Review

JOURNAL OF HEPATOLOGY

Acid-base disorders in liver disease

Bernhard Scheiner[1,2], Gregor Lindner[3], Thomas Reiberger[1], Bruno Schneeweiss[4], Michael Trauner[1], Christian Zauner[1], Georg-Christian Funk[2,*]

Keywords: Acid-base disorders; Liver disease; Cirrhosis; Critically-ill; Acute liver failure.

Received 27 February 2017; received in revised form 21 June 2017; accepted 27 June 2017

Summary

Alongside the kidneys and lungs, the liver has been recognised as an important regulator of acid-base homeostasis. While respiratory alkalosis is the most common acid-base disorder in chronic liver disease, various complex metabolic acid-base disorders may occur with liver dysfunction. While the standard variables of acid-base equilibrium, such as pH and overall base excess, often fail to unmask the underlying cause of acid-base disorders, the physical–chemical acid-base model provides a more in-depth pathophysiological assessment for clinical judgement of acid-base disorders, in patients with liver diseases.

Patients with stable chronic liver disease have several offsetting acidifying and alkalinising metabolic acid-base disorders. Hypoalbuminaemic alkalosis is counteracted by hyperchloraemic and dilutional acidosis, resulting in a normal overall base excess. When patients with liver cirrhosis become critically ill (*e.g.*, because of sepsis or bleeding), this fragile equilibrium often tilts towards metabolic acidosis, which is attributed to lactic acidosis and acidosis due to a rise in unmeasured anions. Interestingly, even though patients with acute liver failure show significantly elevated lactate levels, often, no overt acid-base disorder can be found because of the offsetting hypoalbuminaemic alkalosis.

In conclusion, patients with liver diseases may have multiple co-existing metabolic acid-base abnormalities. Thus, knowledge of the pathophysiological and diagnostic concepts of acid-base disturbances in patients with liver disease is critical for therapeutic decision making.

[1]*Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria*;
[2]*Department of Respiratory and Critical Care Medicine, Otto Wagner Spital, Vienna, Austria*;
[3]*Department of General Internal Medicine & Emergency Medicine, Hirslanden Klinik Im Park, Zurich, Switzerland*;
[4]*Division of Oncology and Hematology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria*

Key point

Patients with liver disease often have various complex acid-base disorders. Pathophysiological and diagnostic concepts as well as potential therapeutic interventions are reviewed in this article.

Introduction

A functioning acid-base balance results in normal blood pH and is critical for regular cellular and organ function.[1,2] Next to the kidneys and lungs, the liver is now recognised as an important organ of acid-base regulation,[3] playing a crucial role in various homeostatic pathways, such as the metabolism of organic acid anions like lactate and certain amino acids.[4] Consequently, patients with liver dysfunction often show acid-base disorders. Interestingly, the literature on acid-base disorders in liver disease is very limited. In addition, standard acid-base variables frequently fail to unmask the underlying acid-base disorders in liver disease.[5,6]

In contrast to the traditional model of acid-base equilibrium based on the Henderson-Hasselbalch-formula,[7,8] the more recent physical-chemical approach (also known as Stewart's approach)[9] provides a better understanding of the underlying mechanisms of acid-base disorders in liver disease. The most common acid-base disturbance in patients with liver disease is respiratory alkalosis; however, various complex metabolic disorders of acid-base equilibrium also occur in patients with both stable and decompensated cirrhosis.[10] This review will thus focus on the pathophysiological role of the liver in acid-base disorders that result from liver injury in the setting of cirrhosis, critical illness and acute liver failure; it will also cover diagnostic approaches, as well as specific therapeutic interventions in order to optimise patient management.

The physiological role of the healthy liver in acid-base regulation

Lactate metabolism and the Cori Cycle

Lactic acidosis is the most important type of metabolic acidosis in intensive care patients. It results from tissue hypoxia secondary to circulatory failure,[11,12] reduced lactate removal due to

sympathoadrenal-induced vasoconstriction and reduced blood flow to the liver, kidney and resting muscles.[13] Lactate is also produced in the working muscle during anaerobic glucose utilisation. The healthy liver acts as the main consumer of lactate and contributes to 30–70% of lactate metabolism (Fig. 1).[14,15] Experimental data indicated that liver lactate consumption is directly related to arterial lactate concentrations,[16] rather than liver blood flow.[17] Even after major hepatectomy with a 50% loss of functional liver tissue, blood lactate concentrations remain unchanged, underlining the functional reserve of a healthy liver to counterbalance lactic acidosis.[18] After hepatic uptake, lactate is first converted to pyruvate and then retransformed to glucose in a process called gluconeogenesis. Together, the release of lactate from the working muscle and its retransformation to glucose in the liver is called the Cori Cycle, and it releases equimolar amounts of HCO_3^-.[19]

