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# 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 $\pm$ 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.

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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

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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