Serum Bicarbonate Concentration and Cognitive Function in Hypertensive Adults

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Abstract

Background and objectives Cognitive function worsens as kidney function declines, but mechanisms contributing to this association are not completely understood. Metabolic acidosis, a common complication of CKD, leads to neural networks overexcitation and is involved in cerebral autoregulation. We aimed to evaluate the association between serum bicarbonate concentration as a measure of metabolic acidosis, and cognitive function in hypertensive adults with and without CKD.

Design, setting, participants, & measurements Five cognitive summary scores were measured (global cognitive function, executive function, memory, attention/concentration, and language) in 2853 participants in the Systolic BP Intervention Trial (SPRINT). Multivariable linear regression models adjusted for demographics, comorbidities, systolic BP, medications, eGFR and albuminuria evaluated the cross-sectional association between bicarbonate and cognition at SPRINT baseline. In a subset (n=681) who underwent brain magnetic resonance imaging, the models were adjusted for white matter hyperintensity volume, vascular reactivity, and cerebral blood flow.

Results The mean age (SD) was 68 (8.5) years. Global cognitive and executive functions were positively associated with serum bicarbonate (estimate [SEM]: 0.014 [0.006]; P=0.01, and 0.018 [0.006]; P=0.003, respectively). Each 1 mEq/L lower bicarbonate level had a similar association with global cognitive and executive function as being 4.3 and 5.4 months older, respectively. The association with global cognition persisted after magnetic resonance imaging findings adjustment (estimate [SEM]: 0.03 [0.01]; P=0.01). There was no association between serum bicarbonate level and memory, attention/concentration, and language.

Conclusions In a large cohort of hypertensive adults, higher serum bicarbonate levels were independently associated with better global cognitive and executive performance. (ClinicalTrials.gov: NCT01206062).

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Introduction

Acid base homeostasis is critically important, and modest fluctuations in blood pH can cause impairment in many vital functions, including neurologic performance. Hydrogen ions are important neuronal signals and are intimately involved in cerebral autoregulation (1). Acidosis has been hypothesized to be a contributing factor to the development of Alzheimer dementia (2) by making the activities between cortical pyramidal neurons and GABAergic neurons imbalanced toward overexcitation, a process similar to neural excitotoxicity (3). Additionally, hydrogen ions are a potent modulator of N-methyl-D-aspartate (NMDA)–activated currents. Low-grade chronic metabolic acidosis inhibits NMDA-activated currents, which would also result in a greater hyperexcitable state (4). However, there is limited data in both animal and human studies on the effects of chronic metabolic acidosis on cognitive function.

The kidneys play an important part in the regulation of acid base metabolism because of their ability to secrete and excrete hydrogen ions (5). Kidney function decline is associated with impaired excretion of nonvolatile acid, resulting in chronic metabolic acidosis (6). Low serum bicarbonate level, a manifestation of metabolic acidosis that often ensues with a lowering in eGFR, has multiple deleterious effects, including adverse kidney and cardiovascular outcomes and greater mortality (7–13). Although cognitive dysfunction is common in patients with CKD, the mechanisms contributing to this association are not completely understood (14–16). A graded relationship has been found between eGFR and cognition, with each 10 ml/min per 1.73 m^2 decline in eGFR being associated with 11% higher prevalence of cognitive impairment (14). Few studies have evaluated the risk conferred by low serum bicarbonate on cognitive function, with mixed results (17,18).

In this study, we evaluated the cross-sectional association between serum bicarbonate and measures of cognitive function in nondiabetic, hypertensive adults, with and without CKD, participating in the

Systolic BP Intervention Trial (SPRINT). We hypothesize that low serum bicarbonate in CKD and non-CKD participants is independently associated with worse cognitive function.

Materials and Methods

Study Design

SPRINT is a multicenter, randomized, clinical trial (ClinicalTrials.gov: NCT01206062) that evaluated whether targeting a systolic BP <120 mm Hg will reduce cardiovascular events and mortality as compared with a systolic BP <140 mm Hg. The study design and methods have been previously published (19). Briefly, between November of 2010 and March of 2013, SPRINT recruited 9361 participants aged ≥50 years with hypertension at 102 clinics in the United States. Eligible participants had a systolic BP between 130 and 180 mm Hg, depending on the number of antihypertensive medications they were receiving during screening, and at least one of four cardiovascular risk factors: the presence of clinical or subclinical cardiovascular disease, an eGFR of 20–59 ml/min per 1.73 m^2, a Framingham 10-year risk score ≥15%, or age ≥75 years (19). Major exclusion criteria included diabetes mellitus, history of stroke, cardiovascular event or procedure in the prior 3 months, symptomatic heart failure in the past 6 months or left ventricular ejection fraction <35%, proteinuria >1 g/d or the equivalent as determined by spot urine measurement, polycystic kidney disease, recent immunosuppression, coexisting disease likely to affect survival, and organ transplant. A subset of 2800 participants, enriched for older SPRINT participants, was targeted to have global cognitive function measured in key specific domains of cognition at study baseline and were included in the SPRINT Memory and cognition IN Decreased hypertension (MIND) cohort. Of these, a subgroup of 677 participants completed baseline brain magnetic resonance imaging (MRI) and were included in the SPRINT MIND MRI substudy. Institutional review boards at all clinical sites approved the study protocol and all participants signed the informed consent.

