{-1}$, $p < 0.05$, resp.), while there was no change in BE in the sham group (5.9 ± 1.9, $6.7 \pm 2.9\,\text{mmol}\,\text{L}^{-1}$). The $P_{SL}CO_2$ did not change significantly over time in the sham-operated group. In the shock group there was also a significant improvement during this period, still these values remained elevated as compared to baseline (T_0). Moreover, at T_5 $P_{SL}CO_2$ was significantly higher than in the sham-operated group (Figure 4(a)). Regarding the $P_{SL}CO_2$ gap, it decreased significantly by T_3 as compared to T_2 in the shock group, but it remained significantly higher as compared to T_0 throughout the resuscitation period. In the sham-operated group the $P_{SL}CO_2$ gap showed a slow nonsignificant increase over time. Between T_3 and T_6 there were no significant differences between the sham and shock groups (Figure 4(b)).

Concerning the microcirculatory measurements, both $RBCV_{SL}$ and CPR_{SL} increased significantly in the shock group compared to T_2, but still they remained decreased compared to the baseline values. At 180 min (T_6), there was no difference in $RBCV_{SL}$ between shock and sham-operated groups (Figure 5(a)), while CPR_{SL} in the shock group remained significantly lower than in the sham-operated group (Figure 5(b)).

Samples of the pictures in each phase can be seen as electronically submitted Supplementary Material (see Figure S1 available online at http://dx.doi.org/10.1155/2015/847152).

Fluid resuscitation resulted in a significant decrease of the $PcvaCO_2$ at T_3–T_6 as compared to T_2, but $PcvaCO_2$ changes within the shock group were significant at T_3 compared to T_0 (Figure 6(a)). $ScvO_2$ showed a statistically significant elevation after resuscitation as compared to T_2 but remained significantly lower as compared to the baseline value at T_0 and to the sham-operated group (Figure 6(b)). In case of the oxygen extraction rate significant differences were observed between the sham and shock groups at T_4–T_6 (Figure 6(c)).

3.3. Correlation Analysis. Statistically significant correlation was found between $P_{SL}CO_2$ gap and $RBCV_{SL}$ ($r = -0.648$; $p < 0.0001$) and $P_{SL}CO_2$ gap and CPR_{SL} ($r = -0.644$; $p < 0.0001$) (Figures 7(a) and 7(b)). The $P_{SL}CO_2$ gap also correlated with $ScvO_2$ and $PcvaCO_2$ ($r = -0.504$ and $p < 0.0001$; $r = 0.623$ and $p < 0.0001$, resp.) (Figures 7(c) and 7(d)). A significant but weaker correlation was found between $P_{SL}CO_2$ and $ScvO_2$ ($r = -0.29$; $p < 0.0001$) and $P_{SL}CO_2$ and $PcvaCO_2$ ($r = 0.405$; $p < 0.0001$).

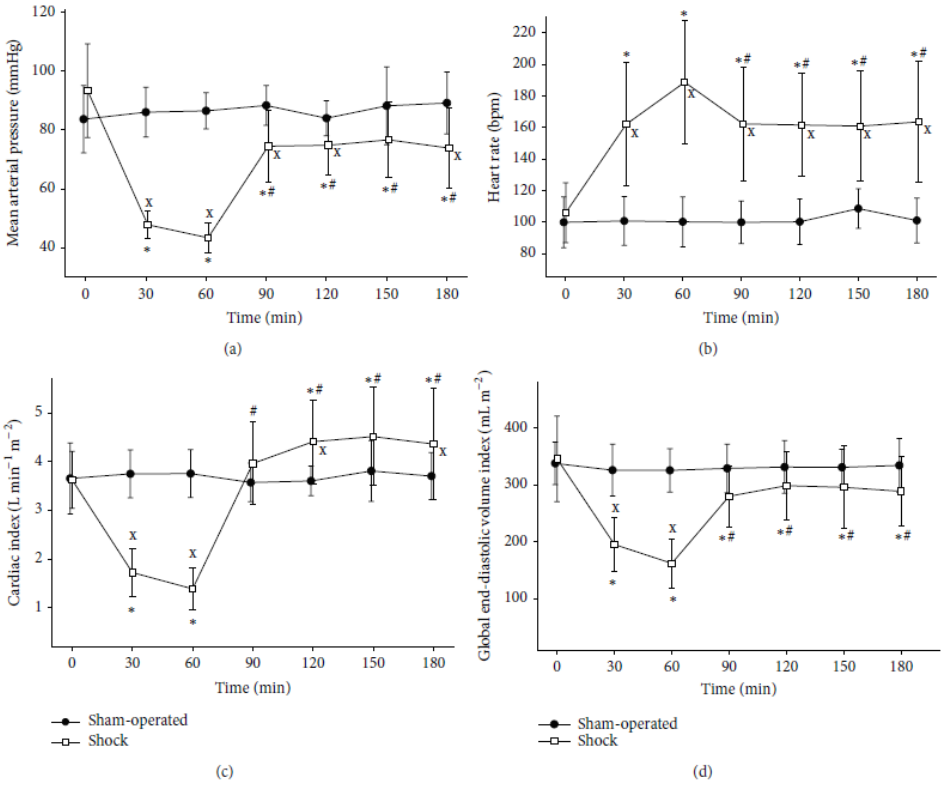

FIGURE 3: Macrohemodynamic parameters. Changes of macrohemodynamic parameters, mean arterial pressure (a), heart rate (b), cardiac index (c), and global end-diastolic volume index (d). $^{*}P < 0.05$ as compared to 0 min (T_0), $^{\#}P < 0.05$ as compared to 60 min (T_2), and $^{x}P < 0.05$ shock group versus sham-operated group.

4. Discussion

In this study we report on the first *in vivo* application of a new sublingual tonometric device. The major finding of this experiment is that this noninvasive monitor accurately followed the changes in submucosal postcapillary blood flow during bleeding and resuscitation. The measured values showed very good correlation with direct indices of microcirculation as determined by the well-established OPS technique and also with global measures of hypovolemia-caused oxygen debt such as $ScvO_2$ and $PcvaCO_2$.

4.1. Sublingual Capnometry and Microcirculation. There are different methods able to detect the increased concentrations of CO_2 in the periphery. Gastric tonometry is based upon the monitoring of gastric mucosal PCO_2 level; sublingual and buccal capnometry measure mucosal PCO_2 of the proximal gastrointestinal tract [19–21]. Mixed venous-to-arterial or central venous-to-arterial CO_2 partial pressure difference is regarded as markers describing the balance between cardiac output and oxygen consumption by peripheral tissues [22, 23].

The concept of monitoring complementary regional/local perfusion parameters in order to guide or fine-tune resuscitation strategies is rather old and well-established. Historically, one of the first methods was gastric tonometry. However, technical difficulties, long equilibration, and other confounding factors [14] hindered the widespread use of the method, leading to the withdrawal of these devices from the market. In recent years several investigators came to the conclusion that PCO_2 values of the oral mucosa correlate well with gastric mucosal PCO_2 parameters [6, 13, 20, 24]. Although the value of sublingual capnometry in the diagnosis of circulatory failure has been reported previously [20, 25], the method is not available for everyday clinical practice. The monitoring tools used for this purpose in the first experimental and clinical studies were highly sophisticated devices with special PCO_2-electrodes or fiber optic sensors [26]. The device we

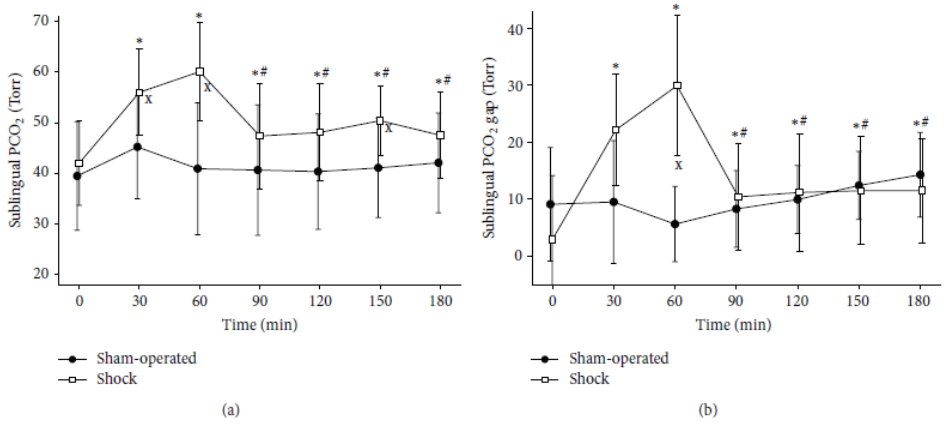

FIGURE 4: Sublingual capnometry. Changes of sublingual tonometric variables measured by the new probe, sublingual PCO_2 (a) and sublingual PCO_2 gap (b). $^{*}P < 0.05$ as compared to 0 min (T_0), $^{\#}P < 0.05$ as compared to 60 min (T_2), and $^{x}P < 0.05$ shock group versus sham-operated group.

