Serum Bicarbonate as a Surrogate for pH in Hemodialysis: A Pilot Study

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Rationale & Objective: Excess morbidity and mortality are associated with both high and low serum bicarbonate levels in epidemiologic studies of patients with end-stage kidney disease (ESKD) receiving hemodialysis. The Kidney Disease Outcomes Quality Initiative (KDOQI) recommends modifying dialysate bicarbonate concentration to achieve a predialysis serum bicarbonate level ≥ 22 mmol/L, measured as total carbon dioxide (CO_2). This practice assumes that total CO_2 is an adequate surrogate for acid-base status, yet its surrogacy performance is unknown in ESKD. We determined acid-base status at the beginning and end of hemodialysis using total CO_2 and pH and tested whether total CO_2 is an appropriate surrogate for acid-base status.

Study Design: Pilot study.

Setting & Participants: 25 veterans with ESKD receiving outpatient hemodialysis.

Tests Compared: pH, calculated bicarbonate level, and total CO_2.

Outcomes: The proportion of paired samples for which total CO_2 misclassified acid-base status according to pH was determined. Bias of total CO_2 was evaluated using Bland-Altman plots, comparing it to calculated bicarbonate.

Results: Among 71 samples, mean pH was 7.41 ± 0.03 predialysis and 7.48 ± 0.05 postdialysis. Compared with interpretation of full blood gas profiles, 9 of 25 (36%) participants were misclassified as acidemic using predialysis total CO_2 measures alone (total CO_2 < 22 mmol/L but pH ≥ 7.38); 1 (4%) participant was misclassified as alkalemic (total CO_2 > 26 mmol/L but pH ≤ 7.42). Among paired samples in which predialysis total CO_2 was < 22 mmol/L, the corresponding pH was acidemic (< 7.38) in just 3 of 13 (23%) instances.

Limitations: Small, single-center, entirely male cohort.

Conclusions: A majority of participants became alkalemic during routine hemodialysis despite arriving with normal pH. 10 of 25 (40%) participants' acid-base status was misclassified using total CO_2 measurements alone; the majority of predialysis total CO_2 values that would trigger therapeutic modification according to practice guidelines did not have acidemia when assessed using pH. Efforts to improve dialysis prescription require recognition that total CO_2 may not be reliable for interpreting acid-base status in hemodialysis patients.

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Hemodialysis is the most common form of kidney replacement therapy used in developed countries to treat patients with end-stage kidney disease (ESKD).[1] Despite clear and convincing evidence that hemodialysis provides life-sustaining therapy, it is increasingly recognized that components of hemodialysis therapy such as acid-base status are potentially modifiable determinants of mortality among patients with ESKD.[2-7]

Editorial, p. 1

Although it is widely accepted that blood gas analysis is the ideal method for evaluating acid-base status, predialysis serum bicarbonate level (typically measured as total carbon dioxide [CO_2]) is the current standard in hemodialysis.[8] In clinical practice, low total CO_2 is considered an adequate indicator of acidemia, and high total CO_2, an adequate indicator of alkalemia. Although clinically convenient, this practice assumes both normal ventilatory function and a predictable relationship between total CO_2 and arterial pH. Importantly, the Kidney Disease Outcomes Quality Initiative (KDOQI) recommends that dialysate bicarbonate prescriptions be adjusted in patients with inferred acid-base derangements, as measured by total CO_2, in an effort to achieve predialysis total CO_2 ≥ 22 mmol/L.[9] However, it is unknown whether total CO_2 performs adequately as a surrogate for acid-base status in patients with ESKD.

Further, to our knowledge, little is known about how acid-base status changes during the course of routine hemodialysis. The Dialysis Outcomes and Practice Patterns Study (DOPPS) hypothesized that the increased mortality observed in patients with ESKD with higher dialysate bicarbonate concentrations was mediated by postdialysis alkalemia, but postdialysis measures of acid-base status were lacking.[10] Acid-base status is not routinely assessed postdialysis, when potential imbalance is largely attributable to hemodialysis. A more detailed understanding of acid-base changes during hemodialysis may inform therapeutic decisions.

