Short Communication

Glycolysis in Patients with Sepsis during Early ICU Hospitalization Shows Differences vis-à-vis Shock Resolution – An Adipose Tissue Microdialysis Study

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Abstract

To assess early-onset differences in glucose metabolism in patients with sepsis during the first day of ICU hospitalization and evaluate these differences vis-à-vis shock resolution, we studied 10 (8 men; mean age+SD: 58+20 years) mechanically ventilated patients with a diagnosis of septic shock. On day 1 blood and microdialysis (MD) samples were collected twelve times per day (every 2 hours) for glucose and lactate in blood and for glucose, pyruvate, lactate and the lactate to pyruvate ratio in tissue (with MD). Six patients recovered from shock within 1-9 days. In patients with shock resolution significant (positive) correlations were noted for MD glucose and MD lactate versus blood lactate and MD pyruvate versus MD lactate, all with no lag. Septic shock patients that showed elements of persistent adipose tissue glycolysis early on had better prognosis compared to those patients that did not show glycolysis.

Keywords: Adipose tissue; Glycolysis; Lactate; Pyruvate; Critical illness; Septic shock

Introduction

In the metabolic pathway of glycolysis, glucose is converted into pyruvate and eventually (under anaerobic conditions) to lactate. Sepsis is a systemic inflammation state that leads to numerous metabolic alterations, including changes in carbohydrate metabolism. [1] In sepsis, entry of glucose carbon into the tricarboxylic acid cycle may be limiting for glucose oxidation, possibly from inhibition of the pyruvate dehydrogenase complex. [1] In critically ill (ICU-hospitalized) septic patients, in spite of corrected blood pressure and cardiac output, microcirculatory (tissue) perfusion is apparently inadequate. The end-result is tissue hypoxia and organ failure, as a consequence of the resulting imbalance at the cellular level of oxygen supply and demand. [2] In case this microcirculation inadequacy is prolonged it may be associated with worse prognosis. Microcirculation has effects on cells and interstitial fluid; the latter reflects cellular metabolic activity. Monitoring of the interstitium can be implemented with minimally invasive techniques, including microdialysis (MD). [3] In MD, compounds in the interstitial fluid of the targeted tissue, are serially recovered via the semi-permeable membrane of a MD catheter, thus permitting quantification of metabolites. Currently MD is increasingly used in critically ill septic patients as a research tool for measuring metabolites, such as lactate, pyruvate and glycerol, thus assessing directly metabolic alterations at the tissue level. [3]

The aim of this study was to assess early-onset differences in glucose metabolism in blood and tissue of patients with sepsis during the first day of ICU hospitalization and evaluate these differences vis-à-vis shock resolution.

Subjects and Methods

We studied 10 (8 men; mean age + SD: 58 + 20 years) mechanically ventilated patients with a diagnosis of septic shock. [4] This study is part of a larger study that included consecutively hospitalized, mechanically ventilated, critically ill patients admitted to the 25-bed medical-surgical adult ICU of a university hospital between March 2008-July 2012. The hospital's Ethics Committee approved the study and informed consent was obtained from patients' relatives. Critically ill patients analyzed in the current study have been shared with other publications by our research group. Inclusion criteria were: mechanically ventilated patients with septic shock (defined according to the SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference). [4] Patients were not enrolled in the study if one of the following exclusion criteria was present: age less than 18 years; glucocorticoid administration prior ICU admission; mechanical ventilation for more than 48 hours before ICU admission; no need for intubation and mechanical ventilation during ICU stay; do-not-resuscitate clinical conditions; brain-death upon ICU entry and HIV infection. Patients with diabetes were excluded as well as those with a diagnosis of systemic inflammatory response syndrome (SIRS), sepsis and severe sepsis. Recovery of shock was defined as maintenance of a systolic blood pressure greater than or equal to

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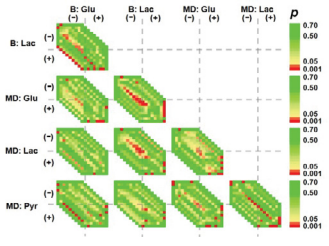
90 mmHg without vasopressor support for 24 h or more. Upon ICU admission a MD catheter (CMA 60, CMA Microdialysis AB, Stockholm, Sweden) was inserted under sterile conditions into the subcutaneous adipose tissue of the upper thigh, as previously described [3,5-8]. (see also Åsberg, A., Insertion of 63 Microdialysis Catheter Into Artificial Adipose Tissue (2014) at https://www.youtube.com/watch?v=g9zj-ktfN0g, Accessed: July 25, 2016). On day 1 blood and MD samples were collected twelve times per day (every 2 hours) in blood for glucose and lactate and in tissue (with MD) for glucose, pyruvate and lactate and the lactate to pyruvate ratio. Six patients recovered from shock within 1-9 days. Comparisons of time-averaged values of the measured parameters were done with Student's t-test; furthermore we analyzed the data on cross-correlation matrices (heat maps) of 2-hours' increments, separately for patients with shock resolution and no shock resolution.

