Association of Arterial Stiffness and Central Pressure With Cognitive Function in Incident Hemodialysis Patients: The PACE Study

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Introduction: Cognitive impairment commonly occurs in hemodialysis patients, with vascular disease potentially implicated in its pathogenesis. However, the relationship of detailed vascular assessment with cognitive function in patients new to hemodialysis has not been demonstrated.

Methods: In a prospective study of incident hemodialysis participants enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) study, we determined aortic stiffness by pulse-wave velocity (PWV), systemic arterial stiffness by the augmentation index (AIx) and central pulse pressure (cPP), and examined their associations with cognitive processing speed, executive function, and global cognitive impairment measured by the Trail making test A (TMTA), Trail making test B (TMTB), and the modified Mini-Mental State Exam (3MS).

Results: Mean baseline age was 55 ± 13 years, 58% were male, 72% were African American, 35% had coronary artery disease, 55% had diabetes, and 10% had cognitive impairment. At baseline, higher PWV and cPP were associated with a longer TMTA, and a higher PWV was associated with a longer TMTB, but the associations were attenuated after multivariable adjustment. At 1 year, PWV was not independently associated with TMTA, TMTB, or 3MS. However, unadjusted and adjusted analyses revealed every 10% increase in AIx and 10 mm Hg increase in cPP were associated with longer TMTB (time difference$_{AIx}$: 0.14; 95% confidence interval [CI]: 0.02−0.25 log-seconds; time difference$_{cPP}$: 0.11; 95% CI: 0.05−0.17 log-seconds) and global cognitive impairment (odds ratio [OR]$_{AIx}$: 10.23; 95% CI: 1.77−59.00; OR$_{cPP}$: 2.88; 95% CI: 1.48−5.59).

Discussion: Higher AIx and cPP, which are indicative of abnormal wave reflections in distal vessels, are associated with, and might contribute to, declining cognitive function in patients starting hemodialysis.

Cognitive impairment and dementia are more prevalent in end-stage renal disease (ESRD) patients who receive hemodialysis compared with an age-matched general population.[1,2] Yet, despite the high prevalence and the adverse impact of cognitive impairment on patient decision-making, adherence, quality of life, and survival,[3,4] the underlying mechanisms and predictors of cognitive impairment in this population remain unclear. Previous observational studies have not reported significant associations between dialysis procedures or uremia and cognitive function,[5–7] and have reported similar rates of Alzheimer's disease between kidney disease patients and control subjects.[8] Taken together, these results suggest that other mechanisms underlie cognitive impairment.

Findings from recent studies of dialysis patients support the hypothesis that small vessel cerebrovascular

disease may be the predominant factor in cognitive impairment in ESRD, and that subclinical cerebrovascular injury may be a consequence of vascular disease and its known risk factors.[9] Past studies have reported higher rates of cerebrovascular disease in chronic kidney disease and have demonstrated an association between cardiovascular disease and poor cognitive function in hemodialysis.[9,10] Central and systemic arterial stiffness can lead to high pulsatile pressure and damage the peripheral microvasculature, which results in increased cerebral white matter lesions associated with cognitive impairment.[11–14] The relationship between aortic stiffness and cognitive function has also been observed in the general population and some populations with chronic kidney disease.[15,16]

The role of exact vascular risk factors, such as arterial stiffness and elevated central blood pressures, in cognitive impairment has not yet been examined in incident hemodialysis patients. In particular, pulse-wave velocity (PWV) could indicate damage of large vessels, whereas central pulse pressure (cPP) and the augmentation index (AIx) could be indicative of systemic arterial stiffness or abnormal wave reflections involving damage of small vessels.[17] If these more specific vascular measures can be implicated in the pathogenesis of cognitive decline as patients start dialysis, then other monitoring and treatment measures might be implemented in the future. The aim of this study was to examine the cross-sectional and follow-up associations of aortic and systemic arterial stiffness, and central pressure with cognitive dysfunction in a large prospective cohort of incident hemodialysis participants from the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) study.

MATERIALS AND METHODS

Study Population and Design
Detailed methods of the PACE study have been previously published.[18] Briefly, 568 adult incident hemodialysis participants within 6 months of dialysis initiation were recruited from 27 outpatient dialysis units in the greater Baltimore area. Participants who completed a baseline cardiovascular visit (n = 397) were eligible for the present study. Participants who did not complete any of the 3 cognitive function assessments (n = 26), pulse-wave measures (n = 31), or had a history of dementia or Alzheimer's disease (n = 7) were excluded. We conducted a cross-sectional analysis at baseline and at 1-year follow-up. The baseline analysis consisted of 333 participants. Of the 333 participants, those with a complete 1-year follow-up study clinic visit were included in the follow-up analyses

(n = 157). The reasons for missing follow-up assessments included death (n = 43), kidney transplantation or transition to peritoneal dialysis (n = 30), moved away (n = 10), end of study (n = 11), unable to follow-up (n = 61), and no follow-up measures of pulsewave or cognitive function (n = 21).

