

## Elevated Serum Bicarbonate Concentration in Chronic Kidney Disease: A Call to Find the Cause

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In this issue, Dobre et al<sup>1</sup> reported an observational study looking at results of annually measured serum bicarbonate concentration in participants with chronic kidney disease (CKD) enrolled in the Chronic Renal Insufficiency Cohort (CRIC) using the marginal structural model, a validated statistical method,<sup>2</sup> to estimate the cumulative effect over the period of the study and their effects on adjudicated heart failure events, atherosclerotic events, renal disease progression, and mortality. In their analysis, they included patients aged 21 to 74 years with estimated glomerular filtration rate of 20 to 70 mL/min per 1.73 m<sup>2</sup> and excluded patients with NYHA Class III/IV heart failure. The final study population of this analysis included 3586 participants. They adjusted all models for age, gender, race/ethnicity, clinical center, estimated glomerular filtration rate, proteinuria, diabetes, systolic blood pressure, cardiovascular disease at baseline, chronic obstructive pulmonary disease, tobacco use, diuretic and alkali medication used, low-density lipoprotein, Fibroblast growth factor-23 (FGF-23), and high-sensitivity C-reactive protein. In their analysis, over an average of 6 years of follow-up, they found a statistically significant higher rate of heart failure events and mortality in participants who maintained serum bicarbonate >26 mmol/L, while participants who maintained serum bicarbonate <22 mmol/L had increased risk of renal disease progression defined as halving of estimated glomerular filtration rate or end-stage renal disease. On the other hand, there was no association between serum bicarbonate levels and atherosclerotic cardiovascular events. In subgroup analysis, the relationship

between serum bicarbonate concentration and heart failure and renal events was consistent across categories of race/ethnicity, diabetes, or baseline kidney function. The strength of association between serum bicarbonate >26 and <22 and heart failure and renal events, respectively, persisted after excluding participants taking alkali therapy, or who had chronic obstructive pulmonary disease (COPD) or cardiovascular disease at baseline. On the other hand, the study was not powered to exclude participants on diuretic therapy (60% of the study cohort were taking diuretics), which is a major cause of metabolic alkalosis.

This observational study discusses a potential link between acid–base abnormalities and cardiovascular and renal outcome in a large cohort of patients with variable stages of CKD. It adds to the existing literature an interesting observation associating serum bicarbonate levels with outcome in this patient population. It employed a novel statistical approach in analyzing observational data that strengthen this association. On the other hand, 2 factors need to be considered with careful analysis of this study:

1. Besides bicarbonate, PCO<sub>2</sub> is the second variable in the Henderson-Hasselbalch equation that determines the acid–base status. Although acid–base status can be predicted by serum bicarbonate concentration alone in some individuals, it might not be the case when examining a large cohort. Current smokers were reported to be <15% in the CRIC cohort, while >60% had a history of >100 cigarettes smoking during their lifetime (ex-smokers). Moreover, spirometry was not routinely used to diagnose COPD in this patient population.<sup>3</sup> Only 3.1% of all participants have a diagnosis of COPD compared with >5% in the US general population.<sup>4</sup> Considering all these factors, there seems to be a reasonable chance that COPD (especially early with borderline FEV<sub>1</sub>/FVC ratio <0.70) was underdiagnosed in this cohort. In support of this trend, it has been shown that fewer than half of the estimated 24 million Americans with airflow obstruction have actually received a diagnosis of COPD.<sup>5</sup> In stable COPD, renal fluid retention and edema are enhanced by hypercapnia-induced renal vasoconstriction and antidiuresis.<sup>6</sup> Patients with edema due to chronic obstructive pulmonary disease have severe retention of salt and water,

