Surgical Innovation
1–9

DOI: 10.1177/1553350615598620
sri.sagepub.com
SAGE

Metabolism-Guided Bowel Resection: Potential Role and Accuracy of Instant Capillary Lactates to Identify the Optimal Resection Site

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Abstract

Background. Strip-based handheld devices can measure lactatemia on capillary blood obtained by needle puncturing. We aimed to assess the kinetic of bowel capillary lactates, metabolomics profiling, and mitochondria respiratory rate in a prolonged model of bowel hypoperfusion. *Materials and Methods*. In 6 pigs, a 3- to 4-cm ischemic segment was created in 6 small bowel loops (total = 36 loops) by clamping the vascular supply, for a duration of 1 to 6 hours. Hourly, 5 blood samples were obtained by puncturing the serosa, and lactates were measured using a handheld analyzer. Samples were made at the following regions of interest (ROIs): center of the ischemic area (1), proximal and distal clinical margins of resection (2a-2b), and vascularized zones (3a-3b). Every hour, surgical biopsies of ROIs were sampled. Activity of bowel mitochondria complexes was measured after 1, 3, and 5 hours of ischemia. Quantification of metabolites was performed on all samples (total N = 180). *Results*. Capillary lactates were significantly higher at ROI 1 versus ROI 3ab at all time points. After 1 hour lactates at the margins were significantly higher than those at vascularized areas ($P = .0095$), showing a mismatch between visual assessment and actual perfusion status. From 2 to 6 hours, there was no difference in lactates between ROIs 2a-2b and 3a-3b. Maximal tissue respiration decreased significantly after 1 hour (ROI 1 vs ROI 3ab). Seven metabolites (lactate, glucose, aspartate, choline, creatine, taurine, and tyrosine) expressed significantly different evolutions between ROIs. *Conclusions*. Capillary lactates could help precisely estimate local bowel perfusion status.

Keywords

capillary lactates, metabolomics profiling, magnetic resonance spectroscopy, oxygraphic mitochondria respiratory rate, bowel hypoperfusion

Introduction

Intestinal perfusion is a crucial parameter to promote optimal digestive anastomotic healing after intestinal resections. Clinical intraoperative evaluation of bowel perfusion is based on macroscopic subjective criteria (eg, the color of the serosa), which are unreliable.[1]

Reduced oxygen supply impairs the mitochondria respiration process and triggers a cytoplasmic low-performance energy-producing process, which is the anaerobic fermentation of 6-carbon sugars. Lactate is the end product of this anaerobic energy shift. The measurement of local production of lactates could precisely inform on the perfusion status of the limited portion of bowel that will be involved in the anastomosis.

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Lactatemia can be measured on capillary blood using strip-based devices[2] within seconds. For example, the Edge lactate analyzer (ApexBio, Taipei, Taiwan, ROC) is a handheld device that measures lactatemia using test strips equipped with a specific biosensor. Only a small amount of blood (<3 μL) is required, and results are obtained in less than 45 seconds.

In previous experiments, we could demonstrate that capillary local lactates measured directly on blood obtained by needle puncturing of the intestinal serosa represent an accurate marker of intestinal perfusion status[3-5] and that pre-anastomotic lactate levels are predictive of anastomotic healing.[6]

In those experiments the level of bowel perfusion to be identified was preset by a software interface, and lactates were used to assess the accuracy of the software. We used a near-infrared fluorescence videography system integrating a proprietary software able to generate a digital cartography of the perfusion based on the fluorescence time-to-peak of the dye indocyanine green (ICG), and to overlap the digital cartography on real-time laparoscopic images. This technique, named FLER (FLuorescence-based Enhanced Reality), showed good accuracy and correlation with metabolic data and the ability to provide quantitative assessment of organ perfusion. However, FLER analysis require extensive technological resources.

Following experimental works from our anesthesiology and vascular surgery departments,[7,8] a clinical trial (ClinicalTrials.gov Identifier: NCT01634815) is currently ongoing to evaluate local capillary lactates as potential markers of recurrent ischemia in revascularized limbs.

In analogy with the application to vascular surgery, this low-price technology could well represent an easy-to-use and readily available biological marker to assist the surgeon during digestive surgery to correctly assess the anastomotic site in gastrointestinal resections.

The aim of this study was to evaluate the kinetic of instant capillary lactates, mitochondria respiratory rate, and metabolomics profiling in a controlled, prolonged model of bowel ischemia in order to validate the use of local capillary lactates as a tool to guide intestinal resection.

Materials and Methods

Animals

A total of 6 female swine (Sus scrofa domesticus, ssp. Large White), mean weight 30.2 ± 3.1 kg, were used in this nonsurvival study. There was no specific reason for sex selection, and the resultant cohort of female-only animals was due to chance. The present experimental study is part of an experimental protocol on intestinal ischemia (No. 38.2012.01.039), which received full approval by the local ethical committee on animal experimentation (ICOMETH, Registration No. 38, agreement from the French Ministry of Higher Education and Research renewed on December 30, 2013). All animals used in the experimental laboratory were managed according to French laws for animal use and care and according to the directives of the European Community Council (2010/63/EU) and the ARRIVE guidelines.[9]

Anesthesia and Animal Monitoring

Premedication was achieved by intramuscular injection of ketamine (20 mg/kg) and azaperone (2 mg/kg) (Stressnil; Janssen-Cilag, Belgium) administered 10 minutes before surgery. Induction was obtained by intravenous propofol (3 mg/kg) combined with pancuronium (0.2 mg/kg). Anesthesia was maintained with 2% isoflurane. A venous central catheter was placed in the jugular vein, and an invasive arterial line was placed in the contralateral carotid artery for continuous invasive pressure registration. Hypothermia was prevented using warming blankets. An esophageal temperature probe was also inserted.