To address these uncertainties, we conducted a pilot study to prospectively determine acid-base status among patients with ESKD at the beginning and end of hemodialysis using total CO_2 and pH. We hypothesized that total CO_2 would serve as a suboptimal surrogate for pH, particularly in those with concomitant respiratory disorders. We further hypothesized that patients with ESKD would arrive to hemodialysis mildly acidemic by pH and become mildly alkalemic following treatment.

METHODS

Participants

Patients with ESKD receiving routine outpatient hemodialysis at the Portland, OR Veterans Affairs (VA) Medical Center were eligible for study entry. Exclusion criteria were low dialysis vintage (< 3 months of hemodialysis) and inability to provide written informed consent. Demographic and clinical data were ascertained from chart review.

Measurements

Pre- and postdialysis blood samples were collected monthly for 3 months. Each month, blood samples were collected on Wednesday for patients dialyzing Monday, Wednesday, and Friday and on Thursday for patients dialyzing Tuesday, Thursday, and Saturday. Blood was collected from the arterial connection of participants' hemodialysis access concurrent with laboratory tests obtained monthly for routine care. Blood gas and chemistry samples were collected within 3 minutes of one another. Blood gas syringes were placed on ice immediately following collection; chemistry samples were left at room air. Study-specific tests measured pre- and postdialysis using blood gas included pH, P_{CO_2}, and P_{O_2} (in mm Hg), lactate, and ionized calcium (each in mmol/L). Ionized calcium was reported without adjustment for pH. Serum bicarbonate level was calculated (in mmol/L) from pH and P_{CO_2} measurements using the Henderson-Hasselbalch equation.[11] In parallel, total CO_2 was measured both pre- and postdialysis through chemistry analysis. Samples were analyzed at the Oregon VA Clinical Laboratory (Portland, OR); blood gas analysis was performed using a Siemens RAPIDLab 1200 automated analyzer (Siemens Healthcare Diagnostics Inc), and total CO_2 was measured using a Roche cobas 6000 photometric assay-based automated analyzer (Roche Diagnostics Corp).

Statistical Analyses

Categorical data on the study population are presented as frequency (percentage), and continuous variables are presented as mean ± standard deviation or median and interquartile range (IQR) as appropriate. Because KDOQI guidelines recommend adjusting dialysate bicarbonate prescriptions to achieve predialysis total $CO_2 \geq 22$ mmol/L, we determined the frequency with which total CO_2 misclassified acid-base status predialysis. Analyzing total CO_2 and pH as categorical variables, we considered total CO_2 to misclassify acidemia if total CO_2 was < 22 mmol/L when pH was "normal" (7.38-7.42) or "high" (pH > 7.42) and misclassify alkalemia if total CO_2 was > 26 mmol/L when pH was normal or "low" (pH < 7.38). To determine whether misclassification was caused by respiratory disorders, bias in total CO_2 estimates, or both, measures of agreement between total CO_2 and calculated serum bicarbonate level were evaluated, and full acid-base profiles were reviewed. We created Bland-Altman plots comparing measured total CO_2 to calculated serum bicarbonate level. To account for repeated measures, we initially performed separate analyses for each month's pre- and postdialysis measurements, but given similar findings each month, the data are presented in aggregate form.

We performed *t* tests and analysis of variance for continuous variables as appropriate and Fisher exact tests for categorical variables. Covariates considered include chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, urine production, hemodialysis access, normalized protein nitrogen appearance, and albumin level. For misclassification rate, exact binomial confidence intervals (CIs) are reported. Given the difference in acid-base components in arterial and venous blood, sensitivity analyses were performed excluding samples obtained from tunneled dialysis catheters. Sensitivity analyses were also performed excluding blood gas samples not processed within 30 minutes of collection in case delayed processing of samples might affect acid-base components. Analyses were performed using Stata 15 (StataCorp LLC). The study was approved by institutional review boards of Portland VA Medical Center and Oregon Health & Science University (study 00016809 M4001). All participants provided written informed consent.