The study protocol was approved by the institutional review board of the Johns Hopkins School of Medicine, DaVita Clinical Research, MedStar Health Systems, and by the medical director of each dialysis unit. All participants provided informed written consent.

Data Collection
Participants underwent a cardiovascular study visit at Johns Hopkins Institute for Clinical and Translational Research (ICTR) at baseline and 1 year. Cardiovascular evaluations were measured by trained technologists or study staff and included pulse-wave analysis and blood pressure (BP) assessments on nondialysis days. Additional data were collected using self-report questionnaires[18] and included many questionnaires that are commercially available, such as the Wide Range Achievement Test-4th edition (WRAT4). The WRAT4 is comprised of 4 subtests: Word Reading, which measures letter recognition and word reading; Sentence Comprehension, which contains 50 items of a few sentences with blank words for participants to fill in; Spelling, which contains letter writing and spelling components; and Math Computation, which includes oral math and computation sections.[19] Davita Clinical Research and MedStar Health Systems provided hemodialysis treatment and laboratory data during outpatient dialysis sessions.

The exposure variables of interest were aortic and systemic arterial stiffness and cPP, which were measured by the Sphygmocor PVx System (AtCor Medical, West Ryde, Australia). Aortic stiffness was measured using carotid-to-femoral PWV, and central AIx was used to measure systemic arterial stiffness.[17] PWV measures were recorded on the nonfistula arm using the carotid and femoral arteries, and the AIx and cPP were measured using radial tonometry.

The main outcome of interest was cognitive function according to the Trail Making Tests A and B (TMTA and TMTB) and the Modified Mini-Mental Status Examination (3MS) as assessed by trained study staff. The TMT was used in this study to assess cognitive executive function. The TMT is widely used to assess the abilities of an individual on the following areas: visual search and scanning, cognitive processing speed, cognitive flexibility, and executive function.[20] It consists of 2 parts that require the participant to draw a trail connecting a set of numbers or numbers with letters. The TMTA

involves drawing a line that connects 25 numbers in sequential order. The TMTB involves drawing a line that connects a set of alternating numbers and letters in sequential order. The time taken to complete the test is recorded as the score, and we imposed 3- and 5-minute time limits for TMTA and TMTB, respectively. There is no one widely used cutoff score for TMTs to define executive function impairment. The 3MS was used in this study to assess global cognitive impairment. The 3MS is an extended version of the Mini-Mental State Examination, which assesses global cognitive function through the following subsets: orientation time, orientation place, registration, concentration, first recall, language, pentagons, animals, date and place of birth, word fluency, similarities, and delayed recall of words.[21] This test has demonstrated high sensitivity for capturing cognitive impairment in those with Alzheimer's disease and in individuals with dementia.[21] The total score ranges from 0 to 100, and the score reflects correctly answered questions. A score <80 is commonly used in studies and clinical settings to define global cognitive impairment. Consequently, we used the same cutoff score to define global cognitive impairment. All 3 tests were administered at study baseline and at the yearly follow-up visit on a nondialysis day at the Johns Hopkins ICTR.

Potential confounders included self-reported participant demographic factors (age, sex, race), and educational level at baseline. In addition, baseline reading comprehension score was measured using WRAT4, and depression severity was measured using Patient Health Questionnaire 9 during the clinic visits. An adjudication committee of physicians reviewed medical records for the 6 months before initiation of dialysis to assign comorbidities of hypertension, cerebrovascular disease, diabetes, and coronary artery disease. Two independent reviews were conducted for each chart, with a corresponding third final review. To account for the roles several trainee committee members had in the process, the third final review was always conducted by a faculty nephrologist. If a consensus was not reached, other members of the committee reviewed the chart, and a majority vote of the committee determined the final comorbidity. These data were combined with baseline self-reported questionnaire data to generate the Charlson comorbidity index. Predialysis laboratory measures, including serum hemoglobin, albumin, Kt/V, and calcium × phosphorus product were examined as 3-month averages before the study clinic visit. Left ventricular ejection fraction was measured at the study baseline visit on a nondialysis day using echocardiography (Toshiba Artida, Otawara, Japan) by trained technologists. Use of antihypertensive medications was recorded during study visits.