Model of Mesenteric Ischemia

A laparotomy was performed and a short 3- to 4-cm ischemic segment was created in 6 small bowel loops in each animal (total = 36 loops) by clamping the vascular supply. Duration of clamping ranged from 1 to 6 hours. Based on the position of the clamping and on the discolored "bluish" aspect of the serosa, 5 regions of interest (ROIs) were visually identified as the ischemic zone (ROI 1), margins of resection (ROIs 2a-2b, "boundaries"), and normally vascularized (ROIs 3a-3b) zones. ROIs were marked with a surgical pen (Figure 1A-D). The ischemic area was removed "en bloc," every hour.

Arterial, Venous, and Capillary Lactates

Every hour, a blood gas analysis was performed on blood samples withdrawn from the carotid artery and the jugular vein, respectively. At the same time points, capillary lactates were measured using the EDGE analyzer, on blood drops obtained by puncturing the pig's groin (supposed to reflect systemic lactatemia) and by puncturing bowel serosa at the ROIs to measure local intestinal lactatemia (Figure 1E).

Mitochondria Respiratory Rate (pmol of Oxygen/Second/mg of Dry Weight)

After 1, 3, and 5 hours, a surgical biopsy of each intestinal ROI was sampled and immediately placed in a 2-mL water-jacketed oxygraphic cell (Oxygraph-2k OROBOROS Instruments, Innsbruck, Austria). The following activities were measured as previously described[5,10,11]:

