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Intestinal Luminal Microdialysis

A New Approach to Assess Gut Mucosal Ischemia

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Background: **The authors developed a microdialysis method for sampling lactate from the gut lumen to evaluate the metabolic state of the intestinal mucosa. The aim of the study was to evaluate the method *in vivo* during nonischemic systemic hyperlactatemia and gut ischemia.**

Methods: **Microdialysis capillaries were inserted in the lumen of jejunum, in the jejunal wall, and in the mesenteric artery and vein in anesthetized, normoventilated pigs. In the first experiment, infusion of lactate was used to clamp the arterial blood lactate at 5 mM and 10 mM (n = 6). In the second experiment, 90 min of intestinal ischemia was induced by total (n = 6) or partial (n = 6) occlusion of the superior mesenteric artery followed by 60 min of reperfusion. Sham-operated animals were used as controls (n = 6).**

Results: **Gut luminal lactate increased only slightly during the nonischemic hyperlactatemia: from a median baseline value of 0.10 (range, 0.06–0.28) to 0.50 (range, 0.15–1.18) and 0.86 (range, 0.35–2.05) mM. Total occlusion of superior mesenteric artery increased luminal lactate from a median of 0.09 (range, 0.06–0.17) to 2.37 (range, 1.29–2.98) and further up to 3.80 (range, 2.55–6.75) mM during reperfusion. Partial occlusion of superior mesenteric artery induced an increase from a median of 0.09 (range, 0.06–0.51) to 1.66 (range, 0.07–3.97) mM. Gut wall microdialysate lactate in deep and superficial layers followed the arterial and mesenteric vein microdialysate lactate.**

Conclusions: **Luminal lactate concentration, as measured by microdialysis, increases substantially during gut ischemia but does not respond to systemic hyperlactatemia *per se*. In contrast, gut wall microdialysis cannot distinguish between gut ischemia and systemic hyperlactatemia. Gut luminal microdialysis provides a method for the assessment of intestinal ischemia with a potential for clinical application. (Key words: Gastric tonometry; lactic acid; sodium lactate; splanchnic circulation.)**

LOW systemic blood flow and hypovolemia induce vasoconstriction in the splanchnic circulation.[1,2] Reduced splanchnic tissue perfusion may contribute to subsequent development of multiple organ dysfunction.[3,4] At the microcirculatory level, the apical part of the intestinal villi have low oxygen partial pressure[5] because of countercurrent exchange of oxygen along the villous vessels,[6,7] plasma skimming,[8] and high metabolic activity of intestinal epithelial cells. These perfusion characteristics make the intestinal mucosa susceptible to ischemia. Monitoring of the adequacy of gut perfusion in the clinical setting is difficult. The only clinically available method so far is the assessment of gastric mucosal carbon dioxide partial pressure (P_{CO_2}) by gastrointestinal tonometry, which provides a surrogate marker for the balance between local perfusion and metabolism.[9,10] Results obtained with gastrointestinal tonometry remain controversial. For example, perioperative gastric mucosal acidosis may be prevented by hemodynamic management,[11] whereas postoperative attempts to improve splanchnic perfusion may paradoxically worsen the mucosal acidosis despite increased splanchnic blood flow.[12–14] In addition, intestinal tissue acidosis has been observed in the presence of either preserved[15,16] or decreased[17] tissue oxygen partial pressure. Thus, additional markers of the adequacy of regional blood flow and regional metabolism are warranted.

Intestinal mucosal ischemia, presumably first affecting the tips of villi,[5] may lead to increased lactate spill into

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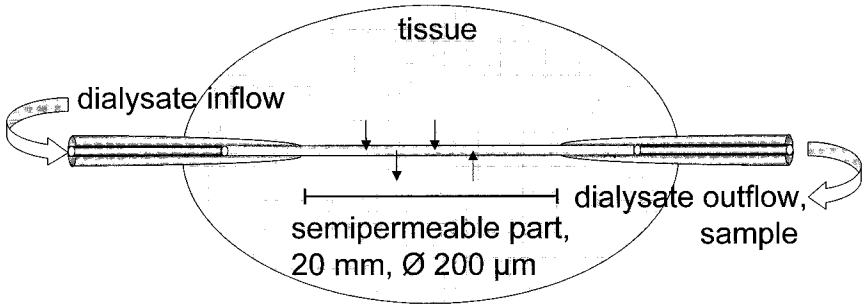

Fig. 1. The structure of the microdialysis capillary. The diffusion of the molecules into dialysate occurs through the semipermeable part of the capillary (arrows).

the lumen of the intestine. Therefore, measurement of the luminal lactate might provide an indicator of the adequacy of gut perfusion or the onset of ischemia.

We developed a microdialysis-based method for intestinal luminal lactate sampling. The aim of the study was to evaluate the method in nonischemic systemic hyperlactatemia and during intestinal ischemia.

Material and Methods

The experimental protocol was approved by the Institutional Animal Care and Use Committee of the University of Kuopio. Female domestic pigs (n = 24; median body weight, 27 kg; range, 24–37 kg) were allocated into two experiments: experiment 1, lactate clamp (nonischemic systemic hyperlactatemia); and experiment 2, gut ischemia. The animals were fasted overnight with free access to water, premedicated with intramuscular azaperone and atropine, and anesthetized with intravenous thiopental. Thiopental was infused continuously at 5 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} to maintain anesthesia, and bolus injections (50 mg in 1–2 min) were added as necessary.

