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CLINICAL RESEARCH

Hypertensive Exposure Markers by MRI in Relation to Cerebral Small Vessel Disease and Cognitive Impairment

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ABSTRACT

OBJECTIVES This study sought to investigate the extent of hypertensive exposure as assessed by cardiovascular magnetic resonance imaging (MRI) in relation to cerebral small vessel disease (CSVD) and cognitive impairment, with the aim of understanding the role of hypertension in the early stages of deteriorating brain health.

BACKGROUND Preserving brain health into advanced age is one of the great challenges of modern medicine. Hypertension is thought to induce vascular brain injury through exposure of the cerebral microcirculation to increased pressure/pulsatility. Cardiovascular MRI provides markers of (subclinical) hypertensive exposure, such as aortic stiffness by pulse wave velocity (PWV), left ventricular (LV) mass index (LVMi), and concentricity by mass-to-volume ratio.

METHODS A total of 559 participants from the Heart-Brain Connection Study (431 patients with manifest cardiovascular disease and 128 control participants), age 67.8 ± 8.8 years, underwent 3.0-T heart-brain MRI and extensive neuropsychological testing. Aortic PWV, LVMi, and LV mass-to-volume ratio were evaluated in relation to presence of CSVD and cognitive impairment. Effect modification by patient group was investigated by interaction terms; results are reported pooled or stratified accordingly.

RESULTS Aortic PWV (odds ratio [OR]: 1.17; 95% confidence interval [CI]: 1.05 to 1.30 in patient groups only), LVMi (in carotid occlusive disease, OR: 5.69; 95% CI: 1.63 to 19.87; in other groups, OR: 1.30; 95% CI: 1.05 to 1.62]) and LV mass-to-volume ratio (OR: 1.81; 95% CI: 1.46 to 2.24) were associated with CSVD. Aortic PWV (OR: 1.07; 95% CI: 1.02 to 1.13) and LV mass-to-volume ratio (OR: 1.27; 95% CI: 1.07 to 1.51) were also associated with cognitive impairment. Relations were independent of sociodemographic and cardiac index and mostly persisted after correction for systolic blood pressure or medical history of hypertension. Causal mediation analysis showed significant mediation by presence of CSVD in the relation between hypertensive exposure markers and cognitive impairment.

CONCLUSIONS The extent of hypertensive exposure is associated with CSVD and cognitive impairment beyond clinical blood pressure or medical history. The mediating role of CSVD suggests that hypertension may lead to cognitive impairment through the occurrence of CSVD. (J Am Coll Cardiol Img 2020;■:■–■) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CI = confidence interval

COD = carotid occlusive disease

CSVD = cerebral small vessel disease

HF = heart failure

LV = left ventricle

LVMi = left ventricular mass index

MRI = magnetic resonance imaging

OR = odds ratio

PWV = pulse wave velocity

VCI = vascular cognitive impairment

Preserving brain health into advanced age has become one of the great challenges of modern medicine. Cardiovascular disease may contribute independently to cognitive impairment (1,2). As a consequence of increasing age in combination with better survival after acute cardiovascular events over the last decades (3), physicians are confronted with a shift to more chronic cardiovascular disease burden with potential detrimental, yet incompletely understood, effects on brain health.

Hypertension is a prominent determinant of chronic (subclinical) cerebral small vessel disease (CSVD), which, owing to advances in neuroimaging, is increasingly recognized as a cause of cognitive impairment (4-7). Exposure of the cerebral microcirculation to higher pressure and pulsatility induces a spectrum of cerebral microvascular remodeling and damage, including thickening of the arterial media, atherosclerotic plaque formation, endothelial dysfunction, increased blood-brain barrier permeability and microbleeds. These pathological microvascular changes may in turn also reduce cerebrovascular reactivity, thus affecting the capability of the brain to maintain adequate blood flow in low pressure or low flow settings and rendering the brain vulnerable to (subclinical) ischemic injury as well (1,8-10).

With a focus on detecting and understanding the early subclinical stages of deteriorating brain health, investigating hypertensive exposure may provide more in-depth insight into the role of hypertensive disease in the pathophysiology of cognitive impairment. However, quantifying hypertensive exposure based on clinical characteristics is hampered by difficulties in assessing or defining factors such as duration, initial severity of hypertension, adequate regulation, number of antihypertensives, and patient compliance, some of which may also vary over time. Alternatively, cardiovascular magnetic resonance imaging (MRI) allows assessment of cardiovascular remodeling in response to hypertension. Hypertensive exposure markers include left ventricular (LV) mass index (LVMi), LV mass-to-volume ratio indicating concentricity, and aortic pulse wave velocity (PWV) indicating arterial stiffness.

The current study investigated the relation of hypertensive exposure markers by cardiovascular MRI with the presence of CSVD assessed by brain MRI and lower cognitive functioning in a population of patients with manifest cardiovascular disease and control participants.

METHODS

STUDY POPULATION. For the current study, baseline data of Heart-Brain Connection Study participants were used. The Heart-Brain Connection Study is a multicenter, prospective, observational study investigating the interplay of cardiovascular and hemodynamic factors in the pathophysiology of cognitive impairment; rationale and methods were described previously (11).