Statistical Analysis

Continuous variables were examined using means ± SD and compared across groups using the Student t-test for normally distributed variables; median (interquartile range) and the Wilcoxon rank-sum test were used for non-normally distributed variables. Categorical variables were examined using frequencies and compared across groups using the χ^2 test.

To investigate the association between various measures of arterial stiffness and cognitive function at baseline and during follow-up, multiple analyses were performed. The TMTA and TMTB scores were log-transformed and kept as continuous variables because no clinically meaningful cutoff scores exist, and the interpretation of the scores involve using normative data sets.[22] The associations of PWV, AIx, and cPP with the TMTA score were examined using a log-linear regression at baseline and at 1-year follow-up. The associations of PWV, AIx, and cPP with the TMTB score at baseline and at 1-year follow-up were examined using a Tobit regression to account for the ceiling effect in TMTB, which was observed in 21% of the participants. The associations of PWV, AIx, and cPP with global cognitive impairment (defined as 3MS score <80) were examined using logistic regression at baseline and at 1-year follow-up.

The final multivariable models were first derived from known associations with cognitive impairment from previous studies. We then used a forward model building approach, which involved manually adding each covariate in the model with the outcome and the main exposure and examining changes in effect size and/or P values. Because of this approach and our limited sample size, we adjusted for the Charlson comorbidity index, which summarizes a range of comorbidities, rather than adjusting for each condition. We also adjusted for the WRAT4 score, which reflects the baseline reading score, rather than educational attainment, because this cohort consisted of younger and predominantly African American participants whose educational quality was better represented with a reading test than with educational attainment.[23] We considered systolic BP based on findings from past observational studies that demonstrated significant association between systolic BP, especially in midlife, and cognitive impairment.[24,25] Systolic BP was an average of 3 seated systolic BP measurements recorded during the study visit that occurred on a nondialysis day. We also considered adjusting for history of cerebrovascular disease; however, in the model building process, adjusting for cerebrovascular disease did not significantly change the main associations.

The final multivariable models included age, sex, race, Charlson comorbidity index, and the WRAT4

reading score. Systolic BP was included in models with PWV and AIx. We performed several sensitivity analyses to assess the robustness of our final models. First, we adjusted for additional variables such as cerebrovascular disease, diastolic BP instead of systolic BP, and education. To evaluate the effect of potential competing risks of death or transplantation, we performed 2 separate analyses: (i) excluded participants, who were later lost to follow-up for various reasons, from the baseline analysis, and (ii) discrete-time pooled logistic regression models excluding those with cognitive impairment at baseline. Finally, we stratified the follow-up associations by participants with and without global cognitive impairment at baseline. We also tested the interaction of PWV, AIx, and cPP with baseline cognitive impairment status. Finally, we stratified our findings by race.

Missing values in linear and logistic models were imputed using the multivariate imputation by chained equations method. Missing covariate data in the Tobit regression models were imputed using means and medians. The imputed variables with missing data were the WRAT4 reading score (8%) and the Charlson comorbidity index (4%). For all analyses, a 2-tailed *P* value of <0.05 was considered significant. All analyses were performed using STATA version 14.0 (Stata Corp., College Station, Texas).

RESULTS

Study Population at Baseline

The final analytical cohort for the baseline cross-sectional analysis consisted of 333 incident hemodialysis participants. The median time between dialysis initiation and baseline study clinic visit was 104 days (interquartile range [IQR]: 78−155 days). The mean ± SD age was 55 ± 13 years (Table 1). The majority were male (58%) and African American (72%), had completed a high school (24%) or postsecondary education (40%), and had a history of depression (50%). At baseline, 55% had diabetes, 35% had coronary artery disease, and 22% had cerebrovascular disease. All patients had hypertension at baseline, and 68% and 43% were on β-blocker therapy and renin-angiotensin-aldosterone system blockade, respectively.

The median PWV was 10.0 m/s (IQR: 7.9−12.5 m/s) and the mean AIx was 14.6 ± 10.2% at baseline. The mean cPP was 55.7 ± 18.7 mm Hg. The median TMTA and TMTB scores were 47 seconds (IQR: 35−65 seconds) and 130 seconds (IQR:93−230 seconds), respectively, and the median 3MS score was 91 (IQR: 85−95). The baseline prevalence of global cognitive impairment was 10% of participants, 32% of whom had a history of cerebrovascular disease.