The trachea was intubated, and the animals were mechanically ventilated (Servo Ventilator 900; Siemens Elema AB, Solna, Sweden) with a constant tidal volume of 10 ml/kg and a fraction of inspired oxygen of 0.30. A 7.5-French flow-directed pulmonary artery catheter (Arrow; Arrow International Inc., Reading, PA) was inserted *via* the right internal jugular vein, and the right carotid artery was cannulated (single-lumen central venous catheter; Arrow) for hemodynamic measurements and blood sampling. The femoral artery was cannulated (single-lumen central venous catheter; Arrow) for blood sampling (experiment 1 only, nonischemic hyperlactatemia). Ventilation was adjusted to maintain arterial P_{CO_2} at 33.75–41.25 mmHg, based on arterial blood gas analysis and continuous monitoring of the end-tidal carbon dioxide. Infusions of Ringer's acetate (Ringersteril; Orion-Medipolar, Oulu, Finland) and hydroxyethyl starch (Plasmafusin; Kabi-Pharmacia, Uppsala, Sweden) were given to maintain pulmonary artery occlusion pressure at 6–8 mmHg until return to baseline measurements. Thereafter, 0.9% saline was infused at 5 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}. The core temperature was maintained constant using external heating when necessary.

Microdialysis capillaries for intraluminal, gut wall, and intravascular lactate sampling were designed and manufactured in our laboratory.[18] Capillary membrane of polysulfone with 60,000-d pore size was used (Fresenius; Fresenius AG, Bad Homburg, Germany). The inner diameter of the capillary was 200 μm. A wire with a diameter of 89 μm was placed inside the capillary. The length of the semipermeable part of the capillary was 2 cm, with a volume of 0.5 μl (fig. 1). The outflow tubing had an inner diameter of 0.134 mm (PTFE transparent; BOC Ohmeda, Espoo, Finland) with total length of 100 cm from the capillary to the sample tube. The time delay from the capillary to the sample tube was 7 min. When the microdialysate flow rate was adjusted to 2 μl/min with microdialysis pumps (Carnagie Medicine, Stockholm, Sweden), the transit time was 15 s/U of dialysate for the semipermeable part of the capillary. Each sample was collected over 30 min. The tubes were kept in ice. *In vitro* recovery was tested in body temperature (37°C) for three capillaries in 0.5 mM, 5 mM, and 10 mM concentrations of sodium lactate in Ringer's acetate (Ringersteril). The dialysate flow rate was 2 μl/min.

A median laparotomy was performed. The mesenteric and the portal veins were cannulated *via* distal mesenteric veins with a single-lumen central venous catheter (Arrow). Microdialysis capillaries were inserted into the mesenteric vein and artery (mesenteric artery only in experiment 1): an 18-gauge needle was guided in and out of the vessel, and the capillary was pulled inside the vessel. In the jejunal wall, both the serosal (deeper layer) and the mucosal side (superficial layer) were assessed; in

the serosal approach, an 18-gauge needle was guided in visual control under the serosa and guided out from the tissue, after which the capillary was pulled into tissue. A blunt-headed metal instrument was first pushed through the jejunal wall for the mucosal approach. The tip was mounted against the mucosa, and with gentle compression against the wall, the instrument was guided inside the tissue 2.5–3 cm. The tip was then pushed out of the wall, and the microdialysis capillary was pulled inside the channel. A needle was pushed in and out the jejunal wall, and a capillary was guided inside the lumen of jejunum for the luminal approach. All of the capillaries were fixed with sutures. A gastrointestinal tonometer (Tonometrics Inc., Hopkinton, MA) was placed into the jejunum through an antimesenteric incision 80 cm distally from duodenum. The placement of the microdialysis capillaries in the jejunal wall was confirmed both macroscopically after each experiment and by histologic preparations.

Experiment 1: Lactate Clamp

After the surgical procedures, the animals were allowed to stabilize for 90 min. After the first 60 min, one 30-min baseline microdialysate lactate sample was collected from each capillary (luminal, superficial, and deeper layer of the gut wall, mesenteric vein, and mesenteric artery). A continuous intravenous infusion of sodium lactate at 4 mmol · kg^{-1} · h^{-1} was started after a priming dose of 6 mmol/kg. The infusion rate was adjusted according to whole-blood lactate measurements taken every 5 min to obtain a steady-state level for two 90-min steps with target values of 5 mM and 10 mM. Two-milliliter samples were drawn and injected immediately into 2-ml tubes (Trisodium-citrate with citric acid and NaF-EDTA, Venoject; Terumo Europe N.V., Leuven, Belgium). The whole-blood lactate was measured within 5 min from sampling (YSI 2300 Stat Plus; Yellow Springs Instruments, Inc., Yellow Springs, OH).

A second bolus of sodium lactate was given after 90 min (12 mmol/kg), and the infusion rate was increased to obtain the higher arterial whole-blood lactate level.

