Pulse Wave Velocity Is Associated With Greater Risk of Dementia in Mild Cognitive Impairment Patients

Laure Rouch, Philippe Cestac, Brigitte Sallerin, Sandrine Andrieu, Henri Bailly, Maëlle Beunardeau, Adrien Cohen, Delphine Dubail, Intza Hernandorena, Marie-Laure Seux, Jean-Sébastien Vidal, Olivier Hanon

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Abstract—To investigate the association between pulse wave velocity, intima-media thickness, carotid artery diameter, carotid plaques, and conversion from mild cognitive impairment to dementia. Three hundred and seventy-five elderly ambulatory subjects with mild cognitive impairment were followed yearly to examine potential conversion to dementia. Vascular function was assessed by carotid-femoral pulse wave velocity. Vascular structure was evaluated by intima-media thickness, carotid artery diameter, and carotid plaques using an ultrasonographic assessment of carotid arteries. One hundred and five patients (28%) converted to dementia during a mean follow-up period of 4.5 years. Higher pulse wave velocity was associated with greater risk of conversion to dementia (1-SD increase of pulse wave velocity: hazard ratio, 1.33; 95% CI, 1.04–1.71; *P*=0.02) independently of age, sex, educational level, systolic blood pressure, cardiovascular diseases, body mass index, calcium channel blockers intake, Mini–Mental State Examination at baseline, and apoE ε4 status. Intima-media thickness, carotid plaques, and carotid artery diameter did not predict conversion to dementia (1-SD increase of intima-media thickness: hazard ratio, 0.93; 95% CI, 0.73–1.18; *P*=0.55; presence of carotid plaques: hazard ratio, 1.08; 95% CI, 0.62–1.87; *P*=0.79; 1-SD increase of carotid artery diameter: hazard ratio, 1.08; 95% CI, 0.89–1.31; *P*=0.44). Pulse wave velocity was associated with conversion to dementia, whereas intima-media thickness, carotid plaques, or carotid artery diameter were not after controlling for age and other confounding factors. Arterial stiffness could identify mild cognitive impairment patients at higher risk of dementia and may be a therapeutic target to delay or prevent the onset of dementia. **(*Hypertension*. 2018;72:1109-1116. DOI: 10.1161/HYPERTENSIONAHA.118.11443.)**

Key Words: blood pressure ■ dementia ■ patients ■ pulse wave analysis ■ risk ■ vascular stiffness

Approximately 48 million people worldwide are living with dementia, and because of a rapidly global increase in population size and life expectancy, this number is predicted to nearly double every 20 years until 2050.[1] Prevention of dementia has, therefore, turned into a major public health challenge and identification of modifiable risk factors is critically important. Accumulating evidence suggests associations between traditional vascular risk factors, such as hypertension, diabetes, hypercholesterolemia, atherosclerosis, and cognitive disorders and dementia, including Alzheimer disease (AD).[2] These associations are complex and sometimes differ depending on when in life the risk factors are assessed. Vascular aging is accompanied by atherosclerosis or arteriosclerosis, noninvasively assessed by structural parameters (carotid intima-media thickness [IMT], carotid artery diameter [CAD] or carotid plaques [CP]) or functional parameter (carotid-femoral pulse wave velocity [PWV] considered to be the gold standard measurement of aortic stiffness[3]). Most studies conducted to date show a positive correlation between PWV and cognitive impairment,[4–7] but inconsistent results are found when predicting dementia.[8–10] Most findings are based on cross-sectional designs. The few longitudinal studies were mainly conducted in general population.[6,7,10] Controversy also remains for IMT that has been associated with poorer cognitive function and dementia in some studies[11–14] but not in others.[15–17] Furthermore, it is not clear whether atherosclerosis, more precisely carotid stenosis and presence of plaques, affects cognition and dementia.[18–23] Moreover, to our knowledge, no study investigated the association between PWV, IMT, CAD, or CP and conversion from mild cognitive impairment (MCI) to dementia, although identification of potential preventive strategies is crucial at early stages. Thus, the aim of our study was to assess

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From the EA 4468, Université Paris Descartes, Sorbonne Paris Cité, France (L.R., H.B., M.B., A.C., D.D., I.H., M.-L.S., J.-S.V., O.H.); Unité INSERM 1027, Toulouse, France (P.C., S.A.); University Paul Sabatier Toulouse III, France (P.C., B.S., S.A.); Pôle Pharmacie, Centre Hospitalier Universitaire de Toulouse, France (P.C., B.S.); Unité INSERM 1048, Toulouse, France (B.S.); Pôle Epidémiologie et Santé Publique, Centre Hospitalier Universitaire de Toulouse, France (S.A.); and Service de gériatrie, Hôpital Broca, AP-HP, Hôpitaux Universitaires Paris Centre, France (H.B., M.B., A.C., D.D., I.H., M.-L.S., J.-S.V., O.H.).

Correspondence to Laure Rouch, EA 4468, Université Paris Descartes, Sorbonne Paris Cité, Hôpital Broca, AP-HP, 54–56 rue Pascal, 75013 Paris, France. Email rouch.l@chu-toulouse.fr

vascular function (PWV) and structure (IMT, CAD, CP) and their role in predicting conversion from MCI to dementia.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

The participants were part of a cohort of elderly ambulatory subjects with memory complaint attending a memory clinic between January 2006 and 2008. We selected 404 consecutive patients with a diagnosis of MCI according to Petersen criteria,[24] defined by a memory complaint reported by the patient or the family, a cognitive or functioning decline reported by the family compared with previous abilities, cognitive impairment (score <1.5 SD on neuropsychological tests), an absence of major repercussions on daily life, as well as an absence of dementia. This concept of MCI is useful in clinical practice to classify the in-between population (ie, individuals who are cognitively impaired but not demented) at risk of conversion to dementia over time. Patients with dementia, major depressive disorders, psychiatric deficits, and metabolic disorders were excluded. Among selected MCI patients, 375 subjects attended follow-up visits and were thus included in our study. All gave written informed consent for their participation in the study, which was approved by the local ethics committee. The procedures followed were in accordance with institutional guidelines. This study was conducted in compliance with the principles of the Declaration of Helsinki and followed the international standards pertaining to protection of human research subjects.