Data Collection

Main Predictor. Serum bicarbonate was measured at SPRINT baseline in frozen serum samples using an enzymatic procedure with phosphoenolpyruvate carboxylase on the Modular P Chemistry analyzer at University of Minnesota Core Laboratory (interassay coefficient of variation 5.0%). Serum bicarbonate were analyzed continuously per 1 mEq/L higher level, and categorically using the following clinically relevant groups: ≤24 mEq/L (low), 25–28 mEq/L (reference group), and >28 mEq/L (high). The low and high groups represent the first (n=643) and fourth (n=572) quartiles of serum bicarbonate distribution respectively, whereas the reference group represents the second and third quartiles (n=1638).

Outcomes. The SPRINT MIND cohort had a set of screening and extended battery cognitive tests at study baseline. Cognitive tests were administered in a private room by SPRINT administrators, all of whom had undergone detailed training on the cognitive test battery. Screening battery tests consisted of Montreal Cognitive Assessment, Digit Symbol Substitution Tests, Logical Memory Immediate Recall, and Logical Memory Delayed Recall. Extended battery included nine tests selected to provide detailed information on multiple cognitive domains: Hopkins Verbal Learning Test Learning Trials 1–3, Hopkins Verbal Learning Test Delayed Recall, Hopkins Verbal Learning Test Delayed Recognition, Trail Making Test A, Trail Making Test B, Boston Naming Test, Rey-Osterrieth Complex Figure, Category Fluency– Animals, and Digit Span Total. The above cognitive tests were *a priori* assigned to five specific cognitive domains. Individual test results were imputed using k nearest neighbors for participants missing up to two test results, and set to missing for participants missing three or more tests. Individual test results were standardized using the SPRINT MIND cohort as (X-median)/interquartile range (IQR). These scores, similar to z-scores, were summed to develop summary cognition domain scores. The five cognitive outcomes were created for the SPRINT MIND subset and are presented in Supplemental Table 1. Higher domain scores represent better performance.

Covariates. Demographic and clinical information were obtained by questionnaires, interviews, and physical examination at baseline visit. Height, weight, and BP were recorded by trained study personnel. History of any cardiovascular disease was defined as self-report or clinical evidence of coronary artery disease, or peripheral arterial disease (19). At each study visit, participants were queried about any medication usage in the prior 30 days. All antihypertensive medications were categorized into drug classes. Smoking status was categorized as current, former, or never smokers. eGFR was calculated using the CKD Epidemiology Collaboration equation, and categorized participants as having CKD if eGFR was <60 ml/min per 1.73 m^2 (20). Serum creatinine concentration was measured by enzymatic procedure traceable to isotope dilution mass spectroscopy on a Roche analyzer. Urine albumin-to-creatinine ratio was calculated from a spot urine sample collected at study baseline and analyzed as a continuous variable after log transformation. Urine albumin was measured by an immunoturbidometric method on a Roche analyzer.

MRI. Brain MRI in SPRINT was performed using 3.0 T scanners and included sagittal three-dimensional fluid-attenuated inversion recovery, T2-weighted, and T1-weighted sequences with whole brain coverage, and an axial arterial spin labeling perfusion sequence (21). The University of Pennsylvania managed the MRI quality control, with each field center performing quarterly phantom scans for the evaluation of scanner stability and image distortion. MRI scanner performance across the clinical centers was stable over the duration of the study. White matter lesions were segmented to characterize brain tissue as normal or abnormal using a supervised learning-based multimodal segmentation technique (22).