Experiment 2: Gut Ischemia–Reperfusion

The pigs were instrumented as in experiment 1 with the exception that the mesenteric arterial microdialysis capillary was not implanted. In addition, the superior mesenteric artery was exposed, and a mechanical occluder and ultrasound flow probe (Transonic Systems Inc., Ithaca, NY) were placed around the vessel. Superior mesenteric artery blood flow was recorded contin-

Table 1. Characteristics of the Lactate Clamp: Experiment 1

	Baseline	Lactate Clamp						*P*
Time (min)	0–30	0–30	31–60	61–90	91–120	121–150	151–180	
Lactate infusion (mmol · kg^{-1} · h^{-1})	—	3.96 (3.80–4.12)	3.47 (3.41–3.69)	3.12 (3.09–3.21)	5.82 (5.70–6.01)	5.99 (5.93–6.24)	5.74 (5.56–5.87)	
CV% of arterial whole blood lactate (%)	5.5 (2.4–15.4)	8.1 (4.7–16.5)	4.4 (2.9–8.7)	3.7 (1.4–14.7)	7.4 (2.7–22.4)	3.9 (1.9–10.7)	3.5 (2.0–14.7)	
Arterial whole blood lactate (mM)	1.05 (0.68–1.82)	4.73 (3.92–5.22)	5.22 (4.40–5.80)	5.18 (4.40–6.00)	9.65 (8.17–10.3)	10.7 (9.33–11.5)	11.2 (10.1–12.3)	
Arterial microdialysis lactate (mM)	1.20 (0.76–2.01)	4.96 (4.43–5.33)	5.60 (4.72–6.40)	5.69 (4.68–6.15)	10.2 (8.3–10.7)	10.9 (9.71–11.5)	11.6 (10.3–12.6)	
Luminal microdialysis lactate (mM)	0.10 (0.06–0.28)	0.27 (0.13–0.80)*	0.38 (0.14–1.13)	0.50 (0.15–1.18)	0.42 (0.25–1.54)	0.40 (0.32–1.39)	0.86 (0.35–2.05)	<0.0001
Gut wall lactate, superficial (mM)	1.02 (0.64–1.94)	2.44 (1.81–3.24)*	2.84 (1.90–3.73)	2.77 (1.96–4.08)	4.06 (2.56–5.63)	4.50 (2.93–6.15)	4.30 (3.36–6.83)	<0.0001
Gut wall lactate, deeper (mM)	0.81 (0.71–1.94)	2.57 (1.81–3.54)*	3.34 (2.44–3.79)	3.80 (2.36–4.21)	5.77 (3.23–6.60)	6.41 (3.64–7.11)	6.35 (4.38–6.91)	<0.0001
Mesenteric venous lactate (mM)	0.81 (0.61–1.71)	2.53 (2.28–4.19)*	3.20 (2.51–4.62)	2.98 (2.51–4.44)	4.84 (3.91–8.41)	5.30 (4.77–9.12)	5.69 (5.14–10.10)	<0.0001
Tonometric-arterial P_{CO_2} gap (mmHg)	5.4 (4.8–6.0)	9.7 (8.7–10.4)*	9.4 (7.9–9.9)	9.6 (6.8–10.7)	10.5 (8.8–11.3)	10.6 (9.1–11.5)	11.6 (9.1–10.0)	<0.0001

CV% = coefficient of variation calculated from six consecutive individual whole blood lactate concentrations.

* Statistical significance of changes within the group was tested with the Friedman test and *post hoc* analysis with the Wilcoxon test, $P < 0.05$.

uously at a frequency of 1 Hz (T101, Transonic Systems Inc.) and stored (Flowtrace, version 2.317, Transonic Systems Inc.). The average of 10 consecutive flow values was calculated to give the flow signal per 10 s. A median of six consecutive values was then calculated to give the flow signal per each minute during the experiment.

During the 90 min of stabilization, one baseline sampling of microdialysate lactate was performed over the last 30 min. After stabilization, animals were randomized into three groups: total occlusion of superior mesenteric artery (n = 6), partial occlusion of superior mesenteric artery (3 ml · kg^{-1} · min^{-1} flow; n = 6), and control (n = 6). The gut ischemia consisted of 90 min of total or partial superior mesenteric artery occlusion followed by 60 min of reperfusion. Total occlusion of the superior mesenteric artery was performed immediately after baseline samples and measurements were taken. Partial occlusion was achieved within 5 min of adjusting the flow. In the control group, the occluder was kept in place for the same period of time without occluding the superior mesenteric artery.

In both experiments, systemic and pulmonary pressures were monitored continuously (AS/3, Datex-Engström, Instrumentarium Corporation, Helsinki, Finland). Pulmonary capillary wedge pressure and cardiac output were measured every 15 min. Cardiac output was measured in duplicate by thermodilution using 10-ml injections of 0.9% saline at room temperature. The dilution curve was evaluated for each measurement, and up to 10% difference between the consecutive measurements was accepted. The hemodynamic data were stored and computer processed. Every 30 min, mean arterial pressure was calculated as the mean of three consecutive 1-min values. Each 1-min value represents the median of six measurements taken at 10-s intervals.

