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ORIGINAL ARTICLE

Relationship of acid–base status with arterial stiffness in community-living elders: the Health ABC Study

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ABSTRACT

Background. Animal studies suggest that acidosis protects against arterial calcification, which contributes to arterial stiffness. The goal of this study was to investigate the associations of serum bicarbonate and pH with arterial stiffness in community-living older adults.

Methods. We performed cross-sectional analyses among 1698 well-functioning participants 70–79 years of age. Bicarbonate and pH were measured by arterialized venous blood gas at the point of care. Bicarbonate was categorized into low (<23 mEq/L), normal (23–27.9) and high (≥28). Arterialized venous pH (AVpH) was categorized into tertiles: ≤7.40, >7.40–7.42 and >7.42. Arterial stiffness was evaluated by pulse wave velocity (PWV) and high ankle-brachial index (ABI; >1.3/incompressible). We used linear and logistic regression to evaluate the association of bicarbonate and AVpH with PWV and high ABI, respectively.

Results. The mean age was 76 years and 15% had an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. The mean bicarbonate was 25.2 ± 2.1 mEq/L and the mean AVpH was 7.41 ± 0.03. Compared with participants in the normal bicarbonate category, those in the low bicarbonate group had 8.8% higher PWV (P = 0.006) and 1.87 greater odds of high ABI (P = 0.04). However, the associations were not significant after adjusting for eGFR (P = 0.24 and 0.43, respectively). There was no difference in PWV or high ABI across AVpH tertiles. Results were similar in those with and without chronic kidney disease and after excluding participants on diuretics.

Conclusions. We did not observe an independent association of bicarbonate or AVpH with arterial stiffness measured by high PWV or ABI in community-living older individuals. Future studies evaluating patients with a greater severity of chronic kidney disease and with more extreme alterations in acid–base status are warranted.

Keywords: acidosis, arterial calcification, arterial stiffness, metabolic acidosis, serum bicarbonate

INTRODUCTION

Arterial calcification is common and is strongly linked with cardiovascular disease mortality in patients with chronic kidney disease (CKD). Arterial calcification may lead to arterial stiffness and systolic hypertension, which in turn predisposes individuals to cardiovascular death. Arterial stiffness measured by high pulse wave velocity (PWV) or high ankle-brachial index (ABI) is a strong independent risk factor for cardiovascular events [1–6].

Chronic metabolic acidosis is a common complication of CKD, with a prevalence ∼30–50% in individuals with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 [7, 8]. It is associated with numerous deleterious effects, such as bone loss, insulin resistance, muscle wasting and progression of kidney disease [7–11]. As a result, oral alkali therapy is often recommended to correct acidosis in CKD [12]. However, animal studies suggest that metabolic acidosis may actually protect against arterial calcification and that alkalosis may worsen it [13, 14]. If this were also true in humans, then it would raise questions regarding the relative risks and benefits of current recommendations for alkali therapy in CKD.

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Few prior studies have evaluated the relationship between metabolic acidosis and arterial stiffness. The goal of this study was to investigate this relationship in the Health, Aging, Body Composition (Health ABC) study. The Health ABC study enrolled generally healthy older individuals with a broad range of kidney function. Participants provided arterialized venous blood gas specimens that were used to calculate serum bicarbonate from arterialized venous pH (AVpH) and the partial pressure of carbon dioxide (pCO_2). The participants were also assessed for measures of arterial stiffness, including PWV and the ABI. *A priori*, we hypothesized that individuals with higher serum bicarbonate levels or AVpH would have greater arterial stiffness compared with those with lower bicarbonate or AVpH and that the associations would be independent of eGFR.

MATERIALS AND METHODS

Study population

The Health ABC is a prospective study designed to evaluate the effect of weight and body composition on age-related physiological and functional changes. The study design has been described in detail previously [5, 15]. Briefly, the study enrolled 3075 participants 70–79 years of age from Memphis, Tennessee and Pittsburgh, Pennsylvania, USA between 1997 and 1998. Participants were eligible if they reported no difficulty in walking a quarter mile, climbing 10 steps or performing basic activities of daily living or a life-threatening illness. The Health ABC study was overseen by institutional review boards at the University of Tennessee and the University of Pittsburgh and was performed under the principles embodied in the Declaration of Helsinki. For this analysis, we included 1698 participants after excluding 788 participants for missing arterialized venous blood gas, 388 for missing PWV and 201 for missing ABI measurements.