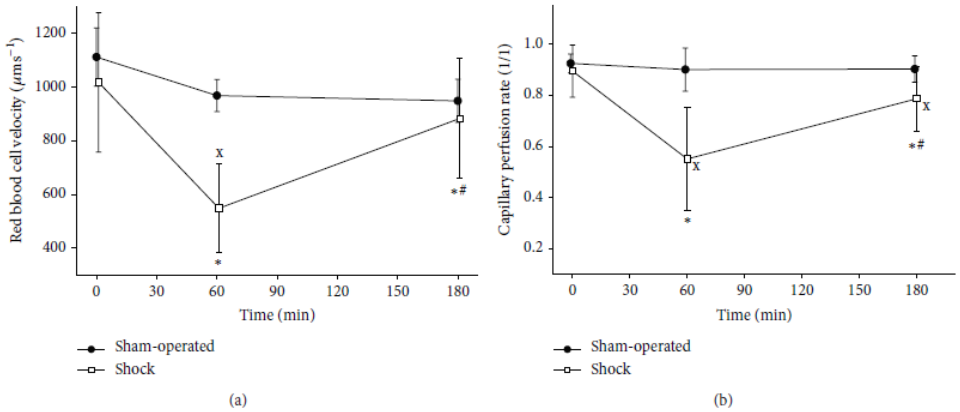

FIGURE 5: Microcirculatory parameters. Changes of microcirculatory parameters measured by orthogonal polarization spectral imaging, red blood cell velocity in postcapillary venules (a) and capillary perfusion rate (b). $^{*}P < 0.05$ as compared to 0 min (T_0), $^{\#}P < 0.05$ as compared to 60 min (T_2), and $^{x}P < 0.05$ shock group versus sham-operated group.

used in the presented experimental protocol proved to be a simple, noninvasive monitor for this purpose.

According to recent studies it was suggested that even the magnitude of blood loss can be estimated by tissue capnometry, and the method may also be useful in guiding fluid resuscitation during hemorrhage. Different authors [27, 28] measured buccal PCO_2 continuously during different severity of hemorrhagic shock in rats and found that tissue PCO_2 monitoring was reliable in the quantitation of acute hemorrhage. Baron et al. [29] measured sublingual PCO_2 in bleeding trauma patients and found similar results. In a porcine model of hemorrhagic shock Xu and colleagues [30] compared different volume replacement protocols based on either sublingual PCO_2 or blood pressure. The animals monitored by sublingual PCO_2 required smaller amount of both crystalloids and transfusion, while the microcirculation, organ functions, and survival were similar in the treatment groups. Although our experiment had different goals, the results give support to both assumptions. Loss of 50% of the circulating blood volume also increased the sublingual PCO_2 by 50%: from $T_0 = 41.6 \pm 8.3$ to $T_2 = 60.1 \pm 9.6$ Torr. On the other hand, sublingual PCO_2 gap increased by 5-fold;

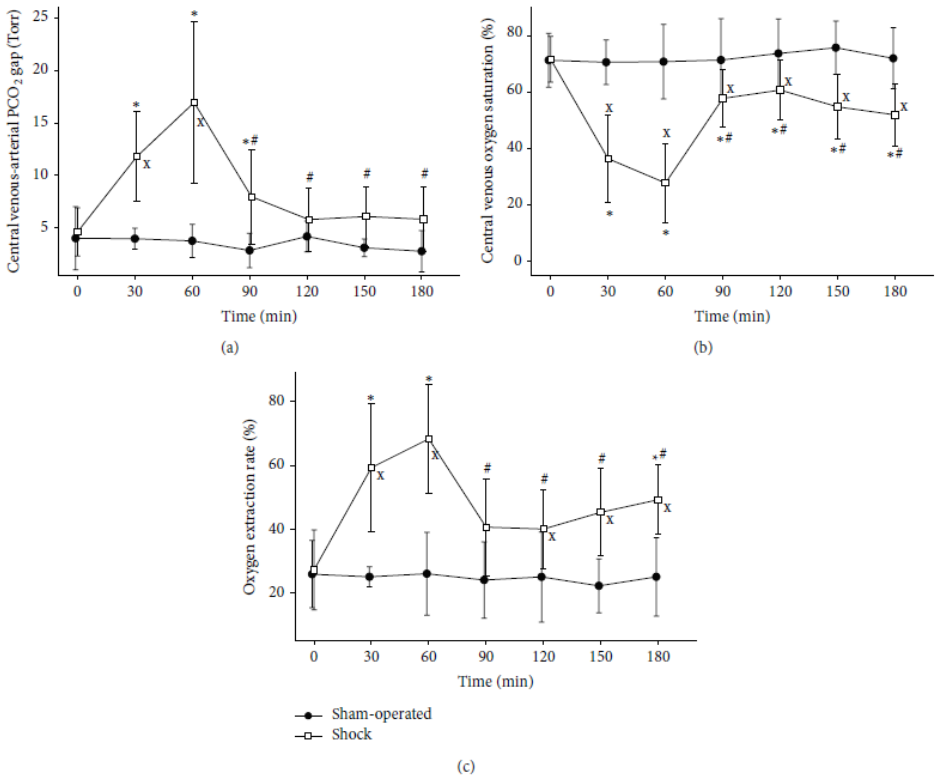

FIGURE 6: Central venous blood gas derived parameters. Changes of central venous blood derived parameters, central venous-arterial PCO_2 gap (a), central venous oxygen saturation (b), and oxygen extraction rate (c). $^{*}P < 0.05$ as compared to 0 min (T_0), $^{\#}P < 0.05$ as compared to 60 min (T_2), and $^{x}P < 0.05$ shock group versus sham-operated group.

therefore it seems that for this purpose this parameter may be more sensitive than sublingual PCO_2 on its own. We did not observe strong, significant differences in the $P_{SL}CO_2$ and the $P_{SL}CO_2$ gap values between the sham-operated and the shock groups in the partial resuscitation phase, but there were significant changes in the shock group reflecting the hemodynamic changes throughout the experiment. We suggest that it is the kinetics of $P_{SL}CO_2$ rather than the absolute value which deserves attention. This has to be investigated in the future. In general it is important to note that $P_{SL}CO_2$ or $P_{SL}CO_2$ gap has different role and interpretation during "rapid" or "massive" and "slow" bleeding. No one needs additional indicators during massive bleeding with severe hypotension to confirm that the patient is in trouble, and neither is there time for these measurements. Therefore sublingual capnometry may prove its merit during slow bleeding and hypovolemia as one of the potential end points of resuscitation of the microcirculation.

Massive bleeding in our study resulted in severe perfusion abnormalities as indicated by significant deterioration of sublingual CPR and RBCV, which was also reflected by changes of the sublingual $P_{SL}CO_2$ gap. Although the close relationship between the sublingual perfusion and PCO_2 has already been described [6, 31], and investigations on mucosal PCO_2 and the microcirculation of the ileum [32] have been performed in hemorrhagic shock, this is the first study to reveal a correlation between sublingual capnometry and directly measured microcirculatory parameters during hemorrhagic shock.

