The liver: The Forgotten Organ in Acid-Base Balance?

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Introduction

Just as mankind is beginning to show more interest in ecological material disposal, clinical medicine, after years of investigating oxygen and nutrient supply, thrives to understand more about the elimination of metabolic endproducts such as carbon dioxide and acid metabolites. It is therefore of the utmost importance to procure knowledge and experience of when we are about to leave shallow water. This led to the discovery that a relevant organ had thus far been ignored, the liver, in particular regarding physiological aspects and clinical as well as physiological chemistry.

The liver is indeed an area in which we for a long time have been missing to ask questions. Still doctors in the field of gastroenterology deal with hepatic failure and in cooperation with nephrologists treat the so-called hepatorenal syndrome. The surgeon has often performed a macroscopically perfect operation during an ostensibly uneventful anesthetic, and up to the moment of deterioration, often days after surgery, the heart rate, blood pressure, urine output etc. that have been recorded laboriously often remain normal; yet the patient may still die. Surgeons perform a liver transplant and the anesthetist takes up the management of the anhepatic patient during surgery. This offers him the opportunity to investigate liver function in particular regarding its influence on the acid-base balance since the immense metabolic activity of the liver must take part in this equilibrium. However, in many situations, physiologic limits have to be extended in anesthesia and intensive care.

Judging by its blood supply and circulation the liver is comparable in importance to the kidneys. With a mean flow of 1.25 l/min it receives approximately 25 % of the cardiac output ¼ of which circulates through the hepatic artery to the hepatic vein and ¼ of which derives from the portal vein which also drains into the hepatic vein. The marked O_2 consumption is 20 % of the total O_2 uptake of the body, 40 % is consumed arterio-venously and 60 % by the portal vein. These numbers alone point out a functional diversion between the two circulation systems of the liver.

Recent findings strength that besides the lung and kidneys, liver metabolism has an essential influence on the regulation of the acid-base balance. Contrary to generally accepted theories, the liver is even the most important regulatory organ in the acid-base balance for it can eliminate as many H^+ ions and therewith liberate HCO_3^- in one hour as the kidneys in 24 hours: depending on the ion challenge the liver can metabolize up to 1000 mmol H^+ ions in 1 hour. This fast H^+ elimination using inorganic acids – such as the lactic acid metabolism (oxidation/gluconeogenesis) – is of particular clinical relevance. The liver can metabolize between 40 (basic metabolism at rest) and 400 mmols (lactic acidosis) of for instance lactic acid under physiological conditions.

The oxidation of the bases such as acetate, lactate, malate or citrate which can be metabolized may lead to an alkalosis because the metabolism of these anions in the form of acetic, lactic, malic, and citric acid uses up to 1 mol (acetic, lactic), or respectively 2 (malic) or even 3 (citric) mols H^+ each of which sets one HCO_3^- ion free. The hepatic elimination of the anions therefore causes an alkalosis of the organism. After treatment of a hypoxic lactic acidosis one often observes a rebound alkalosis as result of the lactate metabolization in the liver. This is similar in the case of infusion of acetate, lactate or malate, or citrate in connection with the transfusion of various blood products.

The metabolism of proteins on the other hand leads to the production of H^+ ions depending on the amino acid and does not set HCO_3^- free causing an alkalosis of the organism. The query whether the urea synthesis of the liver of about 20 g (0.33 mol) per day influences the acid-base balance or not has been controversely discussed in the international literature. However, facts proving the neutral urea synthesis are being provided in the present feature.

Under clinical conditions metabolic alkalosis is often observed in the operative field. This occurs predominantly after surgery or on the intensive care ward because for instance hypothermia, surgical procedure and anesthetics markedly reduce the liver function. Usually this phenomenon is ignored as a passing metabolic disorder or considered a rare curiosity. The main problem with this alkalosis is the consequently commencing hypoventilation. The arterial hypoxemia of the patient, probability of hypoxic tissue as the result of the left-shifted oxyhemoglobin dissociation curve, marked decrease in ionized calcium and the liberation of lipid soluble, neurotoxic NH_3 from NH_4^+ causes the clinical symptoms of somnolence and respiratory depression. The consequence is, for instance, difficult weaning from the ventilator.

