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Serum Bicarbonate in Acute Heart Failure: Relationship to Treatment Strategies and Clinical Outcomes

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Abstract

Background—Though commonly noted in clinical practice, it is unknown if decongestion in acute heart failure (AHF) results in increased serum bicarbonate.

Methods and Results—For 678 AHF patients in the DOSE-AHF, CARRESS-HF, and ROSE-AHF trials, we assessed change in bicarbonate (baseline to 72-96 hours) by decongestion strategy, and the relationship between bicarbonate change and protocol-defined decongestion. Median baseline bicarbonate was 28 mEq/L. Patients with baseline bicarbonate ≥28 mEq/L had lower EF, worse renal function and higher NT-proBNP than those with baseline bicarbonate <28 mEq/L There were no differences in bicarbonate change between treatment groups in DOSE-AHF or ROSE-AHF (all p>0.1). In CARRESS-HF, bicarbonate increased with pharmacologic care but decreased with ultrafiltration (median +3.3 vs. -0.9 mEq/L respectively; p<0.001). Bicarbonate change was not associated with successful decongestion (p>0.2 for all trials).

Conclusions—In AHF, serum bicarbonate is most commonly elevated in patients with more severe heart failure. Despite being used in clinical practice as an indicator for decongestion, change in serum bicarbonate was not associated with significant decongestion.

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Keywords

heart failure; edema; diuretics

Introduction

Acute heart failure (AHF) is common and treatment decisions are often based on an assessment of a combination of clinical conditions and laboratory measures.[1] Many clinicians view increasing serum bicarbonate levels as a sign of volume contraction and use it as a marker of decongestion.[3] However, empirical evidence to support this practice is lacking. Using data from three AHF trials, we sought to describe the characteristics of patients hospitalized for AHF by serum bicarbonate levels at baseline and follow up for different treatment strategies, and describe the association between serum bicarbonate and decongestion.

Methods

Data Source and Study Population

This analysis was performed using data from three National Heart, Lung, and Blood Institute (NHLBI)-sponsored Heart Failure Network trials, Diuretic Optimization Strategy Evaluation in Acute Heart Failure (DOSE-AHF), Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF), and Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF). The design and primary results of these trials have been published previously.[4-9]

All study participants provided written informed consent. The studies were approved by protocol review and data safety monitoring committees as well as each participating site's institutional review board.

Patients enrolled in the DOSE-AHF, CARRESS-HF, and ROSE-AHF trials were included in this study population if they had had a serum bicarbonate level measured at baseline and follow up at 72 hours or 96 hours.

Statistical Analyses

Baseline characteristics were compared between patients with a baseline serum bicarbonate level above and below the median using the Wilcoxon rank-sum test for continuous variables and the Pearson chi-square test for categorical variables. Baseline characteristics were described using medians and 25^{th} and 75^{th} percentiles for continuous variables and frequencies and proportions for categorical variables.

Linear regression was used to estimate the serum bicarbonate change differences across decongestion strategies within each trial. The models were adjusted for baseline serum bicarbonate. For analyses pooling all trials, an indicator variable for trial was also included. Complete decongestion was defined per study protocol as jugular venous distention < 8cm, trace or no peripheral edema, and no orthopnea.[5,7]

Spearman correlations were used to assess the association between the change in serum bicarbonate and the following: change in weight, change in renal function, and change in NT-proBNP.

Results

Of 835 unique patients in the DOSE-AHF, CARRESS-HF, and ROSE-AHF trials, 678 patients had a serum bicarbonate level measured at baseline and at follow-up (72 hours or 96 hours)—225 in DOSE-AHF, 309 in ROSE-AHF, and 144 in CARRESS-HF. Patients with baseline serum bicarbonate above the median (≥ 28 mEq/L) were significantly more likely to have a reduced EF, and at baseline had a lower serum sodium, and higher blood urea nitrogen, creatinine, and NT-proBNP (Table 1).

No difference could be detected in the change in serum bicarbonate between bolus versus infusion ($p = 0.40$) or low-dose versus high-dose diuretics ($p = 0.10$) in DOSE-AHF, or between dopamine versus nesiritide versus placebo ($p = 0.37$) in ROSE-AHF (Table 2). In CARRESS-HF, subjects randomized to stepped pharmacologic care showed an increase in serum bicarbonate from baseline to 96 hours compared to those on ultrafiltration (change +3.3 mEq/L vs -0.9 mEq/L, $p < 0.001$).