4.2. Sublingual Capnometry and Global Hemodynamics. Significant changes in MAP, HR, CI, and GEDVI were detected during the shock phase and during partial resuscitation, with the CI being significantly higher by the end of resuscitation as compared with the baseline, possibly because of the sustained tachycardia caused by the bleeding-related stress response. There are several studies showing that hemorrhage-caused hypovolemia is accompanied by sublingual hypoperfusion and/or the increase in $P_{SL}CO_2$ [13, 20, 29]. Nevertheless, it is

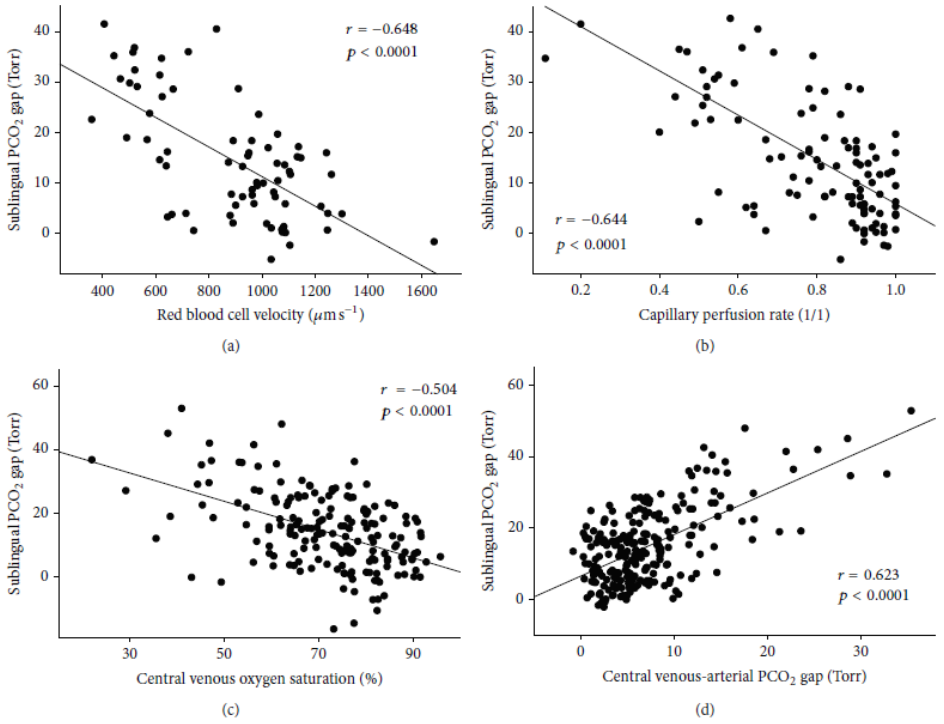

FIGURE 7: Correlations with sublingual capnometry. Relationships between sublingual mucosal-to-arterial carbon-dioxide partial pressure gap and sublingual red blood cell velocity in postcapillary venules (a), sublingual capillary perfusion rate (b), central venous oxygen saturation (c), and central venous-to-arterial carbon-dioxide partial pressure difference (d).

important to acknowledge that $P_{SL}CO_2$ on its own is a poor indicator of regional circulatory changes, unless it is put in the context of the arterial and/or end-tidal PCO_2. Alternatively, in order to eliminate the influence of global respiratory alterations, minute ventilation should be constant. This may explain why in a laboratory model of progressive hypovolemia caused by lower body negative pressure Chung et al. did not confirm the sensitivity of sublingual capnometry in the early phase of cardiovascular collapse [33]. In our opinion the main limitation of that study is that in their model minute ventilation was not constant (subjects were spontaneously breathing), end-tidal PCO_2 decreased significantly, and they measured $P_{SL}CO_2$ and not $P_{SL}CO_2$ gap. By calculating gap values substantial $P_{SL}CO_2 - P_{ET}CO_2$ gap differences could have been detected. There are other important conceptual differences between their model and the earlier experimental protocols; that is, hypovolaemia was not caused by bleeding, the observation period was only 20 min, and the study population was young, healthy, nonsmoking subjects with presumably good physiologic reserves. Finally, the sublingual microcirculation was not monitored in this study, so the changes of sublingual microvascular perfusion during the experiment remain unknown.

4.3. Sublingual Capnometry and Oxygen Delivery/Consumption. Although the most accurate way to assess cardiac output, oxygen delivery, and consumption is invasive hemodynamic monitoring, it is often unavailable in emergencies. Simple blood gas driven variables such as $ScvO_2$ and $PcvaCO_2$ can help the clinician in defining the need for fluid resuscitation and red blood cell transfusion or may serve as therapeutic targets of goal-directed therapy in high-risk surgical or septic patients [34–36]. In our study $ScvO_2$, O_2ER, and $PcvaCO_2$ showed significant changes during hemorrhagic shock and partial resuscitation. Although in cases of impaired oxygen uptake $ScvO_2$ values can be elevated [5, 37], our hemorrhagic shock-resuscitation model gives further support to the theory that low $ScvO_2$ and high $PcvaCO_2$ indicate hypovolemia and they also correlated well with $P_{SL}CO_2$ gap values. In fact correlation of $ScvO_2$ and $PcvaCO_2$ with $P_{SL}CO_2$ gap was better than with $P_{SL}CO_2$, indicating that the actual condition of the microcirculation is

reflected more precisely by gap values than by absolute values of sublingual PCO_2.

5. Conclusions

This new capillary tonometer may be an appropriate tool for the indirect evaluation of the sublingual microcirculation. There are also some limitations to the use of this method, such as the relatively long equilibration time and the need to draw arterial blood samples to determine the $P_{SL}CO_2$ gap. However, the calculation of gap values is probably not necessary if the alveolar ventilation is considered stable. In our opinion, this device can be best utilized during emergency situations (in the ICU or ER and during major/high-risk surgery), where arterial and central venous catheters are commonly used, and excessive invasiveness should therefore not be a concern.

With these restrictions we concluded that capnometry-derived variables followed the microcirculatory changes and correlated with well-established indices of global hemodynamics in hypovolemia and hemorrhagic shock. Combination of these results with central venous oxygen saturation and central venous-to-arterial carbon-dioxide partial pressure differences may be complementary tools for monitoring and treating hypovolemia and hemorrhagic shock in the clinical setting.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Péter Palágyi and József Kaszaki contributed equally to this work.

Acknowledgments

The authors are very grateful to Professor Domokos Boda for his outstanding technical support and guidance by the planning and the implementation of sublingual tonometric measurements. This publication is supported by the European Union and cofunded by the European Social Fund. The project title is Telemedicine-Focused Research Activities on the Field of Mathematics, Informatics and Medical Sciences. The study was also supported by research Grant OTKA K104656.

References

[1] G. Lebuffe, C. Decoene, A. Pol, A. Prat, and B. Vallet, "Regional capnometry with air-automated tonometry detects circulatory failure earlier than conventional hemodynamics after cardiac surgery," *Anesthesia & Analgesia*, vol. 89, no. 5, pp. 1084–1090, 1999.

[2] C. L. Verdant, D. de Backer, A. Bruhn et al., "Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis," *Critical Care Medicine*, vol. 37, no. 11, pp. 2875–2881, 2009.

[3] Y. Sakr, M.-J. Dubois, D. de Backer, J. Creteur, and J.-L. Vincent, "Persistent-microcirculatory alterations are associated with organ failure and death in patients with septic shock," *Critical Care Medicine*, vol. 32, no. 9, pp. 1825–1831, 2004.

[4] P. E. Marik, "Regional carbon dioxide monitoring to assess the adequacy of tissue perfusion," *Current Opinion in Critical Care*, vol. 11, no. 3, pp. 245–251, 2005.

[5] D. de Backer, G. Ospina-Tascon, D. Sagado, R. Favory, J. Creteur, and J.-L. Vincent, "Monitoring the microcirculation in the critically ill patient: current methods and future approaches," *Intensive Care Medicine*, vol. 36, no. 11, pp. 1813–1825, 2010.

[6] J. Creteur, D. de Backer, Y. Sakr, M. Koch, and J.-L. Vincent, "Sublingual capnometry tracks microcirculatory changes in septic patients," *Intensive Care Medicine*, vol. 32, no. 4, pp. 516–523, 2006.

[7] A. Dubin, G. Murias, B. Maskin et al., "Increased blood flow prevents intramucosal acidosis in sheep endotoxemia: a controlled study," *Critical Care*, vol. 9, no. 2, pp. R66–R73, 2005.

[8] A. Pernat, M. H. Weil, W. Tang et al., "Effects of hyper- and hypoventilation on gastric and sublingual PCO_2," *Journal of Applied Physiology*, vol. 87, no. 3, pp. 933–937, 1999.