The study population consisted of patients with a clinical diagnosis of heart failure (HF) (n = 162), vascular cognitive impairment (VCI) (n = 160), or carotid occlusive disease (COD) (n = 109) and a group of control participants (n = 128), enrolled between September 2014 and December 2017 in 4 university medical centers in the Netherlands. HF was defined following European Society of Cardiology Guidelines (12), and patients were clinically stable for at least 6 months before enrollment. VCI was defined as cognitive complaints in the absence of dementia (Clinical Dementia Rating: ≤1 and Mini-Mental State Examination: ≥20), with at least moderate vascular brain injury on brain MRI or mild vascular brain injury in the presence of vascular risk factors or a history of manifest vascular disease. COD was defined as significant stenosis >80% or occlusion of an internal carotid artery not scheduled for surgical intervention. Patients were enrolled from cardiology, memory, and neurology outpatient clinics. Control participants were recruited via advertising leaflets and by approaching spouses of participants when they

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

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fulfilled the selection criteria. Inclusion criteria for all participants were age ≥50 years, ability to undergo cognitive testing, and independence in daily life. We excluded those with a contraindication for MRI, life-threatening disease with life expectancy of <3 years, neurodegenerative disease other than VCI or Alzheimer disease, neurologic or psychiatric diagnosis that could affect cognitive performance, and, for technical reasons, atrial fibrillation upon enrollment (of note, previous or paroxysmal atrial fibrillation was not an exclusion criterion) and premature ventricular contractions of >10% of heartbeats. For control participants, the only additional exclusion criterion was a prior diagnosis of HF, VCI, or COD; that is, controls were not excluded in the case of other manifestations of cardiovascular disease or risk factors.

All participants provided written informed consent. This study was performed in accordance with the Declaration of Helsinki and with approval from the Medical Ethics Review Committee of Leiden University Medical Center and the locally appointed ethics committees of all other participating centers.

CLINICAL CHARACTERISTICS. Sociodemographic characteristics and medical history of cardiovascular and cerebrovascular disease and risk factors were obtained via questionnaires. Anthropometrics included height, weight, waist and hip circumference, and brachial office blood pressure (BP) measurement with a digital sphygmomanometer in the sitting position after 5 min of resting. A waist-hip ratio of ≥0.90 for men and ≥0.85 for women was considered obese, according to the World Health Organization cutoff values (13).

HEART-BRAIN MRI PROTOCOL. Heart-brain MRI was performed on 3.0-T clinical MR scanners (Ingenia or Achieva, Philips, Best, the Netherlands). The cardiovascular MRI protocol consisted of breath-hold electrocardiography-gated, steady-state, free precession cine imaging performed in standard long- and short-axis orientations covering the whole LV. Typical parameters were as follows: spatial resolution: 1.5 × 1.6 × 8.0 mm; repetition time: 3.1 ms; echo time: 1.55; flip angle: 45°; 40 heart phases; and 67% phase percentage. Additionally, for assessment of aortic PWV, through-plane velocity-encoded phase contrast imaging was performed through the ascending and descending aorta at the level of the pulmonary artery. Typical parameters were as follows: spatial resolution: 2.5 × 2.5 × 8.0 mm; TR: 4.7 ms; TE: 2.8 ms; flip angle: 10°; velocity encoding: 150 cm/s; maximal number of heart phases dependent on heart rate (typically approximately 150 to 180 heart phases); temporal resolution: 5 ms.

For the brain MRI protocol, T1-weighted imaging was performed with the following typical parameters: 3-dimensional T1; spatial resolution: 1.0 × 1.0 × 1.0 mm; TR: 8.2 ms; TE: 4.5 ms. Furthermore, fluid attenuation inversion recovery images (spatial resolution: 1.11 × 1.11 × 1.11 mm; TR: 4,800 ms; TE: 313 ms; TI: 1,650 ms) and susceptibility-weighted imaging (spatial resolution: 0.8 × 0.8 × 1.6 mm; TR: 45 ms; TE: 31 ms) were performed.

IMAGE ANALYSIS. Cardiovascular. On short-axis cine images, LV end-diastolic endocardial and epicardial contours and end-systolic endocardial contours were defined by semiautomatic contours with manual correction to calculate LV end-diastolic and end-systolic volumes, LV ejection fraction, and LV (end-diastolic) mass. Papillary muscles were excluded from endocardial contours and included in the LV blood pool. LV end-diastolic myocardial volume was multiplied by 1.05 to calculate LV mass. To correct for the effect of body size, LV mass was divided by body surface area (DuBois & DuBois formula) to calculate LVMi. LV concentricity was assessed by LV mass-to-volume ratio, defined as LV mass divided by LV end-diastolic volume. Aortic PWV, reflecting aortic stiffness, was calculated as distance/transit time, where distance was defined as length of the aortic arch between imaging planes through the ascending and descending aorta, and transit time was defined as the time between pulse waves at the ascending and descending aorta by the foot-to-foot method. All analyses were performed on Mass version August 2017 (Medis medical imaging systems, Leiden, the Netherlands). LV and PWV analyses were performed separately, both by an experienced reader who was blinded to all other patient data.