Assessment of Cognitive Function and Dementia

The global cognitive assessment of patients was based on the Mini–Mental State Examination (MMSE)[25] performed by the physician. A validated comprehensive battery of neuropsychological tests, the cognitive efficiency profile (scored out of 100, higher score, better cognitive function)[9,26] was also performed by trained neuropsychologists. This battery assesses the main cognitive areas: immediate and delayed memory (free and cued recall), language, visuoperceptual and visuospatial capacities, motor planning, executive function, attention, and judgment. Patients were followed yearly up to 6 years in the memory clinic by a neurologist or a geriatrician to examine potential conversion from MCI to dementia according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth revision.[27]

Assessment of Vascular Function and Structure

Arterial stiffness was evaluated by carotid-femoral PWV measurement using an automatic device (Complior; Colson) by 1 physician blind to the cognitive evaluation. In brief, 2 pressure waves were recorded transcutaneously at the base of the neck for the right common carotid artery (CCA) and over the right femoral artery. PWV was determined as the foot-to-foot velocity. Pulse transit time was determined as the average of 10 consecutive beats. The distance traveled by the pulse wave was measured over the body surface as the distance between the 2 recording sites. Aortic PWV was automatically calculated as the ratio of distance to transit time (PWV=D/t[m/s]). The validation of this automatic method and its reproducibility has been described previously with an intraobserver and interobserver repeatability coefficient of 0.935 and 0.890, respectively.[28]

Ultrasound examinations of the carotid arteries were performed with the patient in the recumbent position. We used a Sigma 110 Kontron device with a transducer frequency of 7.5 MHz. This system provides an axial resolution of 0.30 mm. Acquisition and storage of B-mode images were computer-assisted with the M'Ath Std 2.0.0.0 software.[29] All measurements were made by 1 sonographer at the time of examination. IMT was measured on the far wall of the middle segment of the CCA as the distance between the lumen-intima interface and the media-adventitia interface[30] by using an automated edge-detection algorithm. One longitudinal measurement of IMT was completed in the right and left CCA with segment length >10 mm and quality index >50% (quality index being the ratio of valid measurements to all the measurements possibly performed on the studied arterial segment). CCA lumen diameter (CAD) was measured on the same image. All measurements were made at a site free of plaque. Near and far walls of CCA were scanned longitudinally and transversally for plaques which were defined as localized echo structures encroaching into the vessel lumen, for which the distance between the media-adventitia interface and the internal side of the lesion was >1 mm,[31] or as the presence of calcifications. Mean of right and left measurements of IMT, CAD, and CP were used in our analyses.

Systolic blood pressures (SBP) and diastolic blood pressures were measured in each subject 3×, by nurses during the consultation, after at least 5 minutes of seated rest, on the left arm, using a validated electronic device (Omron 750 CP; Omron Healthcare, Co, Ltd, Kyoto, Japan). The average of the 3 measurements was used to determine blood pressure level. Mean arterial pressure (MAP) was calculated as follows: MAP=1/3 (SBP)+2/3 (diastolic blood pressure). Hypertension was defined as SBP ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medication. Cardiovascular diseases were defined by presence of coronary artery disease, atrial fibrillation, chronic heart failure, or stroke.

Statistical Analysis

Distributions of continuous variables were presented in mean (SD). Proportions and numbers were used to describe qualitative variables. Baseline characteristics were analyzed in the whole sample and in patients converting or not from MCI to dementia using Student tests for continuous variables and χ^2 tests or Fisher exact tests for categorical variables. Cox proportional hazards models were performed to assess the role of PWV, IMT, CAD, or CP in prediction of conversion from MCI to dementia. Univariate analyses were done before proceeding to multivariate models. Significance threshold of 0.2 was considered to select potential confounding factors. Proportional hazard assumption was checked graphically for all covariates and using Schoenfeld residuals. Log-linearity hypothesis was also tested for all covariates. Age, sex, educational level, SBP, cardiovascular diseases, body mass index, calcium channel blocker intake, MMSE at baseline, as well as apoE ε4 status were considered as potential confounders. Hazard ratios (HR) and 95% CI were presented per 1-SD increase of PWV, IMT, and CAD or according to the presence of CP. Interaction PWV×age was checked. PWV was also divided into quartiles and Kaplan-Meier curves of the time until conversion from MCI to dementia were drawn. Sensitivity analyses were also performed considering patients who died as having all become demented. All statistical analyses were performed using STATA software version 15. Graph was performed using R statistical software.

Results

Baseline Characteristics of Patients and Arterial Parameters

Among the selected 404 MCI patients, 29 (7.2%) did not participate in the follow-up. Three hundred and seventy-five subjects (100% white; age range, 55–98; 65.6% female; 49.6% university level) were thus included in our study and followed-up during a mean period of 4.5 years (median, 5 years; interquartile range, 4–6 years). Two hundred and seventy-five participants (73%) were seen yearly until conversion or end of follow-up, and 100 participants (27%) were seen at least every 2 years until conversion or end of follow-up. Twenty-five patients (6.7%) died during the study, but information was known about conversion to dementia. Among the 375 patients, 105 (28%) converted from MCI to dementia. Baseline characteristics of the 2 groups are presented in Table 1. Patients showing a conversion from MCI to dementia were significantly