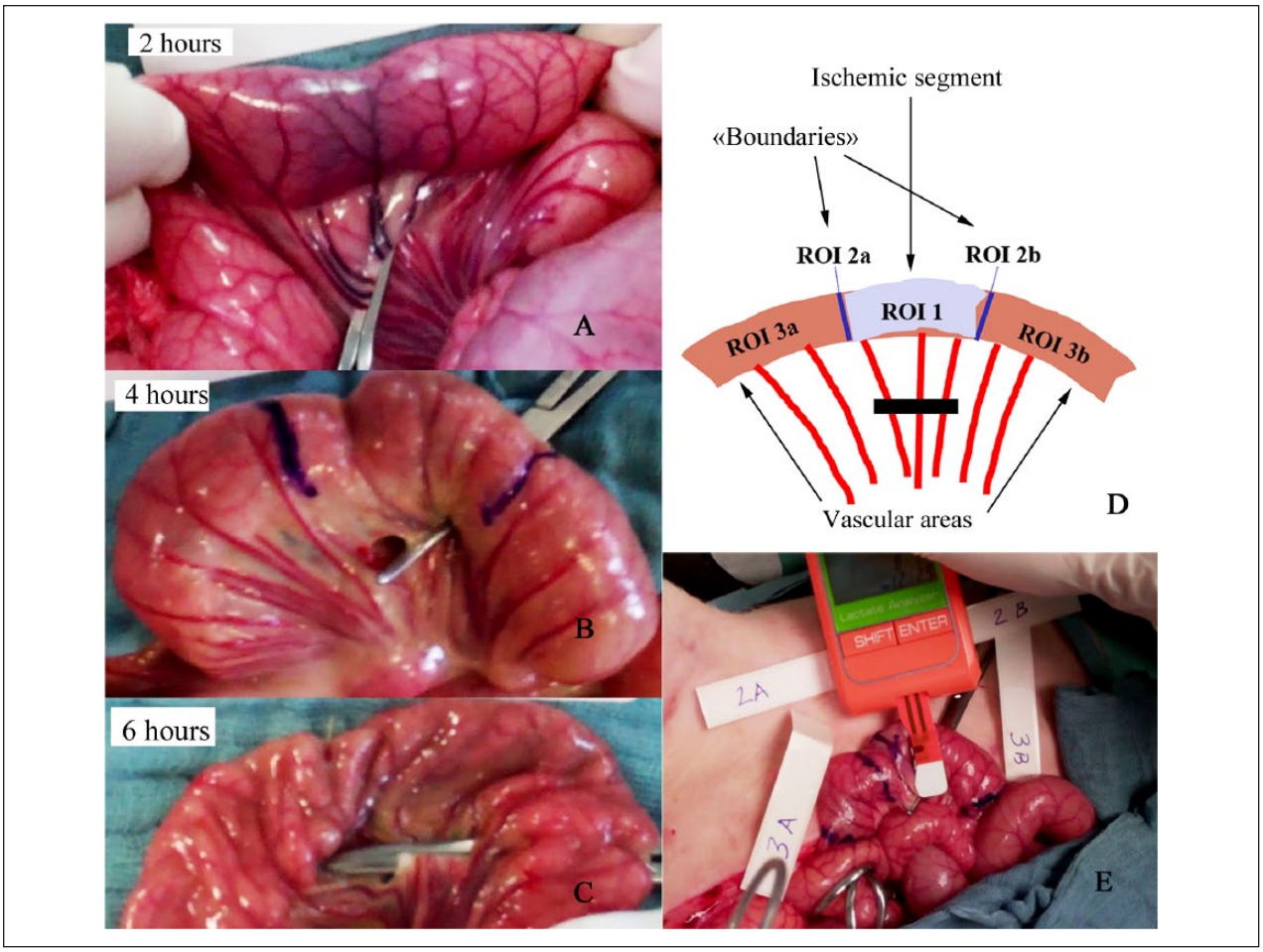

Figure 1. Schema of intestinal regions of interest (ROIs).
Visual aspect of small bowel loops after 2 hours (A), 4 hours (B), and 6 hours (C) of ischemia. Based on the discolored "bluish" aspect of the serosa, 5 ROIs were visually identified as the ischemic zone (ROI 1), margins of resection (ROIs 2a-2b, "boundaries"), and normally vascularized (ROIs 3a-3b) zones (D). Capillary lactates were analyzed using the EDGE lactate analyzer (E).

1. V_0 = basal oxygen consumption
2. V_{ADP} = tissue respiration in the presence of a saturating amount of ADP to evaluate complexes I, III, and IV of mitochondrial respiration
3. V_{MAX} = tissue respiration after stimulation of complex II with succinate, to evaluate complexes I, II, III, and IV
4. V_{AMYTAL} = tissue respiration after complex I is blocked with Amytal, to evaluate complexes II, III, and IV
5. V_{TMPD} = tissue respiration after addition of artificial electron donors to cytochrome c oxidase (complex IV)

Metabolomics Profiling of Ischemia Using High-Resolution Magic Angle Spinning (HRMAS) Nuclear Magnetic Resonance (NMR) Spectroscopy (nmol/mg of Tissue)

Every hour, a piece of the surgical biopsy taken at the different intestinal ROIs was placed in an Eppendorf tube and immediately snap frozen in liquid nitrogen. Subsequently, biopsies were placed into a disposable 30-mL Kelf insert in the presence of 10 mL of D_2O and stored at −80°C until the HRMAS analysis was performed. HRMAS spectra were recorded on a spectrometer (Bruker Advance III 500) equipped with a 4-mm double resonance (^1H, ^{13}C) gradient HRMAS probe as previously reported.[5,12]

Pathology

Every hour, full-thickness bowel biopsies were sampled at the ischemic area and at a control site (vascular areas 3a and 3b alternatively) and placed in 4% buffered formalin for at least 24 hours. Sections (4-µm thick) were cut from paraffin-embedded tissues and stained with hematoxylin and eosin. Six sections per biopsy were analyzed. A standardized semi-quantitative histology score to evaluate ischemia was applied by a blinded pathologist to normal and ischemic

areas. The score was composed as follows: 0 = normal mucosa; 1 = partial epithelial edema and necrosis; 2 = diffuse swelling and necrosis of epithelium; 3 = necrosis with submucosal neutrophil infiltration; 4 = widespread necrosis and massive neutrophil infiltration and hemorrhage.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 6. Bias and agreements between systemic capillary and arterial lactates were assessed using the Bland–Altman method. Pearson's parametric correlation coefficients were also calculated. One-way ANOVA followed by Dunnett's multiple comparison tests were used to calculate *P* values for continuous variables at the different zones of the bowel.

Results

Hemodynamic and body temperature remained stable over the 6-hour experimental procedure time. Subjectively, there was a progressive "recoloring" of the bowel serosa during the progression of ischemia (Figure 1A-C).

Systemic Arterial and Capillary Lactates (mmol/L)

Pearson's *R* correlation between systemic arterial and systemic groin capillary lactates per all time points was 0.9. Rho coefficients between systemic arterial and local capillary lactates were 0.87 (ROI 3a), 0.85 (ROI 3b), 0.75 (ROI 2a), 0.79 (ROI 2b), and 0.53 (ROI 1). The Bland–Altman method showed a good agreement with low bias (difference between the means) for arterial and groin capillary lactates and for arterial and vascularized intestinal areas. High biases were found between arterial and capillary lactates at the ischemic area (Figure 2). Mean capillary lactates (mmol/L) were significantly higher at the ischemic zone (ROI 1) than at the clinically identified margins of resection (ROIs 2ab) at all time points but after 5 hours of ischemia, and higher than at the vascularized zones (ROIs 3ab) at all time points. Mean capillary lactates were statistically significantly higher at the clinically identified margins of resection (ROI 2ab) when compared with ROIs 3ab after 1 hour of ischemia (P = .0095). At longer ischemia times, there was no statistically significant difference (Table 1).

