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ORIGINAL ARTICLE

Stephan Klaus
Matthias Heringlake
Jan Gliemroth
Hans-Peter Bruch
Ludger Bahlmann

Intraperitoneal microdialysis for detection of splanchnic metabolic disorders

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S. Klaus (✉) · M. Heringlake
L. Bahlmann
Department of Anesthesiology,
Medical University of Lübeck,
Ratzeburger Allee 160, 23538 Lübeck,
Germany
e-mail: stephan.klaus@epost.de
Tel.: +49-451-5002765
Fax: +49-451-5003510

J. Gliemroth
Department of Neurosurgery,
Medical University of Lübeck,
Ratzeburger Allee 160, 23538 Lübeck,
Germany

H.-P. Bruch
Department of Surgery,
Medical University of Lübeck,
Ratzeburger Allee 160, 23538 Lübeck,
Germany

Abstract *Background and aims:* Due to its high oxygen demand the gastrointestinal tract is very susceptible to hypoxia or ischemia, which may result in local and systemic dysfunction. Early detection of any profound disorders (e.g., after abdominal surgery) remains an important target for the surgeon. This study investigates whether in vivo microdialysis monitoring of the intraperitoneal space adequately reflects hypoxic conditions. *Methods:* Hypoxic hypoxia by ventilation was induced in 14 rats under general anesthesia with FIO_2 of 0.1 (40 min) followed by reoxygenation with FIO_2 of 0.21. Hemodynamic and blood gas monitoring including blood lactate was performed. Microdialysis catheters were placed in the peritoneal cavity, and lactate, pyruvate, and glycerol were measured out of the ascites. *Results:* A significant decrease in mean arterial pressure and increase in blood lactate level during the hypoxic period was observed. Hypoxia induced an immediate and significant elevation in the intraperitoneal lactate/pyruvate ratio to 446±137% of the baseline values, and glycerol subsequently increased during reoxygenation to 389±109%. Values for the blood compartment showed less profound or no significant differences. *Conclusions:* Biochemical monitoring of the intraperitoneal space by in vivo microdialysis, such as after laparatomy can measure metabolic changes in the gastrointestinal tract produced by hypoxia/ischemia. The surgeon may thus detect postoperative complications at an earlier stage than with routine monitoring devices.

Keywords Monitoring · Microdialysis · Gastrointestinal tract · Metabolism · Surgery

Introduction

The gastrointestinal tract is very sensitive to changes in substrate delivery [1]. In critically ill patients (e.g., postoperatively after major abdominal surgical procedures, mesenterial ischemia and nonocclusive disease). Interruption of this supply causes cellular damage to the mesenteric tract and thus impairs the patient's outcome. For the prevention, early detection, and treatment of these deleterious events it is recommended continuously to monitor the gastrointestinal metabolism to detect derangement of normal physiology at a very early stage. Measurement of blood lactate levels has been suggested to reflect ischemic events, which requires measuring them continuously, but this is a global parameter that provides no information about regional metabolic disorders or the origin of the hyperlactemia. The new monitoring technique, called microdialysis, is useful for detecting and understanding the mechanisms involved in gastrointestinal metabolic disorders. However, it is clear that the surgeon who interprets the clinical data (e.g., clinical examination, temperature, hyperlactemia) and the technical-based results is still the most important factor in the management of critically ill patients.

In the present animal experimental study we measured the interstitial lactate/pyruvate (LP) ratio and glyc-

erol of the intraperitoneal fluid during a period of defined hypoxia (45 min FIO_2 0.1) and subsequent reoxygenation. The LP ratio is one parameter of the (gastrointestinal) anaerobic metabolism, while an increase in glycerol indicates cellular membrane damage. The aim of this study was to investigate whether microdialysis monitoring of the intraperitoneal fluid reflects metabolic gastrointestinal tissue disorders.