Acid–base measurements

Arterialized venous blood gas samples were obtained at the Year 3 visit from a cannulated hand or wrist vein after the participant's hand or wrist had been placed in a warmer set to 42°C and warmed for a minimum of 15 min prior to blood sampling. Samples were obtained after at least 2 h of fasting and analyzed on site at the time of phlebotomy. Each sample was measured for pH and pCO_2 on an ABL5 blood gas analyzer (Radiometer, Copenhagen, Denmark) and was analyzed potentiometrically using a glass membrane and glass/silver/silver chloride electrode, respectively. Arterialized capillary blood gas is less invasive and a reliable substitute for arterial blood gas. According to a meta-analysis, capillary blood gas accurately reflects arterial pH across a wide range (6.77–7.74) [16]. Serum bicarbonate levels were calculated using the Henderson–Hasselbalch equation. Each sample was measured three times and results were averaged. Bicarbonate levels were categorized into low (<23 mEq/L), normal (23–27.9 mEq/L) and high (≥28 mEq/L) based on previously published studies from Health ABC [15]. AVpH was categorized into tertiles: low (≤7.40), normal (>7.40–7.42) and high (>7.42). Participants were categorized into one of seven acid–base statuses previously defined in the Health ABC cohort [15]. Normal acid–base status was defined if average values of AVpH, bicarbonate and pCO_2 were within the normal range. Remaining participants were grouped into one of the abnormal acid–base categories as described in the Supplementary data, Table S1.

Arterial stiffness measurements

Arterial stiffness was assessed by PWV and high ABI. PWV was measured at the year 1 visit (∼2 years before acid–base assessment) from simultaneous Doppler flow signals obtained from the right carotid and right femoral arteries using nondirectional transcutaneous Doppler flow probes (model 810 A, 9.0- to 10-MHz probes; Parks Medical Electronics, Aloha, OR, USA). The distance between the carotid and femoral sample sites was measured above the surface of the body with a metal tape measure. Results from all acceptable runs were averaged for the final PWV measure. Replicate measures of PWV in 14 individuals revealed intraclass correlations of 0.88 between sonographers and 0.84 between readers. A higher PWV indicates stiffer arteries. Prior studies using the PWV measurements in Health ABC have shown strong associations with future cardiovascular disease (CVD) [5].

ABI was measured at the Year 4 visit (∼1 year after acid–base assessment). The ABI was not assessed in those with open wounds including venous stasis ulcers, rashes or bilateral amputations and those who were unable to lie at ≤45°. Pressures were taken in the right arm and both ankles (posterior tibial artery) with standard blood pressure cuffs and a pencil Doppler. The systolic blood pressure of the ankle was divided by the systolic blood pressure of the arm to calculate the leg-specific ABI. Measurements were taken twice and the results were averaged. The lower value between the two legs was used for the patient-specific ABI. ABI values of 0.9–1.3 were considered normal. Arterial stiffness was defined when ABI was >1.3 or when the arteries were incompressible despite inflation of the blood pressure cuff to 250 mmHg. Participants with ABI < 0.9 ($n = 264$) were excluded in the ABI analyses. Prior studies in Health ABC have shown that high ABI measurements were strongly associated with future CVD [4]. Systolic and diastolic blood pressures were obtained by trained and certified clinical staff from the right arm using a conventional mercury sphygmomanometer with the participant in a seated position. Two seated measurements were averaged. Pulse pressure was defined as systolic minus diastolic blood pressure.