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reduction in renal blood flow and glomerular filtration, and neurohormonal activation similar to that seen in patients with edema due to myocardial disease.<sup>7</sup> In isolated cat kidneys, changes in PCO<sub>2</sub> were inversely related to renal blood flow and renal vascular resistance where doubling of PCO<sub>2</sub> decreased renal vascular resistance by 25% with higher chance for salt and water retention.<sup>8</sup> Giannoni et al found increased sensitivity of chemoreceptors to both hypoxia and hypercapnia in systolic heart failure patients—a powerful and independent predictor of mortality. In the early phase of heart failure syndrome, the chemoreceptors may act in a compensatory way, triggering autonomic nervous system changes in the cardiorespiratory system that prevents tissue hypoxia or hypercapnia. However, over time, chemoreceptor upregulation might promote a vicious circle eliciting autonomic imbalance, neurohormonal activation, abnormal ventilatory responses, arrhythmias, and favoring adverse events.<sup>9</sup>

2. Potassium abnormalities, especially hypokalemia, are common and underestimated in patients with CKD.<sup>10,11</sup> The use of diuretics is among the major causes in this patient population. Sixty percent of participant in the CRIC cohort were reported to be on diuretic therapy. In a large cohort of 2500 patient with CKD, mostly stage 3 and 4, hypokalemia (<4 mEq/L) was reported in over one third of the participants. Moreover, hypokalemia was associated with increased risk of end-stage renal disease in this CKD population.<sup>11</sup> In potassium-depletion metabolic alkalosis, a high serum bicarbonate level is maintained by intracellular acidosis in the renal tubular cells, with resulting increased bicarbonate reabsorption at several sites along the nephron. Moreover, pendrin, a luminal chloride-bicarbonate exchanger, is reduced in potassium depletion.<sup>12</sup> Therefore, hypokalemia is considered 1 major factor commonly contributing to maintaining the state of metabolic alkalosis. In a large cohort with heart failure and CKD (estimated glomerular filtration rate <60 mL/min per 1.73 m<sup>2</sup>), hypokalemia was common (>20%) and associated with increased mortality and hospitalizations related to heart failure and cardiovascular disease.<sup>10</sup>

Neurohormonal activation including the sympathetic nervous system, the renin–angiotensin–aldosterone system, and the antidiuretic hormone are beneficial in the short term in patients with heart failure as they tend to restore cardiac output and tissue perfusion toward normal. However, their deleterious effects predominate over the long term. Drugs blocking the sympathetic nervous system and the renin–angiotensin–aldosterone system have been the mainstay of treating heart failure. The relationship between hypokalemia and these neurohormonal adaptive responses in heart failure is complex. Hypokalemia or potassium depletion can result in elevation in

plasma renin activity<sup>13</sup> and diminishes reuptake of norepinephrine by sympathetic nerve terminals.<sup>14</sup> On the other hand and adding to the complexity of this interaction, hypokalemia can be the result of individual activation of these 2 systems.

Endogenous cardiotoxic steroids, also known as digitalis-like factors, natural inhibitors of the Na<sup>+</sup>/K<sup>+</sup> ATPase, have been postulated to play important roles in congestive heart failure. This has been demonstrated in humans and rats by resulting in lowering Na<sup>+</sup>/K<sup>+</sup> ATPase activity.<sup>15,16</sup> Moreover, experimental data also indicate an association between elevated plasma cardiotoxic steroids and cardiovascular remodeling. Ouabain, 1 member of the cardiotoxic steroids family, when infused to sustain physiologic concentrations, induced myocardial hypertrophy in normotensive rats.<sup>17</sup> Hypokalemia has been shown to potentiate the effect of cardiotoxic steroids in inducing left ventricular remodeling and hypertrophy in in vitro and in vivo models.<sup>18–20</sup>

In conclusion, the association between elevated bicarbonate concentration and heart failure exacerbation and mortality in patients with CKD is real and alarming and should raise questions in every patient with CKD. Hypokalemia and respiratory acidosis should not be underestimated as they can be a real threat to this patient population. Further research is needed to take this important observation to a different level and help substantially answer whether bicarbonate is a real player or just a marker of neurohormonal activation.

## Disclosures

None.

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