There was no association between successful decongestion and change in serum bicarbonate from baseline to 72 or 96 hours (Table 3). Across all trials, the mean change in serum bicarbonate was 2.3 mEq/L for those who achieved successful decongestion by 72 or 96 hours and 1.6 mEq/L for those who did not ($p = 0.85$).

Figure 1 demonstrates the relationship between change in serum bicarbonate and other measures of congestion. While correlations were modest, across all trials combined as serum bicarbonate increased from baseline, weight decreased (Panel A), NT-proBNP decreased (Panel B), and serum creatinine decreased (Panel C).

Discussion

Current treatment strategies in AHF rely predominantly on the use of loop and thiazide diuretics. The mechanisms by which the use of these diuretics results in metabolic alkalosis have been well described.[10] “Contraction alkalosis,” due to decreased extracellular fluid volume resulting in increased bicarbonate concentration has only a small effect on serum bicarbonate levels. Diuretic induced acidification of the distal nephron stimulates increased production of bicarbonate, and decreased effective blood volume results in a decrease in the glomerular filtration rate, hindering the amount of bicarbonate filtered.[10,11] Moreover, heart failure represents a state of contracted effective blood volume, setting up a substrate for development of metabolic alkalosis.

In our study, patients with worse heart failure had higher serum bicarbonate at baseline, and all decongestion strategies except ultrafiltration showed an increase in serum bicarbonate, consistent with the known mechanisms by which heart failure and diuretics result in metabolic alkalosis. However, no difference in serum bicarbonate change was detected between low-dose and high-dose diuretic regimens. Furthermore, while patients treated with

ultrafiltration had considerable volume loss there was not an increase in bicarbonate. These results highlight that “contraction” is not the only source of increased serum bicarbonate and metabolic alkalosis during decongestion therapy, and further underscore the complexity of acid-base regulation in the kidney.

Health care providers rely on various subjective and objective features to determine when adequate decongestion has been achieved. In this study, an increase in serum bicarbonate with treatment was associated with other surrogate markers of decongestion, including weight loss and decrease in NT-proBNP. However, change in serum bicarbonate was not associated with worsening renal function or clinical decongestion as determined by history and physical exam findings. The majority of hospitalizations for heart failure are due to congestion, thus adequate decongestion is a primary goal; furthermore inadequate decongestion during hospitalization is associated with poor outcomes.[12-15] Therefore, the finding of an elevated serum bicarbonate level in isolation may not be sufficient evidence for healthcare providers to stop or slow down decongestion efforts in patients with AHF.

Our study has several limitations. First, there is a selection bias inherent to all clinical trials. Second, while both ROSE-AHF and DOSE-AHF enrolled patients within 24 hours of hospital admission and collected serum bicarbonate at baseline and 72 hours after treatment, CARRESS-HF enrolled patients within 10 days of hospital admission—though 78.2% were enrolled within the first 72 hours— and collected serum bicarbonate at the start of the intervention and then after 96 hours. Our study did not account for treatment prior to baseline measurement of serum bicarbonate. Finally, we were limited by the data available. We evaluated lab values and clinical status at 72 or 96 hours after initiation of treatment when only a minority of patients had achieved successful decongestion. We were unable to examine values at other time points, such as later in the hospitalization, at the point of successful clinical decongestion, or at hospital discharge.

In conclusion, an association between change in serum bicarbonate and degree of decongestion for different treatment strategies in AHF could not be detected, though effective decongestion achieved with ultrafiltration was less likely to be associated with an increase in serum bicarbonate compared with a strategy based on pharmacological decongestion. Adequate decongestion is a key goal in the treatment of patients with AHF; thus isolated modest increases in serum bicarbonate should not prompt a decrease or cessation of diuresis.