Jejunal mucosal P_{CO_2} was measured using saline tonometry (Tonometrics Inc.) and 30 min of equilibration. The values were corrected for the equilibration time. The P_{CO_2} of the saline sample and the corresponding arterial blood sample were measured using a clinical blood gas analyzer (ABL 520 radiometer, Copenhagen, Denmark), and the gut mucosal arterial P_{CO_2} gradient was calculated.[9,19]

Statistical Analysis

Results are expressed as median and range unless otherwise indicated. The coefficient of variation for the six consecutive arterial whole-blood lactate values at each blood lactate level was calculated to describe the stability of the clamp. Each of the two different steps of the clamp lasted 90 min. Thus, three coefficients of variation were calculated for each step.

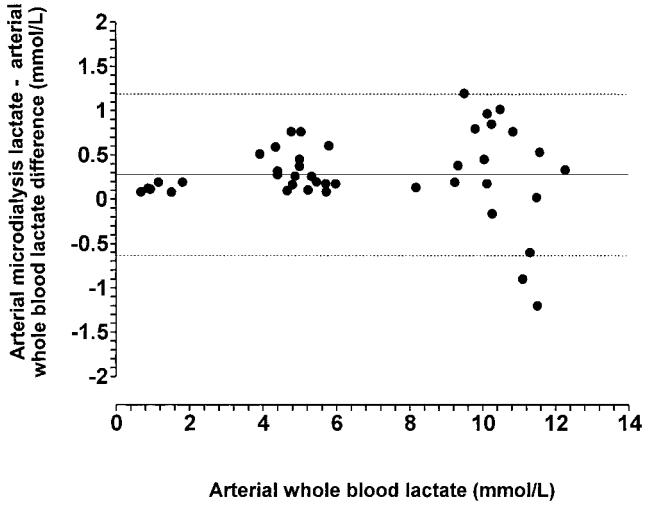

Fig. 2. Individual arterial microdialysis lactate– arterial whole-blood lactate differences *vs.* corresponding arterial whole-blood lactate at each time point. Mean difference ± 2 SD is presented as continuous and dashed lines, respectively.

The agreement between arterial microdialysate lactate and the mean arterial whole-blood lactate corresponding to the 30-min microdialysis lactate sampling period was evaluated according to Bland and Altman.[20] The mean difference of the two methods represents the bias of the microdialysis lactate measurement. The limits of agreement were calculated as ±2 SD of the difference of the two methods. The upper normal limit of the intestinal luminal microdialysis lactate was calculated as mean + 2 SD of the intestinal luminal microdialysis lactate during the baseline sampling. The upper normal limit of the arterial lactate and tonometric-arterial P_{CO_2} gradient were calculated as mean + 2 SD at baseline. The *in vitro* recovery was calculated as percentage of concentration in dialysate *versus* surrounding fluid.

The statistical analysis was performed with the SPSS PC+ software package (version 5.0; SPSS Inc., Chicago, IL). The significance of the differences within the groups was tested with nonparametric Friedman's test. Wilcoxon's signed rank test was used for *post hoc* analysis if there were statistically significant changes within the group. Comparison to baseline was repeated only until the first significant difference was noted. Bonferroni correction was used if repeated *post hoc* tests were needed. A P value < 0.05 was considered significant. Only descriptive statistics are presented for the hemodynamic data.