Table 1. Baseline characteristics of 333 incident hemodialysis participants in the PACE study

| Variables	Participants (*n* = 333)	Mean ± SD, median (IQR), frequency (%)
Sociodemographic measurements		
Age, yrs	333	55 ± 13
Sex		
Male	333	193 (58)
Female		140 (42)
Ethnicity		
African American	333	240 (72)
Non-African American		93 (28)
Education		
<High school	332	120 (36)
High school/vocational		80 (24)
>High school		132 (40)
Cerebrovascular disease risk factors		
Wide Range Achievement Test, out of 70	308	54 (46−61)
Depression	326	164 (50)
Cerebrovascular disease	333	73 (22)
Hypertension	333	333 (100)
Coronary artery disease	333	117 (35)
Diabetes	333	182 (55)
Charlson comorbidity index	320	5 (3−6)
Study visit systolic blood pressure, mm Hg	329	137 ± 25
Study visit diastolic blood pressure, mm Hg	329	75 ± 15
Left ventricular ejection fraction, %	327	66 ± 12
Hemoglobin, g/dl	331	10.8 ± 1.3
Albumin, g/dl	331	3.6 ± 0.4
Calcium × phosphate product, mg^2/dl^2	331	44.4 ± 10.3
Kt/V	327	1.8 ± 0.3
Beta-blocker medication	306	208 (68)
ACEi or ARB[a]	306	132 (43)
Vascular stiffness measurements		
Pulse wave velocity, m/s	278	10.0 (7.9−12.5)
Augmentation index, %	299	14.6 ± 10.2
Central pulse pressure, mm Hg	303	55.7 ± 18.7
Cognitive function measurements		
Trail making test A, s	319	47 (35−65)
Trail making test B, s	312	130 (93−230)
Modified Mini-Mental State exam (3MS), out of 100	324	91 (85−95)
Global cognitive impairment (3MS score <80)	324	33 (10)

IQR, interquartile range.
To convert hemoglobin in grams per deciliter to grams per liter, multiply by 10. To convert albumin in grams per deciliter to grams per liter, multiply by 10. To convert calcium × phosphorus product in square milligrams per square deciliters to square millimoles per square liters, multiply by 0.081.
[a]Renin-angiotensin-aldosterone system blockade included angiotensin-converting enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARB).

Compared with those without cognitive impairment, participants with global cognitive impairment were older (62 ± 12 years vs. 54 ± 13 years; *P* = 0.002) and had a lower baseline WRAT4 score (38 [IQR: 37−48] vs. 55 [IQR: 48−61]; *P* < 0.001), but they had similar PWV, AIx, or cPP at baseline (Figure 1).

Vascular Stiffness and Cognitive Function at Baseline

Higher PWV was associated with longer time to complete TMTA and TMTB in univariable analysis, but
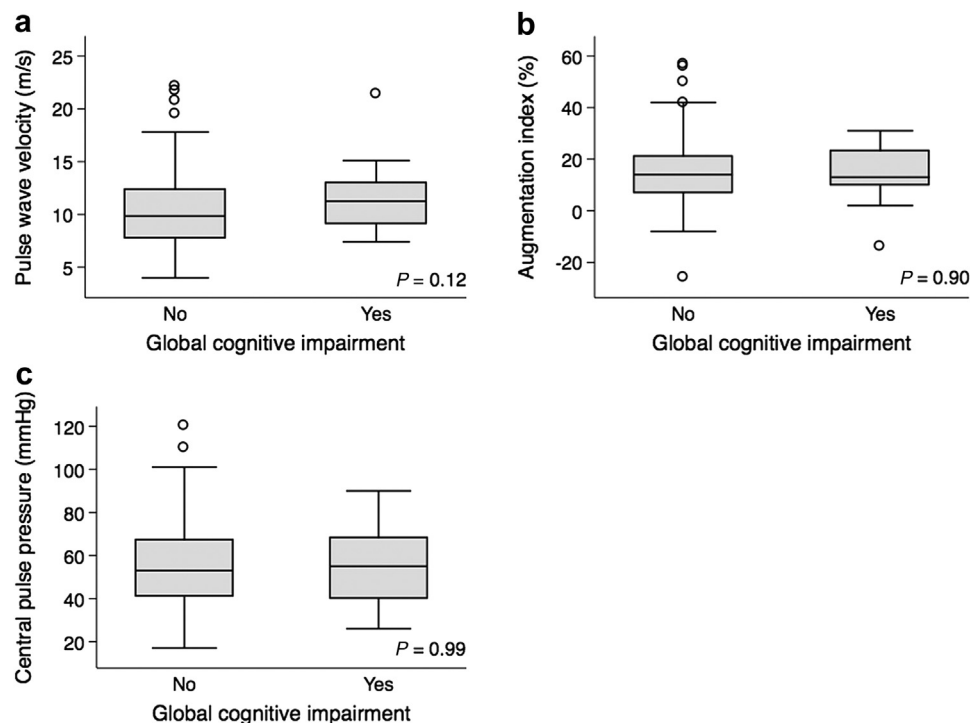
Figure 1. Boxplot of (a) pulse-wave velocity, (b) augmentation index, and (c) central pulse pressure among participants with and without global cognitive impairment at study baseline.

these associations were no longer statistically significant after adjusting for demographic factors, Charlson comorbidity index, systolic BP, and baseline reading score (Table 2). cPP was also associated with TMTA and TMTB; however, the association was attenuated after adjusting for potential confounders. AIx was not associated with TMTA, TMTB, and 3MS. Measures of arterial stiffness were not associated with global cognitive impairment at baseline.