RESULTS

Baseline Characteristics

Among 34 patients receiving outpatient hemodialysis at the Portland VA Medical Center between October and December 2017, a total of 25 (74%) consented and provided blood samples for at least 1 month. Two (6%) additional patients consented but died (n = 1) or transferred to another hemodialysis unit (n = 1) before data collection. Four (12%) patients were excluded due to inability to consent, and 3 (9%) patients declined to participate.

All participants were men and non-Hispanic (Table 1). Mean age was 67 ± 9 years with an estimated dry weight of 91 ± 22 kg. Twenty-one (84%) individuals had received hemodialysis for 12 or more months at enrollment, and 9 (36%) reported producing more than 1 cup (∼250 mL) of urine daily. Hemodialysis access was a fistula, graft, and catheter in 18 (72%), 4 (16%), and 3 (12%) participants, respectively. Six (24%) participants had a baseline dialysate bicarbonate prescription of 30 to 32 mmol/L; 13 (52%), a prescription of 33 to 36 mmol/L; and 6 (24%), a prescription of 37 to 40 mmol/L. Dialysate acetate concentration was 4 mEq/L for all participants.

Seventy-one predialysis blood gas and total CO_2 samples, 70 postdialysis blood gas samples, and 65 postdialysis

Table 1. Characteristics of Study Participants

Characteristic	Total CO_2 < 24 mmol/L (n = 13)	Total CO_2 ≥ 24 mmol/L (n = 12)
Demographics		
Age, y	67 ± 7	66 ± 11
Men	13 (100%)	12 (100%)
Race		
White	9 (69%)	8 (67%)
African American	3 (23%)	4 (33%)
Native American	1 (8%)	0 (0%)
Hispanic	0 (0%)	0 (0%)
Estimated dry weight, kg	99 ± 23	82 ± 15
Medical History		
Diabetes mellitus	11 (85%)	7 (58%)
Hypertension	12 (93%)	9 (75%)
Coronary artery disease	5 (38%)	6 (50%)
Obstructive sleep apnea	8 (62%)	5 (42%)
Chronic obstructive pulmonary disease	4 (31%)	1 (8%)
FEV_1/FVC, n = 5	0.76 [0.67-0.89]	0.6
Restrictive lung disease	2 (15%)	0 (0%)
Tobacco use		
Never	5 (38%)	4 (33%)
Previous	6 (46%)	5 (42%)
Current	2 (15%)	3 (25%)
Dialysis Characteristics		
Vintage		
<12 mo	0 (0%)	4 (33%)
12-24 mo	3 (23%)	2 (17%)
>24 mo	10 (77%)	6 (50%)
ESKD cause		
Diabetes	7 (54%)	5 (42%)
Acute kidney injury	1 (8%)	3 (25%)
Glomerulonephritis	2 (15%)	1 (8%)
Obstruction	0 (0%)	2 (17%)
Polycystic kidney disease	1 (8%)	0 (0%)
Other/unknown	2 (15%)	1 (8%)
Urine production		
None	3 (23%)	6 (50%)
<1 cup (250 mL) daily	6 (46%)	1 (8%)
>1 cup (250 mL) daily	4 (31%)	5 (42%)
Access		
Fistula	11 (85%)	7 (58%)
Graft	2 (15%)	2 (17%)
Catheter	0	3 (25)
Kt/V	1.6 [1.5-1.7]	1.5 [1.5-1.6]
Dialysis filter		
F160	1 (8%)	3 (25%)
F180	8 (62%)	7 (58%)
F250	4 (31%)	2 (17%)
Time prescribed		
3-3.5 h	1 (8%)	4 (33%)
3.75-4 h	8 (61%)	8 (67%)
4.25-4.5 h	4 (31%)	0 (0%)

(Continued)

