NEW THERAPEUTIC ASPECTS IN PATIENTS WITH MULTI-ORGAN FAILURE AND ACIDOSIS

Chair: PD Dr. med. Olaf Boenisch, Hamburg; PD Dr. med. Bernhard Kreymann, Munich

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In this symposium, new therapeutic approaches for the treatment of patients with multi-organ failure and acidosis will be discussed. The importance of the liver in acid-base balance will also be addressed.

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WHAT ROLE DOES THE LIVER PLAY IN ACID-BASE BALANCE?

PD Dr. med. Olaf Boenisch, Hamburg

- The liver significantly influences the acid-base balance through its metabolism activity.
- In acute liver failure, patients with cirrhosis or acute-on-chronic liver failure develop acidemias due to unmeasured anions and lactate azidosis.
- 28-day mortality was directly related to pH in a clinical study. Even mild acidosis significantly increased mortality in critically ill patients.

The lungs and kidneys are essential for maintaining the acid-base balance because of their excretory function. However, many metabolic processes also take place in the liver in which acidic or alkaline substances are produced or reabsorbed, such as albumin synthesis, substrate oxidation or acid metabolism (lactate, amino acids, keto acids). Therefore, liver diseases result in complex disturbances of the acid-base balance, which should be analyzed differencely, reported **PD Dr. med. Olaf Boenisch, Klinik for Intensive Care Medicine, University Medical Center Hamburg-Eppendorf.**

Metabolic acidosis dominates in liver failure. Even mild acidosis is associated with increased mortality. Since all enzymes have a pH optimum, pH deviations lead to disturbances of metabolism, mitochondria, protein structure, cell membrane polarity and electrolytes. The greatest threat to the internal pH environment is the enormous amount of CO_2 produced as an end product of energy metabolism. In addition, there is lactic acid, which is recycled in the body, and other acids that are excreted by the kidneys.

Healthy liver recycles lactate

The liver significantly influences acid-base balance through its metabolism activity. The liver exclusively produces albumin, a buffer substance and weak

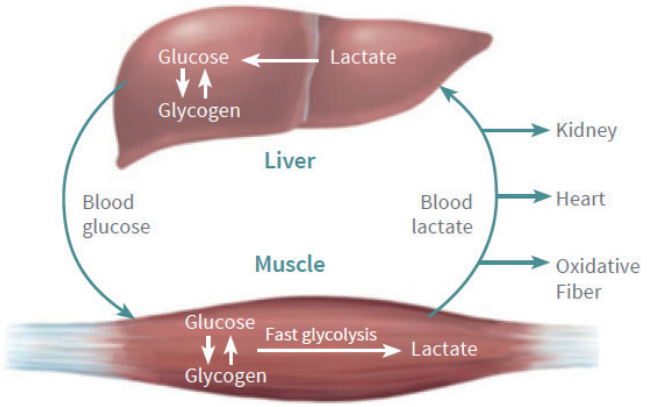

Figure 1: Schematic representation of the lactate recycling (Cori Cycle)

acid. Albumin deficiency causes (mild) metabolic alkalosis. When fats and carbohydrates are burned (substrate oxidation), a lot of CO_2 is produced, which can lead to acidosis. The lactate produced in the muscle during oxidation is recycled in the liver to glucose, which is then made available again as a substrate to the lactate-producing organs (Figure 1). Ketonic acids, which the liver synthesizes from long-chain fatty acids to form bicarbonate, are excreted by the kidney or used as energy sources by organs such as the brain. Amino acids are used for protein synthesis or degraded. However, per100 g protein 1 mol NH_4^+ are formed. This ammonium is converted to urea in the liver with the consumption of bicarbonate or excreted via the kidneys.

Acid-base disorders in liver insufficiency

Patients with liver disease often have respiratory alkalosis because substances that affect the respiratory center, such as ammonia or hormones (including progesterone), are no longer adequately metabolized. Hepatopulmonary syndrome, ascites or hydrothorax also lead to hypoxemia, to which patients react with increased respiratory drive, hyperventilation and respiratory alkalosis.