Table 1. Baseline Characteristics of Subjects—Univariate Cox Analyses

Baseline Characteristics of Subjects, n (%)	All Subjects (N=375)	Conversion to Dementia (n=105)	No Conversion to Dementia (n=270)	*P* Value	Univariate Cox Analyses	
					HR (95% CI)	*P* Value
Age, y, mean (SD)	75.2 (7.0)	78.8 (5.8)	73.7 (6.9)	<0.01	1.09 (1.06–1.13)	<0.01
Female	246 (65.6)	63 (60.0)	183 (67.8)	0.16	0.78 (0.52–1.15)	0.2
Educational level				0.14		0.14
University	183 (49.6)	56 (54.9)	127 (47.6)		1.00	
Middle or high school	100 (27.1)	20 (19.6)	80 (30.0)		0.60 (0.36–1.00)	
Primary school	86 (23.3)	26 (25.5)	60 (22.5)		0.94 (0.59–1.49)	
Hypertension	265 (71.8)	82 (79.6)	183 (68.8)	0.04	1.53 (0.95–2.48)	0.08
Antihypertensive drugs	188 (51.4)	53 (52.0)	135 (51.1)	0.89	1.01 (0.68–1.48)	0.98
Calcium channel blockers	52 (14.3)	10 (10.0)	42 (15.9)	0.15	0.64 (0.33–1.22)	0.18
β-Blockers	74 (20.3)	21 (21.0)	53 (20.1)	0.85	1.03 (0.64–1.67)	0.91
Diuretics	79 (21.7)	20 (20.0)	59 (22.35)	0.63	0.87 (0.54–1.43)	0.59
Angiotensin-converting enzyme inhibitors	39 (10.7)	10 (10.0)	29 (11.0)	0.79	0.88 (0.46–1.69)	0.70
Angiotensin II receptor blockers	45 (12.4)	10 (10.0)	35 (13.3)	0.40	0.73 (0.38–1.41)	0.35
Other antihypertensive drugs*	14 (3.9)	5 (5.0)	9 (3.4)	0.48	1.35 (0.55–3.33)	0.51
Body mass index, kg/m^2, mean (SD)	24.3 (3.4)	23.9 (3.1)	24.5 (3.5)	0.14	0.96 (0.90–1.02)	0.14
Diabetes mellitus	27 (7.4)	8 (7.8)	19 (7.3)	0.85	1.01 (0.49–2.08)	0.97
Dyslipidemia	141 (38.3)	34 (33.0)	107 (40.4)	0.19	0.77 (0.51–1.16)	0.21
Current or former smoker	83 (22.7)	23 (22.3)	60 (22.9)	0.91	0.99 (0.62–1.57)	0.95
Coronary artery disease	35 (10.7)	12 (14.1)	23 (9.5)	0.24	1.54 (0.83–2.84)	0.17
Atrial fibrillation	56 (15.5)	16 (16.3)	40 (15.2)	0.79	1.04 (0.61–1.78)	0.88
Chronic heart failure	9 (2.8)	4 (4.7)	5 (2.1)	0.25	1.72 (0.63–4.70)	0.29
History of stroke or transient ischemic attack	12 (3.7)	3 (3.5)	9 (3.7)	0.94	1.07 (0.34–3.39)	0.91
Cardiovascular diseases	89 (27.0)	30 (34.9)	59 (24.2)	0.05	1.54 (0.99–2.40)	0.06
Family history of dementia	123 (34.2)	38 (38.4)	85 (32.6)	0.30	1.26 (0.84–1.89)	0.26
Mini-Mental State Examination, mean (SD)	27.8 (2.1)	26.6 (2.6)	28.3 (1.6)	<0.01	0.79 (0.74–0.84)	<0.01
Cognitive efficiency profile, mean (SD)	70.5 (13.0)	60.0 (13.4)	74.6 (10.2)	<0.01	0.95 (0.94–0.96)	<0.01
Presence of 1 or 2 apoE ε4 alleles	93 (32.4)	51 (56.0)	42 (21.4)	<0.01	3.23 (2.13–4.90)	<0.01

HR indicates hazard ratio.

*Central antihypertensive agents and α-blockers.

older (78.8 [5.8] versus 73.7 [6.9]; *P*<0.01), more likely to have hypertension (79.6% versus 68.8%; *P*=0.04) and cardiovascular diseases (34.9% versus 24.2%; *P*=0.05). They had significant lower MMSE score (26.6 [2.6] versus 28.3 [1.6]; *P*<0.01), cognitive efficiency profile score (60.0 [13.4] versus 74.6 [10.2]; *P*<0.01) at baseline and were significantly more likely to carry apoE ε4 alleles (56.0% versus 21.4%; *P*<0.01).

Baseline arterial parameters of the 2 groups are presented in Table 2. Patients converting to dementia had significantly higher values of PWV (12.7 [2.2] versus 11.4 [2.1] m/s; *P*<0.01), IMT (0.85 [0.13] versus 0.82 [0.13] mm; *P*=0.03) and were more likely to have CP (41.2% versus 21.3%; *P*<0.01). They also tended to have higher values of SBP (142.3 [18.6] versus 138.5 [17.7] mm Hg; *P*=0.07). Neither diastolic blood pressure (*P*=0.79) nor MAP (*P*=0.29) were significantly different between patients converting or not to dementia. CAD did not differ between the groups (*P*=0.47).

Results of univariate Cox analyses assessing the relationship between baseline characteristics of patients, baseline arterial parameters, and risk of conversion from MCI to dementia are respectively presented in Tables 1 and 2.

Vascular Function (PWV) and Conversion From MCI to Dementia

Kaplan-Meier curves of the time until conversion from MCI to dementia by quartiles of PWV are presented in Figure. Conversion from MCI to dementia was significantly different between quartiles of PWV (*P* log-rank <0.001). Compared with the first quartile of PWV, patients in the third and fourth quartiles had a higher risk of progression from MCI to dementia (HR, 2.13; 95% CI, 1.13–4.02; *P*=0.02 and HR, 3.54; 95% CI, 1.93–6.48; *P*<0.01, respectively).

Multivariate analyses are presented in Table 3. After adjustment for potential confounders (age, sex, educational level,

Table 2. Baseline Arterial Parameters—Univariate Cox Analyses

Baseline Arterial Parameters, mean (SD)	All Subjects (N=375)	Conversion to Dementia (n=105)	No Conversion to Dementia (n=270)	*P* Value	Univariate Cox Analyses	
					HR (95% CI)	*P* Value
Systolic blood pressure, mm Hg	139.6 (18.0)	142.3 (18.6)	138.5 (17.7)	0.07	1.01 (1.00–1.02)	0.11
Diastolic blood pressure, mm Hg	78.4 (10.4)	78.7 (10.0)	78.3 (10.6)	0.79	1.00 (0.98–1.02)	0.88
Mean arterial pressure, mm Hg	98.8 (11.6)	99.8 (11.6)	98.4 (11.5)	0.29	1.01 (0.99–1.02)	0.38
Pulse wave velocity, m/s	11.8 (2.2)	12.7 (2.2)	11.4 (2.1)	<0.01	1.45* (1.25–1.69)	<0.01
Carotid intima-media thickness, mm	0.83 (0.13)	0.85 (0.13)	0.82 (0.13)	0.03	1.22* (1.02–1.46)	0.03
Carotid plaque, n (%)	90 (27.1)	40 (41.2)	50 (21.3)	<0.01	2.10 (1.40–3.15)	<0.01
Carotid artery diameter, mm	7.94 (0.97)	8.00 (0.99)	7.92 (0.97)	0.47	1.08* (0.89–1.31)	0.44