Mitochondria Respiratory Rate (pmol of Oxygen/Second/mg of Dry Weight)

Mean maximal tissue respiration rate (V_{MAX}) was statistically significantly reduced after 1 hour of ischemia when compared to the control area (P = .03). At a longer duration, the difference was not significant. Mean V_{ADP} was significantly decreased after 3 hours of ischemia when compared to viable margins (P = .01) but improved after 5 hours at the ischemic zone. Mean V_{TMPD} was progressively reduced with increased ischemia time without reaching statistical significance at any time point (Figure 3 and Table 2).

HRMAS NMR Spectroscopy (nmol/mg of Tissue)

A total of 25 metabolites could be quantified in small bowel biopsies (lactate, glucose, acetate, alanine, ascorbate, asparagine, aspartate, free choline, creatine, ethanolamine, glutamine, glutamate, reduced glutathione, glycerophosphocholine, glycine, lysine, myo-inositol, phenylalanine, phosphocholine, syllo-inositol, taurine, tyrosine, valine, isoleucine, total choline; Figure 4). At some point, 7 metabolites (lactate, glucose, aspartate, free choline, creatine, taurine, and tyrosine) expressed a statistically significant different values between the ischemic area (ROI 1) and vascular areas (ROI 3ab). Pearson's R correlation between capillary lactates and HRMAS lactates per all time points (n = 180 replicates) was 0.69.

Pathology

Mean ischemia score was invariably zero at control areas at all time points. At the ischemic area, tissue damage was mild and the score presented no statistically significant differences over time at the ANOVA analysis. Minimum score was observed after 4 hours of ischemia (0.5 ± 0.8) while a maximum score was observed after 5 hours (1.33 ± 0.8).

Discussion

Oxygen debt leads to a local rapid accumulation of lactate in ischemic tissues and, more slowly, in the systemic circulation. A simple tool to obtain an intraoperative cartography of bowel perfusion is the measurement of local capillary lactates using strip-based technology.

In the present model, systemic lactates (arterial measured on blood sampled at the femoral artery and capillary lactates measured at the pig's groin) showed a high agreement and were both comparable to local capillary lactates at boundaries (2a-2b) and to those at vascularized areas (3a-3b) per all time points. A low agreement was found with ischemic bowel areas, reflecting that systemic lactatemia is unreliable to identify bowel hypoperfusion, at least when a small portion of the bowel is ischemic. Capillary lactates at the ischemic zone did not display a time-dependent increase, and for this reason one could conclude that local lactates are not a good chronological marker of ischemia. However, per any time point,

