letters to the editor

Acid-base balance: a quest for alkalinity data

To the Editor: Two letters to the editor that were recently published in this journal (1, 13) refer to papers (2, 12) dealing with the role of the liver and the kidneys in blood acid-base balance, namely their contributions to net H^+ or OH^- production. The issues raised focused on whether the overall work of the kidney or the liver results in a net increase or decrease of blood HCO_3^-. Both authors discussed several biochemical reactions that are involved in acid-base regulation, e.g., amino acid oxidation or urea synthesis. Although these reactions occur in a living organism, their relative importance in net acid-base balance cannot be quantitatively assessed as yet due to insufficient experimental data on the actual rates of these reactions in each organ.

Traditionally, changes in acid or base content of physiological solution are determined by evaluating titratable acidity (TA) (7), bicarbonate, and ammonia. For example, urinary net acid excretion (NAE) is equal to $[NH_4^+] + [TA] - [HCO_3^-] \times \dot{V}$ where $\dot{V}$ is urine flow rate. Conceptually correct, this approach suffers from an inability to accurately quantitate the desired parameters. Schwartz and co-workers (10) showed that determination of titratable acid by titrating urine to the pH of plasma is incorrect and the error can be greater than 200%. Furthermore, determination of HCO_3^- is often based on the Henderson-Hasselbalch equation where precise knowledge of pK_1 and CO_2 solubility (α) are required (7). Unfortunately these factors are not precisely known (4, 7) and can change dramatically in urine (3).

These examples highlight the fact that it is difficult to quantitate acid-base changes in complex multibuffer solutions. So the actual question concerning net acid-base balance is: what are the parameters to be measured and by what analytical methods?

The subject of acid-base balance in natural waters has been dealt with successfully by geochemists and marine chemists for over 40 years using the concept of alkalinity (11). Recently we have applied this concept to physiology, and our preliminary studies have been published in an article (4) and abstract (5).

Alkalinity has been defined historically (11) as the number of equivalents of strong acid required to titrate 1 liter (or kg) of seawater to the endpoint corresponding to the formation of carbonic acid from bicarbonate, i.e., when

$$[H^+] = [HCO_3^-] \qquad (1)$$

A recent evaluation of the concept and a suggested exact definition of total alkalinity in seawater as well as a procedure for this estimation from titration data has been given by Dickson (6) and others (8, 9).

Total alkalinity is thus defined as the total concentration (in eq/l) of the ions that will combine with protons at the end point

$$\text{total alkalinity} = \Sigma Q_p + [OH^-] - [H^+] \qquad (2)$$

Q_p is the (negative) charge of a protolytic (proton combining) species i that is neutralized by a proton at the endpoint and $[H^+]$ and $[OH^-]$ are the concentration of hydrogen and hydroxyl ions in solution.

Charge neutrality requires that the charge attributed to total alkalinity be balanced by the charge held by the nonprotolytic ions (e.g., Na^+, K^+, Cl^-, SO_4^{-2}) in solution (6). Consequently, alkalinity is a truly conservative variable, since it follows rigid mass balance rules and can be modified only by acid-base changes. It should be emphasized that alkalinity is not related to the concentration of hydroxyl ions in solution, nor is it related by a simple function to the definition of titratable acidity (7).

In physiological solutions, where bicarbonate and phosphate are the main buffers, alkalinity is defined as

$$\text{total alkalinity} = [HCO_3^-] + 2[CO_3^{2-}] + 2[PO_4^{3-}] + [HPO_4^{2-}[+ [OA^-] + [OH^-] - [H^+] \qquad (3)$$

where brackets denote concentrations and OA^- is the contribution of weak organic acids ($pK_a > 4.5$). The endpoint (i.e., when alkalinity = 0) occurs when $[H^+]$ is equal to the sum of the concentrations of the main protolytic species, e.g., HCO_3^- (8). It is important to note that CO_2 changes have no effect on total alkalinity because they produce (or remove) equivalent amounts of H^+ and HCO_3^- ions, resulting in a net zero change in alkalinity (*Eq. 2*).

Precise measurement of alkalinity can be carried out by the modified Gran titration (4), the equivalence point titration (determination of alkalinity by the point of maximal pH decline per acid increment) (8), or by the fixed endpoint titration method (9).

