Lactate

Glucose is conventionally regarded as the major energy substrate, although lactate can also be an energy source.

Lactate mEq/L CSF 1.6 Arterial plasma 1.0 CSF:plasma ratio 1.6

Although hyperlactatemia is common finding in liver transplant (LT) candidates, association between lactate and organ failures with Acute-on-chronic Liver Failure (ACLF) is poorly studied.

A total of 2,002 patients from LT registry between January 2008 and February 2019 were analyzed. Six organ failures (liver, kidney, brain, coagulation, circulation, and lung) were defined by criteria of EASL-CLIF ACLF Consortium. Variable importance of preoperative hyperlactatemia was examined by machine learning using random survival forest (RSF). Kaplan-Meier Survival curve analysis was performed to assess 90-day mortality.

Median lactate level was 1.9 mmol/L (interquartile range: 1.4, 2.4 mmol/L) and 107 (5.3%) patients showed > 4.0 mmol/L. RSF analysis revealed that the four most important variables for hyperlactatemia were MELD score, circulatory failure, hemoglobin, and respiratory failure. The 30-day and 90-day mortality rates were 2.7% and 5.1%, whereas patients with lactate > 4.0 mmol/L showed increased rate of 15.0% and 19.6%, respectively.

About 50% and 5% of LT candidates showed pre-LT hyperlactatemia of > 2.0 mmol/L and > 4.0 mmol/L, respectively. Pre-LT lactate > 4.0 mmol/L was associated with increased early post-LT mortality. This results suggest that future study of correcting modifiable risk factors may play a role in preventing hyperlactatemia and lowering early mortality after LT [1)]

Metabolism

Neuronal activity is closely associated with energy metabolism. In addition to glucose, astrocyte-derived lactate serves as an energy source for neurons. Chronic inflammation is a common pathological event that is associated with aging and neurodegenerative diseases. However, the mechanisms underlying inflammation-induced neuronal injury are not fully understood. Both microglia and astrocytes participate in the regulation of neuronal functions; therefore, Wang et al. used astrocyte-neuron co-cultures to investigate the effects of chronic microglial activation on neuronal lactate metabolism. Chronic low-grade inflammation was induced by repeated stimulation of primary rat microglia with low-dose lipopolysaccharide (LPS, 10 ng/mL). The medium from the LPS-activated microglia was collected and used to mimic the inflammatory environment in primary cultures. In monocultures exposed to an inflammatory environment, intracellular lactate decreased in neurons but increased in astrocytes. However, astrocyte-neuron co-cultures exhibited increased lactate levels in neurons and decreased lactate levels in astrocytes when exposed to an inflammatory environment. Inhibition of lactate transporters expressed on neurons or astrocytes reduced the intracellular lactate in co-cultured neurons exposed to inflammation, but not in those exposed to physiological conditions. Adenosine triphosphate (ATP) production was reduced in both mono-cultured and co-cultured

neurons. These results indicate that a chronic inflammatory environment increases neuronal lactate supply by promoting the astrocyte-neuron lactate shuttle, but it impairs lactate oxidation in neurons. Additionally, chronic inflammation disrupts the neuronal cytoskeleton. This study highlights the importance of glial cells in regulating neuroenergetics and neuronal function and provides a comprehensive explanation for the neurotoxic effects of neuroinflammation [2].

Experimental and human investigations have convincingly shown that lactate stands as a major actor of cerebral metabolism. Glutamate-induced activation of glycolysis stimulates lactate production from glucose in astrocytes, with subsequent lactate transfer to neurons (astrocyte-neuron lactate shuttle). Lactate is not only used as an extra energy substrate but also acts as a signaling molecule and regulator of systemic and brain glucose use in the cerebral circulation. In animal models of brain injury (e.g., TBI, stroke), supplementation with exogenous lactate exerts significant neuroprotection [3].

For decades, lactate has been considered an excellent biomarker for oxygen limitation and therefore of organ ischemia.

Experimental evidence suggests that lactate is neuroprotective after acute brain injury; however, data in humans are lacking. We examined whether exogenous lactate supplementation improves cerebral energy metabolism in humans with traumatic brain injury (TBI).

Bouzat et al., prospectively studied 15 consecutive patients with severe TBI monitored with cerebral microdialysis (CMD), brain tissue PO2 (PbtO2), and intracranial pressure (ICP). Intervention consisted of a 3-h intravenous infusion of hypertonic sodium lactate (aiming to increase systemic lactate to ca. 5 mmol/L), administered in the early phase following TBI. We examined the effect of sodium lactate on neurochemistry (CMD lactate, pyruvate, glucose, and glutamate), PbtO2, and ICP.

Treatment was started on average 33 ± 16 h after TBI. A mixed-effects multilevel regression model revealed that sodium lactate therapy was associated with a significant increase in CMD concentrations of lactate [coefficient 0.47 mmol/L, 95% confidence interval (CI) 0.31-0.63 mmol/L], pyruvate [13.1 (8.78-17.4) µmol/L], and glucose [0.1 (0.04-0.16) mmol/L; all $p < 0.01$]. A concomitant reduction of CMD glutamate [-0.95 (-1.94 to 0.06) mmol/L, $p = 0.06$] and ICP [-0.86 (-1.47 to -0.24) mmHg, $p < 0.01$] was also observed.

Exogenous supplemental lactate can be utilized aerobically as a preferential energy substrate by the injured human brain, with sparing of cerebral glucose. Increased availability of cerebral extracellular pyruvate and glucose, coupled with a reduction of brain glutamate and ICP, suggests that hypertonic lactate therapy has beneficial cerebral metabolic and hemodynamic effects after TBI [4].

Forty-six patients with an admission Glasgow coma scale score of ≤13 after resuscitation admitted to a dedicated 10-bed Neurotraumatology Intensive Care Unit were included, and 5305 verified samples of good microdialysis data were analyzed.

Lactate levels were above 2.5 mmol/L in 56.9% of the samples. The relationships between lactate and the LPR could not be adequately modeled by any linear or non-linear model. Neither Cohen's kappa nor Gwet's statistic showed an acceptable agreement between both biomarkers to classify the samples in regard to normal or abnormal metabolism. The dataset was divided into four patterns

defined by the lactate concentrations and the LPR. A potential interpretation for these patterns is suggested and discussed. Pattern 4 (low pyruvate levels) was found in 10.7% of the samples and was characterized by a significantly low concentration of brain glucose compared with the other groups.

The study shows that metabolic abnormalities are frequent in the macroscopically normal brain in patients with traumatic brain injuries and a very poor agreement between lactate and the LPR when classifying metabolism. The concentration of lactate in the dialysates must be interpreted while taking into consideration the LPR to distinguish between anaerobic metabolism and aerobic hyperglycolysis [5].

Lactate as tumor biomarker

Lactate as tumor biomarker.

Cerebrospinal fluid lactate

Cerebrospinal fluid lactate

1)
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