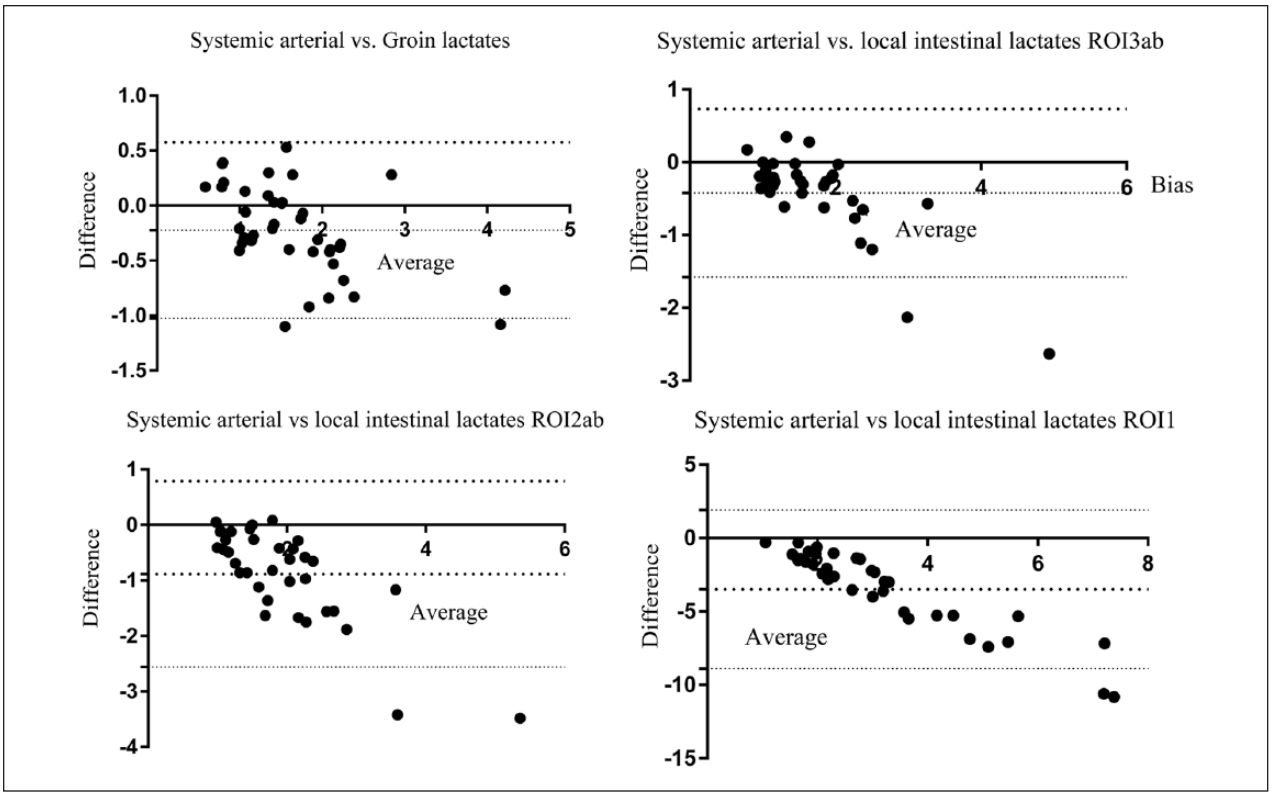

Figure 2. Bland–Altman difference versus average of arterial versus capillary lactates.
The Bland–Altman bias between systemic and capillary lactates was −0.22 (SD 0.4), −0.42 (SD 0.58), −0.88 (SD 0.85), and −3.5 (SD 2.75) for groin, vascular areas (region of interest [ROI] 3ab), boundaries (ROI 2ab), and ischemic area (ROI 1), respectively. Upper and lower 95% limits of agreement with arterial lactates ranged from −1.02 to 0.57 (groin), from −1.58 to 0.73 (ROI 3ab), from −2.55 to 0.79 (ROI 2ab), and from −8.9 to 1.9 (ROI 1).

Table 1. Local Capillary Lactates.

Ischemia Time	ROI 1 (Ischemic Zone)	ROI 2a/2b (Resection Lines)	*P* Value[a] (1 vs 2a/2b)	ROI 3a/3b (Vascular Zones)	*P* Value[a] (1 vs 3a/3b)	*P* Value[a] (2a/2b vs 3a/3b)
1 hour	4.75 ± 2.54	2.38 ± 0.74	**.007**	1.67 ± 0.45	**.0007**	**.0095**
2 hours	7.68 ± 4.16	3.14 ± 1.59	**.003**	2.34 ± 0.78	**.0004**	.13
3 hours	4.5 ± 2.11	2.02 ± 0.56	**.0012**	1.85 ± 0.62	**.0008**	.48
4 hours	4.08 ± 2.85	2.24 ± 0.82	**.04**	1.87 ± 1.13	**.029**	.36
5 hours	4.75 ± 3.21	2.32 ± 2.27	.08	2.09 ± 2.04	**.04**	.79
6 hours	3.82 ± 2.24	2.10 ± 1.17	**.045**	1.74 ± 1.02	**.014**	.43

Abbreviation: ROI, region of interest.
[a]$P < .05$ was considered statistically significant.

capillary lactates allowed to build a clear cartography of bowel perfusion per all time points (except after 5 hours of ischemia). More interestingly, after 1 hour ischemia, lactates at the clinically identified resection line were still significantly higher than those at the vascular zone, demonstrating a mismatch between the visual appreciation and the real metabolic status of the bowel.

Lactate clearance is a sign of improved O_2 supply since the lactate pool can be mobilized as substrate for oxidative energy production and glucose synthesis in the presence of O_2. We surmised that the apparent improved perfusion at the ischemic area, which occurred particularly between 2 hours and 6 hours of ischemia, was probably due to a problem with the model itself. More specifically, the phenomenon could be explained by the limited length of the ischemic segment and by the presence of an overlapping vascular network on the serosa, which might have favored reperfusion starting from the second hour of ischemia. The second potential explanation could be the occurrence of some ischemic preconditioning. This could have occurred