Using any of these methods the endpoint for determination of total alkalinity in physiological solutions such as a Krebs-bicarbonate buffer, normal plasma, and most urine samples has been found in our experiments to vary between pH 4.1 and 4.7.

Since alkalinity is a true measure of net base excess in a solution, alkalinity differences between inflow and outflow (in meq/min) of a given system can be used to determine the rate of production or consumption of acid. If we take the kidney (Fig. 1), for example, where RPF is the afferent plasma flow (l/min), $\dot{V}$ is the urine flow rate (l/min), (RPF − $\dot{V}$) is the efferent plasma flow (l/min), A_1 is the alkalinity of afferent blood (meq/l), A_2 is the alkalinity of urine (meq/l), A_3 is the alkalinity of efferent blood (meq/l), and KA is the net proton consumption or production by the kidney (meq/min). The rate that total alkalinity enters the kidney via the renal artery ($RPF \cdot A_1$ in meq/min) + the renal proton consumption rate (KA in meq/min) must be equal to the rate of alkalinity that leaves the kidney [$\dot{V} \cdot A_2 + (RPF - \dot{V}) \cdot A_3$, in meq/min], and the following relationships hold

$$RPF \cdot A_1 + KA = \dot{V} \cdot A_2 + (RPF - \dot{V}) \cdot A_3 \qquad (4)$$

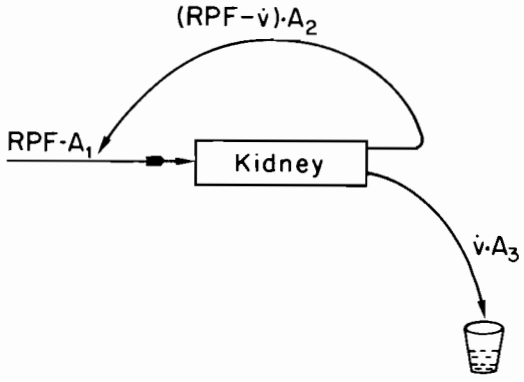

FIG. 1. Alkalinity outflow $(RPF - \dot{V}) \cdot A_2 + \dot{V} \cdot A_3)$ is equal to alkalinity inflow $(RPF \cdot A_1)$ + alkalinity production (proton consumption) by the kidney (KA).

from which we can determine the net acid consumption or production by the kidney

$$KA = [\dot{V} \cdot A_2 + (RPF - \dot{V}) \cdot A_3] - RPF \cdot A_1 \quad (5)$$

and also have an insight for acid or base excretion and reabsorption. Thus it is evident that if $KA > 0$ then net base was produced; if $KA < 0$ then net acid was produced.

Furthermore, if $KA > 0$ and $KA = \dot{V} \cdot A_2$ alkalinity was produced (proton consumed) and all of it was excreted; if $0 < \dot{V} \cdot A_2 < KA$ then alkalinity was produced, part of it was excreted and the rest reabsorbed. The last possibility in this set of $KA > 0$ is that $KA < \dot{V} \cdot A_2$, then the excretion of alkalinity in urine is composed of all the produced alkalinity and some of the filtered alkalinity.

However, if $KA = 0$ then net acid was produced by the kidney (or alkalinity consumed). It is more likely that this net acid production will be reabsorbed, since its excretion requires that $(RPF - \dot{V}) \cdot A_3 > RPF \cdot A_1$, which obligates $\dot{V} \cdot A_2 < 0$ and since physically $\dot{V}$ cannot be negative, A_2 (urinary alkalinity) ought to be negative (*Eq. 5*). Even in the most acidic urine samples (pH 4.6–4.9) we found 9–12 meq/l of alkalinity (unpublished data). Thus it is important to note that the net production of acid by the kidney results in efferent alkalinity flow lower than afferent flow.

If alkalinity is measured in all inflows and outflows of a system (Fig. 1), NH_4^+ will not be part of the net acid base budgeting. Any ammonia change that will interfere with acid base balance will influence one of the measured alkalinities, and the direction of influence will be detected by applying *Eq. 4*. Measurements of ammonia will indicate the metabolic process responsible for an equivalent alkalinity change.