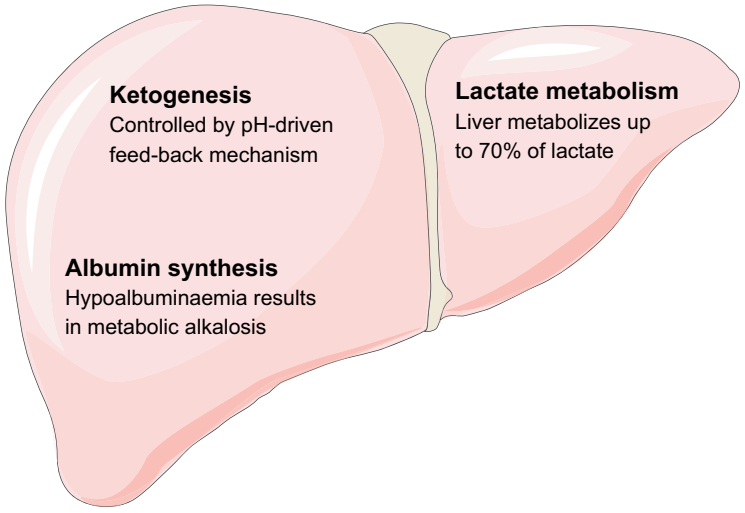

Fig. 1. Summary of the physiological role of the healthy liver in maintaining acid-base

Albumin synthesis

In the physiological range of blood pH, albumin behaves as a weak acid. Hypoalbuminaemia due to decreased production (*e.g.*, in liver disease or malnutrition) or increased loss (*e.g.*, nephrotic syndrome, intestinal loss or large, chronic wounds) results in mild metabolic alkalosis. In contrast, hyperalbuminaemia, which can be seen in patients with severe dehydration but is rarely observed, contributes to mild metabolic acidosis.[20,21]

Ketogenesis and ketoacidosis

Keto acids are produced in the mitochondria of the liver when carbohydrate or fat is incompletely oxidised. The keto acids, 3-hydroxybutyric acid and acetoacetic acid dissociate at physiologic pH, resulting in increased H^+ concentration, and may ultimately lead to ketoacidosis. Therefore, the net production of keto acids as well as their urinary excretion is controlled by a feedback mechanism, leading to reduced endogenous acid production if pH decreases[22] and increased keto acid production if pH rises.[23] This rapid up- or downregulation applies both to hepatic ketogenesis and lactate production. It can be sustained and it reverses completely as an acid-base challenge disappears.[24] Hepatic ketogenesis and its regulation are negligible and do not cause relevant acidosis under normal conditions. However, starvation or massive alcohol consumption can cause ketogenesis with substantial metabolic acidosis.

Urea production

The neurotoxic weak acid NH_4 arises during protein breakdown, with a daily amount of approximately 1 mol NH_4 based on an average protein intake of 100 g per day.[25] In the liver, NH_4 is further processed to urea, which can be excreted via urine. The process of urea production consumes equal amounts of the strong base HCO_3^-.[6] Therefore, urea production is not only a detoxification process; it may also play a role in acid-base regulation.[26] Indeed, early studies suggested that the liver has a direct acid-base regulating effect by altering ureagenesis and therefore HCO_3^- consumption.[5,25] However, these results could not be reproduced in other studies.[27–31] Furthermore, ureagenesis, an acidifying process, increased rather than decreased in experimental human acidosis.[32] Boon *et al.*[33,34] showed that the reduction of urea synthesis in acute and chronic acidosis was due to a marked decrease of hepatic amino acid transport and uptake, rather than a change in the activity of the ornithine cycle *per se*. In summary, ureagenesis has no discernible homeostatic effect on acid-base equilibrium in humans.

The physical-chemical acid-base model

Traditional acid-base analysis according to Siggaard-Andersen acknowledges the influence of $PaCO_2$, as well as organic acids and is based on blood pH.[8] However, it neglects the effects of electrolytes and weak acids (albumin and phosphate) on acid-base balance. The more recent physical-chemical acid-base approach according to Stewart integrates all potential modifiers of the acid-base balance.[9] While Stewart originally proposed a somewhat complex mathematical model, the simplified model by Gilfix *et al.* describes all possible metabolic acid-base disorders based on base excess (BE) subsets (Fig. 2).[20] It includes BE changes explained by variations in the following variables: (i) water (plasma dilution/concentration), (ii) chloride (Cl), (iii) albuminaemia, (iv) lactate and (v) unmeasured anions (UMA). Analogous to the regular BE, negative and positive values of BE subset indicate acidosis and alkalosis, respectively.

* Corresponding author. Address: Department of Respiratory and Critical Care Medicine, Otto Wagner Spital, Sanatoriumstrasse 2, 1140 Vienna, Austria. Tel.: +43 1 91060 41008; fax: +43 1 91060 49853.
E-mail address: georg-christian.funk@meduniwien.ac.at (G.-C. Funk).

Review