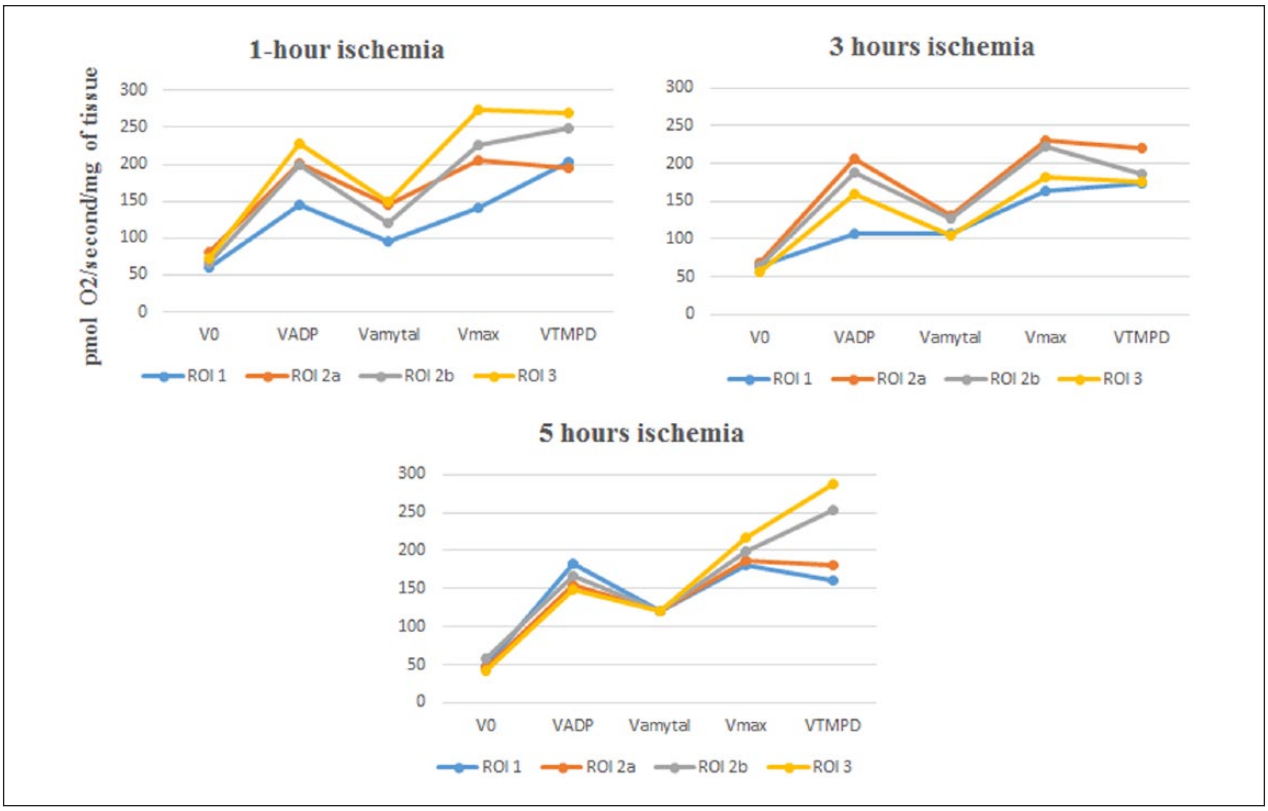

Figure 3. Changes over time in mitochondria respiratory rate.
The figure shows the sequencing of mitochondria respiration rates (V_0, V_{ADP}, V_{AMYTAL}, V_{MAX}, V_{TMPD}) in the ischemic zone (region of interest [ROI] 1), in boundaries (ROI 2a-2b), and in the vascularized control area (ROI 3). Activated complexes: V_0 (I); V_{ADP} (I, III, IV); V_{AMYTAL} (II, III, IV); V_{MAX} (I, II, III, IV); V_{TMPD} (IV). Required substrate: V_0 (glutamate, malate); V_{ADP} (adenosine-diphosphate); V_{AMYTAL} (amytal, inhibitor of complex I); V_{MAX} (succinate, stimulator of complex II); V_{TMPD} (tetramethyl-*p*-phenylenediamine dihydrochloride and ascorbate, electron donors for complex IV, cytochrome C oxidase).

Table 2. Mitochondria Respiratory Rate.

Ischemia Time	Respiration Rate	ROI 1 (Ischemic Zone)	ROI 2a/2b (Boundaries)	*P* Value[a] (1 vs 2a/2b)	ROI 3 (Control)	*P* Value[a] (1 vs Control)
1 hour	V_0	60.38 ± 28.81	73.23 ± 34.51	.44	73.15 ± 39.24	.53
	V_{ADP}	144.51 ± 45.71	200.19 ± 90.46	.17	228.44 ± 89.83	.06
	V_{AMYTAL}	94.79 ± 35.37	132.52 ± 57.72	.16	150.33 ± 51.77	.055
	V_{MAX}	141.57 ± 52.48	215.92 ± 105.48	.12	273.12 ± 116.68	**.03**
	V_{TMPD}	203.2 ± 60.62	221.33 ± 121.64	.73	270.45 ± 156.37	.34
3 hours	V_0	63.85 ± 44.81	67.2 ± 26.18	.84	55.36 ± 18.96	.67
	V_{ADP}	106.88 ± 54.69	196.99 ± 70.29	**.01**	159.42 ± 46.35	.14
	V_{AMYTAL}	107.4 ± 54.76	128.75 ± 37.73	.34	104.55 ± 32.44	.91
	V_{MAX}	163.83 ± 108.13	226.36 ± 75	.16	182.42 ± 46.38	.7
	V_{TMPD}	172.74 ± 84.83	202.68 ± 58.85	.39	175.46 ± 34.73	.94
5 hours	V_0	48.8 ± 28.09	52.22 ± 27.34	.8	42.79 ± 23.39	.69
	V_{ADP}	183.15 ± 82.88	160.65 ± 60.14	.51	149.09 ± 34.53	.37
	V_{AMYTAL}	119.62 ± 58.23	120.58 ± 5.17	.97	119.58 ± 50.35	.99
	V_{MAX}	181.11 ± 99.57	192.87 ± 78.67	.78	216.78 ± 128.34	.78
	V_{TMPD}	160.1 ± 61.22	216.85 ± 116.41	.28	287.39 ± 168.17	.11

Abbreviation: ROI, region of interest.
[a]$P < .05$ was considered as statistically significant.