Material and methods

Animals

After approval of the animal welfare committee 14 adult male CD rats (392–443 g) were anesthetized with thiopentone (200 mg/kg b.w. intraperitoneally; Trapanal 0.5, Byk-Gulden, Konstanz) with repeated injection of 25 mg thiopentone, if necessary. The animal's body temperature was measured rectally and adjusted to 37.5°C. The animals were subjected to a controlled ventilation with a ventilator via the tracheostomy (7025 Rodent Ventilator; Ugo Basile, Varese, Italy) being adjusted individually for normoxic and normocapnic values. Intra-arterial and intravenous lines were inserted into the carotid artery and the jugular vein, respectively. Fluid was supplied by continuous infusion of isotonic saline (2 ml/h) through the central venous catheter. The animals received a total of 10.8±0.8 ml/kg b.w. of saline during the observation period. The inspiratory concentration of O_2 was continuously monitored during the observation period (Muiltcap; Datex-Ohmeda, Helsinki, Finnland). A catheter placed into the carotid artery was used for the invasive measurement of mean arterial pressure and heart rate and for taking the blood samples.

After median laparatomy a microdialysis catheter (CMA 20, CMA Microdialysis, Solna, Sweden) was placed into the peritoneal cave with precaution not to induce any trauma to the intestinal organs. The observation period consisted of the following components: (a) equilibration (45 min; FIO_2=0.21), (b) hypoxic (40 min; FIO_2=0.1), and (c) reoxygenation (50 min; FIO_2=0.21). The hypoxic group (n=7) was ventilated with FIO_2 of 0.1 during the hypoxic period using a volume mixing pump (ISA/27–3F; Wösthoff, Bochum, Germany) by adding nitrogen and a FIO_2 of 0.21 during reoxygenation period. Seven animals served as a control group being ventilated with air (FIO_2 0.21) during the whole experiment.

Arterial blood gas analyses were determined via a blood gas analyzer (ABL 700; Radiometer, Copenhagen, Denmark) at definit time points with particular respect to avoid hypovolemia by blood loss due to too frequent measurements.

Microdialysis

The double lumen microdialysis catheters (CMA 20) had a membrane length of 10 mm, outer diameter of 0.5 mm, and cut-off of 20,000 Da. These were perfused using a CMA 107 microdialysis pump at a flow rate of 1 µl/min with isotonic lactate-free Ringer's solution. The dialysate which streams back in the inner lumen reflects the interstitial concentration of metabolites. Substances of the interstitial and perfusion fluid thereby equilibrate by diffusion depending on the concentration gradient. The use of microdialysis therefore allows the semicontinuous biochemical monitoring of tissue metabolism without repeated traumatization of the tissue. The dialysate and blood samples were analyzed spectrophotometrically for concentrations of lactate, pyruvate, and glycerol via the microdialysis analyzer (CMA 600).

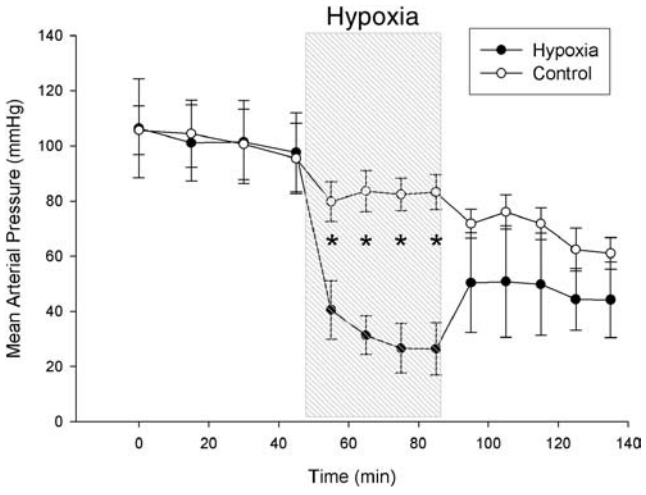

Fig. 1 Mean arterial pressure during normoxia, hypoxia (*shaded area*), and reoxygenation. Significantly lower values for mean arterial pressure were observed during ventilation with lower FIO_2 (0.1). Data are presented as mean ±SD. *P<0.05 between groups

Table 1 Blood lactate, pO_2, pCO_2, and negative base excess during initial normoxia, hypoxia, and reoxygenation