Diagnostics and Methods

To this end a reliable and easy measure of liver deterioration remains the Holy Grail of specialists. The diagnostic possiblities to investigate liver metabolism and its influence on the acid-base balance are either confined to the prospective measurement of the circulation of the gastrointestinal tract by means of intramucosal pCO_2 measurement or the retrospective evaluation of the already existing changes in the metabolite or acid-base balance - such as changes in the lactate concentration of blood or the base excess.

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In this case, the assessment of the gastrointestinal circulation is of particular interest because this would enable us to examine portal circulation quantitatively and non-invasively for the first time. This method uses the CO_2 partial pressure of a CO_2 permeable catheter filled with 0.9% NaCl solution to determine the intramucosal pCO_2 ($piCO_2$, mmHg) as confirmatory parameter for the mesenteric perfusion. Reports in the literature suggest that the technique is of greatest benefit to patients at risk of developing reductions in splanchnic oxygenation in whom early detection of the ischemic episode could possibly guide treatment.

The calculation of the intramucosal pH (pHi) as suggested by the producer and several authors seems dubious and irrelevant. The hypothesis behind this method is that the decreased perfusion of the intestinal tract leads to an increase in mucosal CO_2 partial pressure since the CO_2 transport from the intestines is inhibited: the diagnosis of the 50% decrease in the intestinal circulation would for instance cause the arterio-venous CO_2 partial pressure difference ($avDCO_2$, mmHg) to double. Hypoxic tissue could lead to a concomitant CO_2 production if the anaerobically gained H^+ ions are transformed into CO_2 in the extracellular HCO_3^- barrier.

As we ponder these biochemical and physiological issues, the studies reviewed by this editorial comment appear to face the scientific enterprise with some major quandaries of different kinds. In his study, *Knichwitz* has seen the intramucosal pCO_2 measurement to be useful even though he reported several negative methodological problems. It is not possible to measure the nominal value of a 0.9% NaCl solution for instance equilibrated at 45 mmHg with any of the known blood gas analyzers. As observed in several other studies on this topic, i.e. *Schaffartzik*, *Nöldge-Schomburg* et al. and *Lampert* et al., the author attains the result that the estimation of the pCO_2 nominal value is by 4–58% lower than the actual value depending on the equipment. He suggests using a buffered solution to equilibrate which reduces these deviations but does not omit them. The author, *Knichwitz*, approves intramucosal pCO_2 measurements only if the investigator employs an adequate blood gas analyzer, a buffered solution for equilibration, own correction factors for the pCO_2 measurement and an adequate equilibration time as well as restrains from calculating the pHi. A reference range for the $piCO_2$ cannot be given, only the arterio-intramucosal difference can be used for diagnostic circulation measurements.

The same demands are toughly set by *Nöldge-Schomburg* et al. who derive their results from animal experiments. These studies prove that the intramucosal pCO_2 is as to be expected identical to the mesenteric-venous pCO_2 in that area so that the physiological arterio-intramucosal pCO_2 difference is approximately 10 mmHg ($avDCO_2 \approx aiDCO_2 \approx$ 10 mmHg).

Schaffartzik provides further contrary arguments regarding intramucosal pCO_2 measurements. The pHi reference range reported in literature must be questioned for naturally every alteration of the arterial pH towards acidosis must lead to a decrease in the pHi value which then of course is not caused by a decrease in circulation of the gastrointestinal tract. The calculation of the pHi from the $piCO_2$ has been rejected since every blood gas analyzer calculates the necessary HCO_3^- concentration differently. No explanations are offered in literature for the inconsistency in reported pH values and, although regular users talk of normal and abnormal pHi, this is only as useful as talking about normal and abnormal blood pressure or cardiac output values. The $piCO_2$ measurement or respectively the determination of pHi is not accepted in general clinical practice for many methodological and principle reasons.

The study by *Pichler* et al. on the employment of mucosal pH determination during liver transplant is a very interesting example. During the anhepatic course and the implantation of a veno-venous bypass the arterio-intramucosal pCO_2 difference remained constant and normal with 10 mmHg, yet the equilibration time dependent correction of the $piCO_2$ is 6–7 mmHg. It is rather questionable whether one should conclude that the circulation is really normal under these circumstances.