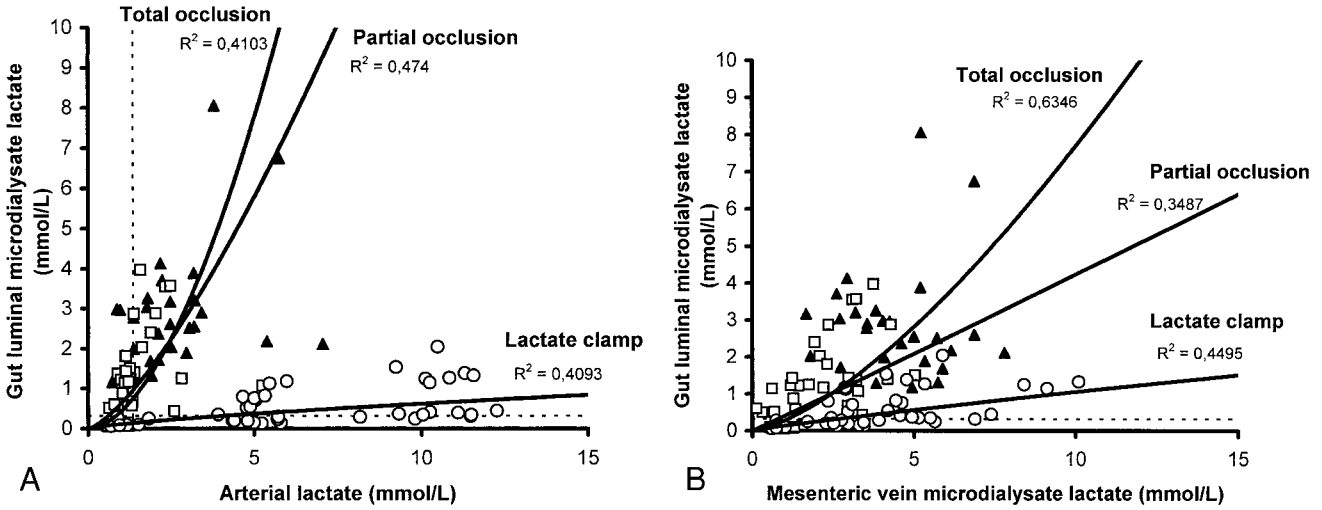

Fig. 3. Individual arterial (*A*) and mesenteric vein (*B*) lactate concentrations *vs.* intestinal luminal microdialysis lactate concentrations in nonischemic hyperlactatemia of lactate clamp (open circle) in the total (triangle) and partial (open rectangle) occlusion of the superior mesenteric artery. The horizontal dashed line indicates the upper normal limit of gut luminal lactate. The vertical dashed line shows the upper normal limit of arterial lactate. The exponential regression curve (least square method) is shown for each group.

Results

Experiment 1: Lactate Clamp

During the lactate clamp, target values were achieved and arterial lactate concentrations were stable (table 1).

High level of agreement was observed between the arterial blood microdialysate lactate and the arterial whole blood-lactate during the lactate clamp. The bias was 0.28 mM (95% limits of agreement, −0.63–1.20 mM; fig. 2). The arterial microdialysate lactate closely tracked the arterial whole-blood lactate concentration during the entire experiment, indicating high recovery (table 1). The *in vitro* recovery was 88% (range, 72–94%).

Hyperlactatemia without regional intestinal ischemia induced a small but consistent increase in the jejunal intraluminal lactate during the lactate clamp at both the

Table 2. Hemodynamics and Intestinal Tonometry of Ischemia and Reperfusion: Experiment 2

	Baseline	Ischemia	Reperfusion					*P*
Time (min)	0	30	60	90	95	120	150	
Total occlusion of SMA								
CI (ml · kg^{-1} · min^{-1})	104 (72–133)	185 (88–256)	112 (82–250)	91 (74–235)	93 (54–123)	95 (59–148)	98 (53–148)	
PCWP (mmHg)	8 (6–8)	4 (1–6)	4 (2–6)	3 (1–7)	3 (1–3)	2 (1–2)	2 (0–2)	
SAP_{mean} (mmHg)	126 (108–141)	147 (125–159)	130 (122–141)	125 (110–133)	69 (52–92)	80 (77–95)	78 (61–95)	
Q_{sma} (ml · kg^{-1} · min^{-1})	15.2 (7.3–26.7)	—	—	—	12.0 (5.7–22.8)	12.2 (8.6–34.2)	20.1 (9.1–39.7)	
d(t-a)P_{CO_2} (mmHg)	14.4 (8.4–22.4)	55.7 (38.6–74.7)*	64.1 (39.2–89.4)	90.7 (39.6–109.1)	—	52.8 (42.7–83.9)	28.7 (13.3–46.3)	0.0001
Partial occlusion of SMA								
CI (ml · kg^{-1} · min^{-1})	102 (81–158)	99 (68–203)	95 (68–193)	98 (70–165)	115 (82–153)	121 (83–131)	114 (87–132)	
PCWP (mmHg)	7 (7–8)	6 (4–7)	5 (5–7)	5 (4–6)	2 (1–5)	2 (1–3)	1 (0–3)	
SAP_{mean} (mmHg)	119 (97–130)	125 (93–129)	123 (84–130)	120 (79–129)	101 (67–119)	97 (74–121)	91 (72–114)	
Q_{sma} (ml · kg^{-1} · min^{-1})	14.5 (9.7–27.1)	3.1 (1.8–3.1)	2.7 (2.2–3.0)	2.6 (2.1–3.1)	18.1 (11.6–23.9)	17.6 (13.3–31.5)	16.4 (11.5–25.7)	
d(t-a)P_{CO_2} (mmHg)	9.7 (4.0–25.4)	40.4 (33.0–75.4)*	49.5 (20.4–88.6)	53.6 (29.1–85.4)	—	20.7 (8.8–33.0)	9.1 (4.0–20.6)	0.0001
Control								
CI (ml · kg^{-1} · min^{-1})	92 (79–163)	84 (68–122)	91 (59–124)	81 (59–125)	84 (68–127)	89 (79–127)	94 (90–113)	
PCWP (mmHg)	7 (6–7)	6 (4–7)	4 (4–7)	4 (3–5)	3 (2–4)	2 (1–4)	2 (1–3)	
SAP_{mean} (mmHg)	113 (104–129)	111 (101–126)	112 (104–125)	115 (97–123)	113 (101–123)	104 (89–123)	100 (83–122)	
Q_{sma} (ml · kg^{-1} · min^{-1})	14.2 (9.1–22.9)	13.4 (9.3–22.2)	12.1 (8.4–24.2)	11.2 (8.1–20.8)	9.1 (7.7–15.0)	11.2 (5.6–13.3)	10.8 (5.2–13.1)	
d(t-a)P_{CO_2} (mmHg)	15.1 (8.4–26.3)	12.3 (2.5–16.3)	8.5 (1.0–25.5)	9.4 (5.8–28.5)	—	11.7 (2.5–24.7)	12.6 (−1.6–22.9)	0.29

CI = cardiac index; PCWP = pulmonary artery wedge pressure; SAP_{mean} = mean arterial pressure; Q_{sma} = superior mesenteric artery flow; d(t-a)P_{CO_2} = tonometric arterial carbon dioxide gradient.