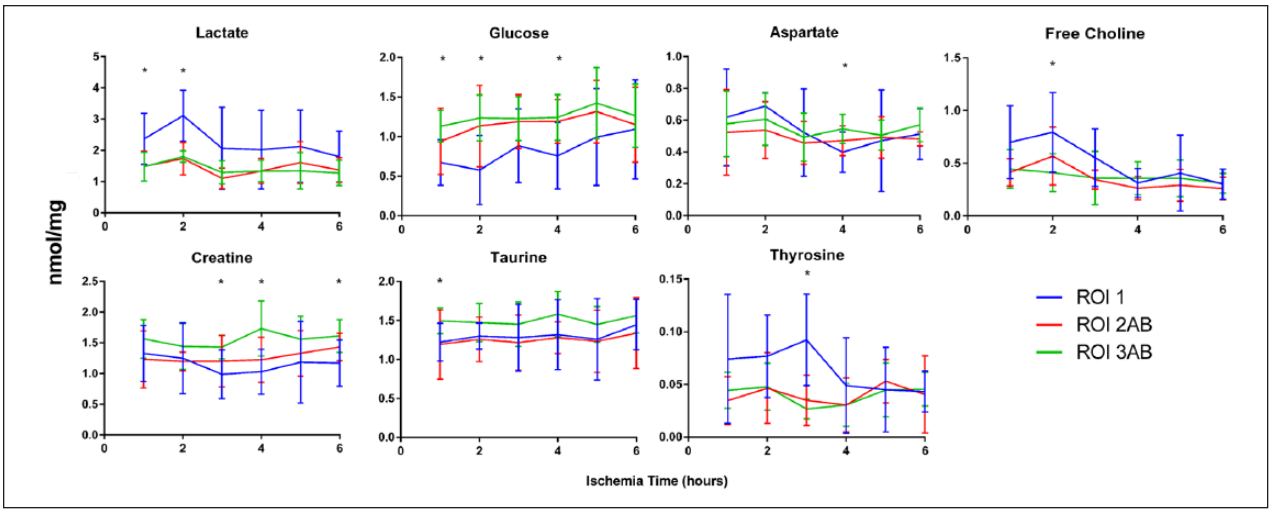

Figure 4. High-resolution magic angle spin nuclear magnetic resonance spectroscopy (nmol/mg of tissue): significant metabolites. Lactate, glucose, aspartate, free choline, creatine, taurine, and tyrosine, expressed at some point statistically significant different values between the ischemic area (region of interest [ROI] 1) and vascular areas (ROI 3ab) at the ANOVA analysis. $P < .05$ was considered statistically significant.

because 6 small bowel loops were simultaneously made ischemic and evaluated subsequently at a 1-hour interval. Although great care was taken to reduce the risk of any reperfusion by removing the ischemic area "en bloc" every hour, some systemic signaling might have induced preconditioning.

In a porcine model of free small bowel flaps, Birke-Sorensen and Andersen used a microdialysis catheter to monitor local lactate and glucose. They could identify an accurate cutoff of the lactate/glucose ratio to discriminate between ischemic and nonischemic segments.[13]

In a 1-hour ischemia experiment, using magnetic resonance spectroscopy to assess the metabolic profile, we also found significantly decreased glucose levels and increased tissue lactate and amino acids, demonstrating a shift toward anaerobic glycolysis.[5] In the present long-lasting model, the lactate/glucose ratio at tissue level remained constant in the ischemic area over time, with an increase in mean glucose levels after 6 hours of ischemia. This increased glucose production is compatible with the occurrence of reperfusion.

On the other hand, Abrahão et al[14] evaluated ischemia-reperfusion injury in a rat small bowel modulated by ischemic preconditioning. The authors found that lactate values were significantly lower in the group receiving 20 minutes of ischemic preconditioning irrespective of morphological aspect of mucosal damage. Pathology evaluation did not show any significant time-dependent progression of mucosal damage. We also found a very mild mucosal damage even after 6 hours of ischemia.

Additional evidence toward the hypothesis of local reperfusion of the ischemic bowel, which occurred in this model, stems from the oxygraphic assessment of the mitochondria respiratory rate. This technique allows for the dynamic assessment of the functional status of mitochondria by measuring the activity of various oxidative phosphorylation enzymatic complexes. Oxidative phosphorylation starts with a series of redox reactions (electron transport chain) in which electrons are transferred to the oxygen, which is the most electronegative acceptor. These reactions generate the energy necessary to actively pump H+ protons in the intermembrane space and create an electrochemical transmembrane gradient, which is used to produce adenosine triphosphate (ATP). There are 3 enzymatic proton pumps: complexes I, III, and IV. While severe impairment of complex IV (cytochrome C oxidase) leads to irreversible lesions, ischemia-induced dysfunction of complexes I and III can be readily reversible during the reperfusion phase.

Ischemia, by reducing the presence of O_2 as terminal electron acceptor, impairs the activity of those complexes, with progressive reduction of the gradient, energy depletion, and ultimately necrosis.

After 1 hour of ischemia, we found a significant respiratory chain impairment in the ischemic zone as compared to the nonischemic segments as expressed by reduced V_{MAX} (1 hour). However, while a relative decrease of basal respiration (V_0) occurred, V_{MAX} remained constant over time, witnessing a preserved function of complex IV activity as well as the absence of decoupling between oxidation and phosphorylation (OXPHOS), which is an additional marker of occurred reperfusion. Decoupling can be calculated with the acceptor control ratio ($ACR = V_{MAX}/V_0$),[15] which was not modified in this model.

