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Treatment of Metabolic Acidosis in Hemodialysis Patients Is Biased by Type of Vascular Access

Lukas Bock[1], Alexander Keil[1], Stefan Flury[1] and Andreas D. Kistler[1,2]

[1]Division of Nephrology, Department of Medicine, Cantonal Hospital Frauenfeld, Frauenfeld, Switzerland; and [2]University of Zurich, Zurich, Switzerland

Correspondence: Andreas D. Kistler, Department of Medicine, Cantonal Hospital Frauenfeld, Pfaffenholzstrasse 4, 8501 Frauenfeld, Switzerland. E-mail: andreas.kistler@stgag.ch

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INTRODUCTION

Considerable debate exists about the optimal treatment of metabolic acidosis in hemodialysis patients,[1,S1,S2] and interventional studies evaluating the effect of different target predialysis bicarbonate levels on outcomes are lacking. Observational studies have found somewhat conflicting results regarding the correlation of predialysis bicarbonate levels with cardiovascular and all-cause mortality but mostly pointed to a U-shaped relationship after adjustment for confounding factors.[2–6] On the basis of these observational studies, guidelines have formulated target predialysis serum bicarbonate levels.[S3–S5]

The type of blood samples used for acid-base assessment in hemodialysis patients varies by type of vascular access: in patients with an arteriovenous access (fistula or graft), arterial blood is sampled, whereas patients with a dialysis catheter have central venous blood analyzed. Owing to the physiological generation of carbon dioxide (CO_2) in the peripheral tissue, acid-base balance systematically differs between arterial and venous blood. Of the studies linking mortality to predialysis serum bicarbonate levels or correlating predialysis bicarbonate levels with nutritional parameters,[7,S6,S7] some systematically excluded patients with catheters,[3–5] but most included patients with both types of vascular access and did not analyze results by type of vascular access or report the percentage of patients with catheters.[2,6,7,S6,S7] Likewise, the cited guidelines do not mention vascular access when providing their target bicarbonate levels.

The aim of the present study was to determine the difference between arterial and venous bicarbonate levels in patients on intermittent outpatient hemodialysis and to assess whether the different nature of the blood samples in patients with catheters versus arteriovenous access resulted in a systematic bias in the treatment of metabolic acidosis.

RESULTS

Predialysis Bicarbonate Values in Arterial Versus Central Venous Blood

Predialysis blood samples were simultaneously drawn from both vascular access sites in 18 hemodialysis patients who temporarily had both an arteriovenous access and a catheter (Supplementary Methods). Patient characteristics are shown in Supplementary Table S1. Actual bicarbonate level was consistently higher in catheter samples compared with those in arteriovenous access (22.4 ± 2.6 mmol/l vs. 20.7 ± 2.3 mmol/l, $P < 0.001$), whereas pH was lower (7.33 ± 0.03 vs. 7.36 ± 0.04, $P < 0.001$) (Figure 1a and c). Bland-Altman plots revealed a mean absolute difference of 1.7 mmol/l for each pair of bicarbonate measurements with substantial variability between patients, as revealed by comparatively large 95% limits of agreement (LOA) (95% LOA −0.3 to 3.6 mmol/l). For pH, the mean absolute difference was −0.03 (95% LOA −0.07 to 0.01) (Figure 1b and d).

Of the 18 paired measurements, 8 were performed in the central laboratory on a blood gas analyzer that reports standard bicarbonate levels. When comparing standard bicarbonate levels between both types of vascular access, measurements did not significantly differ (arteriovenous access: 22.1 ± 2.8 mmol/l; catheter: 22.0 ± 2.7 mmol/l, $P = 0.591$). Compared with actual bicarbonate levels,