Measurements of other covariates

Age, sex, race and smoking status were self-reported. Weight was measured to the nearest 0.1 kg using a balance beam scale with the participants wearing lightweight clothing [17]. Height was measured without shoes to the nearest millimeter using a Harpenden Stadiometer (Holtain, Pantygarn Crymych, UK). Body mass index was calculated in kilograms per meter square. Diabetes was defined as the use of hypoglycemic agents, self-reported history, fasting plasma glucose ≥126 mg/dL or 2-h oral glucose tolerance test ≥200 mg/dL. Hypertension was defined as systolic blood pressure

≥140 mmHg, diastolic blood pressure ≥90 mmHg or current use of antihypertensive medications. Obstructive lung disease was determined based on spirometry using a horizontal dry rolling seal spirometer (SensorMedics, Yorba Linda, CA, USA.) [18]. Participants' medications brought to the study visits were recorded by study personnel and categorized using the Iowa Drug Information System into major therapeutic groups based on ingredients in the medications.

Kidney function was determined using creatinine and cystatin C. Creatinine was measured using a colorimetric assay calibrated to isotope-dilution mass spectrometry–traceable standards [19]. Cystatin C was analyzed using a particle-enhanced immunonephelometric assay [20]. Demographics, creatinine level and cystatin C level were combined to estimate GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine–cystatin C equation [21]. CKD was defined as eGFR <60 mL/min/1.73 m^2. Urine albumin was measured using a particle-enhanced turbidimetric inhibition immunoassay. Urine creatinine was measured by a modified Jaffé method on a clinical chemistry analyzer [22]. Serum calcium was measured with direct quantitative colorimetric determination [23]. Supplementary data, Table S2 indicates the visits at which the above covariates were obtained.

Statistical analyses

The association of baseline participant characteristics across serum bicarbonate categories and AVpH tertiles was examined using analysis of variance for continuous variables or the Kruskal–Wallis test for skewed variables. Chi-squared tests were used for categorical variables. PWV was examined as a continuous variable. After examination of the distribution of PWV, natural log transformation was used to meet normality assumptions for linear regression modeling. Multiple linear regression models were used to evaluate the association of serum bicarbonate and AVpH with PWV. The percentage change in PWV was calculated by transforming the β coefficient [percentage change in PWV = 100 × (e^{β}−1)]. ABI was examined as a categorical variable. Multiple logistic regression models were used to examine the association of serum bicarbonate and AVpH with high ABI. The following covariates were included in sequentially adjusted models: model 1, age, sex, race and clinical sites; model 2, covariates in model 1 plus eGFR; model 3, covariates in model 2 plus heart rate, urine albumin:creatinine ratio, diabetes, systolic blood pressure, diuretics use, renin–angiotensin–aldosterone system blockade and smoking status. Age, sex, race and CKD status (eGFR < 60 mL/min/1.73 m^2) were examined as effect modifiers by using first-order interaction terms.

Several sensitivity analyses were performed. We repeated the analyses after excluding participants on diuretics (n = 464), examined the association between AVpH and arterial stiffness, with AVpH categorized into low (<7.37), normal (7.37–7.43) [24] and high (>7.43) groups instead of AVpH tertiles, and examined the association of serum bicarbonate and AVpH with pulse pressure. In addition, we examined the relationship between acid–base categories and arterial stiffness. Two-sided P-values < 0.05 were considered statistically significant for all analyses, including interaction terms, and analyses were conducted using STATA 14.1 (StataCorp, College Station, TX, USA).

RESULTS

Participant characteristics

The mean age of the study participants was 76 years, 52% were women and 35% were black. The mean serum bicarbonate concentration was 25.2± 2.1 mEq/L and 178 (10.5%) participants had serum bicarbonate concentrations <23 mEq/L. Participants with lower bicarbonate were more likely to be male, white and a smoker, to have diabetes mellitus and to have CKD. They also had higher urine albumin: creatinine ratio (Table 1). In contrast, the low bicarbonate group was less likely to have hypertension and to use diuretics and they had lower eGFR and arterialized venous pCO_2 levels. AVpH was statistically different across the bicarbonate categories, but the distribution of AVpH values was extremely narrow and the mean values were within the normal range. The median PWV for those in the low bicarbonate category was higher than in those in the normal bicarbonate category {866 cm/s [interquartile range (IQR) 678–1107] and 784 cm/s (IQR 630–1024), respectively; P for trend = 0.06}. There were 84 (5%) participants with high ABI group (ABI > 1.30 or incompressible arteries). High ABI was more prevalent in participants with a low bicarbonate level (8% in low, 5% in normal and 4% in the high bicarbonate category; P for trend = 0.09).