Missing values=SBP, 3; DBP, 4; MAP, 4; PWV, 0; IMT, 11; CP, 43; CAD, 18. CAD indicates carotid artery diameter; CP, carotid plaques; DBP, diastolic blood pressure; HR, hazard ratio; IMT, intima-media thickness; MAP, mean arterial pressure; PWV, pulse wave velocity; and SBP, systolic blood pressure.

*HR per 1-SD increase of PWV, IMT, or CAD.

SBP, cardiovascular diseases, body mass index, calcium channel blockers intake, MMSE, and apoE ε4 status), higher baseline PWV remained significantly associated with greater risk of conversion from MCI to dementia (1-SD increase of PWV: HR, 1.33; 95% CI, 1.04–1.71; *P*=0.02). Age, lower MMSE scores at baseline, as well as presence of apoE ε4 alleles were also significantly associated with higher risk of conversion to dementia. Age-stratified analyses were also performed (PWV×age interaction; *P*=0.11). In patients aged <75 years, higher PWV strongly predicted conversion from MCI to dementia (1-SD increase of PWV: HR, 2.51; 95% CI, 1.35–4.69; *P*<0.01). In those aged ≥75 years, higher PWV was also associated with greater risk of conversion from MCI to dementia, although to a lesser extent (HR, 1-SD increase of PWV: HR, 1.29; 95% CI, 0.99–1.68; *P*=0.05). Adjustment on MAP instead of SBP in multivariate models did not alter the results (1-SD increase of PWV: HR, 1.32; 95% CI 1.03–1.69; *P*=0.03). Sensitivity analyses considering patients who died as having all become demented reported an even greater association between PWV and risk of conversion from MCI to dementia (1-SD increase of PWV: HR, 1.36; 95% CI, 1.09–1.70; *P*<0.01).

Vascular Structure (IMT, CAD, CP) and Conversion From MCI to Dementia

As presented in Table 3, after adjustment on potential confounders, neither IMT nor CP predicted conversion from

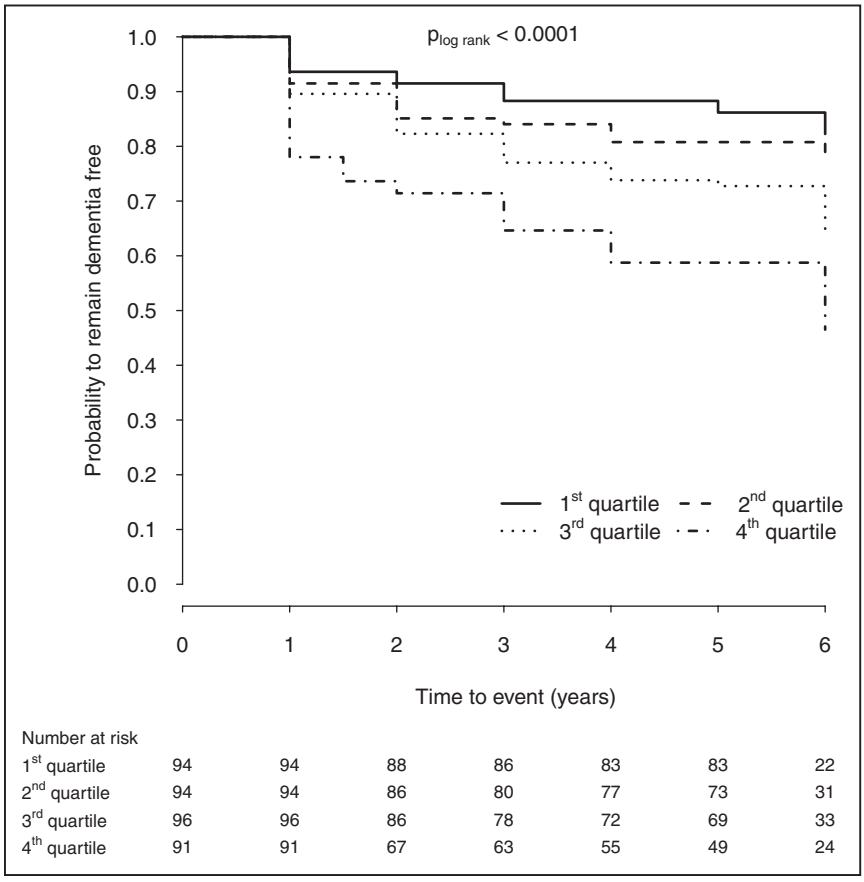

Figure. Kaplan-Meier curves: risk of progression from mild cognitive impairment to dementia according to pulse wave velocity (PWV) quartiles. First quartile includes PWV 6.7 to 10.2; second quartile PWV, 10.21 to 11.52; third quartile PWV, 11.54 to 13.1; and fourth quartile PWV, 13.11 to 22.3.