To encounter respiratory alkalosis, the body excretes bicarbonate. Due to electroneutrality, this leads to increased chloride reabsorption and hyperchloridemic acidosis. In addition, bicarbonate is lost through iatrogenically produced diarrhea (lactulose). Because the various processes balance each other out, compensated liver disease patients have a normal pH: hypalbuminemia causes alkalosis, respiratory alkalosis leads to hyperchloridemic acidosis, and hyponatremia causes dilutional acidosis (the water pH of 7.0 is lower than the blood pH of 7.4).

If collateral damage of the liver disease such as reduced lactate clearance, renal failure, infections, cirrhotic cardiomyopathy or hemorrhage is added, the fragile equilibrium tilts even more towards acidosis. Lactate plays a major role here. In shock, the liver no longer removes lactate but produces it itself. In addition, hypoxia, anemia, increased oxygen consumption, mitochondrial disorders, toxins, thiamine deficiency, and increased concentrations of primarily renally excreted phosphoric and sulfuric acids („unmeasured anions" [UMA]) exacerbate acidosis.

Differential blood gas analysis

Since different acid-base disorders are present in parallel, bicarbonate, pCO_2, and base excess (BE) are not sufficient for assessment. A suitable approach, according to Dr. Boenisch, is the simplified Stewart Model proposed by Story. This model, which includes sodium, chloride, UMA, lactate, and albumin in the analysis, provides a simplified quantitative way to assess the acid-base contributions of the major plasma constituents measured in the Stewart approach[1]. Using a 52-year-old liver cirrhosis patient with spontaneous bacterial peritonitis (CRP 47, elevated procalcitonin) and a BE of -2.6 mEq/l, Dr. Boenisch explained the differential analysis (Figure 2). The patient had marked metabolic acidosis, primarily due to unmeasurable anions (-12.1), i.e. acute renal failure and starvation ketosis, and aggravated by lactic acidosis.

Acidosis kills

In acute liver failure, patients with cirrhosis or acute-on-chronic liver failure develop acidemias due to unmeasured anions and lactate acidosis. 28-day mortality was directly related to pH in a clinical study.[2]
Even mild acidosis significantly increased mortality in critically ill patients. A pH below 7.1 meant 100% mortality. The higher the lactate on hospital admission, the higher the mortality. Lactate levels correlated with bilirubin and INR, i.e. with the extent of liver dysfunction.

Electrolyte effect: $BE_{NaCl} = Na_{mmol/l} - Cl_{mmol/l} - 35$	134-90-35=	9
Albumin effect: $BE_{Albumin} = (42 - Albumin_{g/l})/4$	(42-22)/4=	5
Lactate effect: $BE_{Lactate} = 1 - Lactate_{mmol/l}$	1-5.5=	-4.5
Unmeasured anions (UMA) effect: $BE_{UMA} = BE_{total} - BE_{NaCl} - BE_{Albumin} - BE_{Lactate}$	-2.6-9-5-(4.5)=	-12.1

Figure 2: Analysis of acid-base disorders according to the simplified Stewart Model by Story[1]

THERAPEUTIC OPTIONS FOR AZIDOSIS IN MULTI-ORGAN FAILURE

PD Dr. med. Bernhard Kreymann,
CEO ADVITOS, Munich

- Three organs maintain the acid-base balance: the liver, the lungs and the kidney. The possibilities for compensation are very limited. The failure of one of the three organs can hardly be compensated.

- The ADVOS procedure supports the three essential organs of acid-base balance, the liver (H^+ removal, bicarbonate reabsorption), the lungs (CO_2 excretion) and the kidney (CO_2 and H^+ removal, bicarbonate production). The direct removal of acid equivalents and CO_2 fundamentally distinguishes the ADVOS procedure from previous liver and kidney replacement therapies.

- In Hamburg, 34 critically ill liver cirrhosis patients were treated with the ADVOS multi 102 times. Respiratory acidosis normalized after only one session. The survival rate increased from the expected 20% to 50%.

