

## Defining Acid-Base Status in Hemodialysis: Is Bicarbonate Enough?

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The potential complications of chronic metabolic acidosis have long been a concern among patients with advanced chronic kidney disease. In response, clinical practice guidelines mostly recommend maintaining serum

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bicarbonate at a level  $\geq 22$  mEq/L in patients receiving hemodialysis.<sup>1</sup> One key assumption underpinning these guidelines is that the serum bicarbonate measured from a predialysis blood sample is an accurate indicator of acid-base status. Supporting this assumption is dialysis patients' lack of kidney function, thereby eliminating or at least greatly attenuating the kidney's compensatory response to a respiratory disorder. Thus, changes in serum bicarbonate level larger than 1 to 2 mEq/L are typically assumed to be due to metabolic disturbances.

This assumption is problematic for several reasons. One major consideration is the potential for inaccurate measurement of serum bicarbonate. Several reports have identified falsely low serum bicarbonate values from samples drawn at dialysis facilities.<sup>2-4</sup> Potential causes of spuriously low bicarbonate levels include suboptimal sample handling and processing and the shipping process. Another concern is the presence of concomitant respiratory disorders, which, by altering the pH but not inducing large changes in serum bicarbonate levels in dialysis patients, confound attempts at diagnosis of acid-base disorders using only the predialysis bicarbonate level. In an Italian study of 362 blood gas samples drawn from 53 patients at the start of a hemodialysis session, respiratory acid-base disorders were present in 41%; of samples with a bicarbonate level  $< 22$  mEq/L, 38% had a concomitant respiratory disorder.<sup>5</sup> The implication of this study is that among maintenance hemodialysis patients, low serum bicarbonate level identifies neither the severity of acidemia nor the degree to which acidemia is due to a metabolic disturbance versus a concomitant respiratory acidosis. Additionally, a low serum bicarbonate level may represent a concomitant respiratory alkalosis and an alkalemic pH. One may be forgiven for thinking this sounds similar to the usual acid-base considerations, in which a blood gas measurement is truly the only way to determine what type of acid-base disorder is present.

In this issue of *Kidney Medicine*, Woodell et al<sup>6</sup> prospectively evaluated the utility of serum bicarbonate as the sole measurement determining acid-base treatment decisions. They enrolled 25 male hemodialysis patients and assessed acid-base status pre- and postdialysis for 3 months, using both blood gas and chemistry measurements. Nine patients were misclassified at least once as acidemic using a serum

bicarbonate threshold  $< 22$  mEq/L based on serum chemistry results (note that the chemistry assay does not measure only bicarbonate, but rather the total carbon dioxide [tCO<sub>2</sub>]). Of 13 instances with tCO<sub>2</sub> levels  $< 22$  mEq/L, pH was  $< 7.38$  in only 3. Although a low tCO<sub>2</sub> level did not occur commonly (13 of 71 predialysis samples with both a chemistry and blood gas result), when it did, the utility for clinical decision making was strikingly poor.

Importantly, the major driver of misclassification appeared to be spuriously low values for tCO<sub>2</sub>. In all misclassified samples, tCO<sub>2</sub> level was lower than the bicarbonate value calculated from the blood gas. This is notable because one expects the tCO<sub>2</sub> to be  $\sim 1.2$  mEq/L higher than the calculated bicarbonate level. Therefore, the unexpectedly low tCO<sub>2</sub> values strongly suggest measurement error. Because these chemistries were measured at the local hospital laboratory on the day in which they were collected, the most likely explanation is that the samples remained uncapped in the laboratory for an excessive time before measurement; for each hour of exposure, the measured value can be expected to decline  $\sim 2.5$  mEq/L.<sup>7</sup> This has been a concern in large commercial laboratories, but one wonders how this varies across local hospital laboratories as well. The current report, conducted at a single Veterans Affairs dialysis unit, does not permit us to extrapolate to other centers. However, this is an important question to address.

If this is not a systematic error, that is, the duration of exposure to ambient air varied between samples, then basing treatment decisions on an average of recent monthly laboratory values could reduce the misclassification rate.<sup>8</sup> Woodell et al found that averaging monthly data reduced the number of misclassified patients from 10 to 2. However, such an approach may be difficult to translate to clinical practice and might require that a rolling average be added to the monthly laboratory report, averaging values across several months. In addition, this does not address the possibility of a non-negligible systematic error due to sample processing techniques in certain laboratories. Clearly, accurate and reproducible data are a prerequisite for rational clinical decision making.

The data reported by Woodell et al provide additional insight into the ramifications of misdiagnosed predialysis acidemia. The mean postdialysis pH in all samples was 7.48, indicative of the alkalemia induced by rapidly repleting buffer and bicarbonate stores in several hours when losses occur gradually over days. In the 10 dialysis sessions characterized by misclassified predialysis acidemia, the median postdialysis pH was 7.51. In 7 cases, the dialysate bicarbonate prescription was  $\geq 35$  mEq/L. The use of high-bicarbonate dialysate is typical of nephrology practice in the United States.<sup>9</sup> We do not know whether a high-bicarbonate

dialysate was prescribed specifically to treat a low predialysis bicarbonate level, but this illustrates the potential for inducing significant alkalemia if an increase in dialysate bicarbonate concentration is prescribed inappropriately.

Whether this alkalemia is detrimental remains unclear. Certainly, severe alkalemia has adverse consequences, but the degree to which the usual postdialysis alkalemia affects patients has not been rigorously examined. A large international cohort study reported an association of higher dialysate bicarbonate concentration with increased all-cause mortality, independent of the predialysis serum bicarbonate level.<sup>9</sup> The authors hypothesized that the use of high-bicarbonate dialysate might be dangerous due to postdialysis alkalemia, but their study did not have postdialysis measurements and a subsequent Japanese cohort study found no association of postdialysis alkalemia with adverse outcomes.<sup>10</sup> Hypokalemia and hypocalcemia have been reported with high-bicarbonate dialysis, raising concern over the potential for promoting cardiac arrhythmia.<sup>11-13</sup> Reassuringly, Woodell et al observed no change in ionized calcium levels at the end of dialysis. A recent study of 47 hemodialysis patients dialyzed against a median dialysate bicarbonate concentration of 37 mEq/L found no association between the intradialytic increase in serum bicarbonate level and the rate of ventricular premature contractions.<sup>14</sup> Intradialytic hypoxemia is another potential consequence of high-bicarbonate dialysis, one that has only been examined in small studies and was not addressed by Woodell et al.<sup>15-17</sup> Thus, despite the theoretical concerns regarding high-bicarbonate dialysate and postdialysis alkalemia, more work is needed to define the relevance of these concerns to clinical practice. Avoidance of large rapid perturbations in acid-base status appears prudent, but proposals to avoid such perturbations by using lower bicarbonate concentrations in the dialysate must address the potential long-term risks of predialysis metabolic acidosis.

This report by Woodell et al<sup>6</sup> provides further evidence of the limitations of relying solely on the predialysis serum bicarbonate level. Future studies should include the following objectives: (1) continue to define the optimal method to assess acid-base status in hemodialysis patients, perhaps using a patient-centered rather than a one-size-fits-all approach; and (2) determine whether more accurate assessment improves clinical decision making and whether this translates into improved clinical and patient-centered outcomes. Future guidelines addressing the care of dialysis patients should take these factors into consideration.

## ARTICLE INFORMATION

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