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Highlights

- Elevated serum bicarbonate is a common observation in acute heart failure patients
- In AHF, bicarbonate increased with diuretics but decreased with ultrafiltration
- Bicarbonate change was not associated with clinical signs of decongestion
- Adequate decongestion is a key goal in the treatment of patients with AHF
- Modest increases in bicarbonate should not prompt decrease or cessation of diuresis

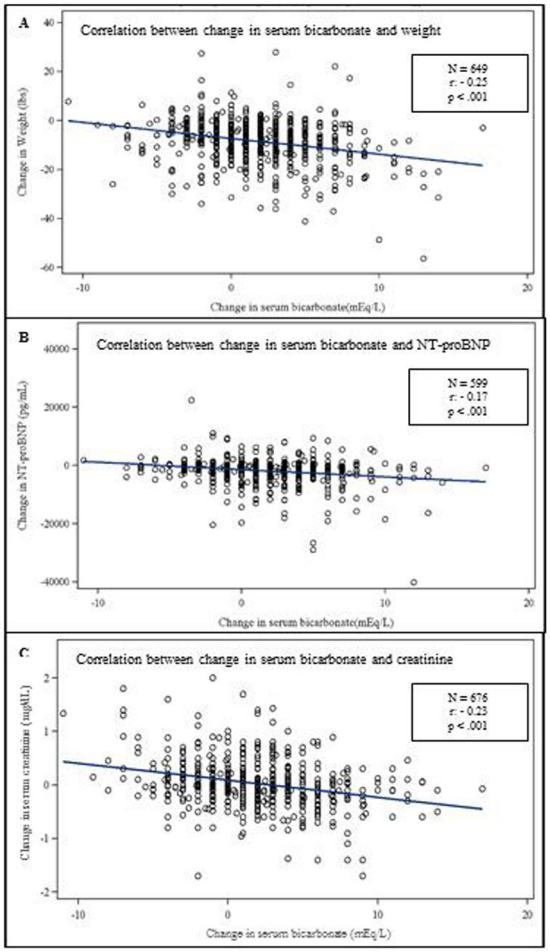

Figure 1.

Scatterplots of change in serum bicarbonate and other measures of congestion. Panel A: Relationship between change in bicarbonate and change in weight. N=649, r: -0.25, $p < 0.001$. Panel B: Relationship between change in bicarbonate and NT-proBNP. N=599, r: -0.17, $p < 0.001$. Panel C: Relationship between change in bicarbonate and change in creatinine. N=676, r: -0.23, $p < 0.001$.

Table 1

Baseline Characteristics by Baseline Median Serum Bicarbonate Level*

Variable	Serum bicarbonate (mEq/L) < 28 N=362	Serum bicarbonate (mEq/L) ≥ 28 N=316	p-value†
Characteristics			
Age, years	68.5 (61.0, 78.0)	68.5 (58.0, 78.0)	0.46
Gender, Male	279 (77.1%)	223 (70.6%)	0.05
Race, White	291 (80.4%)	208 (65.8%)	< 0.001
Ejection fraction, %,	33.6 (28.2, 40.0)	30.4 (25.7, 36.0)	< 0.001
Preserved ejection fraction	121 (33.7%)	80(25.6%)	0.03
Heart failure hospitalization in last year	262 (73.6%)	217 (69.1%)	0.20
Past Medical History			
Ischemia as cause of heart failure	222 (61.3%)	174 (55.1%)	0.10
Atrial fibrillation/flutter	221 (61.0%)	155 (49.1%)	0.002
Diabetes	218 (60.2%)	172 (54.4%)	0.13
Chronic Obstructive Pulmonary Disease	103 (28.5%)	77 (24.4%)	0.23
Medications before Hospitalization			
Beta Blockers	292 (80.7%)	266 (84.2%)	0.23
Aldosterone antagonist	902 (24.9%)	83 (26.3%)	0.68
Furosemide equivalent dose, mg/day	120.0 (80.0, 160.0)	80.0 (80.0, 160.0)	0.002
Baseline Evaluation			
Weight, lbs	216.9 (185.4, 267.4)	196.2 (168.0, 241.8)	< 0.001
Systolic blood pressure, mmHg	114.0 (103.0, 126.0)	116.0 (104.0, 127.0)	0.36
Heart rate, beats/min	75.0 (67.0, 84.0)	76.5 (66.5, 87.5)	0.18
Jugular Venous Pressure ≥ 8 cm	330 (95.7%)	284 (93.4%)	0.21
Orthopnea	317 (91.1%)	276 (92.3%)	0.58
New York Heart Association Class			0.77
I	1 (0.3%)	0 (0.0%)	
II	8 (2.4%)	9 (3.0%)	
III	217 (64.8%)	191 (64.1%)	
IV	109 (32.5%)	98 (32.9%)	
Sodium, mg/L	139.0 (136.0, 141.0)	138.0 (135.0, 140.0)	0.001
Blood urea nitrogen, mg/dl	36.5 (26.0, 51.0)	40.0 (27.0, 59.0)	0.05
Creatinine, mg/dl	1.6 (1.2, 2.0)	1.7 (1.3, 2.3)	< 0.001
NT-pro BNP‡, pg/ml	3929 (1999, 8493)	6230 (2886, 12200)	< 0.001
eGFR‡	43.2 (34.1, 55.9)	38.7 (28.2, 53.6)	0.001