Vascular Stiffness and Cognitive Function at 1-Year Follow-Up

At 1-year follow-up, there were 157 participants who completed the study clinic visit assessments and had at least 1 measure of pulse wave and cognitive assessment. Comparison of baseline cognitive test scores by mortality status at 1 year demonstrated no significant differences (TMTA, $P = 0.61$; TMTB, $P = 0.42$; 3MS, $P = 0.38$). Among those who survived to the 1-year

Table 2. Baseline association of pulse-wave velocity, augmentation index, and central pulse pressure with Trail making tests A and B and Modified Mini-Mental Status examination

		Trail making test A[a]			Trail making test B[a]			Global cognitive impairment (3MS score <80)	
Vascular measurements	n	Time difference (95% CI), log-second	P	n	Time difference (95% CI), log-second	P	n	OR (95% CI)	P
Pulse-wave velocity, per 1 log m/s increase									
Univariable	266	**+0.30 (0.14 to 0.46)**	**<0.001**	259	**+0.37 (0.14 to 0.59)**	**0.002**	270	2.78 (0.69 to 11.24)	0.15
Multivariable[b,c]		+0.09 (−0.08 to 0.26)	0.29		+0.07 (−0.16 to 0.3)	0.56		4.68 (0.44 to 50.02)	0.20
Augmentation index, per 10% increase									
Univariable	286	+0.05 (−0.002 to 0.10)	0.06	280	+0.04 (−0.03 to 0.11)	0.26	290	0.98 (0.68 to 1.41)	0.90
Multivariable[b,c]		+0.01 (−0.05 to 0.06)	0.81		-0.01 (−0.09 to 0.06)	0.72		0.82 (0.47 to 1.42)	0.47
Central pulse pressure, per 10 mm Hg increase									
Univariable	290	**+0.04 (0.01 to 0.07)**	**0.002**	284	+0.04 (−0.002 to 0.08)	0.07	294	1.00 (0.82 to 1.22)	0.99
Multivariable[b]		+0.02 (−0.01 to 0.04)	0.22		+0.01 (−0.03 to 0.04)	0.67		0.90 (0.70 to 1.17)	0.43

CI, confidence interval; 3MS, Modified Mini-Mental Status
[a]Longer time to complete Trail making test indicates worse cognitive processing speed and executive function.
[b]Multivariable model adjusted for age, sex, race, Charlson comorbidity index, Wide Range Achievement Test 4th edition reading score.
[c]Additionally adjusted for systolic blood pressure.
Bolded values indicate statistically significant ($P < 0.05$) associations.

follow-up visit, the baseline characteristics in participants with and without follow-up assessments were similar, although the proportion of African American participants was higher, and PWV and serum albumin were slightly lower among participants who completed follow-up (Supplementary Table S1).

The median PWV at follow-up was 10.0 m/s (IQR: 8.0–12.1 m/s) and was similar to the baseline measure; the mean AIx and cPP were 13.3 ± 8.3 and 52.9 ± 17.8, respectively, and slightly lower at follow-up. The median TMTA and TMTB scores were 49 seconds (IQR: 35–67 seconds) and 135 seconds (IQR: 89–221 seconds), respectively, and were higher at follow-up compared with baseline. The median 3MS score was 91 (IQR: 85–94), and the prevalence of global cognitive impairment at follow-up was 7%. Most of these participants also had global cognitive impairment at baseline. The AIx and cPP levels were significantly higher at follow-up in participants with global cognitive impairment versus participants without global cognitive impairment (Figure 2).

In univariable analysis, higher AIx and cPP were associated with longer time to complete TMTA at follow-up, but the associations were attenuated in multivariable analysis (Table 3). Higher PWV, AIx, and cPP were associated with longer time to complete TMTB in univariable analysis, and higher AIx and cPP remained statistically significantly associated with longer time to complete TMTB even after adjustment

for potential confounders (time difference per 10% increase in AIx: 0.14; 95% CI: 0.02−0.25 log-seconds; time difference per 10-mm Hg increase in cPP: 0.11; 95% CI: 0.05−0.17 log-seconds). Higher AIx and cPP were also significantly associated with higher odds of global cognitive impairment (odds ratio [OR]: 10.23; 95% CI: 1.77−59.00; per 10% increase in AIx, OR: 2.88; 95% CI: 1.48−5.59 per 10-mm Hg increase in cPP). PWV was not associated with global cognitive impairment at follow-up, in either unadjusted or adjusted analyses.