[9] C. Hamilton-Davies, M. G. Mythen, J. B. Salmon, D. Jacobson, A. Shukla, and A. R. Webb, "Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry," *Intensive Care Medicine*, vol. 23, no. 3, pp. 276–281, 1997.

[10] N. Maynard, D. Bihari, R. Beale et al., "Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure," *Journal of the American Medical Association*, vol. 270, no. 10, pp. 1203–1210, 1993.

[11] P. E. Marik and A. Bankov, "Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients," *Critical Care Medicine*, vol. 31, no. 3, pp. 818–822, 2003.

[12] J. Creteur, "Gastric and sublingual capnometry," *Current Opinion in Critical Care*, vol. 12, no. 3, pp. 272–277, 2006.

[13] H. P. Povoas, M. H. Weil, W. Tang, B. Moran, T. Kamohara, and J. Bisera, "Comparisons between sublingual and gastric tonometry during hemorrhagic shock," *Chest*, vol. 118, no. 4, pp. 1127–1132, 2000.

[14] J. J. Kolkman, J. A. Otte, and A. B. J. Groeneveld, "Gastrointestinal luminal P_{CO_2} tonometry: an update on physiology, methodology and clinical applications," *British Journal of Anaesthesia*, vol. 84, no. 1, pp. 74–86, 2000.

[15] D. Boda, J. Kaszaki, and G. Tálosi, "A new simple tool for tonometric determination of the PCO2 in the gastrointestinal tract: in vitro and in vivo validation studies," *European Journal of Anaesthesiology*, vol. 23, no. 8, pp. 680–685, 2006.

[16] P. Palágyi, L. Vimláti, K. Boda, G. Tálosi, and D. Boda, "Practical experiences and in vitro and in vivo validation studies with a new gastric tonometric probe in human adult patients," *Journal of Critical Care*, vol. 25, no. 3, pp. 541.e9–541.e15, 2010.

[17] Z. Rózsavölgyi, D. Boda, A. Hajnal, K. Boda, and A. Somfay, "A newly developed sublingual tonometric method for the evaluation of tissue perfusion and its validation in vitro and in healthy persons in vivo and the results of the measurements in COPD patients," *Critical Care Research and Practice*, vol. 2014, Article ID 534130, 6 pages, 2014.

[18] A. Szabó, B. Suki, E. Csonka et al., "Flow motion in the intestinal villi during hemorrhagic shock: a new method to characterize the microcirculatory changes," *Shock*, vol. 21, no. 4, pp. 320–328, 2004.

[19] S. O. Heard, "Gastric tonometry: the hemodynamic monitor of choice," *Chest*, vol. 123, no. 5, supplement, pp. 469S–474S, 2003.

[20] Y. Nakagawa, M. H. Weil, W. Tang et al., "Sublingual capnometry for diagnosis and quantitation of circulatory shock," *American Journal of Respiratory and Critical Care Medicine*, vol. 157, no. 6 I, pp. 1838–1843, 1998.

[21] T. Pellis, M. H. Weil, W. Tang, S. Sun, P. Csapozi, and C. Castillo, "Increases in both buccal and sublingual partial pressure of carbon dioxide reflect decreases of tissue blood flows in a porcine model during hemorrhagic shock," *Journal of Trauma-Injury Infection & Critical Care*, vol. 58, no. 4, pp. 817–824, 2005.

[22] J. Cuschieri, E. P. Rivers, M. W. Donnino et al., "Central venous-arterial carbon dioxide difference as an indicator of cardiac index," *Intensive Care Medicine*, vol. 31, no. 6, pp. 818–822, 2005.

[23] B. Lamia, X. Monnet, and J. L. Teboul, "Meaning of arteriovenous PCO2 difference in circulatory shock," *Minerva Anestesiologica*, vol. 72, no. 6, pp. 597–604, 2006.

[24] P. E. Marik, "Sublingual capnography: a clinical validation study," *Chest*, vol. 120, no. 3, pp. 923–927, 2001.

[25] M. H. Weil, Y. Nakagawa, W. Tang et al., "Sublingual capnometry: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock," *Critical Care Medicine*, vol. 27, no. 7, pp. 1225–1229, 1999.

[26] A. T. Maciel, J. Creteur, and J.-L. Vincent, "Tissue capnometry: does the answer lie under the tongue?" *Intensive Care Medicine*, vol. 30, no. 12, pp. 2157–2165, 2004.

[27] G. A. A. M. Cammarata, M. H. Weil, C. J. Castillo et al., "Buccal capnometry for quantitating the severity of hemorrhagic shock," *Shock*, vol. 31, no. 2, pp. 207–211, 2009.

[28] H. Lu, J. Zheng, P. Zhao, G. Zhang, and T. Wu, "Buccal partial pressure of carbon dioxide outweighs traditional vital signs in predicting the severity of hemorrhagic shock in a rat model," *Journal of Surgical Research*, vol. 187, no. 1, pp. 262–269, 2014.

[29] B. J. Baron, R. Sinert, S. Zehtabchi, K. L. Stavile, and T. M. Scalea, "Diagnostic utility of sublingual PCO2 for detecting hemorrhage in penetrating trauma patients," *Journal of Trauma*, vol. 57, no. 1, pp. 69–74, 2004.

[30] J. Xu, L. Ma, S. Sun et al., "Fluid resuscitation guided by sublingual partial pressure of carbon dioxide during hemorrhagic shock in a porcine model," *Shock*, vol. 39, no. 4, pp. 361–365, 2013.

[31] X. Jin, M. H. Weil, S. Sun, W. Tang, J. Bisera, and E. J. Mason, "Decreases in organ blood flows associated with increases in sublingual PCO_2 during hemorrhagic shock," *Journal of Applied Physiology*, vol. 85, no. 6, pp. 2360–2364, 1998.

[32] A. Dubin, M. O. Pozo, G. Ferrara et al., "Systemic and microcirculatory responses to progressive hemorrhage," *Intensive Care Medicine*, vol. 35, no. 3, pp. 556–564, 2009.

[33] K. K. Chung, K. L. Ryan, C. A. Rickards et al., "Progressive reduction in central blood volume is not detected by sublingual capnography," *Shock*, vol. 37, no. 6, pp. 586–591, 2012.

[34] S. Kocsi, G. Demeter, J. Fogas, D. Érces, J. Kaszaki, and Z. Molnár, "Central venous oxygen saturation is a good indicator of altered oxygen balance in isovolemic anemia," *Acta Anaesthesiologica Scandinavica*, vol. 56, no. 3, pp. 291–297, 2012.

[35] E. Futier, E. Robin, M. Jabaudon et al., "Central venous O_2 saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery," *Critical Care*, vol. 14, no. 5, article R193, 2010.

[36] P. A. van Beest, M. C. Lont, N. D. Holman, B. Loef, M. A. Kuiper, and E. C. Boerma, "Central venous-arterial P_{CO_2} difference as a tool in resuscitation of septic patients," *Intensive Care Medicine*, vol. 39, no. 6, pp. 1034–1039, 2013.

[37] P. Krafft, H. Steltzer, M. Hiesmayr, W. Klimscha, and A. F. Hammerle, "Mixed venous oxygen saturation in critically III septic shock patients: the role of defined events," *Chest*, vol. 103, no. 3, pp. 900–906, 1993.