The mean AVpH was 7.41 ± 0.03. There were 68 (4%) participants with AVpH <7.37 and 295 (17.4%) with AVpH >7.42. Similar to the participant characteristics by bicarbonate categories, participants with lower AVpH were more likely to be men and to have CKD and less likely to be using diuretics (Supplementary data, Table S3). There was no difference in the PWV or ABI among AVpH tertiles in unadjusted analyses.

Association of bicarbonate concentration and AVpH with PWV

Compared with participants in the normal bicarbonate category, those in the low bicarbonate category had 8.8% [95% confidence interval (CI) 2.2–15.5] higher PWV in unadjusted analysis (Table 2). This association remained statistically significant after adjusting for demographic characteristics and clinical sites but was no longer statistically significant after adjusting for eGFR. There was no significant difference in PWV when comparing those in the normal and high bicarbonate categories. There was no difference in PWV across AVpH tertiles in either unadjusted or adjusted models. Age, sex, race and CKD status did not modify the association of bicarbonate or AVpH with PWV (all interactions had P > 0.12).

Association of bicarbonate concentration and AVpH with high ABI

Compared with participants in the normal bicarbonate category, those in the low bicarbonate category had 1.87 times higher odds of high ABI (P = 0.04) in unadjusted models (Table 3). With every 1 mEq/L higher serum bicarbonate level,

Table 1. Participant characteristics by serum bicarbonate categories

Characteristics	Total, ($n = 1698$)	<23 mEq/L, ($n = 178$)	23–27.9 mEq/L, ($n = 1341$)	≥28 mEq/L, ($n = 179$)	P-value
Demographics					
Age, years	76 (3)	76 (3)	76 (3)	76 (3)	0.17
Sex, *n* (%)					0.007
Women	875 (52)	79 (44)	687 (51)	109 (61)	
Race-ethnicity, *n* (%)					<0.001
Black	602 (35)	59 (33)	448 (33)	95 (53)	
Clinic site, *n* (%)					0.03
Memphis	631 (37)	75 (42)	477 (36)	79 (44)	
Pittsburgh	1067 (63)	103 (58)	864 (64)	100 (56)	
Clinical characteristics					
Body mass index, kg/m^2	27.4 (4.7)	27.2 (4.7)	27.5 (4.6)	27.1 (5.4)	0.57
Smoking status, *n* (%)					0.003
Never smoked	773 (46)	67 (38)	611 (46)	95 (53)	
Former smoker	796 (47)	87 (49)	634 (47)	75 (42)	
Current smoker	128 (8)	24 (13)	95 (7)	9 (5)	
CKD[a], *n* (%)	183 (12)	44 (28)	116 (10)	23 (14)	<0.001
Diabetes mellitus, *n* (%)	322 (19)	46 (26)	239 (18)	37 (21)	0.03
Hypertension, *n* (%)	1275 (75)	131 (74)	995 (74)	149 (83)	0.03
Systolic BP, mmHg	140 (21)	140 (20)	140 (21)	143 (23)	0.13
Diastolic BP, mmHg	74 (11)	73 (10)	74 (11)	76 (11)	0.05
Pulse pressure, mmHg	66 (19)	67 (20)	66 (18)	67 (18)	0.63
Pulse, beats per min	68 (11)	68 (12)	67 (10)	69 (11)	0.18
Antihypertensive medication, *n* (%)					
RAAS blockage	393 (23)	51 (29)	296 (22)	46 (26)	0.10
Diuretics	464 (27)	30 (17)	336 (25)	98 (55)	<0.001
Laboratory data					
AVpH	7.41 (0.03)	7.40 (0.04)	7.41 (0.02)	7.41 (0.03)	<0.001
Serum bicarbonate, mEq/L	25.2 (2.1)	21.5 (1.3)	25.2 (1.3)	28.7 (1.1)	<0.001
Arterialized venous pCO_2, mmHg	40.4 (3.9)	35.5 (3.1)	40.4 (3.0)	45.8 (3.6)	<0.001
Serum albumin, g/dL	4.0 (0.3)	4.0 (0.3)	4.0 (0.3)	4.0 (0.3)	0.14
Serum calcium, mg/dL	8.8 (0.4)	8.8 (0.5)	8.8 (0.4)	8.9 (0.5)	0.27
Hemoglobin A1c	6.3 (1.0)	6.5 (1.2)	6.2 (1.0)	6.4 (1.1)	0.006
eGFR, mL/min/1.73 m^2	80.0 (16.5)	71.3 (20.2)	81.2 (15.4)	79.5 (17.8)	<0.001
Urine albumin:creatinine ratio, median (IQR)	8.0 (4.5–18.4)	11.7 (5.8–27.3)	7.6 (4.2–17.0)	9.6 (5.2–24.0)	<0.001*
PWV, median (IQR), cm/s	793 (632–1033)	866 (678–1107)	784 (630–1024)	791 (606–1027)	0.06*
ABI, *n* (%)					0.09
0.9–1.3	1350 (80)	128 (72)	1079 (80)	143 (80)	
≥1.31 or incompressible	84 (5)	14 (8)	63 (5)	7 (4)	