Arterial spin labeling maps were transformed into cerebral blood flow (CBF) maps, with the values at each voxel in the map representing mean blood flow in ml/100 g per min (23). The CBF maps were then registered to the Jakob atlas so that mean CBF could be calculated for the whole brain and within individual regions of interest. Vascular reactivity was acquired using axial blood-oxygenation-level-dependent

Table 1. Characteristics of SPRINT MIND participants by categories of serum bicarbonate

Characteristic[a]	Total (*n*=2853)	Serum Bicarbonate, mEq/L		
		≤24 (*n*=643)	25–28 (*n*=1638)	>28 (*n*=572)
Demographics				
Age, yr (SD)[b]	68 (9)	67 (8)	69 (9)	69 (9)
Women, *n* (%)[b]	1053 (37)	206 (32)	604 (37)	243 (43)
Race/ethnicity, *n* (%)				
White	1704 (60)	388 (60)	983 (60)	333 (58)
Black	856 (30)	193 (30)	478 (29)	185 (32)
Hispanic	233 (8)	52 (8)	141 (9)	40 (7)
Other	60 (2)	10 (2)	36 (2)	14 (3)
Smoking, *n* (%)[b]				
Current	355 (12)	103 (16)	201 (12)	51 (9)
Former	1246 (44)	292 (45)	709 (43)	245 (43)
Never	1249 (44)	248 (39)	727 (44)	274 (48)
Body mass index, kg/m^2 (SD)[b]	29.8 (5.7)	30.5 (5.7)	29.8 (5.6)	29.2 (5.8)
History of cardiovascular disease, *n* (%)[b]	568 (20)	154 (24)	293 (18)	121 (21)
CKD, *n* (%)[b]	863 (30)	256 (40)	471 (29)	136 (24)
Systolic BP, mm Hg (SD)	139 (16)	138 (16)	139 (16)	140 (17)
Laboratory data				
eGFR, ml/min per 1.73 m^2 (SD)[b]	71 (20)	67 (23)	72 (19)	74 (18)
Urine albumin-to-creatinine, mg/g, median (IQR)[b]	9.7 (5.8–22.5)	10.8 (6.4–33.7)	9.4 (5.6–20.0)	9.3 (5.6–22.3)
Serum creatinine, mg/dl (SD)[b]	1.1 (0.3)	1.2 (0.4)	1.1 (0.3)	1.0 (0.3)
HDL, mg/dl (SD)[b]	53 (15)	52 (14)	54 (14)	55 (15)
LDL, mg/dl (SD)	112 (35)	111 (38)	113 (35)	111 (35)
Medication use, *n* (%)[b]				
Diuretics[b]	1277 (45)	221 (34)	705 (43)	351 (61)
Angiotensin-converting enzyme inhibitor[b]	1058 (37)	258 (40)	613 (38)	187 (33)
Angiotensin receptor blocker	613 (22)	148 (23)	329 (20)	136 (24)
Calcium channel blocker	1024 (36)	231 (36)	597 (37)	196 (34)
β-blocker	884 (31)	206 (32)	487 (30)	191 (33)
Antiacidosis[b]	15 (0.5)	12 (2)	2 (0.1)	1 (0.2)
Aspirin	1465 (51)	325 (51)	841 (51)	299 (53)
Phosphate binders	34 (1)	9 (1)	19 (1)	6 (1)

[a]The following characteristics had missing data: smoking (*n*=3); body mass index (*n*=24); eGFR (*n*=9); urine albumin-to-creatinine ratio (*n*=139); serum creatinine (*n*=9); HDL (*n*=4); LDL (*n*=23); and aspirin (*n*=6). All other 13 covariates had no missing data.
[b]Statistically significant differences were observed between the three groups of serum bicarbonate.

functional MRI (fMRI) sequence during resting and 30-second breath hold, respectively. Blood-oxygenation-level-dependent signal changes for the resting state fMRI and breath-holding task were performed with the same imaging parameters: a two-dimensional gradient-echo echo-planar imaging sequence (field of view=22 cm, matrix =64×64, slice thickness/slice spacing =3.5/0 mm, number of slices =35 covering the whole-brain, TR=2 seconds, TE=25 milliseconds, flip angle =75°, number of time points =120 for resting state fMRI and 105 for breath-holding experiments).

Statistical Analyses

Standard descriptive statistics were used to characterize the study cohort at SPRINT baseline, stratified by groups of serum bicarbonate. Continuous variables were expressed as mean (SD) or median (IQR), and compared using *t* tests or Wilcoxon rank-sum tests as appropriate. Categorical variables were expressed as proportions and compared using chi-squared tests.

Linear regression models were used to estimate the independent association between serum bicarbonate and the five cognitive function outcomes. Covariates used for adjustment in the models included age, sex, race, education, clinical network, tobacco use, history of cardiovascular disease, systolic BP, antihypertensive medications, antiacidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate), baseline eGFR, and spot urine albumin-to-creatinine ratio. Sequential multivariable models for each outcome were created on the basis of our assessment of the covariates likelihood of being a confounder in the relationship between serum bicarbonate and the five cognitive function domains. Because the test scores have been standardized to create a composite measure, their clinical relevance cannot be directly interpreted. Instead we examined the coefficients of other covariates (*i.e.*, age) and compared with the coefficients for serum bicarbonate. Secondary analyses were done to model the association between serum bicarbonate and the performance on individual cognitive tests. All models were tested for linearity of continuous variables of interest. Given the small number of missing covariate data and the large data set, imputation was not performed; participants with missing data were excluded from the multivariable analyses.