Table 1 (Cont'd). Characteristics of Study Participants

Characteristic	Total CO_2 < 24 mmol/L (n = 13)	Total CO_2 ≥ 24 mmol/L (n = 12)
Blood flow rate prescribed		
350 mL/min	0 (0%)	1 (8%)
400 mL/min	11 (85%)	11 (92%)
450 mL/min	2 (15%)	0 (0%)
Dialysate flow rate prescribed		
600 mL/min	10 (77%)	9 (75%)
800 mL/min	3 (23%)	3 (25%)
Dialysate sodium, mmol/L		
135-137	1 (8%)	5 (42%)
138-140	12 (92%)	7 (58%)
Dialysate potassium, mEq/L		
2	9 (69%)	7 (58%)
3	4 (31%)	5 (42%)
Dialysate bicarbonate, mmol/L		
30-32	4 (31%)	2 (17%)
33-36	7 (54%)	6 (50%)
37-40	2 (15%)	4 (33%)
Net ultrafiltration, L	2.6 [1.5-3.7]	3.5 [3-4.4]
Normalized protein nitrogen appearance, n = 22	1.0 [0.85-1.2]	0.90 [0.80-1.10]
Serum albumin, g/dL	3.9 ± 0.3	3.6 ± 0.5

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as median [interquartile range] or mean ± standard deviation.
Abbreviation: CO_2, carbon dioxide; ESKD, end-stage kidney disease; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity.

total CO_2 samples were collected from 25 participants (mean, 2.8, 2.8, and 2.6 samples per person, respectively). The only missing postdialysis blood gas sample was discarded due to sample leakage; 6 postdialysis total CO_2 samples were inadvertently not drawn. Fifty-nine of 71 (83%) predialysis and 55 of 70 (79%) postdialysis blood gas samples were processed within 30 minutes of collection.

Acid-Base Characteristics

Raw data for acid-base measurements are provided for each participant in Table S1. Overall mean pH was 7.41 ± 0.03 predialysis and 7.48 ± 0.05 postdialysis (Table 2); 75% of postdialysis pH measurements were ≥7.45. Mean pH did not differ across months either pre- ($P = 0.60$) or postdialysis ($P = 0.10$).

Overall mean total CO_2 and calculated serum bicarbonate values predialysis were 23.3 ± 2.4 and 24.7 ± 2.4 mmol/L, and postdialysis, were 28.6 ± 2.3 and 30.3 ± 2.6 mmol/L, respectively. Mean P_{CO_2} changed minimally from 40.0 ± 3.8 mm Hg predialysis to 41.9 ± 6.2 mm Hg postdialysis. pH-unadjusted ionized calcium levels remained stable (1.12 ± 0.08 mmol/L predialysis and 1.11 ± 0.04 mmol/L postdialysis). Participants with COPD had a lower mean predialysis pH than those without COPD (7.39 ± 0.03 vs 7.41 ± 0.03, respectively; P = 0.007). Mean predialysis P_{CO_2} was 42.8 ± 3.2 and 39.4 ± 3.6 mm Hg for those with and without COPD, respectively (P = 0.003), while mean predialysis total CO_2 was 24.0 ± 2.0 and 23.2 ± 2.4 mmol/L for those with and without COPD, respectively (P = 0.25). Mean serum lactate concentration was 1.54 ± 0.60 mmol/L predialysis and 1.20 ± 0.43 mmol/L postdialysis.

Misclassification

Among 71 predialysis samples collected from 25 participants for whom paired total CO_2 and pH data were available, 13 (18%) were characterized by total CO_2 < 22 mmol/L. However, the corresponding pH was either normal (pH 7.38-7.42; n = 8) or high (pH > 7.42; n = 2) in 10 of those 13 (77%) instances; 1 participant was misclassified twice, and 8 participants were misclassified once. Among these 10 instances, median postdialysis pH for these 10 samples was 7.51 (IQR, 7.48-7.52). Additionally, 1 participant had a paired sample characterized by total CO_2 > 26 mmol/L but normal pH. Full acid-base profiles for misclassified samples are provided in Table 3. The overall misclassification rate (among 71 samples) was 0.15 (95% CI, 0.08-0.26). Predefined baseline characteristics (COPD, obstructive sleep apnea, urine production, hemodialysis access, and nutrition) did not differ by misclassification status (all P > 0.05).