Note: If normally distributed, values for continuous variables with normal distribution are provided as mean (SD), otherwise they are provided as median (IQR). Categorical variables are presented as absolution number with percentage.

[a]CKD was defined as eGFR < 60 mL/min/1.73 m^2 using the CKD-EPI creatinine–cystatin C equation.

*Kruskal–Wallis equality of population rank tests were used.

BP, blood pressure; RAAS, renin–angiotensin–aldosterone system.

the odds of high ABI decreased by 11% [odds ratio 0.89 (95% CI 0.80–0.99)]. The association was no longer statistically significant after adjusting for demographic characteristics and eGFR. There was no significant association between AVpH and high ABI in either unadjusted or adjusted models. Age, sex, race and CKD status did not modify the association of bicarbonate or AVpH with high ABI (all interactions had $P > 0.28$).

Sensitivity analyses

With AVpH categorized into low (<7.37), normal (7.37–7.43) and high (>7.43) groups, there was no significant association of AVpH with PWV and ABI in unadjusted and fully adjusted models (Supplementary data, Table S4). We did not observe any association of serum bicarbonate and AVpH with pulse pressure (Supplementary data, Table S5). After excluding participants on diuretics, 148 (12.0%) participants had serum bicarbonate <23 mEq/L. Among participants who were not using diuretics (i.e. diuretic nonusers), after adjusting for demographic characteristics and clinical sites, compared with participants in the normal bicarbonate category, those in the low bicarbonate category had 10.6% (95% CI 3.6–18.1) higher PWV, but the association was no longer statistically significant after adjusting for eGFR (Supplementary data, Table S6a). Among diuretic nonusers, there was no difference in PWV across AVpH tertiles and no significant association of serum bicarbonate and AVpH with high ABI or with pulse pressure (Supplementary data, Table S6a–c). Compared with participants with normal acid–base status, those with metabolic acidosis had 8.6% higher PWV ($P = 0.02$), but the association became nonsignificant after adjusting for participant demographics, clinical sites and eGFR (Supplementary data, Table S7).

Table 2. Association of serum bicarbonate categories and AVpH tertiles with PWV (cm/s)

Serum bicarbonate, mEq/L				
Model	<23 ($n = 178$), % change (95% CI)	23–27.9 ($n = 1341$)	≥28 ($n = 179$), % change (95% CI)	Continuous[a], % change (95% CI)
Unadjusted	8.8 (2.4, 15.5)	Ref.	−0.1 (−5.9, 6.1)	−0.3 (−1.2, 0.6)
Model 1	7.4 (1.2, 13.9)	Ref.	−1.5 (−7.2, 4.6)	−0.2 (−1.1, 0.6)
Model 2	3.8 (−2.5, 10.6)	Ref.	−1.0 (−6.8, 5.2)	0.03 (−0.9, 0.9)
Model 3	2.1 (−4.3, 8.9)	Ref.	−3.2 (−9.1, 3.1)	−0.2 (−1.2, 0.8)
AVpH				
Model	≤7.40 ($n = 586$), % change (95% CI)	>7.40–7.42 ($n = 598$),	>7.42 ($n = 514$), % change (95% CI)	Continuous[b], % change (95% CI)
Unadjusted	2.3 (−2.1, 6.9)	Ref.	1.3 (−3.2, 6.0)	1.2 (−5.8, 8.7)
Model 1	0.5 (−3.8, 4.9)	Ref.	2.1 (−2.4, 6.8)	5.8 (−1.6, 13.9)
Model 2	−0.2 (−4.6, 4.4)	Ref.	1.5 (−3.1, 6.3)	7.4 (−0.4, 15.8)
Model 3	0.6 (−4.0, 5.3)	Ref.	0.1 (−4.6, 5.0)	4.6 (−3.4, 13.3)