Sensitivity analyses were done to assess if the association between serum bicarbonate levels and cognitive function is modified by sex, race, educational level, CKD, albuminuria, diuretic use, or systolic BP, using an interaction between serum bicarbonate and each potential modifier. In addition,

Table 2. Performance on cognitive tests by categories of serum bicarbonate in SPRINT MIND participants

Test	Serum Bicarbonate, mEq/L			*P* Value
	≤24 (*n*=643)	25–28 (*n*=1638)	>28 (*n*=572)	
Screening battery				
Logical Memory Immediate Recall	19.3 (4.9)	19.4 (4.9)	19.2 (4.8)	0.80
Montreal Cognitive Assessment	23.3 (4.0)	23.1 (4.1)	22.6 (4.0)	0.02
Digit Symbol Coding	51.5 (14.7)	51.1 (15.0)	50.6 (15.2)	0.59
Logical Memory Delayed Recall	8.2 (3.3)	8.3 (3.4)	8.1 (3.3)	0.36
Extended battery				
Hopkins Verbal Learning Test Learning Trials 1–3	21.5 (5.0)	21.7 (5.3)	21.7 (5.1)	0.54
Trail Making Test A	43.3 (23.4)	43.8 (25.2)	42.7 (19.3)	0.65
Trail Making Test B	122.3 (72.3)	120.1 (71.0)	121.0 (70.0)	0.81
Boston Naming Test	11.9 (3.1)	11.7 (3.2)	11.6 (3.2)	0.35
Rey-Osterrieth Complex Figure	14.3 (4.5)	14.4 (4.7)	14.3 (5.0)	0.80
Category Fluency – Animals	18.1 (5.5)	17.9 (5.0)	17.6 (4.7)	0.24
Digit Span Total	16.8 (4.2)	16.9 (4.2)	16.8 (3.9)	0.57
Hopkins Verbal Learning Test Delayed Recall	5.7 (3.7)	5.6 (3.9)	5.2 (3.9)	0.04
Hopkins Verbal Learning Test Delayed Recognition	10.7 (1.7)	10.7 (1.6)	10.7 (1.7)	0.72

Values are expressed as mean (SD).

given that previous studies have suggested a U-shaped relationship between bicarbonate levels and clinical outcomes, we explored such nonlinear associations further by treating serum bicarbonate as a continuous exposure and using quadratic splines or cubic splines to model the association between serum bicarbonate and each cognitive function summary score.

In the subgroup of participants with MRI data, the models were further adjusted for the MRI findings known to be associated with worse cognitive performance. These confounders included white matter hyperintensity volume and total abnormal volume. Additionally, the models were adjusted for scanner type. Because acid base balance is intimately involved in cerebral autoregulation, the models were adjusted for vascular reactivity and CBF, measures obtained from the 30-second breath-hold fMRI. Demographic characteristics of participants in the MRI subgroup were similar to the entire study cohort.

All analyses were done using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 2853 participants underwent the extended cognitive battery testing and had available serum bicarbonate levels at SPRINT baseline; these participants were included in this analysis. The mean age (SD) was 68 (8.5) years, 1053 (37%) were women, 856 (30%) were black, and 568 (20%) had a history of cardiovascular disease. The mean (SD) bicarbonate level was 26.3 (2.6) mEq/L (median, 26 mEq/L; IQR, 25–28 mEq/L). At study entry, mean (SD) eGFR was 71 (20) (median, 73; IQR, 57–86) ml/min per 1.73 m^2. There were 863 (30%) participants with CKD.

Compared with participants with normal or high serum bicarbonate, participants with serum bicarbonate ≤24 mEq/L were more likely to be younger, to be men, and to have CKD or history of cardiovascular disease at study baseline. They were also more likely to be taking an angiotensin-converting enzyme inhibitor or an antiacidosis medication, and less likely to be on a diuretic (Table 1).

Unadjusted comparisons of performances on individual cognitive tests by categories of serum bicarbonate are presented in Table 2. Statistically significant differences were observed across strata of serum bicarbonate for Montreal Cognitive Assessment score (mean [SD]: 23.3 [3.9], 23.1 [4.1], and 22.6 [4.0]; P=0.02), and Hopkins Verbal Learning Test Delayed Recall score (mean [SD]: 5.7 [3.7], 5.6 [3.9], and 5.2 [3.9]; P=0.04), for serum bicarbonate ≤24, 25–28, and >28 mEq/L, respectively. There were no statistically significant differences in the mean scores in other measures of cognitive function between serum bicarbonate strata (Table 2).