Cause of Misclassification

We next sought to determine whether samples misclassified as acidemia (total CO_2 < 22 mmol/L but pH ≥ 7.38) occurred due to hyperventilation, biased total CO_2 estimates, or both. Among the 10 misclassified samples from 9 individuals, mean P_{CO_2} was 36.2 ± 2.8 mm Hg (Table 4). In contrast, mean P_{CO_2} was significantly higher among samples without misclassification (40.6 ± 3.5 mm Hg; P = 0.02). Bland-Altman plots assessing agreement between predialysis measured total CO_2 and calculated serum bicarbonate level are shown by misclassification status in Figure 1. Total CO_2 measurements were lower than calculated serum bicarbonate levels both pre- and postdialysis (mean difference of total CO_2 estimate compared to calculated serum bicarbonate, −1.4 [95% CI, −1.7 to −1.2] mmol/L predialysis; −1.9 [95% CI, −2.3 to −1.5] mmol/L postdialysis). Bias of predialysis total CO_2 estimates did not statistically differ by misclassification status or blood gas processing time (Item S1).

Sensitivity Analysis

Similar results were observed after separately excluding samples obtained from tunneled dialysis catheters and excluding blood gas samples that were not processed within 30 minutes of collection. Mean pH was unchanged pre- and postdialysis when separately excluding samples from tunneled dialysis catheters and those not processed

Table 2. Pre- and Postdialysis Acid-Base Measurements, by Access Type

Predialysis					Postdialysis				
	pH	P_{CO_2}, mm Hg	Calculated $HCO3^-$, mmol/L	Total CO_2, mmol/L		pH	P_{CO_2}, mm Hg	Calculated $HCO3^-$, mmol/L	Total CO_2,[a] mmol/L
Fistula (n = 50)	7.41 ± 0.04	40.1 ± 4.1	24.8 ± 2.5	23.3 ± 2.5	Fistula (n = 49)	7.48 ± 0.05	42.0 ± 6.4	30.6 ± 2.6	28.8 ± 2.2, n = 46
Graft (n = 12)	7.41 ± 0.03	39.0 ± 3.0	23.9 ± 2.0	22.8 ± 2.3	Graft (n = 12)	7.50 ± 0.03	40.2 ± 2.4	30.2 ± 2.1	28.5 ± 2.1, n = 10
Catheter (n = 9)	7.41 ± 0.01	41.1 ± 2.5	25.3 ± 1.9	23.9 ± 1.5	Catheter (n = 9)	7.44 ± 0.07	43.8 ± 8.1	28.6 ± 2.8	27.0 ± 2.7, n = 9
Overall (n = 71)	7.41 ± 0.03	40.0 ± 3.8	24.7 ± 2.4	23.3 ± 2.4	Overall (n = 70)	7.48 ± 0.05	41.9 ± 6.2	30.3 ± 2.6	28.6 ± 2.3, n = 65

Note: Values are given as mean ± standard deviation.

Abbreviations: calculated $HCO3^-$, calculated bicarbonate (blood gas sample); total CO_2, total carbon dioxide (chemistry sample).

[a]Fewer total CO_2 samples were collected than blood gas samples postdialysis among patients with fistulas and grafts. The number of postdialysis total CO_2 samples is therefore reported separately from the total number of blood gas samples, which is reported by access type.

Table 3. Complete Acid-Base Profiles of Misclassified Samples

Participant (mo)	Total CO_2, mmol/L	pH	P_{CO_2}, mm Hg	Calculated $HCO3^-$, mmol/L	Access	Sit Time, min	Dialysate $HCO3^-$, mmol/L
Total CO_2<22mmol/L and pH≥7.38 (misclassified as acidemic using total CO_2 alone)							
1 (3)	20	7.39	35	21	Fistula	10-20	35
5 (2)	19	7.38	42	24	Fistula	10-20	37
6 (3)	18	7.38	37	21	Fistula	10-20	37
7 (3)	21	7.39	37	22	Graft	10-20	35
8 (1)	21	7.45	34	23	Fistula	21-30	30
8 (3)	21	7.39	39	23	Fistula	31-45	32
11 (3)	21	7.40	36	22	Fistula	10-20	32
14 (2)	18	7.38	35	20	Graft	10-20	35
17 (1)	20	7.45	32	22	Fistula	10-20	35
18 (3)	21	7.41	35	22	Fistula	10-20	37
Total CO_2>26mmol/L and pH≤7.42 (misclassified as alkalemic using total CO_2 alone)							
15 (3)	27	7.38	46	27	Fistula	10-20	34