Should the intramucosal pCO_2 measurement ever be used in general clinical practice it would only be possible with the determination of the correction factor of the blood gas analyzer, the equilibration solution and time. This would only allow the consideration of the arterio-intramucosal pCO_2 difference ($aiDCO_2$) with a normal value of 10 mmHg for the evaluation of the perfusion. Mistakes in the placement of the catheter must be excluded, the acid production of the stomach must be forestalled and the equilibration time must be at least 60 minutes.

The routine measurement of the lactate concentration could enrich the general clinical practice if it were possible to assess the measurement value lactate easily and quickly from blood. The report by *Biedler* and *Mertzlufft* gives information of the first efforts to determine the lactate concentration with an electrode. Whereas the previous method, lactate PAP (Analyticon), which was time consuming and technically complicated gave reliable results with blood as well as plasma, the new electrode (Nova Biomedical) is unacceptably inexact at present and can therefore not be recommended at this time even though the easy measurement method and fast availability of results are obvious advantages of this method. The photometrical method TDxFLx (Abbott) which was also investigated cannot be employed because of value deviation of up to 54%.

In comparative evaluation of data and arguments concerning intramucosal pCO_2 measurements and the assessment of lactate concentration, *Mertzlufft* tries to depict the importance of both methods concerning their clinical value by challenging the more flagrant lapses in responsible literature. It is not surprising that the author comes to the conclusion that neither method is superior to the measurement of base excess in blood and has little clinical benefit for those patients in shock and who are actively resuscitated. More over, *Mertzlufft* reminds the combination of the diagnostic measures for the liver – lactate concentration (as the result of peripheral production and liver metabolism) –, and for measurement of the gastrointestinal perfusion (measurement of the arterio-intramucosal pCO_2 difference) as a parameter-junction that could be of great assistance, for instance in the case of multiple systems organ failure – enabling the clinician to initiate appropriate resuscitative treatment at an earlier stage, with a potential advantage over delayed intervention. This, however, is only possible if there are valid values for the par-

ameters and the momentary analysis duration of 90 minutes is shortened by far without loss of precision.

Contrary to the prior methods the base excess is a diagnostic paramter which has been accepted for several decades and only gives the opportunity to observe the non-respiratory acid-base balance disorder but also enables to commence quantitative treatment. Unfortunately, the calculation of the BE with blood gas analyzers has in the past given rise to incongruencies which had not been considered in the initial studies. In the report by *Müller-Plathe* the classical definitions and conventions are well summarized whereas *Zander* introduces a rather modified calculation of the BE that results in a value which according to definition does not vary with changes in the respiratory parameters pCO_2 and pO_2 (mmHg) or respectively sO_2 (%). This recalculation seems urgent and inevitably results in the demand that the nonrespiratory BE value is the same in the blood in front of the lung (mixed venous) and after the lung (arterial). The BE values of a sample can, however, vary up to 7 mmol/l using the blood gas analyzers offered by various companies whereas the evaluation of 60 equilibrated blood samples shows that the BE difference lies markedly below 1 mmol/l with correct calculation. The suggestion by *Zander* that BE values should only be computed and given including the oxygen saturation so that it is possible to determine the BE value from any arterial, venous and mixed venous blood sample is therefore of lasting importance. Simultaneously the same author introduced for the first time quality controls for the assessment of the base excess.

The consequent development of the classical concept of base excess assessment as a simple respiratory-independent value of the acid-base balance leads to an expansion of the term from being related only to blood or respectively plasma to being measurable in all body fluids which can influence the acid-base balance of the extracellular space metabolically, renally or iatrogenuously. With regard to this, the authors *Blöck* and *Zander* introduce a method to determine the BE in urine and also apply it to all infusion solutions as later explained in the Prophylatics part of this essay.