If alkalinity is not measured in one of the flows, then, based on the assessment that any excretion of NH_4^+ is associated with an equivalent increase of HCO_3^- in the system (NH_4^+ – alkalinity) $\dot{V}$ will be the net acid excretion, as it is in human urine (5).

The main importance of alkalinity is that it is a measurable quantity (6, 8, 9). Although some difficulty might be encountered with high concentrations of organic anions having borderline pK_as in the range of 4 to 5, this problem can be dealt with by a double titration procedure (5) followed by determination of the equivalence point (unpublished data).

Finally we would like to make a brief comment on $M^+ - Cl^-$ as an indicator for acid-base balance as suggested by one of the authors (13). This term, albeit akin to the concept of alkalinity (6), is of limited theoretical and practical value when taken out of the context of the alkalinity. The separation of $M^+ - Cl^-$ from other nonprotolytic ions (over the pH range of interest) and anions of strong organic acids introduces a big error when these compounds are present at significant concentrations, as in the blood of hepatic and portal veins. By contrast, the concept of alkalinity is directly related to the problem of net acid-base balance, and once measured can give a reliable indication of net acid production or consumption.

We thank Dr. S. R. Gullans for his help in preparing this letter and Jim Schafer for his critical review. We thank Michelle Hardiman for her secretarial assistance.

Present address of Z. H. Burbea: Renal Div., Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

REFERENCES

1. ATKINSON, D. E. Ureagenesis and pH homeostasis. *Am. J. Physiol.* 250 (*Renal Fluid Electrolyte Physiol.* 19): F1128–F1129, 1986.
2. ATKINSON, D. E., AND E. BOURKE. The role of ureagenesis in pH homeostasis. *Trends Biochem. Sci.* 291–302, 1984.
3. BURBEA, Z. H., C. CHAIMOVITZ, AND S. BEN-YAAKOV. An increase in urine osmolarity (Vosm) is the primary cause of high urinary pCO_2 ($UpCO_2$) (Abstract). *Clin. Res.* 34: 591, 1986.
4. BURBEA, Z. H., C. CHAIMOVITZ, AND S. BEN-YAAKOV. Determination of carbonate alkalinity and apparent dissociation constants in a multiprotolytic system. *Talanta* 32: 1023–1026, 1985.
5. BURBEA, Z. H., C. CHAIMOVITZ, AND S. BEN-YAAKOV. Net alkalinity balance (NAB). An improved method for measurement of net acid excretion (NAE) (Abstract). *Clin. Res.* 34: 591, 1986.
6. DICKSON, A. G. An exact definition of total alkalinity and a procedure for the estimation of alkalinity and total inorganic carbon from titration data. *Deep Sea Res.* 28A: 609–623, 1981.
7. HENDERSON, L. J. A critical study of the process of acid excretion. *J. Biol. Chem.* 9: 403–424, 1911.
8. MCINTYRE, F. End point and equivalence point attributed to Jon Lyman. *Marine Chem.* 6: 187–192, 1978.
9. PEARSON, F. Fixed end point alkalinity determination. *Water Pol. Cont. Fed.* 53: 1243–1252, 1981.
10. SCHWARTZ, B. W., N. BANK, AND R. W. P. CUTLER. The influence of urinary ionic strength in phosphate pK_2 and determination of titratable acid. *J. Clin. Invest.* 38: 347–356, 1959.
11. SVERDRUP, H. U., M. W. JOHNSON, AND R. H. FLEMING. *The Oceans: Their Physics, Chemistry and General Biology.* Englewood Cliffs, NJ: Prentice-Hall, 1940, p. 1087.
12. WALSER, M. Role of urea production, ammonium secretion and amino acid oxidation in acid-base balance. *Am. J. Physiol.* 250 (*Renal Fluid Electrolyte Physiol.* 19): F181–F188, 1986.
13. WALSER, M. Reply. *Am. J. Physiol.* 250 (*Renal Fluid Electrolyte Physiol.* 19): F1129–F1130, 1986.

Zvi Hai Burbea
Internal Medicine Division
Soroka Medical Center
Beer-Sheva, Israel

Cidio Chaimovitz
Department of Nephrology
Soroka Medical Center
Beer-Sheva, Israel

Sam Ben-Yaakov
Department of Electrical and Computer Engineering
Ben-Gurion University
Beer-Sheva, Israel