mH^+ mobilization model: a new tool to investigate acid-base homeostasis during dialysis

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Introduction

Quite surprisingly, variation of blood bicarbonate concentration ($[HCO_3]$) during hemodialysis is a poorly investigated issue. Our understanding is still mainly limited to the start and end values, and to a few observations showing that $[HCO_3]$ rises rapidly during the first 2 hours of treatment and then remains flat in the second part of the treatment, never reaching the level of dialysis bath $[HCO_3]$. The latter feature is sometimes referred to as the mystery of bicarbonate disappearance, because little is known about what happens to the bicarbonate that diffuses from the bath to the patient in the last few hours of the hemodialysis treatment.

For half a century, nephrologists resorted to the apparent bicarbonate space (ABS) model to approach this acid-base issue. The term "apparent" highlights that bicarbonate distribution volume is larger than its physical space in the body. According to this model the space volume where infused bicarbonate is diluted depends on the initial $[HCO_3]$. Although the ABS model does not provide insights on acid-base events, it has been regarded as *the* tool to predict $[HCO_3]$ during bicarbonate administration.

The availability of blood gas analyzers in hemodialysis units has stimulated new investigations into the acid-base events during a dialysis treatment and put the blood $[HCO_3]$ curve under the spotlights. Sargent, Marano, Marano and Gennari have developed a "mH^+ mobilization model" to shed new light on this mystery. This model shows an impressive fit to experimental data collected by using the OPTI CCA-TS2 system at the Maria Rosaria Clinic in Pompeii, Italy. Fifty years after the great trans-atlantic acid-base debate, a trans-atlantic multidisciplinary effort by physicians and engineers provides a reliable tool to gain insights on acid-base events during dialysis.

Bicarbonate distribution space

The mH^+ mobilization model, in which H^+ stands for hydrogen ion, characterizes and quantifies determinants of $[HCO_3]$ allowing a new look at the physiological response to rapid bicarbonate addition during hemodialysis. According to this model, all the bicarbonate infused is considered to be confined into the extracellular fluid (ECF), a well-defined anatomical compartment. $[HCO_3]$ is the ratio between the amount of bicarbonate in the extracellular space and its volume.

Bicarbonate addition by diffusion

Bicarbonate addition occurs mainly by diffusion from the dialysis bath according to concentration difference between bath and ECF taking also in account the bicarbonate dialysance. Concentration difference (the driving force for bicarbonate entry) progressively decreases as $[HCO_3]$ increases and bicarbonate influx decreases accordingly.

Fluid subtraction within the dialyzer leads to (convective) removal of bicarbonate present in blood coming back to the patient. The amount removed is considered to be somewhere in between blood and bath bicarbonate concentration. In the experiments carried out at Maria Rosaria Clinic a safe volume reduction close to 0,5 l/h was been applied. At any given moment, the mH^+ mobilization model computes the bicarbonate influx net of convective removal (J_{bic}): it amounts to 1.6 mEq/min at the dialysis start but goes down to one-third or less at the end of the treatment.

The acetate contribution

The small content of acetate in dialysis bath, ten times less than bicarbonate, further contributes to base addition during dialysis because of rapid metabolic one-to-one acetate conversion to bicarbonate. Quantitative analysis of this contribution has led to surprising results: one third of bicarbonate added into the ECF comes from acetate diffusion and metabolism (Km Cbac). This occurs because blood acetate concentration is always close to zero and the bath-blood acetate gradient, although narrow, never collapses. Furthermore, the blood exiting the filter contains only one or two mEq/l of acetate, so fluid removal by ultrafiltration does not substantially affect acetate contribution to base addition. These unexpected findings might lead in the near future to changes in dialysis design and bath composition. In fact,dialysis bath containing acetate concentration double than that used in Pompeii study appears to be safe, well tolerated and commercially available.

H^+ mobilization

During dialysis hydrogen ions (H^+) enter the ECF and consume bicarbonate.

Some of these H^+ comes back from intracellular buffers which had combined with H+ in the interdialytic period and others come from newly produced organic acids. H^+ mobilization

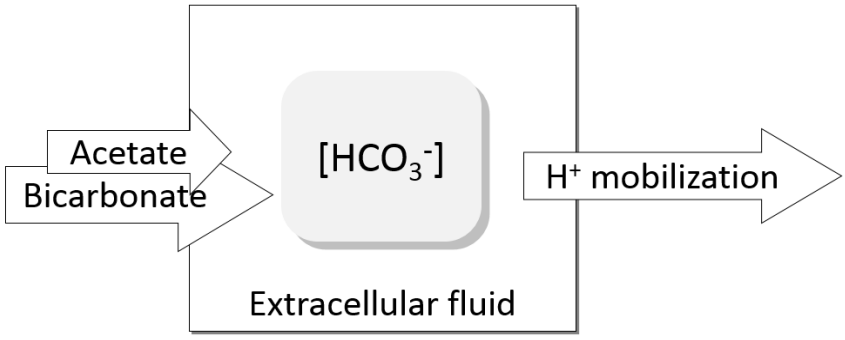
and release into the ECF is intended to offset pH increase due to base addition, but it actually is the cause of disappearance of some of the added bicarbonate.