III

DE GRUYTER OPEN
The Journal of Critical Care Medicine 2016;2(1):30-37 RESEARCH ARTICLE
DOI: 10.1515/jccm-2016-0002

Recent Advances Of Mucosal Capnometry And The Perspectives Of Gastrointestinal Monitoring In The Critically Ill. A Pilot Study

Péter Palágyi[1*], Sándor Barna[2], Péter Csábi[3], Péter Lorencz[1], Ildikó László[1], Zsolt Molnár[1]

[1] Department of Anaesthesiology and Intensive Therapy, University of Szeged, Hungary
[2] Department of Anaesthesiology and Intensive Therapy, Bács-Kiskun County Hospital, Teaching Hospital of the University of Szeged, Hungary
[3] Department of Anaesthesia and Intensive Care, Wexham Park Hospital, United Kingdom

Abstract

Mucosal capnometry involves the monitoring of partial pressure of carbon dioxide (PCO2) in mucous membranes. Different techniques have been developed and applied for this purpose, including sublingual or buccal sensors, or special gastrointestinal tonometric devices. The primary use of these procedures is to detect compensated shock in critically ill patients or patients undergoing major surgery. Compensatory mechanisms, in the early phases of shock, lead to the redistribution of blood flow towards the vital organs, within ostensibly typical macro-haemodynamic parameters. Unfortunately, this may result in microcirculatory disturbances, which can play a pivotal role in the development of organ failure. In such circumstances mucosal capnometry monitoring, at different gastrointestinal sites, can provide a sensitive method for the early diagnosis of shock. The special PCO2 monitoring methods assess the severity of ischaemia and help to define the necessary therapeutic interventions and testing of these monitors have justified their prognostic value. Gastrointestinal mucosal capnometry monitoring also helps in determining the severity of ischaemia and is a useful adjunctive in the diagnosis of occlusive splanchnic arterial diseases. The supplementary functional information increases the diagnostic accuracy of radiological techniques, assists in creating individualized treatment plans, and helps in follow-up the results of interventions. The results of a pilot study focusing on the interrelation of splanchnic perfusion and gastrointestinal function are given and discussed concerning recent advances in mucosal capnometry.

Keywords: capnometry, carbon-dioxide gap, perfusion, oxygenation, enteral feeding, motility

Received: 21 September 2015 / Accepted: 05 December 2015

Introduction

The clinical significance of monitoring the gastrointestinal circulation is based on several factors. It is well recognized that in the early phase of shock, compensatory mechanisms lead to the redistribution of blood flow from the gut to other organs, resulting in the normalization of macrohemodynamic parameters. Consequently, in spite of normal values of global oxygen delivery, gastrointestinal hypoperfusion may occur and remains undiagnosed by conventional monitoring tools. This phenomenon explains the sensitivity of mucosal capnometry for the diagnosis of compensated shock. Unfortunately, during this redistribution phase, increased intestinal permeability and microcirculatory insufficiency can result in tissue hypoxia, which may eventually lead to toxin translocation from the gut into the circulation, causing organ dysfunction and the development of multiple organ failure [1,2]. In haemorrhagic shock, buccal PCO_2 monitoring proved to be useful in both the diagnosis and the quantification of bleeding [3-5]. In animal experiments, buccal PCO_2 values were found to be sensitive to hypoperfusion, and also showed a strong correlation with outcomes,

* Correspondence to: Péter Palágyi MD., University of Szeged, Department of Anaesthesiology and Intensive Therapy, 6. Semmelweis St, 6725 Szeged, Hungary.
E-mail: peter@med.u-szeged.hu
· Sándor Barna: Department of Anaesthesiology and Intensive Therapy, Bács-Kiskun County Hospital, Teaching Hospital of the University of Szeged, 6000 Kecskemét, Nyíri út 38, Hungary
· Péter Csábi: Department of Anaesthesia and Intensive Care, Wexham Park Hospital, United Kingdom, Wexham, Slough, Berkshire, SL2 4HL
· Péter Lorencz: University of Szeged, Department of Anaesthesiology and Intensive Therapy, 6. Semmelweis St, 6725 Szeged, Hungary.
· Ildikó László: University of Szeged, Department of Anaesthesiology and Intensive Therapy, 6. Semmelweis St, 6725 Szeged, Hungary.
· Zsolt Molnár: University of Szeged, Department of Anaesthesiology and Intensive Therapy, 6. Semmelweis St, 6725 Szeged, Hungary.

compared to traditional vital signs or blood gas parameters. Similar findings have been reported, using sublingual capnometric monitoring during bleeding, in both human and animal studies [6,7]. The results of a haemorrhagic shock model in pigs, when complex hemodynamic and blood gas measurements were performed in addition to sublingual capnometry and orthogonal polarisation spectral imaging (OPS) during severe bleeding, were recently detailed [8]. The results suggest that, sublingual to arterial PCO_2 gap values, correlated well with microcirculatory parameters gained by videomicroscopy, and the combination of capnometric monitoring with arterial and central venous blood gas parameters may improve the diagnostic accuracy of haemodynamically relevant haemorrhage or other types of hypoperfusion. The utility of mucosal PCO_2 monitoring was also verified in septic shock in pigs when the early signs of circulatory insufficiency were detected by simultaneous intestinal mucosal capnometry monitoring and microcirculatory assessment using OPS, but not by conventional clinical parameters like arterial blood pressure, urinary output or lactate levels [9].

Mucosal capnometry and respiratory monitoring

In patients with stable haemodynamics and good peripheral circulation tissue PCO_2 changes closely follow the arterial PCO_2 alterations. The first application of a ballooned gastric tonometer in a pediatric population with respiratory paralysis was based on this principle [10]. As these patients did not suffer from circulatory failure, they only had a minor difference of 2-3 mmHg between their gastric and arterial PCO_2. In such circumstances, sudden changes of the absolute value of gastric or other gastrointestinal mucosal PCO_2 may indicate respiratory disturbances. This was the case of a nine-month infant, born with combined congenital cardiac abnormalities, in whom an abrupt increase in gastric PCO_2 was detected during aggressive mechanical ventilation, and was followed by the diagnosis of a severe respiratory complication of tension pneumothorax [11]. In a validation study of a new sublingual capillary tonometer, performed in COPD patients, sublingual PCO2 values decreased in parallel with arterial blood PCO2 during hyperventilation [12]. These observations suggest that in patients without compromised circulation sublingual capnometry may indicate short term changes in arterial PCO2.

Gastric tonometry in the diagnosis of splanchnic artery stenosis

Acute gastrointestinal ischemia has a high incidence in shock, which condition is a common scenario in perioperative medicine and intensive care [13,14]. In most cases it is not related to significant anatomical stenoses of gastrointestinal tract vessels, but it is due to compensatory vasoconstriction. This condition is also named non-occlusive mesenteric ischemia (NOMI). The main goals of its therapy include the restoration of circulating blood volume and stabilization of haemodynamics. Splanchnic ischemia, however, may also be due to arteriosclerosis or external compression of the coeliac and mesenteric arteries. Various vague ischaemic symptoms may develop, which depend on the duration and the degree of blood flow reduction. Strong abdominal pain and "acute abdomen" is characteristic in acute splanchnic syndrome (ASS), while postprandial pain and weight loss are typical but non-specific symptoms in chronic splanchnic syndromes (CSS) [15]. Gastrointestinal tonometry has a role in the diagnosis of ongoing ischemia, as the association of hypoperfusion with increased PCO_2 has been observed in ischaemic models and animal experiments [16-18]. While the diagnosis of an acute abdominal catastrophe is simple, recognizing chronic ischemia may be extremely difficult. Kolkman developed a diagnostic approach in which gastrointestinal tonometry played a pivotal role [19,20]. The sensitivity of gastric tonometry was increased by using a ten-minute bicycle exercise test or a test meal, and coined the term, gastric exercise tonometry (GET). These tests can provoke and detect mucosal ischaemia, and can be successfully used for the diagnosis of different occlusive arterial diseases [21]. Combined non-invasive screening with exercise tonometry and duplex ultrasonography showed excellent accuracy in detecting chronic gastrointestinal ischemia while the application of various imaging methods can give morphological diagnosis only. Besides, in this series of investigations, GET proved its practicability in the selection of patients who can most benefit from surgery or PTA/stent placement.

The correlation between gastric mucosal perfusion and emptying in a pilot study

Enteral feeding is undoubtedly superior to parenteral nutrition [22,23]. Effective enteral nutrition, however, requires functioning gastrointestinal tract, often missing in the critically ill patient [24]. The factors neces-

sary for the maintenance of the physiological structure and mucosal perfusion (Figure 1), are often compromised due to circulatory disturbances in patients in an ICU. Although good peripheral circulation is unlikely when unstable haemodynamics exist, regional hypoperfusion may be present due to normal macro-hemodynamic and oxygenation parameters [9,25,26]. This fact underlines the potential importance of monitoring regional perfusion in this group of patients.