Table 3. Multivariate Cox Analyses: PWV, IMT, CP, and Risk of Progression From MCI to Dementia

	PWV Model		IMT Model		CP Model	
Conversion From MCI to Dementia	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
1-SD increase of PWV	1.33 (1.04–1.71)	0.02				
1-SD increase of IMT			0.93 (0.73–1.18)	0.55		
CP					1.08 (0.62–1.87)	0.79
Age, y	1.09 (1.04–1.13)	<0.01	1.11 (1.06–1.15)	<0.01	1.11 (1.06–1.15)	<0.01
Female	1.07 (0.62–1.84)	0.80	0.94 (0.56–1.59)	0.83	0.89 (0.52–1.50)	0.66
Educational level		0.16		0.16		0.19
University	1 (ref)		1 (ref)		1 (ref)	
Middle or high school	0.53 (0.27–1.04)	0.06	0.51 (0.25–1.03)	0.06	0.52 (0.25–1.05)	0.07
Elementary school	0.94 (0.52–1.71)	0.84	0.94 (0.52–1.71)	0.84	0.86 (0.46–1.58)	0.62
Systolic blood pressure	1.00 (0.99–1.02)	0.78	1.01 (0.99–1.02)	0.24	1.01 (1.00–1.02)	0.19
Cardiovascular diseases	1.06 (0.62–1.79)	0.84	1.09 (0.63–1.86)	0.76	1.07 (0.61–1.85)	0.82
Body mass index	1.00 (0.92–1.08)	0.92	0.99 (0.91–1.07)	0.77	0.99 (0.90–1.07)	0.74
Calcium channel blockers intake	0.89 (0.41–1.94)	0.78	0.97 (0.45–2.12)	0.95	1.13 (0.52–2.46)	0.75
Mini–Mental State Examination	0.78 (0.70–0.86)	<0.01	0.78 (0.70–0.86)	<0.01	0.80 (0.72–0.89)	<0.01
Presence of 1 or 2 apoE ε4 alleles	3.33 (1.99–5.56)	<0.01	2.87 (1.72–4.78)	<0.01	2.93 (1.74–4.93)	<0.01

CP indicates carotid plaques; HR, hazard ratio; IMT, carotid intima-media thickness, MCI, mild cognitive impairment; and PWV, pulse wave velocity.

MCI to dementia (1-SD increase of IMT: HR, 0.93; 95% CI, 0.73–1.18; *P*=0.55 and presence of CP: HR, 1.08; 95% CI, 0.62–1.87; *P*=0.79). Adjustment on MAP instead of SBP in multivariate models did not alter the results (1-SD increase of IMT: HR, 0.93; 95% CI, 0.73–1.19; *P*=0.57; presence of CP: HR, 1.10; 95% CI, 0.63–1.89; *P*=0.74). CAD was not associated with progression from MCI to dementia in univariate analyses (1-SD increase of CAD: HR, 1.08; 95% CI, 0.89–1.31; *P*=0.44). Sensitivity analyses considering patients who died as having all become demented did not change our results for IMT, CP, or CAD.

Discussion

In this population of MCI patients, subjects with higher PWV had a greater risk of conversion to dementia. This relationship was independent of age, sex, educational level, SBP, cardiovascular diseases, body mass index, calcium channel blockers intake, MMSE at baseline, and apoE ε4 status. Arterial stiffness appeared to be an independent determinant of conversion from MCI to dementia. Conversely, IMT, CP, and CAD were not associated with progression to dementia. Our findings suggest the emergence of PWV as a unique vascular biomarker to identify MCI patients at higher risk of dementia.

To our knowledge, no study investigated the association between PWV and conversion from MCI to dementia. Cross-sectional studies have suggested a relationship between arterial stiffness and dementia. A meta-analysis supported the hypothesis that greater arterial stiffness is a contributor to microvascular brain disease.[32] Recently, high cerebral artery pulsatility was found to be an independent predictor of dementia in individuals with subjective memory decline or MCI.[33]

Several mechanisms may explain how functional changes of arterial system could be involved in the onset of dementia.[9] PWV reflects arterial stiffness which is one of the earliest indicators of changes in vascular function. Arterial stiffness may contribute to microvascular brain injury by exposing small vessels of cerebral vasculature to high-pressure fluctuations and flow pulsatility.[34] An increasing epidemiological, clinical, and experimental evidence suggested a significant role of systemic hemodynamic pulsatility on alteration of structure and function of the brain.[35] The increased pulsatile load may induce a microvascular remodeling response leading to hypoperfusion.[36] Arterial stiffness has been related to atherosclerosis or arteriosclerosis in large[37] and small vessels[38] and associated with small infarcts (lacunar stroke) and white matter lesions. Dementia may be the direct consequence of these ischemic brain lesions, depending on the volume, location, and number of these vascular lesions. In the Rotterdam study, PWV was an independent predictor of stroke in apparently healthy subjects.[39] In the Framingham Third Generation cohort study,[40] higher PWV was associated with greater burden of white matter hyperintensities. Moreover, a significant association between PWV and medial temporal lobe atrophy suggests a role of arterial stiffness in the pathogenesis of AD.[41] Medial temporal lobe is particularly known for its sensitivity to ischemia. Vessel remodeling and hypoperfusion after arterial stiffness might affect the volume of this structure.[42] Recently, lower cerebral blood flow, measured with magnetic resonance imaging), was found to be associated with accelerated cognitive decline and increased risk of dementia.[43] Further studies focusing on testing the impact of carotid blood flow on dementia risk would be of interest. Lesions in cerebral microvessels may compromise the function of blood-brain barrier increasing vascular permeability and

protein extravasation in cerebral parenchyma. Accumulation of different vasculotoxic and neurotoxic byproducts, as β-amyloid peptide, would result in neuronal dysfunction and neurodegenerative changes.[44] Moreover, changes in pulsatile flow dynamics following from aortic stiffening may alter the movement of cerebrospinal fluid along perivascular spaces, disrupting the clearance of metabolic waste from the brain.[45] Interestingly, arterial stiffness was found to be associated with an increased risk of having β-amyloid deposition on positron emission tomography–imaging, independently of blood pressure level in nondemented older adults.[46] Recently, in the ARIC-PET study (Atherosclerosis Risk in Communities–Positron Emission Tomography),[47] greater PWV was significantly associated with having lower brain volumes in AD susceptible regions, high white matter hyperintensities burden, as well as concomitant high white matter hyperintensities and Aβ positive scans. These associations were strongest among individuals with MCI. A recent experimental work also reported that pulsatile stretch of brain vascular endothelial cells, strongly associated with higher values of PWV, could lead to upregulation of APP (amyloid precursor protein) expression and amyloidogenic processing enzyme, β-secretase 1, and Aβ42 secretion.[48] Vascular stiffness, particularly higher PWV, is also related to endothelial dysfunction where nitric oxide (NO)-mediated endothelium-dependent vasodilatation, facilitated by the eNOS (endothelial NO synthase), is diminished. Deficiency of eNOS was found to be associated with higher APP protein expression and secretion of Aβ.[48,49] Finally, in the present investigation, PWV was able to better qualify the risk of conversion with respect to SBP. It could be suggested that long-standing hypertension from midlife is accompanied by an arterial aging process, whereby arterial stiffness becomes more prominent compared with high blood pressure. However, our study was not designed to address this contrast and measurement of blood pressure was limited to 3 readings on a single occasion.