Clinical Physiology

Nöldge-Schomburg et al. were able to observe remarkable results concering the acid-base metabolism in animal experiments. The function of the liver as regards the acid-base balance in both cirulatory systems with four different arterio-hepatovenous and porto-hepatovenous parameters was assessed for the first time with the BE for the determination of the H^+ ion turnover, the pCO_2 for the measurement of the CO_2 concentrations, the plasma HCO_3^- concentration to evaluate the HCO_3^- turnover and the lactate concentration for the characterization of the metabolizable anions. Furthermore the flow rates of the circulation systems were determined. According to these results the liver is capable of transforming or respectively metabolizing 10 - 45 mmol H^+ ions per hour under physiological conditions as well as in the case of an endotoxemia which means that it sets free 45 mmols HCO_3^- into the plasma in one hour. If these results are transferred to the human being with a mean weight of 65 kg (instead of 24 kg of the animals) this would mean that the human liver can metabolically consume 30 - 120 mmol H^+ ions per hour. It is assumed that the transformation of H^+ ions is entered into the metabolism of lactate. It is of particular interest that ¼ of this consumption of H^+ ions is in the portal circulation. Thus, the authors provide the first proof of a CO_2 uptake in the liver which can be derived from a pCO_2 decrease during the passage through the portal vein to the hepatic vein. These observations are unique and are only comparable to the CO_2 partial pressure difference in the lung. Since CO_2 is produced and liberated into the blood during the passage from the hepatic artery to the hepatic vein as seen in all other organs, here CO_2 can only be consumed while circulating from the portal vein to the hepatic vein.

This is a significant observation concerning the urea synthesis: If CO_2 is taken up in the intrahepatic portal circulation the "modern" hypothesis on the urea synthesis from HCO_3^- ions with the liberation of CO_2 cannot be correct and the "traditional" theory of a neutral synthesis with CO_2 uptake must be retained.

In comparison to the kidneys with a daily H^+ ion elimination rate of 50 - 100 mmols the liver function with a similar hourly elimination rate is obviously superior in the non-respiratory regulation of the acid-base balance.

The association between liver metabolism and acid-base balance is investigated more thoroughly in the study by *Zander*. The uncharged endproducts of the metabolism of carbohydrates, fat, and proteins, which are CO_2, NH_3 and SO_3 with their compulsory reactions in the organism such as hydration, association, and dissociation result in the development of charged reaction partners such as H^+, NH_4^+, HCO_3^- and SO_4^{--} - which in turn can obviously influence the acid-base balance. This leads to the metabolic effect of organic acids and their metabolizable anions such as acetate, lactate, malate and citrate with complete oxidation as well as of the amino acids such as asparagine acid, glutamine acid, lysine, arginine, methionine, and cysteine.

The question whether the urea synthesis can influence the acid-base balance can be answered with a simple stoichiometric analytical study: The "traditional" hypothesis of the urea synthesis from CO_2 and NH_3, which is neutral concerning the acid-base balance is still valid whereas the so-called "modern" idea of a synthesis from HCO_3^- and NH_4^+ with an influence on the acid-base balances is refutable. This would mean that HCO_3^- is not a "waste product" which is derived from amino acid metabolism and elimination through urea synthesis but a "valuable" extracellular buffer-base whose existence is maintained with high energy input: 4,500 mmols are completely retained by the kidneys each day. New observations of liver function gained with animal experiments, the simple stoichiometrical considerations and the fact that children with congenital urea synthesis defect rarely develop metabolic alkalosis prove beyond doubt that the urea synthesis transforms the substances neutrally as regards the acid-base balance. All of these observations must be taken into consideration when giving enteral or parenteral nutrition.

After shock, trauma or sepsis hypoxic tissue can arise in the liver causing liver dysfunction which can be lead back to a decrease in circulation and microcirculatory disorders. Using fluorescence microscopy *Vollmar* showed that the assessment of liver microcirculation is possible and of clinical value. The treatment should take the pathophysio-

logical alteration of the microcirculation in the case of shock and sepsis into consideration.

The influence of the conservation conditions on the reperfusion after liver transplant is described by *Walcher* and *Marzi*. The optimal conditions for a sufficient postoperative organ function depend mainly on the different concepts of organ protection. These should inhibit cell edema, acidosis and energy depletion in order to prolong the conservation duration.

Clinical Practice

In general clinical practice the diverse therapeutical measures obviously only insufficiently allow for the in comparison to the kidneys and lung time-dependent possibilities of the liver to influence the acid-base balance. Infusion solutions for instance can therewith cause a dilution acidosis (a dilution of the HCO_3^- ions in the extracellular space) or an infusion acidosis (H^+ ion supply) or even an infusion alkalosis (too great a supply of metabolizable anions) depending on its composition. Under clinical conditions *Singbartl* et al. were the first to observe a dilution acidosis in a large number of patients if they were followed up to a Hb concentration of 6 g/dl under normovolemic hemodilution. The BE decreases as to be expected by approximately 6 mmol/l since more than 5 litres of bicarbonate-free infusions accordingly decrease extracellular HCO_3^- ion concentration.