Liver support therapies should also affect acid-base balance. Patients with acidosis often die very quickly, but direct acid removal can improve survival. Early use of the ADVOS procedure therefore appears to make pathophysiological sense, explained **PD Dr. med. Bernhard Kreymann, CEO of ADVITOS GmbH, Munich.**

A pH below 7.15 corresponds to 4 points in the APACHE score. This is the same as a mean blood pressure below 50 mmHg, which is practically equivalent to a death sentence. The validity of this classification is supported by a French study of 2,550 sepsis patients[3]. Of 155 patients with metabolic or mixed severe acidosis (pH<7.2), 57% died. All patients had multiple organ failure (MOF). While in an American study hyperchloremic acidosis only slightly increased hospital mortality, more than half of the patients with lactic acidosis died.[4] In an Australian study, 8% of patients died with normal pH, 12% with compensated hypercapnic acidosis, and nearly 22% with hypercapnic acidosis.

Liver, lungs and kidney crucial

Three organs maintain the acid-base balance: the liver, the lungs and the kidney. However, MOF patients have 80% lung failure, 40% kidney failure and 20% liver failure. The compensation possibilities are therefore very limited and the failure of one of the three organs can hardly be compensated. Most patients with severe acidosis therefore die quickly. Only if it is possible to normalize the pH very quickly, there is a chance of survival.

Consequences of acidosis

A pH decrease from 7.5 to 6.5 reduces the activity of respiratory chain enzymes by approximately 40%. Hypercapnic acidosis impairs the immune response, disrupts cell differentiation, alters receptors for bacteria, reduces the amount of energy provided (less ATP synthesis), and decreases ion transport across cell membranes.[5] CO_2 is a potent immunosuppressive substance, Dr. Kreymann emphasized. Many sepsis patients have significantly elevated CO_2 levels, which significantly worsens the prognosis.

Acidosis leads to significant organ dysfunctions. Cardiac muscle contractility decreases, patients respond poorly to catecholamines, have arrhythmias, beta receptors are downregulated, and cytokine production increases. Other consequences include somnolence, coma, glucose metabolism disorders, insulin resistance, protein degradation, hyperkalemia, intestinal wall permeability, organ edema, vasodilation, increased pulmonary vascular resistance with right heart strain, and hyperventilation.

Sodium bicarbonate infusions enhanced acidosis

In acidic patients, H^+ ions react with HCO_3^- to form CO_2. CO_2 diffuses into the cells and leads to intracellular acidosis. This pathophysiological process has direct clinical consequences: In patients with cardiac arrest and severe acidosis, bicarbonate increases mortality as a result of CO_2 increase.[6] Classical acidosis treatment is based on bicarbonate infusions. However, this does not remove the acid directly, the patient also needs a well-functioning lung to breathe out the CO_2 produced. The same applies to dialysis with increased bicarbonate concentration. Here, too, CO_2 is generated in the dialysate.

In an in vitro comparison between the ADVOS (Advanced Organ Support) procedure and continuous venovenous hemofiltration (CVVH), the metabolic acidosis (pH 7.2) in the CVVH group was compensated with bicarbonate.[7] Due to lack of aeration, pCO_2 increased sharply (> 90 mmHg) and pH decreased below 7.0, whereas the ADVOS procedure normalized pH and bicarbonate in less than one hour. Due to the high CO_2 removal with the ADVOS multi at a dialysate pH of 9.0, an additional 15 ml/min CO_2 had to be added to maintain the blood pH between 7.35 and 7.45.

ADVOS procedure

The ADVOS procedure includes a second albumin dialysate circuit in addition to the normal aqueous dialysis circuit. The procedure normalizes electrolytes, removes water, removes protein-bound toxins and recycles albumin.

The dialysate loaded with toxins is processed in two parallel filter circuits connected in parallel. By convection/

ultrafiltration in the filter, the adjusted ultrafiltrate is pressed off and the now unbound toxins are filtered out. The dialysate pH is lowered by adding dilute hydrochloric acid (HCl). This loosens the binding of positively charged toxins (e.g. copper or CO_2) to albumin. The dialysate pH is raised by adding diluted sodium hydroxide (NaOH). In addition, the temperature of the dialysate is increased. This loosens the bond between negatively charged toxins (e.g. bilirubin or bile acid) and albumin.