The magnitude of H^+ mobilization is proportional to [HCO_3] increase from its predialysis value (times the mobilization constant: mH^+). Accordingly, the H^+ influx abruptly increases to 0.86 mEq/min at 60 mins and remains strong thereafter, mirroring dynamic of [HCO_3]. From a quantitative point of view H^+ mobilization is meaningful: at the end of the treatment so much H^+ are mobilized that 90% of delivered bicarbonate has been neutralized. From an acid-base perspective, the H^+ mobilization makes dialysis less efficient. The largest part of mobilized H^+ is for restoring body buffers, a physiological process needful to maintain acid-base homeostasis, but at least one-third of H^+ comes from production of new organic acids such as lactic acid and β-hydroxybutyric acid. This process is energy consuming, potentially catabolic and irreversible, because anions of these acids are subsequently lost in dialysis bath. In addition, the bicarbonate consuming reaction with organic acids produces carbon dioxide, further increasing lung workload. In many respects, organic acid production is a maladaptative response to base addition.

Concentration or content?

Finally, we have to address the issue of *concentration* versus *content*. We usually look at, and OPTI TS2 provides, the [HCO_3] value but we have to think also in terms of content as well as concentration because dialysis treatment changes both the numerator and denominator of the ratio of bicarbonate content and ECF volume: bicarbonate is added at the same time as ECF volume is decreased. Obviously, blood bicarbonate concentration - [HCO_3] – is nothing else than the amount of bicarbonate dissolved in its distribution volume, the ECF in our case. In the last half of dialysis treatment more bicarbonate is consumed by H^+ mobilization than is added in the ECF, meaning that the content of bicarbonate decreases. Because ECF volume also decreases, the ratio, namely [HCO_3], does not. Regardless any therapeutic implication of this relevant and unexpected finding, it should be acknowledged that [HCO_3] value is not a reliable hallmark of bicarbonate dynamics during dialysis. This work indicates that mH^+ mobilization model is useful tool to investigate base addition.

Figure 1: mH^+ Mobilization Model



Legend: On the left the influx of Bicarbonate net of convective removal by ultrafiltration and Acetate contribution to blood bicarbonate concentration in the extracellular fluid. On the right Bicarbonate removal by H^+ mobilization. [HCO_3^-] stands for blood bicarbonate concentration.

Figure 2: Model Equations

$$\frac{d}{dt}(Cb\,V_{ecf}) = J_{bic} + K_m\,Cb_{ac} - mH^+(Cb - Cb_0)$$

$$J_{bic} = D(Cd - Cb) - Q_f\frac{Cd + Cb}{2}$$

Top equation is differential equation ruling the H^+ mobilization model where ***Cb*** stands for blood bicarbonate concentration and $\boldsymbol{V_{ecf}}$ for extracellular fluid volume. The first term on the right $\boldsymbol{J_{bic}}$ is net bicarbonate flux, depicted in detail below. The second term $\boldsymbol{K_m\,Cb_{ac}}$ is acetate contribution computed as blood acetate concentration $\boldsymbol{Cb_{ac}}$ times its metabolic clearance $\boldsymbol{K_m}$. The third term $\boldsymbol{-mH^+(Cb\text{-}Cb_0)}$ is bicarbonate subtractive component due to hydrogen ions mobilization, computed as mobilization constant $\boldsymbol{mH^+}$ times blood bicarbonate increase from pre-dialysis value $\boldsymbol{Cb_0}$.

Bottom equation is bicarbonate influx $\boldsymbol{J_{bic}}$ from dialysis bath to the extracellular fluid. It is equal to bath-blood bicarbonate concentration difference ***Cd-Cb*** times bicarbonate dialysance ***D***. From this amount has to be subtracted the amount of bicarbonate removed by ultrafiltration. This is equal to ultrafiltration rate ***Qf*** times bicarbonate concentration in blood exiting the filter computed as the average between bath and blood bicarbonate concentration ***(Cd+Cb)/2***.

Reference:

Sargent JA, Marano M, Marano S, Gennari FJ.
Acid-base homeostasis during hemodialysis: New insights into the mystery of bicarbonate disappearance during treatment.
Semin Dial. 2018 May 29. doi: 10.1111/sdi.12714.