Sensitivity Analyses

Our sensitivity analyses revealed several important findings. When we included additional variables in our follow-up analysis, such as history of cerebrovascular disease, diastolic BP instead of systolic BP, and educational attainment instead of the WRAT4 score, the associations of PWV, AIx, and cPP with global cognitive impairment were similar in direction and magnitude compared with our main findings, even after adjusting for additional variables (Supplementary Table S2). In both models, we excluded participants who were later lost to follow-up from the baseline analysis and when we used the models for discrete-time pooled logistic regression, the results were comparable in direction, magnitude, and statistical significance to our original findings from Table 2 (data not shown). Our sensitivity analysis, in which we stratified the
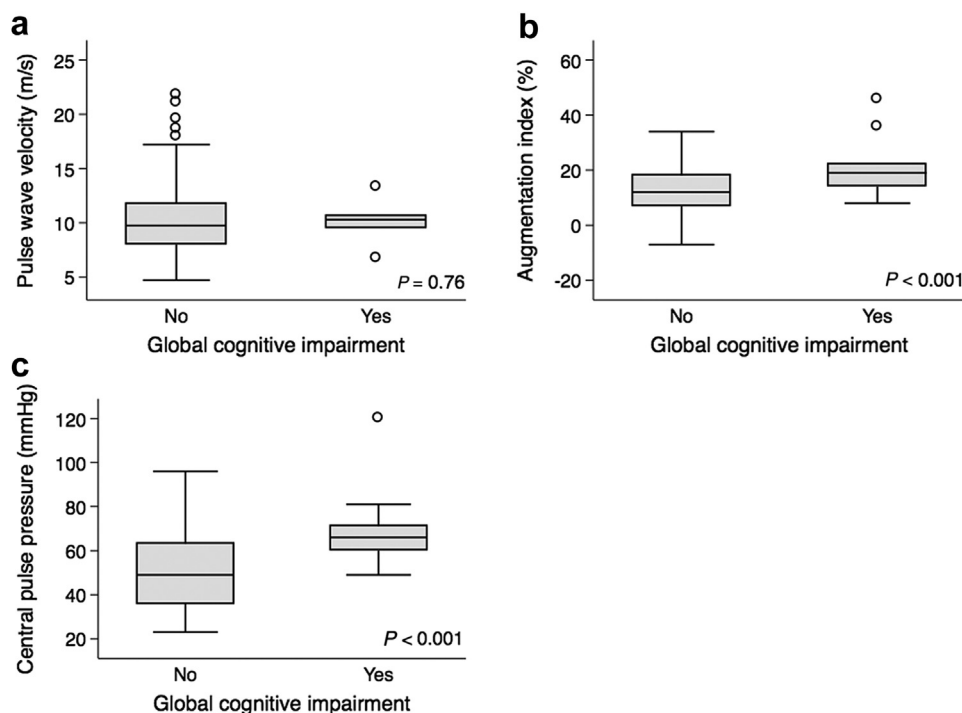
Figure 2. Boxplot of (a) pulse-wave velocity, (b) augmentation index, and (c) central pulse pressure among participants with and without global cognitive impairment at 1 year of follow-up.

Table 3. Follow-up association of pulse-wave velocity, augmentation index, and central pulse pressure with Trail making tests A and B and Modified Mini-Mental Status examination

Vascular measurements	Trail making test A[a] (log transformed)			Trail making test B[a] (log transformed)			Global cognitive impairment (3MS score <80)		
	n	Time difference (95% CI), log-second	P	n	Time difference (95% CI), log-second	P	n	OR (95% CI)	P
Pulse-wave velocity, per 1 log m/s increase									
Univariable	135	+0.25 (−0.03 to 0.53)	0.08	130	**+0.39 (0.05 to 0.73)**	**0.02**	128	1.26 (0.08 to18.85)	0.87
Multivariable[b,c]		+0.17 (−0.47 to 0.13)	0.28		-0.08 (−0.42 to 0.26)	0.64		0.12 (0.001, 23.72)	0.43
Augmentation index, per 10% increase									
Univariable	132	**+0.11 (0.01, 0.22)**	**0.04**	128	**+0.19 (0.06 to 0.33)**	**0.01**	125	**3.32 (1.51 to 7.31)**	**0.003**
Multivariable[b,c]		+0.01 (−0.12 to 0.13)	0.94		**+0.14 (0.02 to 0.25)**	**0.02**		**10.23 (1.77 to 59.00)**	**0.01**
Central pulse pressure, per 10 mm Hg increase									
Univariable	134	**+0.06 (0.01 to 0.11)**	**0.01**	130	**+0.11 (0.05 to 0.17)**	**<0.001**	127	**1.83 (1.22 to 2.74)**	**0.003**
Multivariable[b]		+0.02 (−0.02 to 0.07)	0.32		**+0.08 (0.03 to 0.13)**	**0.002**		**2.88 (1.48 to 5.59)**	**0.002**