* Significance for within group changes was tested with Friedman's test with Wilcoxon test as post hoc analysis.

Table 3. Arterial Plasma and Regional Microdialysate Lactate in Gut Ischemia and Reperfusion: Experiment 2

	Baseline	Ischemia	Reperfusion				*P*
Time (min)	0	30	60	90	120	150	
Total occlusion of SMA							
Luminal microdialysis lactate (mM)	0.09 (0.06–0.17)	1.36 (1.15–2.37)*	2.09 (1.32–2.97)	2.37 (1.29–2.98)	3.80 (2.55–6.75)	3.11 (2.03–8.06)	0.0001
Gut wall lactate, superficial (mM)	1.21 (0.78–1.47)	2.20 (1.42–2.88)*	2.49 (1.65–3.45)	2.17 (1.67–3.89)	2.66 (1.51–4.44)	1.93 (1.25–3.51)	0.0011
Gut wall lactate, deeper (mM)	0.58 (0–0.87)	1.63 (1.07–2.69)*	2.44 (1.55–5.24)	2.55 (1.45–4.97)	1.99 (0.69–3.97)	1.32 (0.12–2.69)	0.0001
Mesenteric venous lactate (mM)	0.78 (0.56–1.25)	3.42 (2.72–4.94)*	5.52 (4.08–6.14)	5.64 (3.53–7.80)	4.41 (2.61–6.87)	2.95 (1.67–5.21)	0.0002
Arterial plasma lactate concentration (mM)	0.74 (0.55–1.12)	1.21 (0.71–2.11)*	2.44 (0.96–5.38)	1.66 (0.86–7.06)	2.70 (1.79–5.75)	2.85 (1.77–3.79)	0.0002
Partial occlusion of SMA							
Luminal microdialysis lactate (mM)	0.09 (0.06–0.51)	0.63 (0.09–1.37)*	1.42 (0.10–2.88)	1.66 (0.07–3.97)	1.21 (0.05–3.57)	0.97 (0.06–2.4)	0.006
Gut wall lactate, superficial (mM)	1.08 (0.99–1.26)	2.00 (1.22–2.44)*	2.49 (1.79–2.79)	2.56 (1.61–3.42)	2.14 (0.83–2.58)	1.48 (0.62–2.58)	0.0004
Gut wall lactate, deeper (mM)	0.75 (0.06–1.09)	1.38 (0.01–2.43)*	1.84 (0.09–3.02)	1.79 (0.04–2.75)	0.85 (0.01–1.66)	0.71 (0.10–1.51)	0.006
Mesenteric venous lactate (mM)	0.77 (0.56–1.55)	2.20 (0.82–3.40)*	2.55 (1.19–4.28)	2.71 (0.62–5.03)	1.98 (0.32–3.21)	1.26 (0.13–3.27)	0.027
Arterial plasma lactate concentration (mM)	0.76 (0.63–1.22)	1.15 (0.75–2.59)	1.33 (0.67–2.03)	1.20 (0.56–2.33)	1.29 (0.61–2.81)	1.09 (0.60–5.25)	0.27
Control							
Luminal microdialysis lactate (mM)	0.10 (0.03–0.16)	0.10 (0.01–0.17)	0.10 (0.02–0.22)	0.08 (0.02–0.22)	0.07 (0.02–0.24)	0.06 (0.01–0.22)	0.15
Gut wall lactate, superficial (mM)	1.00 (0.87–1.13)	0.89 (0.84–1.19)	0.88 (0.80–1.22)	0.88 (0.84–1.14)	0.91 (0.80–1.22)	0.83 (0.73–1.28)	0.30
Gut wall lactate, deeper (mM)	0.80 (0.72–0.91)	0.78 (0.59–0.85)	0.69 (0.19–0.77)	0.65 (0.45–0.79)	0.68 (0.47–1.19)	0.69 (0.44–1.04)	0.34
Mesenteric venous lactate (mM)	0.78 (0.76–1.23)	0.75 (0.65–0.99)*	0.72 (0.64–0.90)	0.66 (0.59–0.80)	0.64 (0.54–1.02)	0.60 (0.46–1.13)	0.02
Arterial plasma lactate concentration (mM)	0.69 (0.61–1.00)	0.66 (0.61–1.05)	0.66 (0.62–1.13)	0.70 (0.54–0.92)	0.67 (0.51–10.9)	0.72 (0.51–1.53)	0.79

* Statistical significance of changes within the group was tested with Friedman's test and *post hoc* analysis with Wilcoxon test, $P < 0.05$.

lower and the higher level of the clamp (table 1). The upper normal limit of luminal microdialysate lactate was 0.32 mM (figs. 3A and 3B)

Microdialysate lactate concentrations of both the deeper and superficial layer of the intestinal wall increased during the lactate clamp. Lactate concentration in both layers followed the arterial and mesenteric venous lactate levels (table 1). The tonometric-arterial P_{CO_2} gradient remained low throughout the experiment, although a statistically significant increase during lactate infusion was detected (table 1). The lactate concentration in the mesenteric vein was constantly lower than in the artery during the two steps of the clamp (table 1). Two luminal lactate values are missing because of technical problems.

