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Intraperitoneal Microdialysis as a Monitoring Method in the Intensive Care Unit

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Studies on surgical patients provide some evidence of prompt detection of enteric ischemia with microdialysis. The purpose of the study was to measure intraperitoneal microdialysis values (glucose, glycerol, pyruvate, and lactate) in patients hospitalized in an intensive care unit (ICU) with an underlying abdominal surgical condition and to correlate these values with patients' outcomes. Twenty-one patients, 10 female, were enrolled in the study. The intraperitoneal metabolite values were measured for 3 consecutive days, starting from the first day of ICU hospitalization. Descriptive and inferential statistics were performed. The t-test, repeated measures analysis, Holm's test, and a logistic regression model were applied. Level of statistical significance was set at $P = 0.05$. Mean age of participants was 68.10 ± 8.02 years old. Survivors exhibited statistically significantly higher glucose values on day 3 (6.61 ± 2.01 against 3.67 ± 1.62; $P = 0.002$). Mean lactate/ pyruvate (L/P) values were above 20 (35.35 ± 27.11). All non-survivors had a mean three day L/P values greater than 25.94. Low L/P values were related to increased survival possibilities. High microdialysis glucose concentration, high L/P ratio and low glucose concentration were the major findings during the first three ICU hospitalization days in non-survivors. Intraperitoneal microdialysis may serve as a useful tool in understanding enteric ischemia pathophysiology.

Key words: Microdialysis – Peritoneum – Ischemia – Surgery – Outcome

Microdialysis is a novel technique enabling the study of the biochemistry of extracellular space in living tissue. It is used *in vivo* to determine concentration of endogenous substances and drugs

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in humans. The microdialysis technique entails the insertion of a small catheter (also referred to as microdialysis probe) into the tissue. The microdialysis probe is a double lumen, concentric catheter that is perfused with an aqueous solution. The tip of the probe contains a semipermeable membrane. Small solutes from the extracellular compartment can cross this membrane. After a period of equilibration, the solution, dialysate leaving the probe, is collected. A special analyst then measures the concentration of certain solutes. In this study the tissue of interest was the peritoneal cavity. The substances studied—glucose, glycerol, lactate, and pyruvate[1–3]—are related to cell metabolism and integrity.

Microdialysis is used in abdominal surgery to predict early ischemia that renders the gastrointestinal tract a source of bacteria, endotoxins, free radicals, and inflammatory agents with detrimental effects to health. Lactate and pyruvate and their ratio (lactate / pyruvate, L/P) is of particular interest.[3–5]

Lactate is increased in cases of increased physical stress (*i.e.*, in cases of severe sepsis, cardiogenic shock, etc.) with severe effects to mesenteric circulation and gastrointestinal tract perfusion. Lactate is also increased in cases of localized digestive system and peritoneal cavity physical stress, such as bacterial peritonitis or local ischemia. In other words, either global or local bowel ischemia promotes the generation of lactate. Regardless of the cause, lactate behaves similarly in both the intestinal tract and the peritoneal cavity.[5–7]

In anaerobic conditions, energy is produced when pyruvic acid is reduced to lactic acid mediated by lactic dehydrogenase. Therefore, the L/P (lactate-to-pyruvate) ratio serves as an indirect index of the balance between aerobic and anaerobic metabolism. During ischemia, lactate concentration normally increases and pyruvate concentration normally decreases or, alternatively, there is a disproportionate increase of lactate in relation to pyruvate, which is metabolized into lactate, due to the delayed activation of oxidative phosphorylation. This results in an increase in the L/P ratio and a decrease in the consumed glucose concentration. During a serious inflammation, there is also a high lactate concentration, due to hypermetabolism. Intraperitoneal microdialysis offers a unique way of diagnosing local ischemia and/or inflammation, two conditions essential in surgical patient outcome prognosis.[7,8]

High glycerol levels have been reported in inducible ischemia models in guinea pigs. Glycerol is a component of the cell membrane. In anaerobic conditions, phospholipase is activated and glycerol is released into the surrounding environment, and the increased levels indicate cellular destruction.[9,10]

The purpose of this study was to measure intraperitoneal microdialysis values (glucose, glycerol, pyruvate, and lactate) in patients hospitalized in ICU with an underlying abdominal surgical condition and to correlate these values with patients' outcomes.

Materials and Methods

The sample study comprised 21 patients (11 males) with a variety of underlying diseases, all being related to abdominal surgery. These patients were admitted to ICU during a 3-year period and their closest relative or the patients gave informed consent to study participation. Anonymity was a prerequisite. Thirteen patients had undergone surgery before or during ICU hospitalization. The case mix of patients is a mixture of acute and programmed admissions. The acute admissions are comprised of patients with acute abdomen and severe deterioration of homeostasis. The programmed admissions refer to patients that had major abdominal surgery and also had significant comorbidities.