Association of Serum Bicarbonate with Cognitive Function

Table 3 depicts the results of multivariable linear regression models evaluating the association between serum bicarbonate as continuous variable and cognitive function scores. There was a positive linear association between serum bicarbonate and global cognitive function summary score that was consistent in hierarchical models adjusted for demographics (estimate [SEM]: 0.02 [0.005]; P<0.01), clinical characteristics (estimate [SEM]: 0.02 [0.006]; P<0.01), and eGFR and albuminuria (estimate [SEM]: 0.01 [0.006]; P=0.01). Similarly, there was a positive linear association between serum bicarbonate and executive function summary score that was consistent after adjustment for demographics (estimate [SEM]: 0.02 [0.006]; P<0.01), clinical characteristics (estimate [SEM]: 0.02 [0.006]; P=0.004), and eGFR and albuminuria (estimate [SEM]: 0.02 [0.006]; P=0.002). Each 1 mEq/L lower serum bicarbonate concentration had a similar association with global cognitive and executive function as being 4.3 and 5.4 months older, respectively (estimate [SEM] for age in the final model: −0.040 [0.002] and −0.039 [0.002], respectively). There was no statistically significant association between serum bicarbonate level and memory, attention/concentration, and language summary scores (Table 3). The association between serum bicarbonate and individual cognitive test results is presented in Supplemental Table 2.

Table 3. Association between continuous serum bicarbonate and summary cognitive function domains in SPRINT MIND participants

Domain	Model 1, *n*=2853		Model 2, *n*=2853		Model 3, *n*=2804	
	Estimate (SEM)	*P* Value	Estimate (SEM)	*P* Value	Estimate (SEM)	*P* Value
Global cognitive function	0.02 (0.005)	<0.01	0.02 (0.006)	<0.01	0.01 (0.006)	0.01
Executive function	0.02 (0.006)	<0.01	0.02 (0.006)	0.004	0.02 (0.006)	0.002
Memory	0.01 (0.006)	0.07	0.008 (0.006)	0.20	0.006 (0.006)	0.35
Attention/concentration	0.01 (0.006)	0.06	0.01 (0.006)	0.04	0.01 (0.006)	0.06
Language	−0.008 (0.006)	0.19	−0.009 (0.006)	0.15	−0.009 (0.006)	0.17

Model 1 adjusted for age, network, education, sex, and race. Model 2 adjusted for model 1 components as well as cardiovascular disease, systolic BP, use of diuretics, and antiacidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate). Model 3 adjusted for model 2 components as well as eGFR and log-transformed urine albuminuria.

In exploratory models by categories of serum bicarbonate, participants with serum bicarbonate ≤24 mEq/L had lower performance on global cognitive and executive function summary scores, compared with participants with serum bicarbonate 25–28 mEq/L, although these associations did not reach statistical significance (estimate [SEM]: −0.06 [0.04]; *P*=0.18, and −0.06 [0.04], *P*=0.15, respectively) (Supplemental Tables 3 and 3.1). The association between categories of serum bicarbonate and individual cognitive test results is presented in Supplemental Table 4.

Sensitivity analyses of the association between serum bicarbonate level and cognitive function scores were conducted in the following subgroups by sex, race, education, CKD status, systolic BP, albuminuria, and diuretic use. No significant interactions were observed (Supplemental Table 5).

Association of Serum Bicarbonate with Cognitive Function in the MRI Substudy

We tested the association between serum bicarbonate and cognitive function in a subgroup of 681 participants who underwent brain MRI. The positive linear association between serum bicarbonate and global cognitive function persisted after adjustment for MRI structural and functional measurements to include white matter hyperintensity volume, vascular reactivity, and CBF (estimate [SEM]: 0.03 [0.01]; *P*=0.01). There was a positive association between serum bicarbonate and executive function when adjustments were made for demographics and traditional cardiovascular risk factors (estimate [SEM]: 0.03 [0.01]; *P*=0.02); however, these associations were attenuated and became not statistically significant after adjustments for structural brain abnormalities (estimate [SEM]: 0.02 [0.01]; *P*=0.06) as well as functional brain abnormalities (estimate [SEM]: 0.02 [0.01]; *P*=0.07) (Table 4). Characteristics of participants in the MRI subgroup are presented in Supplemental Table 6. There was no statistical significant association between serum bicarbonate level and white matter volume, CBF, and vascular reactivity (Supplemental Table 7).