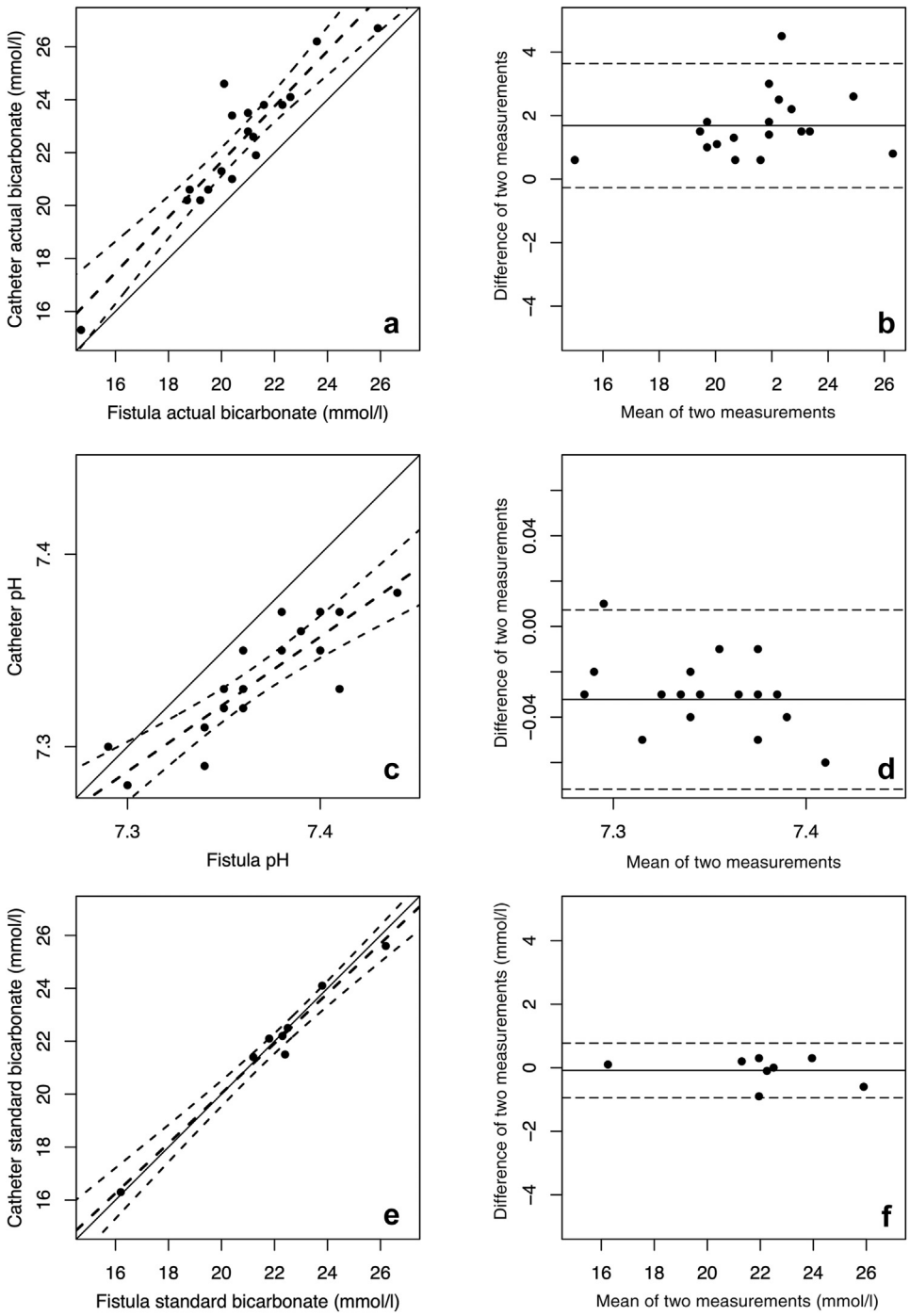

Figure 1. Actual bicarbonate (a), pH (c), and standard bicarbonate (e) levels in samples from the arteriovenous access (fistula/graft) versus samples from the dialysis catheters, line of equality (continuous), and linear regression with 95% CIs (dashed). Corresponding Bland-Altman plots of actual bicarbonate (b), pH (d), and standard bicarbonate (f) levels with mean of measurement pairs vs. respective absolute difference, mean absolute difference of measurements (straight), and 95% limits of agreement (dashed).

variability of the absolute differences of each pair of measurements was considerably lower with a mean absolute difference of −0.1 mmol/l and less scatter (95% LOA −0.9 to 0.8) (Figure 1e and f). Mean standard bicarbonate level was higher than mean actual bicarbonate level for samples drawn from the arteriovenous access (22.1 ± 2.8 mmol/l vs. 21.4 ± 3.2 mmol/l; Supplementary Figure S1A) and lower than mean actual bicarbonate level for samples drawn from catheters (22.0 ± 2.7 mmol/l vs. 22.9 ± 3.5 mmol/l; Supplementary Figure S1B).