Mucosal capnometry is the monitoring of the partial pressure of carbon dioxide (PCO_2) in mucous membranes. Its history began with the invention of gastro tonometry [10], which method allowed the measurement of intraluminal PCO_2 and the calculation of intramucosal pH (pHi) in the gastric mucosa. The method was first used in the University of Szeged, Hungary for the adjustment of ventilators in poliomyelitic children with respiratory insufficiency [10]. As these patients were haemodynamically stable, the gastric carbon-dioxide levels closely followed systemic arterial carbon-dioxide values. This observation was confirmed in animal experiments and in human volunteers with normal perfusion, in whom the changes in alveolar ventilation and arterial PCO_2 resulted in parallel changes of the tonometric variables [27-29]. The significance of gastric tonometry, in detecting the failure of regional perfusion, was recognized later, when substantial differences were found between gastric and arterial PCO_2 in various clinical and experimental studies [30]. The magnitude of this difference, the so-called gastric-to-arterial PCO_2 gap ($PgaCO_2$), corresponds with the severity of the disease and splanchnic perfusion failure and proved to be an important prognostic factor [31,32]. More than 3000 articles have been published on this topic, in the areas including intensive care, perioperative and transplantation medicine, traumatology, sepsis, and cardiology, yet gastric tonometry is still not used as much as would be expected. This might be due to pitfalls of pHi calculation, the interference of gastric acid and enteral feeding, and technical difficulties [16,33] which have lead to the gradual abandonment of tonometric monitors. Despite the development of gastric tonometry. [34], interest turned to the capnometric monitoring at other sites of the gastrointestinal mucosa. In the last decades, several investigators have reported a correlation between the PCO_2 values of the oral and gastric mucosa in different pathological conditions [35,36] and has resulted in the use of sublingual or buccal mucosal capnometry. These methods do not have the limitations of gastric tonometry and are increasingly used for the measurement of PCO_2 in the mucosa, and the calculation of mucosal-to-arterial PCO_2 gap [3,37]. Currently buccal or sublingual mucosal capnometry has wide range applications in medical research and a remarkable potential for patient monitoring.

The aim of the study is to present the results of a preliminary investigation concerning the relationship between gastric emptying and regional perfusion detected by gastric mucosal capnometry in critically ill patients.

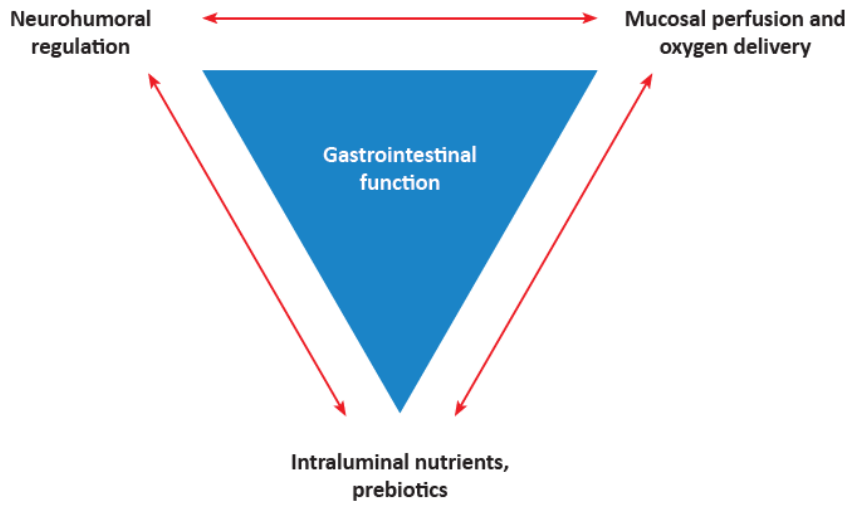

Fig. 1. Factors contributing to the physiologic function of the gastrointestinal tract. (For explanation, see text.)

METHODS

Critically ill, mechanically ventilated patients were included in our prospective observational study. The study was approved by the Regional Human Biomedical Research Ethics Committee of the University of Szeged. All patients were informed of the procedures and gave written concent.

A conventional nasogastric tube was introduced into the stomach to provide enteral feeding, and a silicon gastrotonometric device was inserted through the other nostril, for gastric mucosal PCO_2 measurements. The features of this special probe have been described earlier [38]. The patients were given proton-pump inhibitors twice a day in order to reduce the interference of gastric acid. After early cardiopulmonary stabilization 1 kcal/ml standard enteral formula (Nutrison Standard, Nutricia) was started via the feeding tube. The caloric requirements were defined as 20-25 kcal/kg, for obese patients with a BMI > 30 kg/m2. In case of delayed gastric emptying, with higher residual gastric volume (RGV), the algorithm depicted on Figure 2. was used for dose adjustments. Feeding was stopped two hours before tonometric measurements, to minimize the confounding effects of nutrition. At the end of these feeding pauses, overall arterial and central venous blood-gas analysis and gastric tonometric measurements were performed twice a day (Figure 3). The main clinical end-points were the amount of RGV in eight-hour periods and the enteral caloric intake in the last 24 hours (actual energy=Ea) divided by the previously calculated optimal daily caloric intake (total energy=Et). The Ea/Et ratio reflected the daily status of enterally administered nutrients compared to total caloric needs. The occurrence of feeding intolerance and complications eg. aspiration, regurgitation, vomitus, bowel distention, and diarrhea were also recorded. Subgroups were created in a post hoc fashion according to the median $PgaCO_2$ value and divided into "low" (LG) and "high" (HG) $PgaCO_2$ groups.

The main outcome parameters were the differences in RGV and Ea/Et ratios. The numeric data in the text and values on the figures are given as median and 25th and 75th percentiles.

The Bartlett test was used to verify if samples were from populations with equal variances and the Kolmogorov-Smirnov test used to determine normal distribution. Individual groups were compared by Mann-Whitney test. Data analysis was done using the statistical software package SigmaStat for Windows (Jandel Scientific, Erkrath, Germany). The level of statistical significance was set at $\alpha = 0.05$.

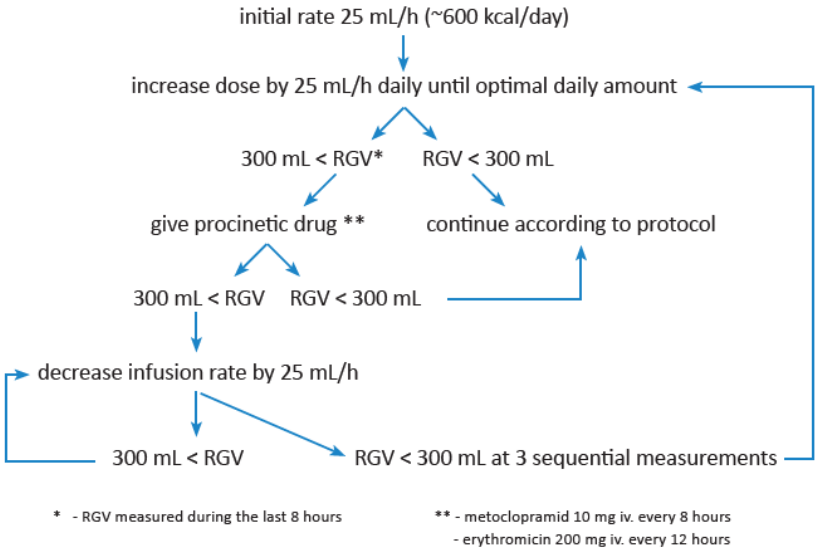

Fig. 2. Protocol for dose adjustments during early enteral feeding. (RGV, residual gastric volume. For further explanation see text.)

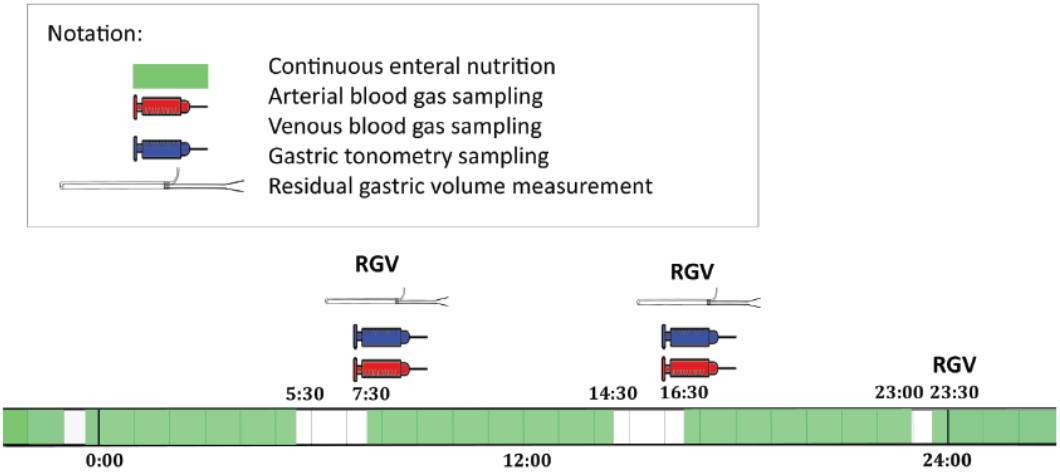

Fig. 3. Sampling protocol during early enteral nutrition. (For explanation see text.)