Experiment 2: Gut Ischemia–Reperfusion

The onset of hypoperfusion during total and partial occlusion of superior mesenteric artery was reflected as an increase of the tonometric arterial P_{CO_2} difference (table 2). The P_{CO_2} gradient recovered during the reperfusion phase (table 2). The upper normal limit of the P_{CO_2} gradient was 26.6 mmHg. Venoarterial lactate difference over the intestinal bed increased from the baseline level of 0.10 mM (range, 0.05–0.16 mM) to 4.28 mM (range, 0.20–7.53 mM) and from 0.14 mM (range, −0.01–0.32 mM) to 1.9 mM (range, 0.39–4.90 mM) after 90 min of total and partial occlusion, respectively.

The upper normal limit of arterial lactate concentration was 1.35 mM. Arterial plasma lactate concentrations increased over the upper normal limit during the total occlusion of the superior mesenteric artery, whereas in partial occlusion of the superior mesenteric artery, only a modest increase in arterial lactate was detected (table 3). The hemodynamic pattern of the different groups is shown in table 2.

Intestinal luminal microdialysate lactate increased from low baseline levels to > 10-fold after 30 min of total occlusion of the superior mesenteric artery and > fivefold after 30 min of partial occlusion. After 30 min of ischemia, the luminal lactate concentration was higher in the total occlusion of the superior mesenteric artery than in the partial occlusion (table 3). The difference between the total and partial occlusion groups disappeared later during the ischemia, but after the release of the occlusion there was a further increase in the luminal lactate in the total-occlusion group, whereas in the partial occlusion group it decreased during reperfusion. Luminal lactate remained at stable and low levels in the control group throughout the experiment (table 3).

The pattern of luminal microdialysate lactate and tonometric-arterial P_{CO_2} gradient was different during ischemia and reperfusion in both total and partial occlusion of the superior mesenteric artery. Parallel changes were observed only during total occlusion (fig. 4).

Discussion

Intestinal luminal microdialysis has not been used previously to evaluate intestinal mucosal lactate release. The

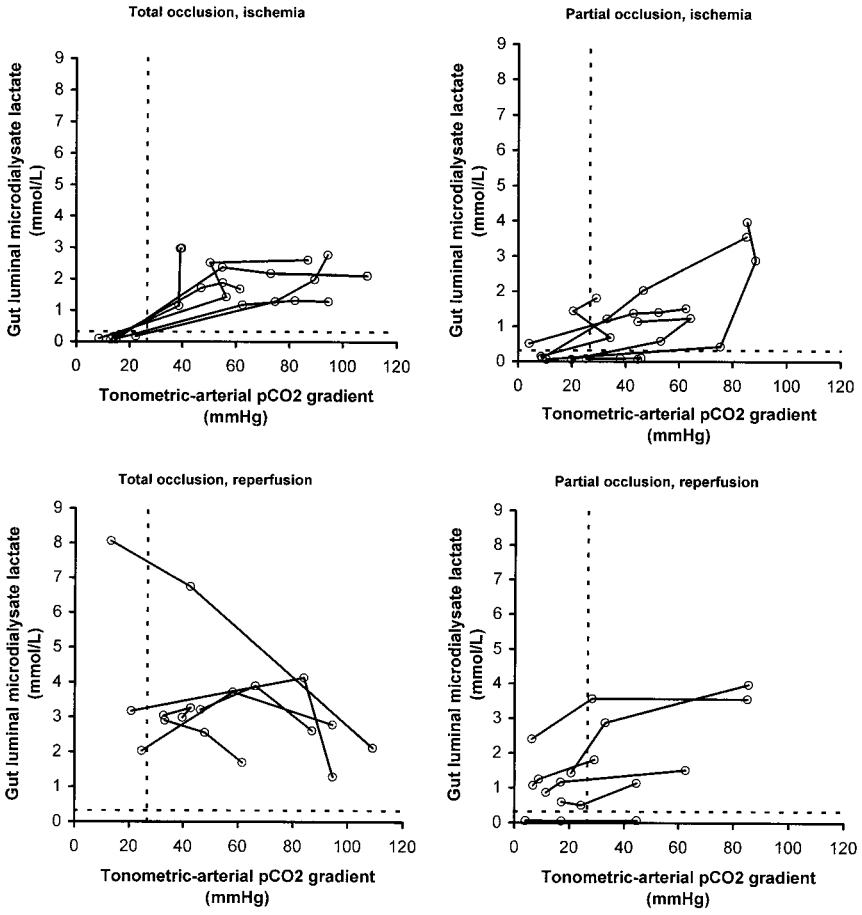

Fig. 4. The individual comparison of tonometric-arterial P_{CO_2} gradient and jejunal luminal microdialysate lactate. (*Upper*) Total (*left*) and partial (*right*) occlusion of the superior mesenteric artery at baseline with three consecutive samples during 90 min of ischemia. (*Lower*) Total (*left*) and partial (*right*) occlusion, reperfusion phase, the last ischemic sample with the two consecutive samples during 60 min of reperfusion. The upper normal limits of P_{CO_2} gradient (vertical dashed line) and luminal lactate (horizontal dashed line) are shown.

main finding of this study was the consistent early increase of intestinal luminal microdialysate lactate both in partial and total occlusion of the superior mesenteric artery. Systemic nonischemic hyperlactatemia increased intestinal luminal lactate only at very high arterial lactate levels.