Acid-Base Parameters and Acidosis Treatment by Type of Vascular Access

We next compared predialysis and postdialysis acid-base parameters as well as the prescribed dialysate bicarbonate level in 67 chronic hemodialysis patients

with an arteriovenous access versus 45 patients with a dialysis catheter (Supplementary Methods). Although mean predialysis bicarbonate levels were identical in the 2 vascular access groups, the mean prescribed bicarbonate level was 1.7 mmol/l higher in patients with an arteriovenous access compared with patients with a catheter (Table 1). Postdialysis actual bicarbonate level was significantly higher in patients with an arteriovenous access, and both predialysis and postdialysis pH were significantly lower in patients with a catheter (Table 1). Bicarbonate level and pH increased more during a single hemodialysis session in the arteriovenous access group (Supplementary Figure S2A and B).

Given the differing dialysate bicarbonate prescriptions, we evaluated whether predialysis and postdialysis levels of standard bicarbonate differed between the vascular access groups. Standard bicarbonate values were available for 75 of 112 patients, and they were significantly lower in patients with a catheter compared with patients with an arteriovenous access, with the postdialysis difference being more pronounced than the predialysis difference (Table 1 and Supplementary Figure S2C).

DISCUSSION

Our study revealed the following 2 major findings: First, actual bicarbonate levels differed significantly and to a degree of potential clinical relevance between arterial samples retrieved from arteriovenous access and venous samples drawn from dialysis catheters. Second, we found that this systematic difference between the sampling sites resulted in a treatment bias of metabolic acidosis with a lower prescribed dialysate bicarbonate level in patients with a catheter compared with patients with an arteriovenous access.

From a physiological perspective, it is evident that acid-base parameters differ between the arterial and the venous blood, and arterial versus venous bicarbonate level has been previously compared through simultaneous blood sampling in several patient cohorts.[8,S8–S16] However, these studies were performed in acutely ill patients in emergency departments or intensive care units. Our study is, to the best of our knowledge, the first one comparing arterial and venous blood gas analyses in hemodialysis patients.

Despite the lack of definitive evidence, guidelines provide target ranges for the predialysis bicarbonate level based on the available observational data.[S3–S5] Most dialysis centers regularly measure predialytic bicarbonate levels, and many adjust dialysate bicarbonate concentration to them. Of note, the cited guidelines do not specify target bicarbonate levels according to vascular access type nor even elaborate on a potential role of blood sampling site. Likewise, although some observational studies were limited to patients with fistulas,[3–5] most did not specify vascular access type.[2,6,7,S6,S7] Our study clearly reveals that the source of blood samples influences analysis of acid-base balance and bicarbonate prescription in hemodialysis patients if the same bicarbonate target values are used irrespective of vascular access type. Although use of dialysis catheters is associated with a number of potential complications and arteriovenous access should generally be preferred over catheters,[S17] many patients initiate chronic hemodialysis by a catheter and a significant minority continues treatment by a catheter for various reasons. Thus, it seems important to consider the type of vascular access when treating acidosis to a target bicarbonate level, when interpreting serum bicarbonate values and in the future design of clinical studies.

An obvious approach would be to use target bicarbonate values of 1.5 to 2.0 mmol/l higher in patients with catheters. This correction may, however, be unreliable given the large interindividual variability of the arteriovenous difference in bicarbonate levels that we observed. An alternative approach is to use standard bicarbonate instead of actual bicarbonate, for which our exploratory analysis revealed less variability between the arterial and the venous samples. As its measurement requires the simultaneous assessment of hemoglobin, not all point-of-care blood gas analyzers

Table 1. Predialysis and postdialysis acid-base parameters and prescribed dialysate bicarbonate concentration in patients with an arteriovenous access or a catheter

Acid-base parameters	AV access	Catheter	*P* value (crude)	*P* value (adjusted)[a]
Actual bicarbonate, predialysis (mmol/l), mean (SD)	21.7 (2.5)	21.7 (2.2)	0.872	0.770
Actual bicarbonate, postdialysis (mmol/l), mean (SD)	27.7 (2.2)	26.5 (1.9)	0.003	0.026
Standard bicarbonate,[b] predialysis (mmol/l), mean (SD)	22.0 (2.0)	21.1 (1.8)	0.042	0.055
Standard bicarbonate,[b] postdialysis (mmol/l), mean (SD)	28.1 (1.9)	25.6 (1.9)	<0.001	<0.001
pH, predialysis, mean (SD)	7.38 (0.04)	7.34 (0.05)	<0.001	<0.001
pH, postdialysis, mean (SD)	7.48 (0.04)	7.41 (0.04)	<0.001	<0.001
Prescribed dialysate bicarbonate (mmol/l), mean (SD)	33.2 (2.4)	31.5 (2.3)	<0.001	0.012

