

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

Summary of PhD Thesis

Péter Palágyi MD

Department of Anaesthesiology and Intensive Therapy
& Institute of Surgical Research
University of Szeged

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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. 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 occurrence 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. 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. 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 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. 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. 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 availability 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 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. In vitro and in vivo measurements with a new capillary gastric tonometric probe

New balloonless gastric tonometric probes were applied in our investigations made entirely of silicone rubber. It has already been introduced in an animal study, the former human investigations were carried out exclusively in infants and children. For the comparison of the in vitro uptake of CO₂ by the probe and the catheter investigations were performed using an equilibrium chamber and applying different carbon-dioxide concentrations. During the first human adult in vivo application of the new gastric tonometric method the insertion and measurement with the probe was tested in healthy volunteers. Both fasting and postprandial tonometric measurements were performed on

two consecutive days, inserting a new probe each day. In the clinical part of the examinations anaesthetized adult patients scheduled for neurologic, orthopedic, trauma, and cardiac surgery were enrolled in order to perform intraoperative mucosal capnometric monitoring. In a subgroup of these patients parallel measurements were performed after inserting both the catheter and the probe. The catheters were used as reference during the simultaneous in vivo measurements, similarly to the in vitro experiments.

3.2. Sublingual tonometric monitoring in an experimental model of haemorrhagic shock.

A new sublingual mucosal capnometric probe was tested in an animal model of haemorrhagic shock. The experimental protocol enabled us to investigate the alterations of different macro- and microcirculatory parameters, and sublingual capnometry in two well separated periods: severe shock and moderate hypovolemia. After baseline measurements in the shock group, hemorrhagic shock was induced by bleeding the animals through the right carotid arterial catheter into a heparin 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. At 60 min volume resuscitation was started with colloid solutions in order to reach 75% of the starting MAP in 10-15 min. This means that the pigs were

partially resuscitated and remained hypovolemic in the following period between 60 and 180 min. Hemodynamic-, arterial- and central venous blood-gas measurements and tissue capnometry were repeated and recorded every 30 min for duration of 3 hours. Intravital videomicroscopy was performed at baseline, at 60 and 180 min. 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. Haemodynamics, blood gas analysis and microcirculatory measurements were performed at the same time points. We studied the correlation of the results of sublingual capnometry and direct microcirculatory measurements by intravital microscopy (IVM), and investigated how the capnometry-derived values relate to global indicators of haemodynamic changes during haemorrhage and resuscitation.

3.3. Gastric tonometry during early enteral nutrition of critically ill patients

Critically ill, mechanically ventilated patients were included in this prospective observational study. 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. After early cardiopulmonary stabilization a standard enteral formula was started via the feeding tube. Residual gastric volume (RGV) was determined and recorded every 8 hours. Twice a day overall arterial and central venous blood-gas analysis, and gastric tonometric measurements were performed. Tube feeding was stopped two hours before these measurements. 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= E_a) divided by the previously calculated optimal daily caloric intake (total energy= E_t). The E_a/E_t ratio was calculated each day in each individuals, and reflected the daily status of enteral feeding 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 $P_{\text{ga}}\text{CO}_2$ value and divided into “low” (LG) and “high” (HG) $P_{\text{ga}}\text{CO}_2$ groups. The main outcome parameters were the differences in RGV and E_a/E_t ratios.

4. RESULTS

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

According to 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) 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. The probe is easily applicable in clinical practice. Its use is well tolerated by the patients and does not cause more inconveniences than does the simple use of a feeding tube. The tonometric measurements performed with the probe in the 50 surgical cases few technical problems were encountered. Nevertheless, we consider most of these difficulties as the results of inexperience, because they occurred mainly in the initial phase of the study. The results of gastric tonometric measurements performed in anaesthetized 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, as higher ASA classification corresponded to higher gastric tonometric values. The statistical analysis of the intraoperative cases revealed that both the absolute values of gastric mucosal PCO_2 and the gastric mucosal to arterial gap values were significantly lower in the low-risk categories. The results of the simultaneous in vivo tonometric measurements performed with

the catheter and the probe showed predominantly higher mucosal PCO_2 values obtained with the new probe.

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

During the haemorrhagic shock model in this study we performed complex macro-haemodynamic monitoring and microcirculatory assessment during severe bleeding and moderate hypovolaemia. Regarding the sublingual capnometric parameters significant increases were detected both in the P_{SLCO_2} and the P_{SLCO_2} gap values during the haemorrhagic shock phase, while during partial resuscitation a significant improvement of P_{SLCO_2} and P_{SLCO_2} gap was detected, still these values remained elevated as compared to baseline. The P_{SLCO_2} did not change significantly over time in the sham operated group. The sublingual postcapillary red blood cell velocity (RBCV_{SL}) and the sublingual capillary perfusion rate (CPR_{SL}) determined by intravital videomicroscopy decreased significantly in severe shock. During partial resuscitation both RBCV_{SL} and CPR_{SL} increased in the shock group, but still they remained decreased compared to the baseline values. At 180min, 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. 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 P_{cvaCO_2} increased. 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 P_{cvaCO_2} . $ScvO_2$ showed a statistically significant elevation after resuscitation, but remained significantly lower as compared to the baseline value and to the sham-operated group. In case of the oxygen extraction rate significant differences were observed between the sham and shock groups. The correlation analysis of the sublingual capnometric and the direct microcirculatory parameters obtained by intravital videomicroscopy revealed a statistically significant correlation between P_{SLCO_2} gap and $RBCV_{SL}$ ($r = -0.648$; $p < 0.0001$) and P_{SLCO_2} gap and CPR_{SL} ($r = -0.644$; $p < 0.0001$). The P_{SLCO_2} gap also correlated with $ScvO_2$ and P_{cvaCO_2} ($r = -0.504$ and $p < 0.0001$; $r = 0.623$ and $p < 0.0001$, respectively).

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

In 50% of the patients, the average P_{gaCO_2} was lower, while in the other 50% higher than 29 mmHg. This was the median value to develop the low and high P_{gaCO_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, $p < 0.001$. 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 with our protocol.

6. SUMMARY/MAJOR FINDINGS

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 CO₂ 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.

FULL PAPERS DIRECTLY RELATED TO THE THESIS:

- I. Palágyi P, Vimláci 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

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ABSTRACTS

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