RESULTS

The data of eighty separate measurement points in eighty critically ill patients were analyzed. The clinical characteristics of the study population are summarized in Table 1. The average APACHE II score of the whole sample was twenty-six points with a calculated mortality risk of about 55%. In 50% of the patients, the average $PgaCO_2$ was lower while in the other 50% higher than 29 mmHg. This was the median value to develop the two groups (LG and HG). The amount of RGV was found significantly lower in the LG as compared to the HG: 0 (0-50) compared to 50 (30-200) ml, $p < 0.001$ (Figure 4). Differences in physiological parameters, such as central venous oxygen saturation ($ScvO_2$), serum lactate (seLac) and central venous-to-arterial CO_2

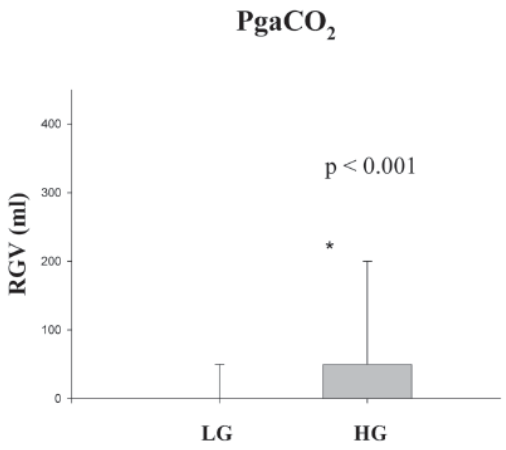

Fig. 4. Differences in the average residual gastric volume (RGV) between patients with low (LG) and high (HG) $PgaCO_2$ levels. (* $p < 0.001$ Mann-Whitney Rank Sum test.)

Table 1. Clinical characteristics of the patients involved in the study

Age (years)	**74 (59-87)**
Gender (m/f)	4/4
APACHE II. score	26
Mortality risk (%)	55
Mortality (%)	37
Diagnosis (n)	
intracranial haemorrhage	3
subarachnoid haemorrhage	2
sepsis, MOF	1
cardiogenic shock	2

Data are expressed as mean (min-max), respectively.

Table 2. Differences in physiological parameters. LG, "low" group; HG, "high" group; $PcvaCO_2$, central venous-to-arterial CO_2 gap; $ScvO_2$, central venous oxygen saturation; seLac, serum lactate. Values are expressed as median and 75th and 25th percentiles.

	LG	**HG**
$PcvaCO_2$ (mmHg)	6.0 (4.6.7.0)	7.0 (5.0-8.0)
$ScvO_2$ (%)	80 (77-82)	75 (68-81)
seLac (mmol/L)	1.1 (0.9-1.2)	1.6 (1.1-3.2)

gap ($PcvaCO_2$) levels are summarized in Table 2. There was no statistically significant difference in the rate and escalation of enteral feeding, and the Ea/Et quotient was also found similar in the groups. Complications attributable to early enteral feeding were uncommon, short-term diarrhea stopped by feeding-pause were reported in two individuals and suspected regurgitation and aspiration in one case.

Discussion

During critical illness, the provision of enteral feeding is crucially important. Unfortunately, gastrointestinal dysfunction, including dysmotility and malabsorption, may hinder nasogastric tube feeding. According to the literature, its aetiology is multicausal [22,23,39,40], and concomitant complications may inhibit the application of a more physiologic way of providing nutrition. As the severity of the illness is associated with higher incidence of gastrointestinal complications and insufficient enteral calorie delivery, this vicious circle worsens the clinical outcome and delays recovery. Consequently, barriers to feeding are of great significance in high risk patients [40]. Normal splanchnic blood flow is a key factor in the maintenance of the healthy bowel system. The relationship between regional and global blood flow and gastric emptying was investigated in this pilot study. Mucosal capnometry devices allowed the indirect monitoring of gastrointestinal regional perfusion [38,41], while from simultaneously drawn arterial and central venous blood gas parameters assessed patients' macro-hemodynamic and oxygenation status. The different blood gas values have particular implications for systemic oxygen balance: $ScvO_2$ refers to the proportion of global oxygen delivery and consumption, $PcvaCO_2$ describes the relationship of cardiac output to global metabolism and microvascular blood flow, and seLac is a well-known parameter of inadequate tissue perfusion related anaerobic metabolism [42]. Although the measurement of RGV is a rough estimation of gastric emptying, it has been used frequently as an indicator of hindered gastric emptying ang motility. Because of the lack of other practical techniques it was decided to monitor RGVs at eight-our intervals to track gastric motility. During the study, early enteral nutrition was given to eight critically ill patients, whose calculated mortality risk exceeded 55%. The applied feeding concept was found to be feasible with adverse effects rarely encountered. Splanchnic hypoperfusion - reflected by increased $PgaCO_2$ gap, was a common finding, being detected in 70% of all measurements. These abnormalities would have remained hidden without regional perfusion monitoring, and could have contributed to the development of organ dysfunction, and worsen clinical outcome. Thirty-seven percent of patients died in the intensive care unit.

Abnormal values of arterial and central venous blood gas parameters were infrequent. Pathological values were recorded for seLac, $ScvO_2$ and $PcvaCO_2$ in 16%, 14% and 39% of all measurements, respectively. These result demonstrate the relative stability of global oxygenation and perfusion parameters compared to those of regional perfusion. The main finding is, that patients with elevated $PgaCO_2$ had significantly higher RGVs. As the prediction of feeding intolerance is rather diffucult, the increased amount of gastric residuals in the patients with compromised tonometric parameters suggest that normalization of these parameters may positively affect the motility of the stomach. The concept of improving cardiovascular performance to reduce gastrointestinal complications in the perioperative period has already been justified in several studies [43-47]. In an examination performed in neonates decreased Doppler sonographic blood flow in the superior mesenteric artery has been linked to intestinal dysmotility and feeding intolerance [48]. These data support the assumption that perfusion of the bowel system directly affects its motility. A literature review suggests that the association between elevated mucosal PCO_2 due to decreased splanchnic perfusion and the direct influence of circulatory parameters on gastric emptying and enteral feeding has not been reported.

Conclusion

The use of mucosal capnometry and the measurement of mucosal-to-arterial PCO_2 gap in different gastrointestinal areas proved to be useful in numerous laboratory and clinical studies. At present, the most important clinical aspect is probably the assessment of splanchnic regional blood flow in special gastrointestinal diseases. Besides compensated shock can be detected in acutely ill patients with normal macro-hemodynamic parameters, while selective gut hypoperfusion can be diagnosed in special populations with chronic gastrointestinal ischemia. In the present study, a new application field of a new gastric tonometry device was tested. The splanchnic blood flow of high-risk ICU patients receiving early enteral feeding was monitored, and significant

differences in gastric emptying were found in patients with elevated mucosal-to-arterial CO_2 gap. These data suggest that the extension of similar examinations to a greater ICU population may be worthwhile. Taking into consideration the intensive research and continuous evolution of mucosal capnometry monitoring methods, the widespread use of such devices in special medical or surgical patient groups may just be a question of time.

Acknowledgements

The authors are very grateful for the selfless help of the nursing staff of the Department of Anaesthesiology and Intensive Therapy of the Medical University of Szeged.

Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Pastores SM, Katz DP, Kvetan V. Splanchnic ischemia and gut mucosal injury in sepsis and the multiple organ dysfunction syndrome. Am J Gastroenterol. 1996;91:1697-710.
2. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med. 2004;32:1825-31.
3. Pellis T, Weil MH, Tang W, Sun S, Csapozi P, Castillo C. Increases in both buccal and sublingual partial pressure of carbon dioxide reflect decreases of tissue blood flows in a porcine model during hemorrhagic shock. J Trauma. 2005;58:817-24.
4. Cammarata GA, Weil MH, Castillo CJ, et al. Buccal capnometry for quantitating the severity of hemorrhagic shock. Shock. 2009;31:207-11.
5. Lu H, Zheng J, Zhao P, Zhang G, Wu T. Buccal partial pressure of carbon dioxide outweighs traditional vital signs in predicting the severity of hemorrhagic shock in a rat model. J Surg Res. 2014;187:262-9.
6. Baron BJ, Sinert R, Zehtabchi S, Stavile KL, Scalea TM. Diagnostic utility of sublingual PCO2 for detecting hemorrhage in penetrating trauma patients. J Trauma. 2004;57:69-74.
7. Xu J, Ma L, Sun S, et al. Fluid resuscitation guided by sublingual partial pressure of carbon dioxide during hemorrhagic shock in a porcine model. Shock. 2013;39:361-5.
8. Palágyi P, Kaszaki J, Rostás A, et al. Monitoring microcirculatory blood flow with a new sublingual tonometer in a porcine model of hemorrhagic shock. BioMed Research International. 2015; 847152. http://dx.doi.org/10.1155/2015/847152.
9. Verdant CL, De Backer D, Bruhn A, et al. Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis. Crit Care Med. 2009;37:2875-81.
10. Boda D, Murányi L. Gastrotonometry: an aid to the control of ventilation during arteficial respiration. Lancet. 1959;1:181-2.
11. Boda D, Tálosi G, Hódi Z. Development of gastrotonometry and the future of its use in the monitoring of critically ill patients. Orv Hetil. 2005;146:153-7.
12. Rózsavölgyi Z, Boda D, Hajnal A, Boda K, Somfay A. A Newly Developed Sublingual Tonometric Method for the Evaluation of Tissue Perfusion and Its Validation In Vitro and in Healthy Persons In Vivo and the Results of the Measurements in COPD Patients. Crit Care Res Pract. 2014;2014:534130.
13. Kolkman JJ, Mensink PB. Non-occlusive mesenteric ischaemia: a common disorder in gastroenterology and intensive care. Best Pract Res Clin Gastroenterol. 2003;17:457-73.
14. Ackland G, Grocott MP, Mythen MG. Understanding gastrointestinal perfusion in critical care: so near, and yet so far. Crit Care. 2000;4:269-81.
15. Kolkman JJ, Bargeman M, Huisman AB, Geelkerken RH. Diagnosis and management of splanchnic ischemia. World J Gastroenterol. 2008;28;14:7309-20.
16. Kolkman JJ, Otte JA, Groeneveld AB. Gastrointestinal luminal PCO2 tonometry: an update on physiology, methodology and clinical applications. Br J Anaesth. 2000;84:74-86.
17. Dubin A, Edul VS, Pozo MO, et al. Persistent villi hypoperfusion explains intramucosal acidosis in sheep endotoxemia. Crit Care Med. 2008; 36:535-42.
18. Knichwitz G, Rötker J, Möllhoff T, Richter KD, Brüssel T. Continuous intramucosal PCO2 measurement allows the early detection of intestinal malperfusion. Crit Care Med. 1998;26:1550-7.
19. Mensink PB, van Petersen AS, Geelkerken RH, Otte JA, Huisman AB, Kolkman JJ. Clinical significance of splanchnic artery stenosis. Br J Surg. 2006;93:1377-82.
20. Otte JA, Geelkerken RH, Huisman AB, Kolkman JJ. What is the best diagnostic approach for chronic gastrointestinal ischemia? Am J Gastroenterol. 2007;102:2005-10.
21. Mensink PB, van Petersen AS, Kolkman JJ, Otte JA, Huisman AB, Geelkerken RH. Gastric exercise tonometry: the key investigation in patients with suspected celiac artery compression syndrome. J Vasc Surg. 2006;44:277-81.
22. Kozeniecki M, Fritzshall R. Enteral nutrition for adults in the hospital setting. Nutr Clin Pract. 2015;30:634-51.
23. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. Am J Clin Nutr. 2001;74:534-42.
24. Gungabissoon U, Hacquoil K, Bains C, et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. J Parenter Enteral Nutr. 2015;39:441-8.
25. Maynard N, Bihari D, Beale R, et al. Assessment of splanchnic

oxygenation by gastric tonometry in patients with acute circulatory failure. JAMA. 1993;270:1203-10.

26. Creteur J, De Backer D, Sakr Y, Vincent JL. Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med. 2006;32:516-23.
27. Pernat A, Weil MH, Tang W, et al. Effects of hyper- and hypoventilation on gastric and sublingual PCO2. J of Appl Physiol. 1999;87:933–7.
28. Salzman AL, Strong KE, Wang H, Wollert PS, Vandermeer TJ, Fink MP. Intraluminal "balloonless" air tonometry: a new method for determination of gastrointestinal mucosal carbon dioxide tension. Crit Care Med. 1994;22:126-34.
29. Kolkman JJ, Steverink PJ, Groeneveld AB, Meuwissen SG. Characteristics of time-dependent PCO2 tonometry in the normal human stomach. Br J Anaesth. 1998;81:669-75.
30. Fiddian-Green RG, Pittenger G, Whitehouse WM Jr. Back-diffusion of CO2 and its influence on the intramural pH in gastric mucosa. J Surg Res. 1982;33:39-48.
31. Gutierrez G, Palizas F, Doglio G, et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet. 1992;339:195-9.
32. Heino A, Hartikainen J, Merasto ME, Alhava E, Takala J. Systemic and regional pCO2 gradients as markers of intestinal ischaemia. Intensive Care Med. 1998;24:599-604.
33. Carlesso E, Taccone P, Gattinoni L. Gastric tonometry. Minerva Anestesiol. 2006;72:529-32.
34. Bennett-Guerrero E, Panah MH, Bodian CA, et al. Automated detection of gastric luminal partial pressure of carbon dioxide during cardiovascular surgery using the Tonocap. Anesthesiology. 2000;92:38-45.
35. Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL. Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med. 2006;32:516-23.
36. Povoas HP, Weil MH, Tang W, Moran B, Kamohara T, Bisera J. Comparisons between sublingual and gastric tonometry during hemorrhagic shock. Chest. 2000;118:1127-32.
37. Nakagawa Y, Weil MH, Tang W, Sun S, Yamaguchi H, Jin X, Bisera J. Sublingual capnometry for diagnosis and quantitation of circulatory shock. Am J Respir Crit Care Med. 1998;157:1838-43.
38. Boda D, Kaszaki J, Tálosi G. A new simple tool for tonometric determination of the PCO2 in the gastrointestinal tract: in vitro and in vivo validation studies. Eur J Anaesthesiol. 2006;23:680-5.
39. Chapman MJ, Deane AM. Gastrointestinal dysfunction relating to the provision of nutrition in the critically ill. Curr Opin Clin Nutr Metab Care. 2015;18:207-12.
40. Chapman MJ, Nguyen NQ, Deane AM. Gastrointestinal dysmotility: evidence and clinical management. Curr Opin Clin Nutr Metab Care. 2013;16:209-16.
41. Palágyi P, Vimláti L, Boda K, Tálosi G, Boda D. Practical experiences and in vitro and in vivo validation studies with a new gastric tonometric probe in human adult patients. J Crit Care. 2010;25:541.e9-15.
42. Joosten A, Alexander B, Cannesson M. Defining goals of resuscitation in the critically ill patient. Crit Care Clin. 2015;31:113-32.
43. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg. 1995;130:423-9.
44. Mythen MG. Postoperative gastrointestinal tract dysfunction. Anesth Analg. 2005;100:196-204.
45. Giglio MT, Marucci M, Testini M, Brienza N. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Br J Anaesth. 2009;103:637-46.
46. Kirov MY, Kuzkov VV, Molnar Z. Perioperative haemodynamic therapy. Curr Opin Crit Care. 2010;16:384-92.
47. Futier E, Robin E, Jabaudon M, et al. Central venous O_2 saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery. Crit Care. 2010;14:R193.
48. Robel-Tillig E, Knüpfer M, Pulzer F, Vogtmann C. Blood flow parameters of the superior mesenteric artery as an early predictor of intestinal dysmotility in preterm infants. Pediatr Radiol. 2004;34:958-62.