Abbreviations: calculated $HCO3^-$, calculated bicarbonate (blood gas sample); total CO_2, total carbon dioxide (chemistry sample).

within 30 minutes of collection, while mean total CO_2 and calculated serum bicarbonate values were within 0.3 mmol/L of estimates in the full analysis (Table S2).

When monthly total CO_2 and pH measures were averaged for each participant, the number of participants with misclassification decreased from 10 to 2.

DISCUSSION

In this pilot study, a considerable subset of total CO_2 samples misclassified acid-base status, illustrating the inherently flawed assumptions made when using total CO_2 as a surrogate for pH in this population. Further, the majority of patients with ESKD ended hemodialysis alkalemic after arriving with pH in the normal range. Because clinical decisions on bicarbonate delivery are based on predialysis total CO_2 measurements, our findings suggest that more work is needed to determine how and when acid-base status should be assessed in patients with ESKD.

This work underscores the relatively high frequency with which nephrologists make incorrect inferences about acid-base status of patients with ESKD when using total CO_2 alone in routine clinical practice. This is consistent with work by Marano et al[12] in which a significant proportion of patients with ESKD were retrospectively found to have respiratory alkalosis rather than metabolic acidosis when looking beyond total CO_2 measurements alone. Our findings add to their work by demonstrating that such misclassification may not be due only to hyperventilation, but also measurement bias. Total CO_2 measurements repeatedly disagreed with serum bicarbonate calculations in a way that suggested a more acidemic state than was measured using pH. For example, if measured total CO_2 values from participant 5 during month 2 (see Table 3) were used with the measured P_{CO_2} to calculate pH using the Henderson-Hasselbalch equation, calculated pH would be far lower than that directly measured from the gas (calculated pH of 7.28 compared to measured pH of 7.38). Importantly, total CO_2 samples misclassifying acid-base status may trigger modifications in hemodialysis prescriptions, only to exacerbate alkalemia. KDOQI guidelines would have recommended increasing bicarbonate delivery on 13 occasions during the study period, yet the predialysis pH was actually normal (7.38-7.42) or even high (> 7.42) on 10 of those occasions, and the median postdialysis pH among this subset was already > 7.50. These observations cause one to consider whether misclassification triggers well-intentioned decisions in clinical practice that have inadvertent consequences on acid-base status and, more importantly, clinical outcomes.

The number of participants with misclassification decreased from 10 to 2 when considering average rather than single measures. This observation is similar to that reported by Patel et al[13] in which about half the total CO_2 measurements that were considered abnormal one month normalized the following month. These 2 findings further support the notion that total CO_2 may not provide a reliable picture of acid-base status in patients with ESKD receiving hemodialysis. More work is needed to better characterize which patients are more likely to have misleading total CO_2 measurements compared to pH. Clinicians are aware that COPD may compromise the

Table 4. Acid-Base Characteristics by Misclassification Status

Acid-Base Measure	Misclassified as Acidemic Using Total CO_2 Measures Alone[a] (n = 10)	Correctly Classified Using Total CO_2 Measures Alone[a] (n = 61)
pH	7.40 ± 0.03	7.41 ± 0.04
P_{CO_2}, mm Hg	36.2 ± 2.8	40.6 ± 3.5
Total CO_2, mmol/L	20 ± 1.2	23.9 ± 2.0
Calculated $HCO3^-$, mmol/L	22 ± 1.2	25.2 ± 2.2

Note: Values expressed as mean ± standard deviation.
Abbreviations: calculated $HCO3^-$, calculated bicarbonate (gas sample); total CO_2, total carbon dioxide (chemistry sample).
[a]Measures where pH ≥ 7.38, total CO_2 < 22 mmol/L.