	Hypoxia	Control
Blood lactate (mM)		
Steady state	1.7±0.4	1.6±0.7
End of hypoxia (FIO_2 0.1)	9.6±4.2*	1.55±0.3
Reoxygenation (30 min)	5.5±2.8*	1.4±0.2
Reoxygenation (50 min)	5.7±2.9*	1.5±0.4
Arterial pO_2 (mmHg)		
Steady state	93±7.4	89.6±9.5
End of hypoxia (FIO_2 0.1)	51±14*	87±10.8
Reoxygenation (30 min)	104±16	78.4±6.3
Reoxygenation (50 min)	101±19	81±9.8
Arterial pCO_2 (mmHg)		
Steady state	36.4±3.6	34.7±7.3
End of hypoxia (FIO_2 0.1)	24.3±7.5*	37.2±5.4
Reoxygenation (30 min)	32.6±6.7	37.2±5.0
Reoxygenation (50 min)	32.0±9.2	36.4±4.0
Negative base excess (mM)		
Steady state	2.0±2.4	2.9±2.2
End of hypoxia (FIO_2 0.1)	16.5±7*	2.6±1.8
Reoxygenation (30 min)	10.7±6*	2.7±2.1
Reoxygenation (50 min)	9.7±5.5*	2.6±3.0

* P<0.05 vs. controls

Statistical analysis

The results for the microdialysis values are presented for their relative changes. The mean value of the three concentrations determined during the equilibration period (0–45 min) was set as reference for the baseline values (100%). The results are presented as a mean value ±standard deviation. The two groups were compared statistically by Student's t test, with a P value less than 0.05 as indicating statistical significance.

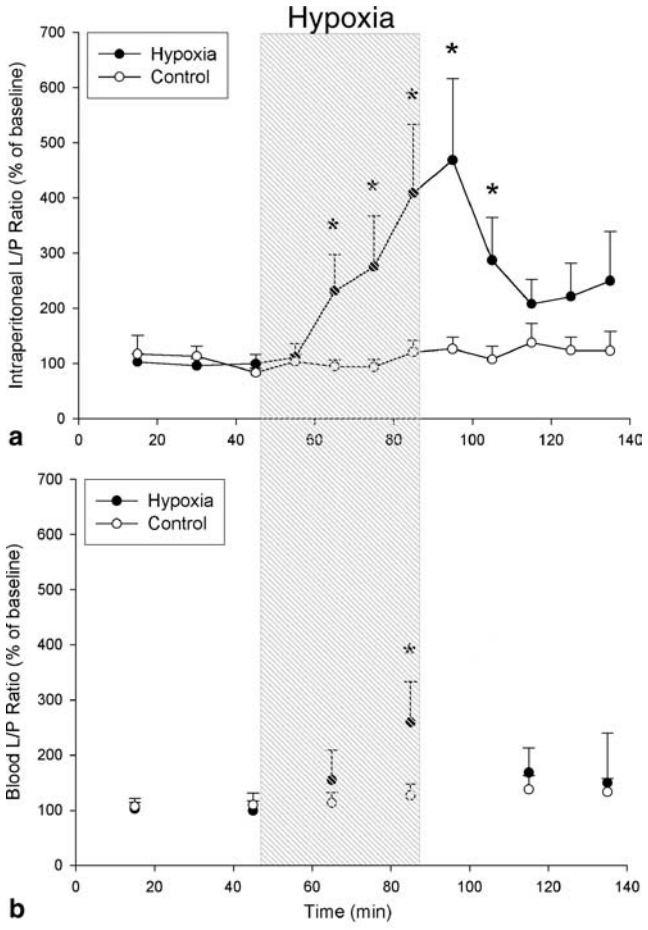

Fig. 2 Lactate/pyruvate (*LP*) ratio in the intraperitoneal space (**a**) during normoxia, hypoxia (*shaded area*), and reoxygenation measured by in vivo microdialysis and blood (**b**). The hypoxic period induced immediate and significant increase in the intraperitoneal LP ratio, while it was less profound in the blood compartment. Data are presented as mean ±SD as percentage of baseline values. **P*<0.05 between groups