The recovery rate of lactate for the microdialysis capillary we used was high as tested *in vivo* in the arterial blood stream (table 1). The apparent higher concentration of lactate in the dialysate compared with the surrounding whole blood may be because microdialysate reflects the plasma concentration rather than the concentration in the whole blood. The whole-blood lactate concentrations are lower than the corresponding plasma concentrations when measured by the L-lactate-oxidase–based method. *In vitro* recovery is less informative than the *in vivo* calibration with clamp or other methods.[21] Nevertheless, 88% of *in vitro* recovery together with the arterial clamp results indicate high yield of the capillary. The agreement with the arterial whole-blood lactate was good, although the limits of agreement were wider for the higher level of the clamp.

Intestinal lactate production may develop as a consequence of low systemic blood flow or low regional blood flow despite normal systemic hemodynamics.[22] In the clinical setting, when gut perfusion is inadequate, systemic arterial hyperlactatemia may be present. Depending on the overall hemodynamic state and liver function, systemic lactate concentration may vary widely.[23–26] In our experiment, gut luminal microdialysis revealed intestinal hypoperfusion when systemic signs of inadequate perfusion were still absent and arterial lactate levels were normal or marginally increased (figs. 3A and 3B). It may also help to evaluate the source of hyperlactatemia. Although luminal lactate increased slightly during the highest arterial blood lactate concentrations during nonischemic hyperlactatemia (fig. 3A), the increase was within the variability of the method (fig. 2). Accordingly, systemic hyperlactatemia does not confound the detection of intestinal ischemia unless very severe.

Assessment of tissue perfusion or oxygenation using tonometry may be confounded by a decrease in aerobic carbon dioxide production concomitantly with decreasing oxygen delivery to tissues, flow dependence of tissue P_{CO_2},[27,28] and the Haldane effect,[29] which all render tissue P_{CO_2} a complex parameter as a marker of tissue oxygenation. Therefore, intestinal luminal lactate measurement can provide complementary information about the metabolic state of the intestinal wall. The different patterns of jejunal tonometric-arterial P_{CO_2} gradient and jejunal luminal microdialysate lactate during both ischemia and reperfusion (fig. 4) suggest that the two variables reflect different aspects of perfusion and metabolism.

The further increase in luminal lactate during reperfusion after total occlusion of the superior mesenteric artery and sustained higher level of lactate during reperfusion in the partial-occlusion group may indicate that luminal lactate is a marker of continuing cellular dysfunction associated with reperfusion (table 3 and fig. 4). Alternatively, washout of lactate from the intestinal lumen may be slow or the breakdown of the mucosal barrier may lead to a leakage of lactate from the tissue or the venous blood.

The lactate concentrations in the luminal microdialysate cannot be directly extrapolated to absolute luminal concentrations of lactate. Nevertheless, the good recovery of lactate in the blood stream and the high concentrations of lactate observed during gut ischemia suggest a marked increase in luminal lactate during hypoperfusion. To perform quantitative luminal lactate measurements, the *in vivo* calibration described by Lönnroth *et al.*[21] should be used. Because this requires adding known concentrations of the substrate of interest to the dialysate and zero point of substrate flux extrapolation by linear regression, it is not feasible in the non–steady-state conditions such as an acute ischemia–reperfusion experiment.

Intestinal wall microdialysate and arterial blood lactate concentrations have been shown to increase during experimental endotoxemia.[30] It is possible that gut luminal lactate also increases in sepsis or endotoxemia if mucosal dysoxia appears. High levels of intestinal wall microdialysate lactate can be achieved without regional intestinal ischemia, as demonstrated in the present study. In contrast, gut luminal microdialysate lactate is not confounded by systemic hyperlactatemia without intestinal ischemia, unless severe. In addition, it offers a relatively noninvasive approach with a potential for clinical application. Hence, the applicability of the method in sepsis needs further evaluation. Luminal lactate release in experimental gut ischemia has been described previously using a segmental perfusion technique.[31] Because this requires occlusion of a segment of intestine, the method may further interfere with the local perfusion of the gut wall and is unlikely to be applicable clinically.[32] In contrast, microdialysis can be combined with gastrointestinal tonometry and provide independent additional information about perfusion when placed in the gut, *e.g.*, endoscopically.

In conclusion, gut luminal microdialysis can reveal ischemia-induced gut lactate production. The measurement of lactate from the gut lumen is not confounded by systemic hyperlactatemia, unless severe. Gut luminal microdialysis has a potential for clinical application as a method for the assessment of intestinal hypoperfusion and dysoxia.

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