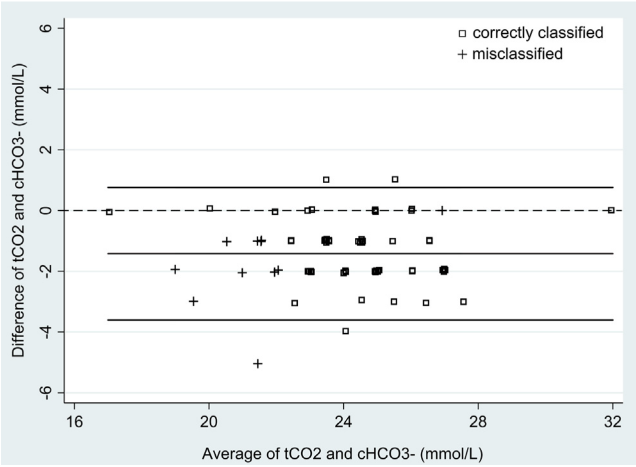

Figure 1. Solid black lines represent the mean difference between paired total carbon dioxide (tCO_2; chemistry sample) and calculated $HCO3^-$ (c$HCO3^-$; blood gas sample) values (in mmol/L) and the 95% limits of agreement.

surrogacy of total CO_2 for pH by causing respiratory acidosis.[14] However, our data suggest that future studies should also examine the frequency and impact of respiratory alkalosis in the context of hemodialysis.

Measured total CO_2 provided lower estimates than calculated serum bicarbonate level, an observation at odds with current teaching.[15] Though unexpected, Nasir et al[16] observed similar findings in the general population; a significant number of total CO_2 estimates were lower than calculated serum bicarbonate levels. One plausible explanation for this is loss of CO_2 gas from serum during processing or underfilling of vacuum tubes.[17,18] Our study did not record processing time of chemistry samples, and the duration of time that tubes were uncapped in the laboratory was not standardized. However, results were typically reported within a few hours of collection, and trained laboratory personnel were responsible for handling the samples. These conditions are similar to if not more expeditious than the processing of chemistry samples for patients receiving hemodialysis at large dialysis organizations, for which samples are often transported to nationally centralized laboratories for processing. Thus, even if this observation is assumed to be due to laboratory mishandling, the clinical implications remain significant because this is believed to reflect common processing technique. Previous work also suggests that the acid dissociation constant (pK) may vary in hemodialysis patients to a degree sufficient to meaningfully affect bicarbonate balance.[19] If 1 or more of these factors alters the composition of total CO_2, the ability of total CO_2 to provide meaningful information about acid-base status may be compromised.

Our study has several strengths. The simultaneous measurement of total CO_2, P_{CO_2}, and pH before and after hemodialysis is to our knowledge the first such evaluation in a US cohort, providing critical data necessary to definitively determine acid-base status. Additionally, the prospective design eliminates potential for confounding by indication. Last, participants' demographics and hemodialysis prescriptions were robustly characterized.

Our study also has important limitations. The single-center design of a small entirely male ESKD population limits generalizability, and similar investigations at hemodialysis units with diverse demographics are needed. Additionally, the dialysate bicarbonate concentration that was delivered to hemodialysis patients was not independently confirmed and may thus differ from the prescribed concentrations.

In conclusion, the majority of individuals with ESKD in this pilot study became alkalemic during hemodialysis despite arriving with normal acid-base status, and 40% had acid-base status misclassified using total CO_2 measurements alone due to hyperventilation, low total CO_2 estimates, or both. Ten of 13 total CO_2 samples that would trigger increased dialysate bicarbonate delivery based on KDOQI guidelines occurred in settings in which pH was actually normal or high. More work is needed to effectively evaluate and manage acid-base status for patients with ESKD receiving hemodialysis.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Bias of total CO_2 according to misclassification status and processing time.

Table S1: Raw acid-base data predialysis (a) and postdialysis (b), by participant.

Table S2: Acid-base characteristics excluding samples obtained from (a) tunneled dialysis catheters and (b) paired samples for which gas was not processed within 30 minutes of collection.

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