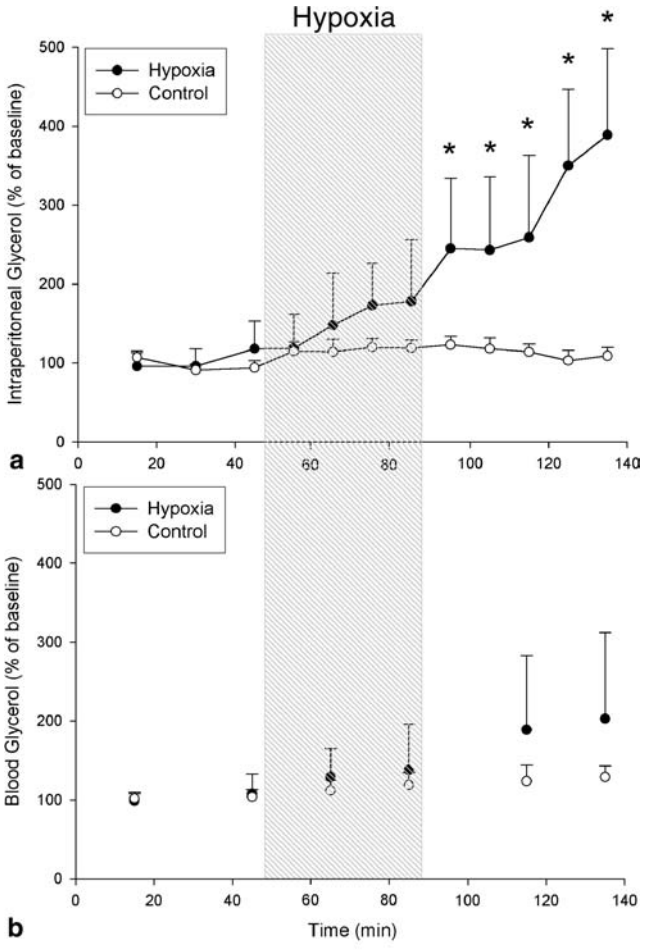

Fig. 3a, b Glycerol concentrations of the intraperitoneal fluid (**a**) and blood (**b**) presented as changes in percentage of the baseline values. In contrast to the intraperitoneal LP ratio, a marked and significant increase was induced during the reoxygenation period, while the values were only moderately elevated during hypoxia. Blood glycerol concentrations did not differ significantly between groups. Data are presented as mean ±SD. **P*<0.05 between groups

Results

No significant differences were found in any of the following parameters between the two groups regarding baseline values.

Hemodynamics and blood gas monitoring

Hypoxia immediately induced a significantly lower mean arterial pressure than in normoxic animals (Fig. 1; $P<0.05$). Reoxygenation resulted in a gradual increase in mean arterial pressure but not significantly lower than in control group. No significant differences in heart rate were observed throughout the entire observation time. Values for blood lactate, pO_2, pCO_2, and base excess are shown in Table 1.

Microdialysis

Baseline values for the LP ratio in the microdialysate were 14±3 (=100%) without any significant differences in the blood values (Fig. 2). After the onset of hypoxia LP of the peritoneal fluid significantly increased and peaked at 446±137% of baseline levels ($P<0.05$) while blood values presented a significant but less marked increase to 260±74%. The control group remained virtually unchanged throughout the observation period. The peritoneal LP ratio in the hypoxic group after reoxygenation persisted at a higher level of 249±89% of the initial levels while blood LP ratio approximated those of the control group (both n.s.).

Baseline glycerol concentrations (=100%) in the intraperitoneal fluid were 71±26 µmol/l those in the blood were 59+23 µmol/l (Fig. 3). During hypoxia only

moderate increases in glycerol concentrations were noted (n.s.). In the peritoneal cavity they began to increase dramatically with the onset of reoxygenation (389%± 109%), showing significantly higher values than control animals ($P<0.05$), while the increase in blood glycerol to 203±109% was less and was nonsignificant.

Discussion

Glycolysis can proceed by either anaerobic or aerobic mechanisms. Anaerobic glycolysis is much less efficient than aerobic glycolysis because it produces less high-energy phosphate per molecule of glucose. The gastrointestinal tract produces *lactate* from glycolysis when oxygen becomes limiting. *Pyruvate* is customarily considered the last molecule produced in glycolysis. Under aerobic conditions pyruvate is transformed into acetyl-coenzyme A, which then enters the citric acid cycle. Under anaerobic conditions, however, something else must be done to oxidize all the NADH formed in glycolysis. Lactate/pyruvate ratios higher than 15:1 suggest that oxygen delivery is inadequate to meet metabolic demand [2]. *Glycerol* is released when degradation of the double-layer phospholipid membrane due to cell damage occurs.