The association between IMT and cognitive disorders yields conflicting results. Some studies reported significant associations,[12–14] whereas others did not.[15–17] Buratti et al[50] reported a correlation between increased values of IMT and progression from MCI to dementia. Wendell et al[11] only found an association between dementia and the upper quintile of IMT but not when IMT was considered as a continuous variable. We did not find a significant association between IMT and conversion from MCI to dementia after adjustment for age and other confounding factors, possibly because IMT also represents nonatherosclerotic age-associated changes in the vessel wall.[11] Our findings are consistent with a previous study that also found a lack of predictive value of CP on the risk of conversion from MCI to dementia.[51] The hypothesis of a competing risk of mortality could be suggested to explain these negative findings. Furthermore, CP are strongly associated with lipids, smoking, and other traditional risk factors[52] more than with age or blood pressure. They are also more closely related to coronary artery diseases than stroke. Thus, they may not be causally involved in progression to dementia.

Our study has some limitations that are worth noting. First, our findings are based on an observational study, and residual confounding may still exist. Second, we assessed conversion from MCI to dementia but were not able to distinguish AD from vascular dementia. Neither magnetic resonance imaging nor cerebrospinal fluid biomarkers for AD were available in our study. However, all patients underwent a computed tomography brain scan allowing to rule out a diagnosis of pure vascular dementia. Third, our sample was comprised mostly of highly educated whites, limiting the generalizability of the results. Fourth, PWV, as well as IMT, CP, and CAD were only measured at baseline. Fifth, the study was conducted among older adults with a long-term follow-up, so attrition was unavoidable. However, only 7.2% of subjects did not participate in the follow-up. Their baseline characteristics did not significantly differ from those of patients remaining in the study. They only tended to be slightly older. Moreover, our sensitivity analyses considering patients who died as having all become demented revealed no impact on our findings. Finally, we did not have any qualitative and quantitative data on CP, although their respective association with dementia remains to be investigated.

Nevertheless, our study has several strengths. It was conducted on a relatively large sample size, with a longitudinal design and a long-term follow-up, in a specific population of MCI patients at risk of conversion to dementia. The rate of progression from MCI to dementia we found was consistent with previous findings.[53] An extensive vascular investigation was done, including both structural and functional assessment. All measures were done using standardized protocols with a validated and widely-used device. The association between PWV and conversion from MCI to dementia was observed after adjustment for age, sex, education level, SBP, cardiovascular diseases, body mass index, calcium channel blocker intake, baseline cognitive function, and apoE ε4 status suggesting that the relationship is independent of these variables. Finally, assessment of dementia was performed in a memory clinic by trained neurologists or geriatricians.

Perspectives

In the present study, arterial stiffness, measured as PWV, was associated with conversion from MCI to dementia. However, neither IMT, CP nor CAD was found to be associated with progression from MCI to dementia after controlling for age and other confounding factors. Overall, our findings suggested that arterial stiffness could identify MCI patients at higher risk of dementia and may be a therapeutic target to delay or prevent the onset of dementia.

Disclosures

None.

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement*. 2013;9:63–75.e2. doi: 10.1016/j.jalz.2012.11.007
2. Gorelick PB, Scuteri A, Black SE, et al; American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart

association/american stroke association. *Stroke*. 2011;42:2672–2713. doi: 10.1161/STR.0b013e3182299496
3. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–2605. doi: 10.1093/eurheartj/ehl254
4. Li X, Lyu P, Ren Y, An J, Dong Y. Arterial stiffness and cognitive impairment. *J Neurol Sci*. 2017;380:1–10. doi: 10.1016/j.jns.2017.06.018
5. Singer J, Trollor JN, Baune BT, Sachdev PS, Smith E. Arterial stiffness, the brain and cognition: a systematic review. *Ageing Res Rev*. 2014;15:16–27. doi: 10.1016/j.arr.2014.02.002
6. Tsao CW, Himali JJ, Beiser AS, Larson MG, DeCarli C, Vasan RS, Mitchell GF, Seshadri S. Association of arterial stiffness with progression of subclinical brain and cognitive disease. *Neurology*. 2016;86:619–626. doi: 10.1212/WNL.0000000000002368
7. Watfa G, Benetos A, Kearney-Schwartz A, Labat C, Gautier S, Hanon O, Salvi P, Joly L; PARTAGE Study Investigators. Do arterial hemodynamic parameters predict cognitive decline over a period of 2 years in individuals older than 80 years living in nursing homes? The PARTAGE Study. *J Am Med Dir Assoc*. 2015;16:598–602. doi: 10.1016/j.jamda.2015.01.098
8. Meyer ML, Palta P, Tanaka H, Deal JA, Wright J, Knopman DS, Griswold ME, Mosley TH, Heiss G. Association of central arterial stiffness and pressure pulsatility with mild cognitive impairment and dementia: the Atherosclerosis Risk in Communities Study-Neurocognitive Study (ARIC-NCS). *J Alzheimers Dis*. 2017;57:195–204. doi: 10.3233/JAD-161041
9. Hanon O, Haulon S, Lenoir H, Seux ML, Rigaud AS, Safar M, Girerd X, Forette F. Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. *Stroke*. 2005;36:2193–2197. doi: 10.1161/01.STR.0000181771.82518.1c
10. Nilsson ED, Elmståhl S, Minthon L, Pihlsgård M, Nilsson PM, Hansson O, Nägga K. No independent association between pulse wave velocity and dementia: a population-based, prospective study. *J Hypertens* 2017;35:2462–2467. doi: 10.1097/HJH.0000000000001480
11. Wendell CR, Waldstein SR, Ferrucci L, O'Brien RJ, Strait JB, Zonderman AB. Carotid atherosclerosis and prospective risk of dementia. *Stroke*. 2012;43:3319–3324. doi: 10.1161/STROKEAHA.112.672527
12. Wang A, Chen G, Su Z, Liu X, Yuan X, Jiang R, Cao Y, Chen S, Luo Y, Guo X, Wu S, Zhao X. Carotid intima-media thickness and cognitive function in a middle-aged and older adult community: a cross-sectional study. *J Neurol*. 2016;263:2097–2104. doi: 10.1007/s00415-016-8234-9
13. Zeki Al Hazzouri A, Vittinghoff E, Sidney S, Reis JP, Jacobs DR, Yaffe K. Intima-media thickness and cognitive function in stroke-free middle-aged adults: findings from the Coronary Artery Risk Development in Young Adults Study. *Stroke* 2015;46:2190–2196. doi: 10.1161/STROKEAHA.115.008994
14. Zhong W, Cruickshanks KJ, Schubert CR, Acher CW, Carlsson CM, Klein BE, Klein R, Chappell RJ. Carotid atherosclerosis and 10-year changes in cognitive function. *Atherosclerosis*. 2012;224:506–510. doi: 10.1016/j.atherosclerosis.2012.07.024
15. Suemoto CK, Nitrini R, Grinberg LT, Ferretti RE, Farfel JM, Leite RE, Menezes PR, Fregni F, Jacob-Filho W, Pasqualucci CA; Brazilian Aging Brain Study Group. Atherosclerosis and dementia: a cross-sectional study with pathological analysis of the carotid arteries. *Stroke*. 2011;42:3614–3615. doi: 10.1161/STROKEAHA.111.628156
16. Weimar C, Winkler A, Dlugaj M, Lehmann N, Hennig F, Bauer M, Kröger K, Kälsch H, Mahabadi AA, Dragano N, Moebus S, Hoffmann B, Jöckel KH, Erbel R; Heinz Nixdorf Recall Study Investigative Group. Ankle-brachial index but neither intima media thickness nor coronary artery calcification is associated with mild cognitive impairment. *J Alzheimers Dis*. 2015;47:433–442. doi: 10.3233/JAD-150218
17. Lim SL, Gao Q, Nyunt MS, Gong L, Lunaria JB, Lim ML, Ling A, Lam CS, Richards AM, Ling LH, Ng TP. Vascular health indices and cognitive domain function: singapore longitudinal ageing studies. *J Alzheimers Dis*. 2016;50:27–40. doi: 10.3233/JAD-150516
18. Wardlaw JM, Allerhand M, Eadie E, Thomas A, Corley J, Pattie A, Taylor A, Shenkin SD, Cox S, Gow A, Starr JM, Deary IJ. Carotid disease at age 73 and cognitive change from age 70 to 76 years: a longitudinal cohort study. *J Cereb Blood Flow Metab*. 2017;37:3042–3052. doi: 10.1177/0271678X16683693
19. Kitagawa K, Miwa K, Yagita Y, Okazaki S, Sakaguchi M, Mochizuki H. Association between carotid stenosis or lacunar infarction and incident dementia in patients with vascular risk factors. *Eur J Neurol*. 2015;22:187–192. doi: 10.1111/ene.12553
20. Wang T, Mei B, Zhang J. Atherosclerotic carotid stenosis and cognitive function. *Clin Neurol Neurosurg*. 2016;146:64–70. doi: 10.1016/j.clineuro.2016.03.027
21. Lal BK, Dux MC, Sikdar S, Goldstein C, Khan AA, Yokemick J, Zhao L. Asymptomatic carotid stenosis is associated with cognitive impairment. *J Vasc Surg*. 2017;66:1083–1092. doi: 10.1016/j.jvs.2017.04.038
22. Rogne SO, Solbu MD, Arntzen KA, Herder M, Mathiesen EB, Schirmer H. Albuminuria and carotid atherosclerosis as predictors of cognitive function in a general population. *Eur Neurol*. 2013;70:340–348. doi: 10.1159/000353701
23. Arntzen KA, Schirmer H, Johnsen SH, Wilsgaard T, Mathiesen EB. Carotid atherosclerosis predicts lower cognitive test results: a 7-year follow-up study of 4,371 stroke-free subjects - the Tromsø study. *Cerebrovasc Dis*. 2012;33:159–165. doi: 10.1159/000334182
24. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56:303–308.
25. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
26. De Rotrou J, Forette F, Hervy M, Tortrat D, Fermanian J, Boudou M, Boller F. The cognitive efficiency profile: description and validation in patients with Alzheimer's disease. 1991;6:501–509.
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington, DC: American Psychiatric Association; 1994.
28. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension*. 1995;26:485–490.
29. Touboul PJ, Prati P, Scarabin PY, Adrai V, Thibout E, Ducimetière P. Use of monitoring software to improve the measurement of carotid wall thickness by B-mode imaging. *J Hypertens Suppl*. 1992;10:S37–S41.
30. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation*. 1986;74:1399–1406.
31. Zureik M, Touboul PJ, Bonithon-Kopp C, Courbon D, Berr C, Leroux C, Ducimetière P. Cross-sectional and 4-year longitudinal associations between brachial pulse pressure and common carotid intima-media thickness in a general population. The EVA study. *Stroke*. 1999;30:550–555.
32. van Sloten TT, Protogerou AD, Henry RM, Schram MT, Launer LJ, Stehouwer CD. Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2015;53:121–130. doi: 10.1016/j.neubiorev.2015.03.011
33. Chung CP, Lee HY, Lin PC, Wang PN. Cerebral artery pulsatility is associated with cognitive impairment and predicts dementia in individuals with subjective memory decline or mild cognitive impairment. *J Alzheimers Dis*. 2017;60:625–632. doi: 10.3233/JAD-170349
34. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertens Dallas Tex 1979* 2005;46:200–204. doi: 10.1161/01.HYP.0000168052.00426.65
35. Avolio A, Kim MO, Adji A, Gangoda S, Avadhanam B, Tan I, Butlin M. Cerebral haemodynamics: effects of systemic arterial pulsatile function and hypertension. *Curr Hypertens Rep*. 2018;20:20. doi: 10.1007/s11906-018-0822-x
36. Cooper LL, Woodard T, Sigurdsson S, van Buchem MA, Torjesen AA, Inker LA, Aspelund T, Eiriksdottir G, Harris TB, Gudnason V, Launer LJ, Mitchell GF. Cerebrovascular damage mediates relations between aortic stiffness and memory. *Hypertens Dallas Tex 1979* 2016;67:176–182. doi: 10.1161/HYPERTENSIONAHA.115.06398
37. van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, Hoeks AP, van der Kuip DA, Hofman A, Witteman JC. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke*. 2001;32:454–460.
38. Baumbach GL, Siems JE, Heistad DD. Effects of local reduction in pressure on distensibility and composition of cerebral arterioles. *Circ Res*. 1991;68:338–351.
39. Mattace-Raso FUS, van der Cammen TJM, Hofman A, van Popele NM, Bos ML, Schalekamp MADH, Asmar R, Reneman RS, Hoeks APG, Breteler MMB, Witteman JCM. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation* 2006;113:657–663. doi: 10.1161/CIRCULATIONAHA.105.555235
40. Pase MP, Himali JJ, Mitchell GF, Beiser A, Maillard P, Tsao C, Larson MG, DeCarli C, Vasan RS, Seshadri S. Association of aortic stiffness with cognition and brain aging in young and middle-aged adults: the