The blood products are often distinguished by the fact that they cause an acidosis because of the acid stabilizers and lactic acid production during storage whereas one also observes an alkalosis depending on the citrate concentration and the metabolic rate of the liver. The number and velocity of transfusions determines whether the patient has a transfusion acidosis or alkalosis. This problem is thoroughly investigated in the *Schmitt* study. In comparison to blood transfusions with an initial acid load followed by a later potential base load the different component therapy tends to acid overloads. Fresh frozen plasma (FFP) acts as an alkalosis inducing agent since it contains approximately 70% citrate derived from stabilizers. Erythrocyte concentrates as obtained by auto transfusion devices which will not be further discussed in this study induce an acidosis for their HCO_3^- content is reduced to practically nil by the washing process.

According to *Schranz* et al. metabolic alkalosis after heart surgery in children is an important complication on pediatric wards which can cause BE values to increase to more than 20 mmol/l. This phenomenon can most probably be lead back to infusion of anions primarily in the form of citrate through blood products which are metabolized postoperatively because the anesthetics and hypothermia had more or less suppressed liver function intraoperatively. It cannot yet be evaluated which roll the missing renal compensation plays in the development of this alkalosis.

The liver metabolism can be systematically brought into action during dialysis in order to compensate the renal acidosis with metabolizable anions which can be transformed by the liver. The liver becomes the substitute of the kidneys concerning acid-base balance. The dialysis solutions can cause acidosis (HCO_3^- depletion during dialysis) or alkalosis (metabolism of anions following dialysis) if it contains acetate or lactate. During acetate hemodialysis a loss of 900 mmol of HCO_3^- must be compensated with the infusion of 1100 mmol acetate (potent HCO_3^- donor).

Peritoneal dialysis calls for the infusion of approximately 300 mmol lactate a day to compensate the loss of 200 mmol of HCO_3^-. The latter is the subject of *Quellhorst*: The same patients are observed during peritoneal dialysis as regards the reaction of the acid- base balance in the presence of acetate, lactate or bicarbonate.

In general, each of the three substances is described as well-suitable in case of intermittent (IPD) or continuous ambulatory peritoneal dialysis (CAPD) as well. However, despite evident advantages of peritoneal dialysis using bicarbonate (the physiologic buffer), the respective disadvantages (especially instability) as well as the unsolved complaints due to side effects following application of acetate give reason, to the author's opinion, for recommendation of lactate as the dialyzing agent to be still in practice.

Prophylactics

The infusion solutions are only marked according to their contents and not their influence on the acid-base status of the patient. According to *Zander* the declaration should be improved and show the actual, i.e. pH dependent composition. It would be particularly important to add the declaration of the base excess (BE, mmol/l) and the BE_{pot} (mmol/l) in order to show the alteration of the acid-base balance after infusion and metabolization. The sample of over 30 infusion solutions shows that the BE values are too high resulting in a BE of approximately – 2 to – 5 mmol/l in a 65 kg patient before metabolization of the anions and amino acids and without renal compensation. The potential BE values are described as being within the range of + 8 and – 198 mmol/l. A litre infusion would therewith lead to BE values of approximately 0 to – 13 mmol/l in the same patient with metabolization of the anions and amino acids but without renal compensation. The example set by Ringer's solution elucidates that a missing HCO_3^- concentration of 24 mmol/l with the complication of a dilution acidosis can under optimal conditions (liver function fully intact) be compensated by 27 mmol/l lactate. The lactic acidosis, however, is a contraindication for the application of Ringer's solution since liver metabolism obviously does not suffice to transform the lactic acid which derives from hypoxic chemical reactions. The rebound acidosis elucidates that the remaining lactate after treatment of lactic acidosis – the lactic acid and not the lactate causes the acidosis – can create problems for the patient and the doctor initiating therapy as well.

Liver function and its interrelation with the acid-base balance in the pre-, peri-, and postoperative phases of clinical management discloses as being more subtle and common than believed. Decisions that once might have been carefully considered now seem urgent. To conclude, as the "idea of liver" is not yet in general use, we are faced with an opportunity to audit its introduction, something we have failed to do for other clinical considerations.