Discussion

In a large cohort of hypertensive adults with and without CKD, we found a positive linear association between serum bicarbonate level and global cognitive and executive functions, independent of the degree of albuminuria, eGFR, diuretic use, or traditional cerebrovascular risk factors (age, cardiovascular disease, and BP). Each 1 mEq/L lower serum bicarbonate concentration had a similar association with global cognitive and executive function as being 4.3 and 5.4 months older, respectively. To our knowledge, this is the first study to evaluate the association between serum bicarbonate level and rigorous multiple cognitive function domain measurements in patients with and without CKD.

The relationship between serum bicarbonate and global cognitive function was maintained after adjustments for

Table 4. Association of serum bicarbonate with cognitive function domains in the SPRINT MIND MRI subgroup

Domain	Model 1, *n*=681		Model 2, *n*=681		Model 3, *n*=594	
	Estimate (SEM)	*P* Value	Estimate (SEM)	*P* Value	Estimate (SEM)	*P* Value
Global cognitive function	0.0391 (0.01)	0.001	0.0358 (0.01)	0.003	0.0328 (0.01)	0.01
Executive function	0.0304 (0.01)	0.02	0.0246 (0.01)	0.06	0.0246 (0.01)	0.07
Memory	0.0255 (0.01)	0.05	0.0256 (0.01)	0.05	0.0203 (0.01)	0.14
Attention/concentration	0.0240 (0.01)	0.07	0.0196 (0.01)	0.15	0.0164 (0.01)	0.26
Language	0.0024 (0.01)	0.86	−0.0005 (0.01)	0.97	0.0078 (0.01)	0.59

Model 1 adjusted for age, network, education, sex, race, cardiovascular disease, systolic BP, use of diuretics and antiacidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate), eGFR, and log-transformed urine albuminuria. Model 2 adjusted for model 1 components as well as scanner type, intracranial volume, and total abnormal volume. Model 3 adjusted for model 2 components as well as vascular reactivity and cerebral blood flow.

structural white matter abnormalities, cerebral vascular reactivity, and CBF, suggesting that chronic low levels of bicarbonate within the brain may be detrimental to neuronal function. Our models showed a trend toward a statistically significant association between serum bicarbonate and executive function in the MRI subgroup. Important to note, this was observed in a subset of SPRINT participants with available brain MRI data, so further studies on larger cohorts would be needed to assess this association. We found no association between serum bicarbonate level and memory, attention/concentration, and language domains, suggesting a potential distinct pathophysiologic process. In exploratory analyses by categories of serum bicarbonate, the lack of statistical significant association is likely explained by the loss of statistical power.

Previous studies evaluating the mechanisms of acidosis induced neuronal dysfunction described the role of impaired GABAergic neurons responsible to coordinate the activities of principal neurons and help manage well organized cognitions (24,25). A potential mechanism of acidosis leading to impaired cognition may be through overexcitation of neural networks by being a potent inhibitor of NMDA-activated currents. The possible effect of acidosis on neuronal function and not structure is also supported by the null association found between bicarbonate and structural MRI measurements. It is reasonable to assume that chronic, low degree metabolic acidosis induced by a Western diet irrespective of the level of eGFR (26) can promote neural excitotoxicity and subsequently cognitive impairment. Because pH was not available in SPRINT, it is possible that a small proportion of SPRINT participants with low bicarbonate had respiratory alkalosis. Mechanisms underlying alkalosis-induced brain dysfunction are much less understood, but they seem to be related to impairment in excitatory synaptic transmission and spike initiation in cortical GABAergic neurons (27).

A larger body of evidence describe the effect of acidosis on neurons and glia, primarily in the setting of cerebral ischemia, with most pointing toward regional lactic acidosis as a key neurotoxic insult to ischemic brain leading to direct impairment of cellular metabolism (28–31). Cognitive dysfunction, and in particular changes in processing speed, shifting between mental tasks, executive function, concentration, and attention have been long thought to be a consequence of cerebral vascular damage (32,33).

Cardiovascular disease and metabolic acidosis are common complications of CKD. Cognitive impairment is another common occurrence in CKD, and the risk of cognitive decline is dependent on the severity of CKD. The exact mechanisms of CKD promoting neuronal damage remain vaguely unknown. This study may provide a mechanistic insight into why patients with CKD have poor cognitive function. Future randomized trials with alkali supplementation should clarify if correction of metabolic acidosis in CKD will also lead to better cognitive outcomes in this population at high cardiovascular risk. The strength of the association between serum bicarbonate level and global cognitive and executive functions was relatively modest in our observational study, and should be confirmed in clinical trials testing alkali supplementation or dietary modifications to correct metabolic acidosis.