CI, confidence interval; 3MS, Modified Mini-Mental Status.
[a]Longer time to complete Trail making test indicates worse cognitive processing speed and executive function.
[b]Multivariable model adjusted for age, sex, race, Charlson comorbidity index, Wide Range Achievement Test 4th edition reading score.
[c]Additionally adjusted for systolic blood pressure.
Bolded values indicate statistically significant (P < 0.05) associations.

follow-up associations by participants with and without global cognitive impairment at baseline, revealed that most interactions of PWV, AIx, and cPP with baseline cognitive impairment status were not statistically significant (Supplementary Table S3). The interaction terms in the associations of the AIx with TMTB and global cognitive impairment were statistically significant; however, the stratified estimates in these associations were in the same direction. Furthermore, the number of cases in the global cognitive impairment group were also too small to provide stable estimates in the stratified analysis. Therefore, we were unable to detect meaningful effect modification by baseline cognitive impairment status. Finally, our sensitivity analysis stratifying by race found no statistically significant relationships (Supplementary Table S4).

DISCUSSION

Our study demonstrated that higher AIx and cPP, which are measures of systemic arterial stiffness and central pressure, were significantly associated with longer time to complete the TMTB and a higher risk of global cognitive impairment at follow-up independent of confounders. This suggested that arterial stiffness and central pressure might potentially contribute to cognitive executive function decline and global function in incident hemodialysis patients.

Our results demonstrated that the associations of AIx and central pressures with cognitive function were more significant at follow-up than at baseline. This suggested that the relationship between arterial stiffness and cognitive impairment might not be prominent until cognitive function declines substantially over time and

might be more detectable as vascular changes continue to exert effects over time. Because our cohort of incident hemodialysis participants was relatively young compared with studies of prevalent dialysis patients and older participants from the general population, we could potentially find stronger associations as the participants become older. Our findings were nonetheless consistent with studies in a population that demonstrated a similar and significant longitudinal relationship.[26] A cross-sectional analysis of community-based cohort of 70- to 90-year-old participants also found no significant relationship between PWV and cognitive function.[16]

Reported prevalence rates of cognitive impairment in the dialysis population ranged from 40% to 70%, depending on the measurements used to assess cognitive function.[2,27,28] In this study, only 10% of participants had cognitive impairment at baseline, as defined by a 3MS cutoff score of 80 alone, presumably because this study included a cohort of incident hemodialysis patients rather than prevalent dialysis patients. Participants with baseline cognitive impairment in PACE were older and had a lower baseline WRAT4 score compared with those without baseline cognitive impairment. The mean 3MS score at baseline was also higher compared with past studies of hemodialysis patients,[1] but this could be attributed to the relatively younger age of our cohort (55 years). In comparison to the general population, the mean 3MS score was similar to that of 65- to 69-year-old individuals without kidney disease (3MS score of ∼90),[29] which suggested that having ESRD contributed to cognitive dysfunction with a magnitude similar to aging a decade.[10,30,31] Also, the median times of TMTA and TMTB were considerably higher compared with studies in the general

population of similar age (TMTA median 32, range: 19–72 and 74; TMTB median 74, range 42–127),[22] which reflected a substantial difference in executive functional skills.

We demonstrated that significant vascular disease as measured by cPP was associated with worsening executive and global cognitive function. The mechanism leading to the worsening function could be related to underlying vascular cognitive impairment involving deep subcortical white matter damage, which can impair cognitive attention, processing, and executive function.[32,33] Observational studies of older general and Hispanic populations previously demonstrated an association of central pressures with subcortical infarcts and thinning of the left inferior frontal gyrus cortical thickness. These findings suggested that high central pressure could lead to poor executive function.[34,35] The significant association between measures of arterial stiffness and memory-based 3MS scores or global cognitive function suggested that the underlying pathogenesis for cognitive impairment in incident hemodialysis patients might also involve neuronal or synaptic dysfunction that is often associated more with memory loss.[33] The significant follow-up association between central pressure and global cognitive function was also similar to the findings from the Baltimore Longitudinal Study of Aging, which showed that higher pulse pressure was associated with a faster decline in global cognition.[36]