Model 1: adjusted for age, sex, race, clinical sites.
Model 2: adjusted for covariates in Model 1 plus eGFR.
Model 3: adjusted for covariates in Model 2 plus heart rate, urine albumin:creatinine ratio, diabetes, systolic blood pressure, diuretics, renin–angiotensin–aldosterone system blockade and smoking status.
[a]Per 1 mEq/L higher in serum bicarbonate.
[b]Per 0.1 higher in AVpH.

Table 3. Association of serum bicarbonate categories and AVpH tertiles with high ABI

Serum bicarbonate (mEq/L)				
Model	<23 ($n = 142$), OR (95% CI)	23–27.9 ($n = 1142$)	≥28 ($n = 150$), OR (95% CI)	Continuous[a], OR (95% CI)
Unadjusted	1.87 (1.02–3.43)	Ref.	0.84 (0.38–1.87)	0.89 (0.80–0.99)
Model 1	1.81 (0.98–3.35)	Ref.	0.95 (0.42–2.15)	0.91 (0.81–1.01)
Model 2	1.33 (0.65–2.69)	Ref.	0.88 (0.37–2.12)	0.94 (0.83–1.05)
Model 3	1.29 (0.62–2.69)	Ref.	0.86 (0.35–2.13)	0.93 (0.82–1.06)
AVpH				
Model	≤7.40 ($n = 487$), OR (95% CI)	>7.40–7.42 ($n = 506$)	>7.42 ($n = 441$), OR (95% CI)	Continuous[b], OR (95% CI)
Unadjusted	1.00 (0.59–1.71)	Ref.	1.07 (0.62–1.84)	1.80 (0.75–4.32)
Model 1	0.95 (0.55–1.64)	Ref.	1.11 (0.64–1.92)	2.02 (0.83–4.96)
Model 2	0.81 (0.44–1.47)	Ref.	0.97 (0.53–1.78)	2.10 (0.85–5.19)
Model 3	0.80 (0.43–1.47)	Ref.	0.92 (0.49–1.72)	2.17 (0.81–5.80)

Model 1: adjusted for age, sex, race, clinical sites.
Model 2: adjusted for covariates in Model 1 plus eGFR.
Model 3: adjusted for covariates in Model 2 plus heart rate, urine albumin:creatinine ratio, diabetes, systolic blood pressure, diuretics, renin–angiotensin–aldosterone system blockade and smoking status.
[a]Per 1 mEq/L higher in serum bicarbonate.
[b]Per 0.1 higher in AVpH.

DISCUSSION

Low serum bicarbonate concentration was associated with high PWV and high ABI in univariate analyses, but after adjusting for eGFR, these associations were rendered null. Sensitivity analyses using different cut-off points for AVpH and pulse pressure as a measure of arterial stiffness, after excluding participants on diuretics, and categorizing participants into different acid–base status categories provided similar results. Contrary to our hypothesis, there were no associations of higher serum bicarbonate or AVpH with arterial stiffness measures. Thus our results do not support an independent association of bicarbonate or AVpH with arterial stiffness in well-functioning community-living older adults.

Using the Multi-Ethnic Study of Atherosclerosis (MESA), a community-based cohort free of cardiovascular disease at baseline, Kendrick *et al.* [25] found that among diuretic nonusers, bicarbonate ≥25 mEq/L was associated with 1.0 mmHg higher aortic pulse pressure (95% CI 0.4–2.0) compared with those with bicarbonate 23–24 mEq/L. Our sensitivity analyses of diuretic nonusers showed no association between acid–base status and arterial stiffness. Reasons for the discrepancy in results could be the different study populations, with participants from

the MESA being younger than the Health ABC study (mean age 60 versus 70 years) and different measurements for arterial stiffness (aortic pulse pressure versus PWV/ABI/pulse pressure).