Framingham Third Generation Cohort Study. *Hypertens Dallas Tex 1979* 2016;67:513–519. doi: 10.1161/HYPERTENSIONAHA.115.06610
41. Lilamand M, Vidal JS, Plichart M, De Jong LW, Duron E, Hanon O. Arterial stiffness and medial temporal lobe atrophy in elders with memory disorders. *J Hypertens*. 2016;34:1331–1337. doi: 10.1097/HJH.0000000000000954
42. de Jong LW, Forsberg LE, Vidal JS, Sigurdsson S, Zijdenbos AP, Garcia M, Eiriksdottir G, Gudnason V, van Buchem MA, Launer LJ. Different susceptibility of medial temporal lobe and basal ganglia atrophy rates to vascular risk factors. *Neurobiol Aging*. 2014;35:72–78. doi: 10.1016/j.neurobiolaging.2013.07.009
43. Wolters FJ, Zonneveld HI, Hofman A, van der Lugt A, Koudstaal PJ, Vernooij MW, Ikram MA; Heart-Brain Connection Collaborative Research Group. Cerebral perfusion and the risk of dementia: a population-based study. *Circulation*. 2017;136:719–728. doi: 10.1161/CIRCULATIONAHA.117.027448
44. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci*. 2011;12:723–738. doi: 10.1038/nrn3114
45. Bilston LE, Fletcher DF, Brodbelt AR, Stoodley MA. Arterial pulsation-driven cerebrospinal fluid flow in the perivascular space: a computational model. *Comput Methods Biomech Biomed Engin*. 2003;6:235–241. doi: 10.1080/1025584031000160611 6
46. Hughes TM, Kuller LH, Barinas-Mitchell EJ, Mackey RH, McDade EM, Klunk WE, Aizenstein HJ, Cohen AD, Snitz BE, Mathis CA, Dekosky ST, Lopez OL. Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults. *Neurology*. 2013;81:1711–1718. doi: 10.1212/01.wnl.0000435301.64776.37
47. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, Wong D, Zhou Y, Knopman D, Mosley TH, Gottesman RF. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET Study. *Neurology*. 2018;90:e1248–e1256. doi: 10.1212/WNL.0000000000005259
48. Gangoda SVS, Avadhanam B, Jufri NF, Sohn EH, Butlin M, Gupta V, Chung R, Avolio AP. Pulsatile stretch as a novel modulator of amyloid precursor protein processing and associated inflammatory markers in human cerebral endothelial cells. *Sci Rep*. 2018;8:1689. doi: 10.1038/s41598-018-20117-6
49. Austin SA, Santhanam AV, Katusic ZS. Endothelial nitric oxide modulates expression and processing of amyloid precursor protein. *Circ Res*. 2010;107:1498–1502. doi: 10.1161/CIRCRESAHA.110.233080
50. Buratti L, Balestrini S, Altamura C, Viticchi G, Falsetti L, Luzzi S, Provinciali L, Vernieri F, Silvestrini M. Markers for the risk of progression from mild cognitive impairment to Alzheimer's disease. *J Alzheimers Dis*. 2015;45:883–890. doi: 10.3233/JAD-143135
51. Viticchi G, Falsetti L, Vernieri F, Altamura C, Bartolini M, Luzzi S, Provinciali L, Silvestrini M. Vascular predictors of cognitive decline in patients with mild cognitive impairment. *Neurobiol Aging*. 2012;33:1127.e1–1127.e9. doi: 10.1016/j.neurobiolaging.2011.11.027
52. Spence JD. Carotid intima-media thickness and cognitive decline: what does it mean for prevention of dementia? *J Neurol Sci*. 2004;223:103–105. doi: 10.1016/j.jns.2004.05.012
53. Roberts RO, Knopman DS, Mielke MM, Cha RH, Pankratz VS, Christianson TJH, Geda YE, Boeve BF, Ivnik RJ, Tangalos EG, Rocca WA, Petersen RC. Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. *Neurology* 2014;82:317–325. doi: 10.1212/WNL.0000000000000055

Novelty and Significance

What Is New?

- Our study reported that higher pulse wave velocity is associated with greater risk of conversion from mild cognitive impairment to dementia. Arterial stiffness could identify mild cognitive impairment patients at higher risk of dementia.

What Is Relevant?

- In the present investigation, pulse wave velocity is able to better predict the risk of conversion from mild cognitive impairment to dementia with respect to systolic blood pressure, intima-media thickness, carotid plaques, or carotid artery diameter. These findings suggest the emergence of pulse wave velocity as a unique vascular biomarker to identify mild cognitive impairment patients at higher risk of dementia. However, further investigations, designed to address this contrast, are needed.

Summary

Higher pulse wave velocity was associated with greater risk of conversion from mild cognitive impairment to dementia. However, neither intima-media thickness, carotid plaques nor carotid artery diameter was found to be associated with progression from mild cognitive impairment to dementia after controlling for age and other confounding factors.