Monitoring the adequacy of tissue oxygenation, particularly in the gastrointestinal tract, is an important goal in the care of the postoperative critically ill patient. Global alterations in tissue oxygenation are inferred from changes in systemic oxygen transport and total oxygen consumption [3]. However, global parameters (e.g., blood lactate levels) cannot measure the level of oxygenation of specific tissue beds, in particular those that are first affected by hypoxia, such as the gastrointestinal tract [4].

Recovery of the intestinal tract after major abdominal surgery or during mesenterial ischemia is hidden from inspection. Thus the surgeon assesses only the patient's parameters of clinical status and probably global blood markers to judge the benefit of the operation. The decision regarding a possible relaparatomy, with the associated higher morbidity and mortality, must be made on these grounds [5]. This places a great responsibility on the surgeon, because preoperative, intraoperative, and postoperative factors may be life threatening for the patient. It seems preferable to involve further monitoring devices in the assessment of gastrointestinal disorders of critical ill patients to objectify regional biochemical alterations. Our data suggest that biochemical measurement of the intraperitoneal fluid by simply leaving a microdialysis probe inside the abdominal cave after laparatomy – comparable to a standard drain – or insertion via a Verres needle during capnoperitoneum can indicate pathophysiological disorders of the gastrointestinal tract. In our study the initial profound increase in the LP ratio as a marker for anaerobic carbohydrate metabolism was followed by a dramatic elevation of the glycerol concentration. The latter indicates subsequent cellular membrane damage after hypoxic stress even when oxygen is resupplied. Neitheroth parameter for tissue and organ disturbance was adequately reflected by the respective blood concentration, due, respectively, to a later onset and less profound increase. According to our results, assessment of tissue metabolism by measuring microdialysis parameters (e.g., splanchnic ischemia) allows earlier detection and subsequent therapeutic intervention during reversible organ dysoxia (LP ratio increase) to avoid irreversible tissue damage (glycerol increase).

Measuring of tissue oxygen and CO_2 tension, blood lactate levels, and also gastrointestinal mucosal pH has been recommended as the best monitoring systems clinically available for this purpose [6, 7, 8, 9, 10,11]. Further approaches for functional monitoring of the gastrointestinal tract have been proposed such as histological examination [12], in vivo magnetic resonance imaging of the oxygenated hemoglobin of the mesenteric veins [13], and hepatic venous oxygen saturation [14], but none has proven to ideal for clinical routine. Vahl et al. [15] suggested gastrointestinal endoluminal pulsoxymetry in the mucosa and serosa to be a valuable tool for detecting ischemia after abdominal aortic surgery. However, adequate measurement of gastrointestinal tissue oxygenation appears to require local organ metabolism to be determined, as is possible by in vivo microdialysis.

Microdialysis was introduced in the early 1970s as a method of measuring the dynamic release of substances in the brain [16,17]. In vivo microdialysis measures the chemical composition of the interstitial fluid which is directly exposed to the cells where biochemical and pharmacological events take place.

The technique has been refined over the past three decades due to the development of new materials for dialysis membranes and commercial availability of smaller, more consistently fabricated probes. Several studies have confirmed microdialysis to be a valuable tool for assessing the metabolic state of organs during critical conditions [18, 19, 20,21]. To our knowledge, no data are available on the *intraperitoneal* microdialysis of the ascites as a reflection of biochemical disorders in the mesenteric region (e.g., ischemia, hypoxia). Intraperitoneal microdialysis after laparatomy seems to be a relatively less-invasive device, and the results of our study suggest that it measures metabolic changes produced by hypoxia/ischemia. Because of the sensitive nature of the gastrointestinal tissue these changes often occur well in advance of other, global indices of hypoxia (blood lactate) [1]. Translated into the clinical situation, this might allow an objective insight to the amount of possible postoperative mesenterial complications at an earlier stage than routine monitoring devices currently do.

Conclusions

Increases in O_2 demand (and delivery) and subsequent metabolic alteration due to critical circumstances should be guided by monitoring of regional tissue dysoxia as is possible by microdialysis. This technique may provide support to early detect mesenteric ischemia or hypoxia (e.g., nonocclusive disease) and thus improve the patients posttherapeutic outcome. This would give the surgeon an additional tool for determining whether resuscitative efforts during the postoperative period are too little, too much, or just right.

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