The potential protective effect of multiple ischemic loops could have played the same role on mitochondrial respiration as stressed for lactate/glucose ratio, since ischemic preconditioning has been shown to specifically restore activities of complexes I and II in ischemic skeletal muscle by our group.[16]

To provide insights in order to better understand what happened in this short segment ischemia model, we performed a metabolomics analysis of small bowel full-thickness biopsies, using nuclear magnetic resonance spectroscopy (NMRS). This is a powerful research tool, which provides a quantitative snapshot of the tissue metabolism in a given condition.[17]

In a rat model of intestinal ischemia/reperfusion by mesenteric artery or portal vein occlusion, Vincenti et al performed NMRS quantification of intestinal metabolic impairment in both conditions.[18] The authors found that portal vein occlusion leads to more severe metabolic changes in terms of accumulation of lactates, amino acids, and fatty acids, and decrease of glucose, while a more intense oxidative stress is observed in arterial occlusion, with reduction of reduced glutathione.

In our experiment, among the 25 metabolites that could be identified, only 7 (lactate, glucose, aspartate, free choline, creatine, taurine, and tyrosine) expressed some statistically significant differences during the evolution of the hypoperfusion. Critical metabolites involved in oxidative stress, such as reduced glutathione, although lower in the ROI 1 when compared to vascular areas, showed no statistically significant differences.

Aspartate is a nonessential amino acid that participates in gluconeogenesis. In this model, aspartate presented a bimodal evolution in the ischemic area when compared to vascular areas (increased after 2 hours, significantly decreased after 4 hours to increase again after 6 hours). This evolution might correlate with a modification in gluconeogenesis during the alternate anaerobic/aerobic metabolic phases that occurred in the model.

Choline is an essential component of cell membranes.[19] The significant peak of choline levels observed after 2 hours in the ischemic area when compared to controls could well correlate with the most intense period of cellular turnover with a higher release of membrane components in response to the hypoxic injury. This phenomenon was probably slowed down once functional recovery occurred.

Creatine metabolism plays a crucial role in intestinal mucosal homeostasis and adaptive response to stress factors such as hypoxia.[20] In our model, creatine constantly expressed lower values at the ischemic area reaching statistically significant difference after 3, 4, and 6 hours of ischemia.

Taurine has an antioxidant activity, which protects mitochondria from excessive superoxide production (radical of oxygen mediated damage) by stimulating the electron transport chain.[21] Taurine was significantly decreased after 1 hour in the ischemic region when compared to perfused areas, and remained lower over time, but without reaching statistically significant differences from 2 to 6 hours. Conversely, tyrosine, which also expresses antioxidant activities,[22] but more specifically against reactive nitrogen intermediates damage,[23] was significantly higher in the ischemic zone and decreased over time.

What must be remembered concerning this highly controlled study is the following: (*a*) that the measurement of local capillary lactates using strip-based low-cost technology can very accurately build a metabolic cartography of the bowel in almost real time and (*b*) that there was a concordance between kinetics of capillary lactates, mitochondria respiratory rate, and metabolomics profiling of ischemia, witnessing the robustness of the experimental model. The ability to precisely discriminate well-perfused areas using capillary lactates was preserved during the progression of ischemia per all time points. To obtain capillary blood samples in the laparoscopic setting, we have used in previous experiments a motorized sterile pipette[10] introduced through one of the laparoscopic ports. Capillary blood is aspirated from the bowel and then transferred on the strip of the lactate analyzer. A clinical trial will be promoted soon at the University Hospital of Strasbourg to evaluate the accuracy of indocyanine green fluorescence and capillary lactates in identifying the optimal resection site in laparoscopic colorectal resections. More generally, the indications for the use of capillary lactates in gastrointestinal surgery are all those requiring some resection (eg, sleeve gastrectomy) or resection-anastomosis (eg, colorectal surgery). The barrier for clinical adoption today is mainly the absence of any data on patients (except the trial performed currently at the University of Strasbourg on limb perfusion after vascular surgery). Capillary lactates have been largely used by athletes to self-monitor their pre and post effort levels. In medicine, the largest use of real-time lactate assessment is done in obstetrics (scalp or umbilical cord lactates) to exclude an acidotic status of the baby. The cost is 2 Euros (approximately US$2.5) per strip, and the time to obtain results is 45 seconds, which means a mild impact on global costs. Should the serial lactate measure be of clinical impact in reducing the rate of anastomotic leakage, this simple technology will certainly gain popularity.

Conclusions

Intraoperative measurement of capillary lactates is accurate to identify optimal resection margins and future anastomotic sites in digestive resections. Oxygraphic evaluation of mitochondria respiratory rate and evolution of the metabolomics profiling over time showed concordant kinetics in this experimental model. The next step is the translation to the clinical setting of this simple technology to evaluate the potential impact to establish the optimal resection site in digestive resections.

Acknowledgments

The authors are grateful to Christopher Burel and Guy Temporal, professionals in medical English editing, employees of IRCAD-IHU, for their valuable help with the proofreading of the manuscript.

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Study supervision: Pierre Diemunsch, Izzie-Jacques Namer, Bernard Geny, Jacques Marescaux

Authors' Note

Part of the data of this study were presented at the International Anesthesia Research Society Annual Meeting in San Diego, CA, on May 4-7, 2013.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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