This study has several strengths, including concurrent assessment of serum bicarbonate level, kidney function, albuminuria, cognitive function tests, and brain MRI. Furthermore, a large battery of tests was used to assess cognitive function, allowing for differentiation of cognitive deficit subtypes associated with a low bicarbonate level. Also, SPRINT recruited a large sample of individuals with CKD who are more likely to have acid base abnormalities.

This study has several limitations. First, it is a cross-sectional analysis and causality cannot be inferred. Second, the acid base status assessment with a blood gas analysis was not available. Some participants might have high bicarbonate as a compensatory mechanism for respiratory acidosis, or a low bicarbonate as a compensatory response for respiratory alkalosis. Third, these analyses are on the basis of a single measurement of serum bicarbonate; whether changes in bicarbonate levels over time add incremental predictive value to the development of cognitive dysfunction will need further study. Also, using a lower category of serum bicarbonate <22 mEq/L on the basis of the current guidelines of alkali supplementation was not possible because of the small number of participants in that group. However, in exploratory analyses the same direction of the association was observed for bicarbonate ≤ 22 and 23–24 mEq/L groups when compared with 25–28 mEq/L group, for four of the five cognitive summary measures (Supplemental Table 3s). Lastly, given that many cofactors used for adjustments (age, BP, history of cardiovascular disease, *etc.*) correlate with the exposure, but they also can be a direct cause of the outcome (cognitive function), residual confounding might in part influence the study findings.

In summary, in a large cohort of hypertensive individuals at high cardiovascular risk, lower levels of serum bicarbonate were associated with worse cognitive performance. In particular, lower serum bicarbonate level was associated with reduced global cognitive function and lower performance on executive function. These findings suggest that low bicarbonate level may be detrimental to neuronal activity. Future intervention trials aimed at correcting chronic metabolic acidosis with alkali therapy are required to test a beneficial effect on the cognitive function.

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For a full list of contributors to SPRINT, please see the supplemental acknowledgment list.

Disclosures

None.