In addition, the ADVOS procedure can be used to specifically change the pH value. At a dialysate pH of 9, there is a strong H^+ gradient compared to the blood pH. H^+ ions diffuse into the dialysate in the direction of the higher pH. There is also a gradient for CO_2, which is virtually absent at a pH of 9.0. H^+ remaining in the blood are bound to albumin or phosphate, bicarbonate increases, and CO_2 is reduced. Now the erythrocytes release CO_2 and a new equilibrium with lower CO_2 concentration is reached. That way, large amounts of CO_2 can be removed with the ADVOS procedure.

Acid-base correction can be customized using different alkaline concentrates. A bicarbonate-containing concentrate is available for patients with metabolic acidosis, and a concentrate with a low bicarbonate content is available for CO_2 removal.

The ADVOS therapy supports the three essential organs of acid-base balance, the liver (H^+ removal, bicarbonate production), the lungs (CO_2 removal) and the kidney (CO_2 and H^+ removal, bicarbonate production). The direct removal of acid equivalents and CO_2 fundamentally distinguishes the ADVOS procedure from previous liver and kidney replacement therapies. With the ADVOS multi, up to 146 ml/min CO_2 and up to 3 mmol /min H^+ were removed in vitro.[7] CO_2 elimination with the ADVOS multi depends on H^+/CO_2 amount, blood flow and dialysate composition (bicarbonate concentration, dialysate pH) (Figure 3).

Clinical Data

In Hamburg, 34 critically ill liver cirrhosis patients (SOFA Score 17, 75% ventilated, 100% dialyzed) were treated a total of 102 times with the ADVOS multi. Respiratory acidosis normalized after only one session. Bicarbonate increased slightly, pCO_2 decreased from 65 to 54 mmHg and ventilatory pressures were reduced. Survival increased from an expected 20% to 50%.

In eleven patients with severe metabolic acidosis (pH<7.2), bicarbonate increased relatively slowly with ADVOS multi treatment, CO_2 remained the same, base excess increased, and lactate was reduced. Due to pH normalization, catecholamine response improved and norepinephrine administration was significantly reduced.

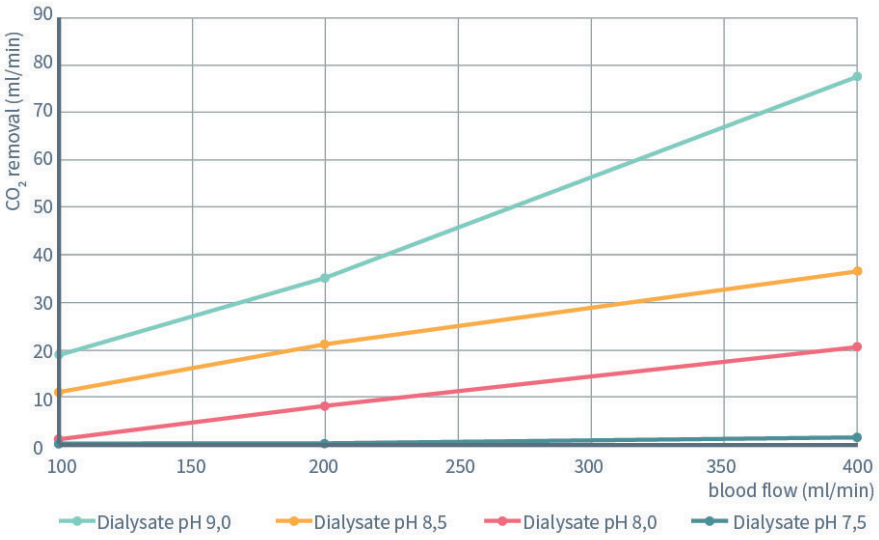

Figure 3: Correlation between blood flow, dialysate and CO_2 removal

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