*Presented as Presented as N (%) or median (25^{th}, 75^{th} percentile)

†p-values obtained using Wilcoxon rank-sum test for continuous variables and Pearson chi-square test for categorical variables

‡Abbreviations: NT-proBNP: N-terminal brain natriuretic peptide, eGFR: indexed glomerular filtration rate

Table 2

Change in Serum Bicarbonate and Frequency of Significant Rise in Serum Bicarbonate by Decongestion Strategy

Trial/Decongestion Strategy	Baseline Bicarbonate (mEq/L) Mean (SD)	72 or 96 hours Bicarbonate (mEq/L) Mean (SD)	Change in Bicarbonate (mEq/L) Mean (SD)	p-value*
DOSE-AHF				
Bolus (N=117)	28.2 (4.2)	29.3 (3.8)	1.1 (3.5)	0.40
Infusion (N=108)	28.0 (4.2)	29.5 (4.0)	1.5 (3.8)	
Low Dose (N=110)	28.0 (4.1)	29.0 (3.9)	1.0 (3.6)	0.10
High Dose (N-115)	28.2 (4.2)	29.8 (3.9)	1.6 (3.7)	
ROSE-AHF				
Dopamine (N=105)	27.4 (4.5)	30.0 (4.6)	2.5 (3.6)	0.37
Nesiritide (N=102)	27.0 (4.0)	29.0 (4.0)	2.1 (3.7)	
Placebo (N=102)	27.4 (3.4)	29.7 (3.8)	2.2 (3.3)	
CARRESS-HF				
Stepped pharmacologic care (N=75)	27.9 (4.4)	31.2 (4.1)	3.3 (3.9)	<0.001
Ultrafiltration (N=69)	28.1 (4.6)	27.2 (4.8)	-0.9 (3.9)	

* p values obtained from linear regression model. Models were adjusting for baseline serum bicarbonate.

Table 3
Association of Success of Decongestion and Change in Serum Bicarbonate by Trial

Trial/Decongestion Status	Baseline	72 or 96 hours	Change	p-value*
All Trials				0.85
Successful Decongestion† (N=83)				
Bicarbonate (mEq/L), Mean (SD)	26.4 (4.3)	28.7 (3.6)	2.3 (4.0)	
Unsuccessful Decongestion (N=580)				
Bicarbonate (mEq/L), Mean (SD)	27.9 (4.1)	29.6 (4.2)	1.6 (3.7)	
DOSE-AHF				0.26
Successful Decongestion (N=33)				
Bicarbonate (mEq/L), Mean (SD)	26.1 (4.9)	28.9 (3.7)	2.8 (4.3)	
Unsuccessful Decongestion (N=187)				
Bicarbonate (mEq/L), Mean (SD)	28.4 (4.0)	29.5 (3.9)	1.1 (3.3)	
ROSE-AHF				0.79
Successful Decongestion (N=39)				
Bicarbonate (mEq/L), Mean (SD)	26.4 (4.1)	28.8 (3.7)	2.4 (3.3)	
Unsuccessful Decongestion (N=263)				
Bicarbonate (mEq/L), Mean (SD)	27.4 (4.0)	29.6 (4.2)	2.2 (3.5)	
CARRESS-HF				0.48
Successful Decongestion (N=11)				
Bicarbonate (mEq/L), Mean (SD)	26.9 (2.6)	27.8 (3.7)	0.9 (5.2)	
Unsuccessful Decongestion (N=130)				
Bicarbonate (mEq/L), Mean (SD)	28.2 (4.5)	29.4 (4.9)	1.2 (4.3)	

*p values obtained from linear regression model. Models were adjusting for baseline serum bicarbonate (and trial when all trials were combined)

†Successful decongestion is defined as JVP < 8cm, no orthopnea, and trace or no peripheral edema