Metabolites values were measured for three consecutive days, the first being the admission day. The first 2 measurements were discarded in order to exclude false measurements because of catheter insertion technique. A thin peritoneal catheter was inserted in the abdominal cavity of all participants. Samples were collected at 4-hours intervals. Lactate, pyruvate, glucose, and glycerol were measured. Each patient was equipped with a catheter for microdialysis (CMA 70 Brain Microdialysis Catheter, 10 mm membrane length, 20 kDa cut off, CMA, Stockholm, Sweden), bearing a gold tip, for CT scan. The duration of peritoneal monitoring for study purpose was continued for 3 days.

The CMA 600 analyzer (Harvard Apparatus, M Dialysis AB, Sweden) was used for photometric sample analysis (LABpilot TM Software). The CMA 62 microdialysis catheter was used for peritoneal study. The one tip was connected to an effusion pump (CMA 107) and the other to a collection chamber. Microdialysis solution features were as follows: Na 147 mmol/L, K 4 mmol/L, Ca 2.3

Table 1 Underlying disease and outcome

	Outcome		
	Survival	Death	Total
Colectomy	6	4	10
Acute pancreatitis	2	2	4
Gastric hemorrhage	1	0	1
Acute abdomen	1	0	1
Multi-injured/Liver rupture	0	1	1
Ileus	2	2	4
LR = 0.531	12	9	21

mmol/L, Cl 1.56 mmol/L, ph 6.0, osmolarity 290 mOsm/kg. Microdialysis values are all expressed in mmol/L.

Statistics

Descriptive and inferential statistics were performed. Normality was explored with Shapiro–Wilk test. Likelihood ratio and Fisher's exact test were applied for nominal variables as appropriate and t-test for quantitative ones. A logistic regression model was also applied for outcome prognosis. Statistical significance was set at $P = 0.05$. Statistics were processed with SPSS 17.0 (SPSS Statistics for Windows, SPSS Inc, Chicago, IL).

Results

Thirteen patients had undergone surgery. Mean patient age was 68.10 ± 8.02 years. Nine patients died. Mean age of deceased patients was 69.66 ± 6.57 years versus 66.5 ± 8.45 of survivors (difference not statistically significant). Regarding simplified acute physiology score (SAPS), survivors had statistically significantly lower score than deceased 42.58 ± 14.13 versus 64.22 ± 16.29 ($P = 0.004$).

No statistically significant difference was observed based on underlying disease (Table 1).

Survivors had greater lactate (mean: 3 days value) values than deceased 41.98 ± 29.84 versus 21.25 ± 5.92, P = 0.07 (Table 2), while third day glucose was significantly different between the two groups: 6.61 ± 2.01 versus 3.67 ± 1.62 respectively (Table 3).

All survivors had a mean 3-day L/P ratio over 25.94 compared with deceased group (difference statistically significant at $P = 0.006$; Table 4).

When a logistic regression model adjusted for age was applied with outcome as the dependent variable and third glucose and L/P ratio as independent variables, lower L/P values were related to increased survival probability by 59% (1/0.628; Table 5).

Table 2 Metabolic marker values in relation with outcome and days of hospitalization

	Outcome	*N*	Mean value	*SD*	*P*
Glucose - first day	Survivors	12	5.3606	1.19624	0.454
	Deceased	9	4.8674	1.76651	
Glucose - third day	Survivors	12	6.6178	2.01749	0.002
	Deceased	9	3.6778	1.62771	
Lactate - first day	Survivors	12	4.4456	1.79419	0.100
	Deceased	9	9.3985	9.77735	
Lactate - third day	Survivors	12	11.7933	19.89394	0.633
	Deceased	9	13.0089	14.15575	
Pyruvate - first day	Survivors	12	208.3944	70.38514	0.111
	Deceased	9	275.6593	101.62642	
Pyruvate - third day	Survivors	12	207.5000	78.23682	0.293
	Deceased	9	263.8889	157.41303	
Glycerol - first day	Survivors	12	106.0556	48.45467	0.619
	Deceased	9	120.9630	86.02332	
Glycerol - third day	Survivors	12	104.0192	42.61271	0.430
	Deceased	9	163.5641	253.06335	
L/P 1 day	Survivors	12	22.2057	6.69008	0.177
	Deceased	9	29.7840	17.18618	
L/P 3 day	Survivors	12	47.0647	66.67089	0.838
	Deceased	9	52.8867	59.04737	
t-test					

Discussion

Microdialysis was used to explore changes in biochemical parameters related to peritoneal cell energy balance and peritoneal cell viability. A high concentration of glycerol, a high L/P ratio, and low concentration of glucose were the main findings during the first days of hospitalization in the patients who finally died. Those patients had higher intraperitoneal glycerol concentration than survi-

*Table 3 Metabolic markers values the first 3 days of ICU hospitalization**

	Outcome	*N*	Mean value	*SD*	*P*
Lactate	Survivors	12	8.54	7.77	0.588
	Deceased	9	10.58	9.09	
Pyruvate	Survivors	12	206.43	65.02	0.153
	Deceased	9	254.62	83.52	
Glycerol	Survivors	12	104.44	29.27	0.469
	Deceased	9	134.39	137.48	
Glucose	Survivors	12	5.11	1.25	0.353
	Deceased	9	8.54	3.39	
L/P (mean 3-day value)	Survivors	12	21.25	5.92	
	Deceased	9	41.98	29.84	0.072

*Mean 3 days' value.