AV, arteriovenous.
[a]Two patients in the catheter group did not have their residual renal function documented (no urine collection available) and were excluded from adjusted analyses.
[b]Standard bicarbonate values were only available for patients treated in the Frauenfeld dialysis unit; 75 of 112 patients.
Crude *P* values as calculated by the 2-sided *t* test, and adjusted *P* values as per multivariable linear regression.

are able to calculate standard bicarbonate levels. Standard bicarbonate eliminates the respiratory component from the analysis of acid-base balance, which might be advantageous also in the analysis of the arterial blood, because concomitant respiratory acid-base disorders are present in a large proportion of hemodialysis patients.[9] However, a Japanese study found an association of all-cause and cardiovascular mortality with predialysis pH, but not bicarbonate level, suggesting pH might be more relevant than bicarbonate.[5] It thus remains to be established whether dialysis treatment should primarily focus on correcting the metabolic component of acidosis and target specific bicarbonate or standard bicarbonate values or whether pH represents a more meaningful treatment target. Of note, pH also differed between the 2 types of vascular access in our study, with lower values in the blood drawn from catheters. This difference was even more pronounced between the 2 groups in the retrospective analysis of patients with catheters versus arteriovenous access (owing to lower dialysate bicarbonate prescriptions in the former). Targeting specific predialysis pH values irrespective of the type of vascular access would bias acidosis treatment in the opposite direction compared with the targeting of bicarbonate values.

Although bicarbonate level is usually determined by blood gas analysis in Germany, Italy, and Switzerland, enzymatic assays of "total CO_2" are frequently used in the United States, the United Kingdom, France, and Spain.[3] Total CO_2 comprises dissolved CO_2 in addition to bicarbonate. Because venous partial pressure of CO_2 is higher than arterial partial pressure of CO_2, the arteriovenous difference of total CO_2 is even slightly higher than the arteriovenous difference of bicarbonate, and our results are generally applicable to settings where enzymatic assays of total CO_2 are used instead of blood gas analysis.

Of interest, although predialysis bicarbonate level was not different between the 2 vascular access groups, postdialysis bicarbonate level was lower in patients with catheters. Likewise, the difference in standard bicarbonate level was more pronounced for the postdialysis samples. This may be due to the following factors: first, postdialysis bicarbonate level is strongly influenced by dialysate bicarbonate concentration, which was lower in patients with catheters. Second, patients with catheters had less efficient dialysis sessions (lower kT/V probably owing to lower blood flow), which might limit bicarbonate transfer from the dialysate to the blood. Finally, cardiopulmonary recirculation may increase bicarbonate levels determined from the arterial line in patients with arteriovenous access at the end of dialysis. Importantly, most patients with catheters were far from reaching postdialysis alkalosis, which is considered to have potentially detrimental effects.[1,7] Hence, metabolic acidosis was likely undertreated in patients with catheters and a moderate increase in dialysate bicarbonate level would not expose these patients to postdialysis alkalosis.

Our study has several limitations. First, the number of patients for the first part of the study was limited and standard bicarbonate level was available only for a subset of patients. Hence, estimates of the systematic and random bias are not precise. Second, this is a single-center study and might not be fully representative of common practice in other dialysis centers. Finally, owing to the limited size and the cross-sectional nature of the analysis, we cannot comment on the clinical consequences of the observed treatment bias. Nevertheless, our results point to a source of systematic bias in the treatment of acidosis in hemodialysis patients.

In conclusion, future studies investigating the management of metabolic acidosis in hemodialysis patients should account for the effect of vascular access type on acid-base assessment and the type of vascular access should be considered in clinical practice when interpreting serum bicarbonate levels and applying bicarbonate target values.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Comparison of standard bicarbonate versus actual bicarbonate in samples from arteriovenous access (fistula/graft) (a) or dialysis catheter (b) with line of equality (continuous), linear regression, and 95% confidence intervals (dashed).

Figure S2. Predialysis and postdialysis actual bicarbonate (a), pH (b), and standard bicarbonate (c) in samples from patients with arteriovenous access (fistula/graft) (red) and patients with dialysis catheter (blue).

Table S1. Baseline characteristics of patients included in study part 1 (simultaneous blood sampling from catheter and arteriovenous access).

Table S2. Baseline characteristics of patients included in the cross-sectional analysis (study part 2).

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