The reasons for our null findings are not certain, but we considered three potential explanations. First, our hypothesis was based on the results from preclinical experiments, which may not be applicable to humans. Specifically, we hypothesized that older individuals with higher serum bicarbonate levels or pH would have greater arterial stiffness compared with those with lower bicarbonate or pH. In an *in vitro* study [13], when rat aortas were intermittently exposed to medium with pH increased from basal levels of 7.4 to 7.5 for 5 h every other day, aortic calcification increased 2.5-fold compared with aortas exposed to a constant pH of 7.4. This finding may not be generalized to *in vivo* settings or to humans. Metabolic acidosis may not only affect arterial calcification, but also bone resorption. As bone is a major proton buffer, metabolic acidosis stimulates mineral dissolution of the bone, causing efflux of calcium and phosphate to the blood [26]. In rats, chronic metabolic acidosis decreased total bone mineral density [27]. In humans, low serum bicarbonate has been associated with lower bone mineral density as well [28]. Thus, although metabolic acidosis may decrease arterial calcification by increasing the solubility of calcium and phosphate, it may also promote arterial calcification via its effects on bone resorption to increase circulating calcium and phosphate concentrations.

Second, the association between acidosis and vascular stiffness and calcification may be different among patients with and without CKD. In the animal study that examined the effects of acidosis on vascular calcification, rats with 5/6 nephrectomy (i.e. remnant kidney model of uremia) were used [14]. Administration of calcitriol to these uremic rats resulted in significant aortic calcification, but calcitriol-treated uremic rats with acidosis did not develop aortic calcification. Our null findings could reflect the substantially smaller variation in bicarbonate and AVpH and lower severity of acidosis evaluated in the Health ABC study compared with the changes in bicarbonate or pH in the CKD animal model or in humans with advanced CKD. In our study cohort, the mean AVpH was 7.41 $\pm$ 0.03 and the mean serum bicarbonate concentration was 25.2 $\pm$ 2.1 mEq/L, whereas in the uremic rat study, administration of 0.5% ammonium chloride decreased pH from 7.46 to 7.06 and bicarbonate from 28.1 to 11 mEq/L [14]. There were 12% who had an eGFR $<$ 60 mL/min/1.73 m^2 in our study in Health ABC. As metabolic acidosis typically starts when GFR falls below 40 mL/min/1.73 m^2 [29], it is not surprising that only 10.5% of this relatively healthy cohort had serum bicarbonate $<$23 mEq/L. Besides the low prevalence and severity of acidosis in the Health ABC cohort, low bicarbonate could also represent respiratory alkalosis. We have previously shown that the prevalence of respiratory alkalosis in the Health ABC cohort was 16.3% [15].

Third, stiff arteries may not only be from arterial calcification, but also from atherosclerosis, loss of elastic properties, advanced glycation end products and other mechanisms [30]. It is difficult to differentiate arterial calcification from atherosclerosis clinically because they often accompany each other [31]. However, they differ pathophysiologically. Arterial calcification is pathological deposition of calcium and phosphate salts into arterial walls and shares many features with bone formation [32]. The major factors leading to arterial calcification are disturbances in mineral metabolism (e.g. calcium and phosphate) and vascular smooth muscle cells. Under a pathogenic environment, vascular smooth muscle cells can transition into cells that resemble osteoblasts and initiate mineralization of arterial walls [33]. Atherosclerosis is chronic vascular inflammation induced by lipids, followed by endothelial cell injury and leukocyte infiltration and inflammation [34]. While metabolic acidosis may protect against arterial calcification, as shown in animal studies [13, 14], it may accelerate the progression of atherosclerosis by promoting oxidation of low-density lipoprotein [35]. Therefore, examining arterial stiffness rather than vascular calcification alone may also contribute to the null findings reported here.