Table 4 Three-day L/P and outcome

	L/P (3 days)		
	Survival	Death	Total
Outcome			
≤25.94	12	4	16
>25.94	0	5	5
Total	12	9	21
Fisher's exact test = 0.006			

vors from the very beginning of their hospitalization, being raised to 50% on the third day. High glycerol levels have been observed in animal ischemia models. Glycerol is a key component of cell membrane and, in anaerobic conditions, phospholipase and glycerol are released to extracellular interstitial space as a result of cell destruction.[11,12]

Glucose metabolism in the intensive care setting is quite complex. The neuroendocrine and inflammatory response to stress leads to alterations in glucose metabolism. The end result is the appearance of stress related hyperglycaemia. Glucose levels in the blood are further influenced by the concomitant administration of intravenous insulin, the nutritional status of the patient, liver function, and the existence or not of diabetes. Mesenteric ischemia leads to significant reduction of glucose that is offered to the intestinal cells. In animal experiments, strangulation of intestinal vessels eventually provokes severe depletion of glucose. Glucose levels are reduced inside the mesenteric vessels, intraluminally, but also intraperitoneally.[13]

During this study, the L/P ratio remained at high levels for the first 3 days of hospitalization. In fact, an L/P ratio of 25.94 is recommended as a baseline value, over which the survival rate is significantly decreased, as clearly observed in this study. Previous studies, in patients who had undergone colectomy, showed that the intraperitoneal L/P ratio went over 20, and did not decrease during the first postoperative days, indicative of a visceral ischemia as well as a prognostic factor for avoiding future anastomosis breakdown.[14–16]

The intraperitoneal microdialysis is useful in assessing local ischemia and/or inflammation both being critical for outcome prognosis in surgical patients. Previous studies in patients who underwent colectomy have shown that when intraperitoneal L/P ratio values exceed 20 and L/P ratio is not decreasing during the first postsurgery days, splanchnic ischemia is strongly suspected. It is also a sign of anastomotic leak in the near future.[17] In the present study, L/P ratio remained during the first 3 days of hospitalization. We further propose the value 25, 94 as a reference value. Above this cutoff point, the odds of survival are considerably diminished. This is probably a sign that in surgical patients with unfavorable outcome, marked anaerobic metabolism, indicative of ischemia, takes place early in the postoperative course. Detecting subtle metabolic changes early may enhance prompt treatment with obvious benefits.

A high L/P ratio suggests an increased intraperitoneal lactate concentration along with a decreased pyruvate concentration. Glucose is the main supplier of intracellular pyruvate, with pyruvate concentration decreasing when glucose supply is decreased and aerobic glycolysis is concluded, as in cases of ischemia, and when there is a decreased substrate and oxygen supply; in other words, the cell does not have the required resources to continue its normal functions.[18] This suggests that these changes take place early in surgical patients, with unfavorable outcomes, during their hospitalization, and early detection could potentially mean a more successful treatment intervention.

The findings of the present study indicate that inflammation is triggered by local enteric ischemia leading to decreased flow of substrates and oxygen

Table 5 Outcome prediction model

			95% Wald ΔE		Hypothesis test				95% Wald ΔE Exp(B)	
Variable	B	Std. Error	Upper bound	Lower bound	Wald Chi-square	df	*P*	Exp(B)	Upper bound	Lower bound
(constant)	2.301	0.301	1.710	2.892	58.237	1	0.000	9.982	5.528	18.023
(3 days' L/P ≤25, 94)	−0.466	0.237	−0.918	−0.014	4.079	1	0.043	0.628	0.399	0.986
[3-days L/P >25, 94]	0[a]	.	.	.	.	.	.	1	.	.
Third day glucose	−0.087	0.042	−0.169	−0.004	4.240	1	0.039	0.917	0.844	0.996
Age	−0.038	0.164	−0.360	0.283	0.055	1	0.815	0.962	0.698	1.328
Survival = 1, Death = 2										

and tissue necrosis. Given the heterogeneity of the underlying diseases in the sample study, this mechanism appears to be common in surgical patients, regardless of the underlying disease. The potential early prognosis of a surgical patient's outcome based on microdialysis values may enhance prompt localization of septic foci and proper treatment. Intraperitoneal microdialysis may be a useful research tool in understanding the pathophysiology of enteric ischemia and predicting outcome. The metabolites measured may be useful markers in clinical trials targeting at reducing enteric ischemia in surgical patients. The findings of the present study facilitate the creation of a conceptual framework for a future, larger study on peritoneal microdialysis and outcomes in surgical ICU patients.

Limitations

The small number of patients and the short duration of follow-up together with the heterogeneity of the underlying disease do not allow generalization of the proposed cutoff values. Also, possible association of microdialysis values with clinical signs was not evaluated.

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