References

1. Chu XP, Xiong ZG: Physiological and pathological functions of acid-sensing ion channels in the central nervous system. *Curr Drug Targets* 13: 263–271, 2012
2. Pirchl M, Humpel C: [Does acidosis in brain play a role in Alzheimer's disease?]. *Neuropsychiatr* 23: 187–192, 2009
3. Zhao H, Cai Y, Yang Z, He D, Shen B: Acidosis leads to neurological disorders through overexciting cortical pyramidal neurons. *Biochem Biophys Res Commun* 415: 224–228, 2011
4. Yuen AW: Low-grade chronic metabolic acidosis is a contributory mechanism in the development of chronic epilepsy. *Epilepsy Behav* 8:347–349, 2006
5. Brown D, Bouley R, Păunescu TG, Breton S, Lu HA: New insights into the dynamic regulation of water and acid-base balance by renal epithelial cells. *Am J Physiol Cell Physiol* 302: C1421–C1433, 2012
6. Kraut JA, Kurtz I: Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. *Am J Kidney Dis* 45: 978–993, 2005
7. Kovesdy CP, Anderson JE, Kalantar-Zadeh K: Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. *Nephrol Dial Transplant* 24: 1232–1237, 2009
8. Menon V, Tighiouart H, Vaughn NS, Beck GJ, Kusek JW, Collins AJ, Greene T, Sarnak MJ: Serum bicarbonate and long-term outcomes in CKD. *Am J Kidney Dis* 56: 907–914, 2010
9. Shah SN, Abramowitz M, Hostetter TH, Melamed ML: Serum bicarbonate levels and the progression of kidney disease: A cohort study. *Am J Kidney Dis* 54: 270–277, 2009
10. Navaneethan SD, Schold JD, Arrigain S, Jolly SE, Wehbe E, Raina R, Simon JF, Srinivas TR, Jain A, Schreiber MJ Jr., Nally JV Jr.: Serum bicarbonate and mortality in stage 3 and stage 4 chronic kidney disease. *Clin J Am Soc Nephrol* 6: 2395–2402, 2011
11. Raphael KL, Wei G, Baird BC, Greene T, Beddhu S: Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. *Kidney Int* 79: 356–362, 2011
12. Dobre M, Yang W, Chen J, Drawz P, Hamm LL, Horwitz E, Hostetter T, Jaar B, Lora CM, Nessel L, Ojo A, Scialla J, Steigerwalt S, Teal V, Wolf M, Rahman M; CRIC Investigators: Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: A report from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidny Dis* 62: 670–678, 2013
13. Raphael KL, Murphy RA, Shlipak MG, Satterfield S, Huston HK, Sebastian A, Sellmeyer DE, Patel KV, Newman AB, Sarnak MJ, Ix JH, Fried LF; Health ABC Study: Bicarbonate concentration, acid-base status, and mortality in the health, aging, and body composition study. *Clin J Am Soc Nephrol* 11: 308–316, 2016
14. Kurella Tamura M, Wadley V, Yaffe K, McClure LA, Howard G, Go R, Allman RM, Warnock DG, McClellan W: Kidney function and cognitive impairment in US adults: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Am J Kidney Dis* 52: 227–234, 2008
15. Kurella Tamura M, Muntner P, Wadley V, Cushman M, Zakai NA, Bradbury BD, Kissela B, Unverzagt F, Howard G, Warnock D, McClellan W: Albuminuria, kidney function, and the incidence of cognitive impairment among adults in the United States. *Am J Kidney Dis* 58: 756–763, 2011
16. Kurella M, Chertow GM, Fried LF, Cummings SR, Harris T, Simonsick E, Satterfield S, Ayonayon H, Yaffe K: Chronic kidney disease and cognitive impairment in the elderly: The health, aging, and body composition study. *J Am Soc Nephrol* 16: 2127–2133, 2005
17. Afsar B, Elsurer R: Association between serum bicarbonate and pH with depression, cognition and sleep quality in hemodialysis patients. *Ren Fail* 37: 957–960, 2015
18. Egbi OG, Ogunrin O, Oviasu E: Prevalence and determinants of cognitive impairment in patients with chronic kidney disease: A cross-sectional study in Benin City, Nigeria. *Ann Afr Med* 14: 75–81, 2015
19. Ambrosius WT, Sink KM, Foy CG, Berlowitz DR, Cheung AK, Cushman WC, Fine LJ, Goff DC Jr., Johnson KC, Killeen AA, Lewis CE, Oparil S, Reboussin DM, Rocco MV, Snyder JK, Williamson JD, Wright JT Jr., Whelton PK; SPRINT Study Research Group: The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: The Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials* 11: 532–546, 2014
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009
21. Tamura MK, Pajewski NM, Bryan RN, Weiner DE, Diamond M, Van Buren P, Taylor A, Beddhu S, Rosendorff C, Jahanian H, Zaharchuk G; SPRINT Study Research Group: Chronic kidney disease, cerebral blood flow, and white matter volume in hypertensive adults. *Neurology* 86: 1208–1216, 2016
22. Zacharaki EI, Kanterakis S, Bryan RN, Davatzikos C: Measuring brain lesion progression with a supervised tissue classification system. *Med Image Comput Comput Assist Interv* 11: 620–627, 2008
23. Wang Z, Aguirre GK, Rao H, Wang J, Fernández-Seara MA, Childress AR, Detre JA: Empirical optimization of ASL data analysis using an ASL data processing toolbox: ASLtbx. *Magn Reson Imaging* 26: 261–269, 2008
24. Li F, Liu X, Su Z, Sun R: Acidosis leads to brain dysfunctions through impairing cortical GABAergic neurons. *Biochem Biophys Res Commun* 410: 775–779, 2011
25. Zhou C, Xiao C, Deng C, Hong Ye J: Extracellular proton modulates GABAergic synaptic transmission in rat hippocampal CA3 neurons. *Brain Res* 1145: 213–220, 2007
26. Amodu A, Abramowitz MK: Dietary acid, age, and serum bicarbonate levels among adults in the United States. *Clin J Am Soc Nephrol* 8: 2034–2042, 2013
27. Sun L, Zhang K, Li J, Liu D, Lu Y, Zhang Z: An impairment of cortical GABAergic neurons is involved in alkalosis-induced brain dysfunctions. *Biochem Biophys Res Commun* 419: 627–631, 2012
28. Myers RE, Yamaguchi S: Nervous system effects of cardiac arrest in monkeys. Preservation of vision. *Arch Neurol* 34: 65–74, 1977
29. Welsh FA, Ginsberg MD, Rieder W, Budd WW: Deleterious effect of glucose pretreatment on recovery from diffuse cerebral ischemia in the cat. II. Regional metabolite levels. *Stroke* 11: 355–363, 1980

30. Kalimo H, Rehncrona S, Söderfeldt B, Olsson Y, Siesjö BK: Brain lactic acidosis and ischemic cell damage: 2. Histopathology. *J Cereb Blood Flow Metab* 1: 313–327, 1981
31. Plum F: What causes infarction in ischemic brain?: The Robert Wartenberg Lecture. *Neurology* 33: 222–233, 1983
32. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, Bowler JV, Ballard C, DeCarli C, Gorelick PB, Rockwood K, Burns A, Gauthier S, DeKosky ST: Vascular cognitive impairment. *Lancet Neurol* 2: 89–98, 2003
33. Graham NL, Emery T, Hodges JR: Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. *J Neurol Neurosurg Psychiatry* 75: 61–71, 2004

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