Results

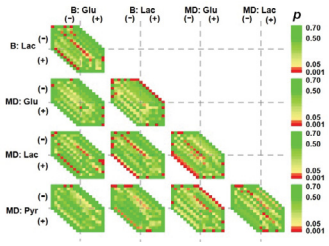
There were no notable differences between the two groups in the measured parameters [Table 1]. There were no differences for cross-correlation of blood glucose versus blood lactate in both groups [Figure 1]. However, in patients with shock resolution significant (positive) correlations were noted for MD glucose and MD lactate versus blood lactate and MD pyruvate versus MD lactate, all with no lag [maximum r=+0.838; p=0.001; Figure 1a]; the corresponding correlations in patients with no shock resolution were more disorderly and scattered in the heatmap diagrams [Figure 1b].

Table 1: Measured parameters values, mean ± SE; MD: Microdialysis.

		Shock resolution (n=6)	No shock resolution (n=4)	*p-value*
Blood	Glucose (mmol/L)	7.72 ± 0.22	7.16 ± 0.33	0.18
	Lactate (mmol/L)	1.54 ± 0.06	1.38 ± 0.05	0.09
MD	Glucose (mmol/L)	7.73 ± 0.54	7.07 ± 0.40	0.40
	Pyruvate (μmol/L)	179 ± 17	130 ± 6	0.06
	Lactate (mmol/L)	2.55 ± 0.19	1.93 ± 0.16	0.06
	Lactate to pyruvate molar ratio	14.3 ± 0.6	15.3 ± 0.6	0.29



(a)



(b)

Figure 1: Cross correlation's *p* values for septic patients with shock resolution (panel 1a) and no shock resolution (panel 1b). Note the clustered high correlation *p* values in and around the no lag points for *B Glu vs. B Lac*, *B Lac vs. MD Glu* and *B Lac vs. MD Lac* only in patients with shock resolution (panel 1a), but not in patients with no shock resolution (panel 1b); *B: Blood; MD: Microdialysis; Glu: Glucose; Lac: Lactate; Pyr: Pyruvate; (+) Positive lag; (-) Negative lag; Dotted lines indicate no lag.*

Discussion

In this study we found that the parameters of glycolysis in blood or adipose tissue (with MD) were more correlated in critically ill patients that eventually resolved their shock status compared to those that did not. Thus, despite overall similar averaged levels for glucose, lactate or pyruvate, the dynamics of glycolysis were more organized and persistent in those patients with septic shock that had a better prognosis.

Glycolysis in the cytoplasm produces pyruvate (an intermediate metabolite). Under aerobic conditions, cells convert pyruvate to acetylCo-A to enter Kreb's cycle (to produce energy) whereas under relative anaerobic conditions (ischemia, hypoxia or primary mitochondrial dysfunction), pyruvate is converted to lactate by lactate dehydrogenase, resulting in much lower energy production (2 ATPs generated, instead of 36). [9]. Glycolysis is an evolving field of research, since facets of it are still obscure, particularly in tissues other than muscle, such as adipose tissue. Energy use - and eventual manipulation of it - is important in critically ill patients. The latter, if their condition persists, need tailored nutritional support. In the past, carbohydrate-based caloric over-alimentation in septic patients was shown not to be beneficial to septic ICU patients. [10]. Nevertheless, based on the present study, we could speculate that it was in patients with no discernible glycolysis that this nutritional energy support was not beneficial (whereas in patients with persistence of glycolysis carbohydrates might indeed be needed).

Most biochemical events take place in tissues, and MD may detect metabolic events that would go undetected by conventional sampling approaches, as described in neuro intensive care. [7]. In this study the persistence of glycolysis both in blood and adipose tissue of septic shock patients that fared better than others lends credence to the implementation of metabolic monitoring of critically ill patients with techniques such as MD. This is of practical importance, since already in critically ill patients, monitoring of the lactate to pyruvate ratio with MD is a potent indicator of tissue damage and a prognostic tool. Additionally, it has been previously shown that in experimental human sepsis, lactate production does not occur in the muscles [11] and this study may point to the possibility that a site of lactate generation in sepsis might be the subcutaneous adipose tissue.

Limitations

Despite our results we have to bear in mind the limitations of this study. The small number of patients and absence of blood pyruvate measurements are major limitations; nevertheless the total number of measurements for each parameter was large (assuming for simple bivariate correlations effect sizes of f2 = 0.005-0.10, α = 0.05-0.10 and (1-β) = 0.90 would have required 67-133 measurements, whereas in this study there were 120 values for each parameter). [12]. The averaged measured parameters' overall similarity in both patients' groups may be

partially explained by the small study sample size; usually in septic shock high tissue lactate, pyruvate, and lactate to pyruvate ratio are related to poor clinical outcome. [5]. Furthermore, while the metabolism of glucose to pyruvate and of pyruvate to lactate is practically instantaneous, the metabolic route of lactate is more complicated. The origin of tissue lactate in sepsis is apparently multifactorial and a matter of debate and the evolution of tissue lactate levels are dependent on production (either aerobic or anaerobic) and clearance. So, if for instance lactate levels decrease, this may be caused by decreased production or increased clearance or both; this was not addressed by the present study. Additionally, half of the produced lactate is back-transformed to glucose. Finally, the equilibrium between plasma and tissue interstitial space in the setting of sepsis may be incomplete – and hence MD measurements may reflect evolving processes - due to interstitial edema, impairment of the microcirculation or administration of vasopressor agents.

Conclusion

In conclusion, septic shock patients that showed elements of persistent adipose tissue glycolysis early on had better prognosis compared to those patients that did not show glycolysis.

Acknowledgement

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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