The significant association of AIx, which is indicative of systemic arterial stiffness, in addition to central pressure with cognitive function, suggested that abnormal wave reflections, rather than the stiffness of the aorta, underlay cognitive decline. Increased vascular stiffness and pulse pressure can be influenced by central stiffness or alterations in either the branching of the peripheral vessels or vascular properties of the distal arteries and arterioles.[17,37–39] The lack of association between PWV and cognitive function in this study suggested that in younger dialysis patients, cognitive function is influenced to a greater extent by the modifications to the microvascular network—possibly in cerebral microvessels—that change the vascular resistance, number, and composition of vessels, and increase pulse pressure and systemic stiffness.[17,37–39] Similar findings of increased pressure and cognitive function were demonstrated in the Women's Health and Aging Study II.[26] Further studies will be required to examine the impact of systemic vascular disease and central pressure on cerebrovascular changes using magnetic resonance imaging in incident dialysis patients.

Although PWV is a direct measure of aortic stiffness, we did not find significant associations between PWV and cognitive function. This corroborated findings from the Framingham Offspring cohort study, which demonstrated that higher pulse pressure, but not PWV, was associated with worse global cognitive function in the general population.[40] A recent study of 72 hemodialysis patients found a significant association between PWV and cognitive impairment as measured by the 3MS examination; however, this study included prevalent hemodialysis patients with a mean dialysis history of 10 years, and examined only cross-sectional associations.[15] Our study differed from the previous study because we examined longitudinal associations in a multiethnic incident study population recruited from multiple dialysis units. Furthermore, due to the relatively younger age of our study population, changes in carotid-to-femoral PWV might not yet be prominent, and thus not a significant early predictor of cognitive impairment. Because the effect of aging and change in central pressure measurement is more marked in younger (younger than 50 years) individuals as opposed to increased PWV, which is prominent in older individuals (older than 50 years) with higher aortic stiffness, this might account for the lack of association with cognitive decline.[41]

A few limitations of this study included participant recruitment from a single region, and limited assessment of cognitive function and cerebrovascular disease, with a lack of an extended battery of tests and brain imaging. There were a number of issues that affected the follow-up visit, such as hospitalizations, transition to transplantation or peritoneal dialysis, and significant early mortality that might have affected the statistical power for longitudinal analyses, but the results were consistent as shown in our sensitivity analysis. The subgroup of participants who were lost to follow-up had higher PWV and lower survival, and less adherence, all of which could be associated with worse cognitive impairment. This would have biased our findings toward the null; however, we still demonstrated that there was a statistically significant association of the AIx and central pressure with measures of executive and global cognitive impairment at follow-up. Lastly, future studies should consider following a larger study population over a longer time to perform any competing risk analysis.

Despite these limitations, the main strengths of this study included the large well-characterized cohort of incident hemodialysis participants who were assessed using standardized methods of cardiovascular and cognitive function assessments on nondialysis days, because both can be affected by dialysis treatment. This was also important because there are also intermittent shifts in electrolytes and fluids during dialysis that might have affected BP, cardiac function, and possibly intradialytic hypotension, which greatly

affect arterial stiffness measures. Moreover, because our study cohort was predominantly African Americans, who are often underrepresented in studies or trials, our results might be generalizable to more racially diverse communities or populations at high risk for cardiovascular or kidney disease. In our cohort of relatively younger patients, we were able to examine the relationship between vascular stiffness and cognitive function over time using comprehensive follow-up information.

CONCLUSIONS

Among relatively younger incident hemodialysis patients, global cognitive impairment is common. A higher AIx and cPP are associated with worsening executive and global cognitive function during follow-up, which suggests that abnormal wave reflections potentially involving small vessel injuries may significantly contribute to cognitive decline in incident hemodialysis patients. Further imaging studies with longitudinal data in a larger cohort are required to examine cerebrovascular changes in relation to arterial stiffness and central pressure.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

SUPPLEMENTARY MATERIALS

Table S1. Comparison of baseline characteristics between participants in the study analyses who completed a follow-up visit and participants who did not complete a follow-up visit among those who survived to 1 year after the first study clinic visit.

Table S2. Follow-up association of pulse wave velocity, augmentation index, and central pulse pressure with global cognitive impairment using additional modeling.

Table S3. Stratified analysis of the follow-up associations by baseline global cognitive impairment status and interactions of pulse wave velocity, augmentation index, and central pulse pressure with baseline cognitive impairment status.

Table S4. Stratified analysis of the follow-up associations by race and interactions of pulse wave velocity, augmentation index, and central pulse pressure with race.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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