Our study has several strengths. First, the large cohort with blood gas measurements is a unique feature that allowed us to assess the relationship between ABI and PWV with both serum bicarbonate and AVpH. Second, AVpH and bicarbonate concentrations were determined at the point of care. Other large cohort studies have measured bicarbonate after processing and shipment to a central lab, and measurement delays may underestimate bicarbonate values due to volatile loss of CO_2 [36, 37]. Furthermore, measurements were made three times at the point of care and averaged, providing greater precision. Third, we used both creatinine and cystatin C to determine GFR, which likely minimizes residual confounding by the severity of CKD [21].

This study also has important limitations. The Health ABC study enrolled ambulatory well-functioning older adults, only 12% had eGFR $<$ 60 mL/min/1.73 m^2 and few had advanced stages of CKD. Thus the findings cannot be generalized to patients with more advanced CKD, in which metabolic acidosis is more common and often more severe. We do not have centrally measured serum bicarbonate and recognize that calculation of bicarbonate by the Henderson–Hasselback equation can be different in some settings [38, 39]. There was also very little variability in AVpH in the Health ABC study. This limits generalization of our findings to circumstances that have more extreme acid–base variability, such as the pH changes seen in patients with advanced CKD or on dialysis. The main variables were noncontemporaneously measured; acid–base status, PWV and ABI measured at the 3, 1 and 4 year visits, respectively. This noncontemporary measurement could also explain the difference between the results of our study and the ones from MESA [25]. However, development of arterial stiffness is a slow process. A 1- to 2- year difference in the measurement is unlikely to have a clinically meaningful influence on the PWV and ABI measurements at the time of acid–base assessment relative to the time they were measured in Health ABC. Finally, metabolic acidosis can increase ionized calcium by increasing calcium efflux from bone and enhancing the release of albumin-bound calcium in the circulation [40], which may contribute to arterial stiffness. Ionized calcium levels would complement our

findings, but they were not measured at the time of collection and cannot be measured in the stored samples from the Health ABC Study [41].

In conclusion, we found no association of serum bicarbonate concentrations or AVpH with arterial stiffness as assessed by PWV or high ABI values after adjusting for kidney function in healthy and community-living older persons. Future studies should evaluate the relationship between acidosis and arterial calcification in patients with CKD who have a higher prevalence and severity of acidosis.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST

W.C., A.B.N., L.F.F., D.E.R., M.G.S., M.J.S., R.K., M.M., K.L.R., D.A.B. and J.H.I. declare that they have no conflicts of interest. Results presented in this article have not been published previously in whole or part, except in the abstract format.

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ORIGINAL ARTICLE

Value of biomarkers for predicting immunoglobulin A vasculitis nephritis outcome in an adult prospective cohort

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ABSTRACT

Background. Henoch–Schönlein purpura, more recently renamed immunoglobulin A vasculitis (IgAV), is a systemic vasculitis characterized by IgA deposits. The current markers used to assess IgAV inaccurately evaluate the risk of nephritis occurrence and its long-term outcomes. The current study assessed biomarkers of nephritis outcomes.

Methods. This French multicentre prospective study enrolled 85 adult patients at the time of disease onset. Patients were assessed for clinical and biological parameters and re-examined after 1 year. Immunoglobulins, cytokines, IgA glycosylation, IgA complexes and neutrophil gelatinase-associated lipocalin (NGAL) concentrations were assessed in blood and urine.

Results. We identified 60 patients with IgAV-related nephritis (IgAV-N) and 25 patients without nephritis (IgAV-woN). At the time of inclusion (Day 1), the serum levels of galactose-deficient IgA1 (Gd-IgA1) and urinary concentrations of IgA, IgG, IgM, NGAL, interleukin (IL)-1β, IL-6, IL-8, IL-10, IgA–IgG and IgA–sCD89 complexes were higher in the IgAV-N patients than in the IgAV-woN patients ($P < 0.005$ for all comparisons). After follow-up (1 year), 22 patients showed a poor outcome. Among the tested markers, urine IgA at disease onset adequately reclassified the risk of poor outcome over conventional clinical factors, including estimated glomerular filtration rate, proteinuria and age (continuous net reclassification improvement = 0.72, $P = 0.001$; integrated discrimination improvement = 0.13, $P = 0.009$) in IgAV patients.

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