Brain. Brain MRI markers of CSVD (white matter hyperintensities and lacunes of presumed vascular origin, microbleeds, and moderately to severely enlarged perivascular spaces in the basal ganglia) were visually scored on T1-weighted fluid attenuation inversion recovery and susceptibility-weighted images. White matter hyperintensities were graded by using the Fazekas scale (0 to 3). The Staals classification was used to determine presence of CSVD (defined as a Staals classification of >1, which consists of 1 or more of the following findings: white matter hyperintensities with Fazekas score >1; ≥1 microbleed; ≥1 lacunar infarct; and moderately to severely enlarged perivascular spaces in the

TABLE 1 Characteristics of the Study Participants

	All Participants (N = 559)	HF (n = 162)	VCI (n = 160)	COD (n = 109)	Control Participants (n = 128)
Age, yrs	67.8 ± 8.8	69.7 ± 10.0	68.8 ± 8.4	66.4 ± 8.0	65.6 ± 7.4
Female	200 (35.8)	54 (33.3)	61 (38.1)	25 (22.9)	60 (46.9)
Education, yrs	13.4 ± 4.4	13.2 ± 4.7	13.8 ± 4.2	12.3 ± 3.8	14.2 ± 4.4
Mini Mental State Exam score	29 (27-30)	29 (28-30)	28 (26-29)	28 (27-29)	29 (28-30)
Current smoking	91 (16.3)	24 (14.9)	29 (18.1)	30 (27.8)	8 (6.3)
Former smoking	318 (57.1)	91 (56.5)	92 (57.5)	72 (66.7)	63 (49.2)
Body mass index >25 kg/m^2	361 (65.0)	111 (69.4)	94 (59.1)	79 (73.2)	77 (44.5)
Waist-to-hip ratio, obese	430 (78.9)	129 (83.8)	121 (77.6)	97 (89.8)	83 (65.4)
Hypertension	315 (56.8)	86 (53.8)	115 (71.9)	81 (75.7)	33 (25.8)
Untreated hypertension	28 (8.9)	5 (5.8)	11 (9.6)	8 (9.9)	4 (12.1)
Hypercholesterolemia	311 (56.3)	75 (47.2)	106 (67.1)	92 (86.0)	38 (29.7)
Untreated hypercholesterolemia	37 (11.9)	8 (10.7)	15 (14.3)	4 (4.3)	10 (26.3)
Diabetes mellitus	82 (14.7)	29 (18.0)	19 (11.8)	31 (28.9)	3 (2.3)
Myocardial infarction	120 (21.6)	82 (50.9)	18 (11.3)	16 (15.0)	4 (3.1)
Percutaneous coronary intervention	107 (19.2)	62 (38.5)	17 (10.6)	22 (20.6)	6 (4.7)
Coronary artery bypass grafting	57 (10.3)	31 (19.3)	6 (3.8)	16 (15.0)	4 (3.1)
Transient ischemic attack	140 (25.2)	16 (9.9)	38 (23.9)	79 (73.8)	7 (5.5)
Cerebrovascular attack	130 (23.2)	9 (5.6)	66 (41.3)	55 (50.5)	0 (0.0)
Office systolic BP, mm Hg	142 ± 21	135 ± 19	142 ± 22	152 ± 22	143 ± 19
Office diastolic BP, mm Hg	80 ± 11	77 ± 11	81 ± 11	82 ± 12	82 ± 10
Office heart rate, beats/min	67 ± 11	65 ± 11	68 ± 11	69 ± 11	66 ± 11
Office Bp >140/90 mm Hg	305 (55.3)	68 (42.8)	88 (55.3)	78 (73.6)	71 (55.5)
Office Bp >130/80 mm Hg	440 (79.7)	110 (69.2)	127 (79.9)	97 (91.5)	106 (82.8)
Cardiac magnetic resonance					
LV end-diastolic volume, ml	161 (134-199)	206 (162-243)	147 (121-173)	160 (143-175)	151 (129-177)
LV end-systolic volume, ml	71 (53-100)	116 (85-154)	60 (48-79)	66 (52-79)	61 (49-74)
LV ejection fraction, %	55 (46-61)	43 (36-49)	58 (53-63)	58 (54-64)	59 (55-63)
LV mass, g	97 (79-117)	110 (88-128)	93 (74-109)	108 (91-123)	84 (71-103)
LV mass index, g/m^2	50 (43-58)	56 (47-64)	49 (41-54)	53 (46-62)	44 (39-50)
LV mass-to-volume ratio, g/ml	0.60 ± 0.12	0.55 ± 0.11	0.62 ± 0.10	0.69 ± 0.11	0.57 ± 0.09
Aortic pulse wave velocity, m/s	8.4 (6.8-10.8)	7.9 (6.2-10.2)	9.0 (7.3-11.1)	9.0 (7.5-12.1)	8.2 (6.3-10.4)

Values are mean ± SD, n (%), or median (interquartile range).
BP = blood pressure; COD = carotid occlusive disease; HF = heart failure; LV = left ventricular; VCI = vascular cognitive impairment.

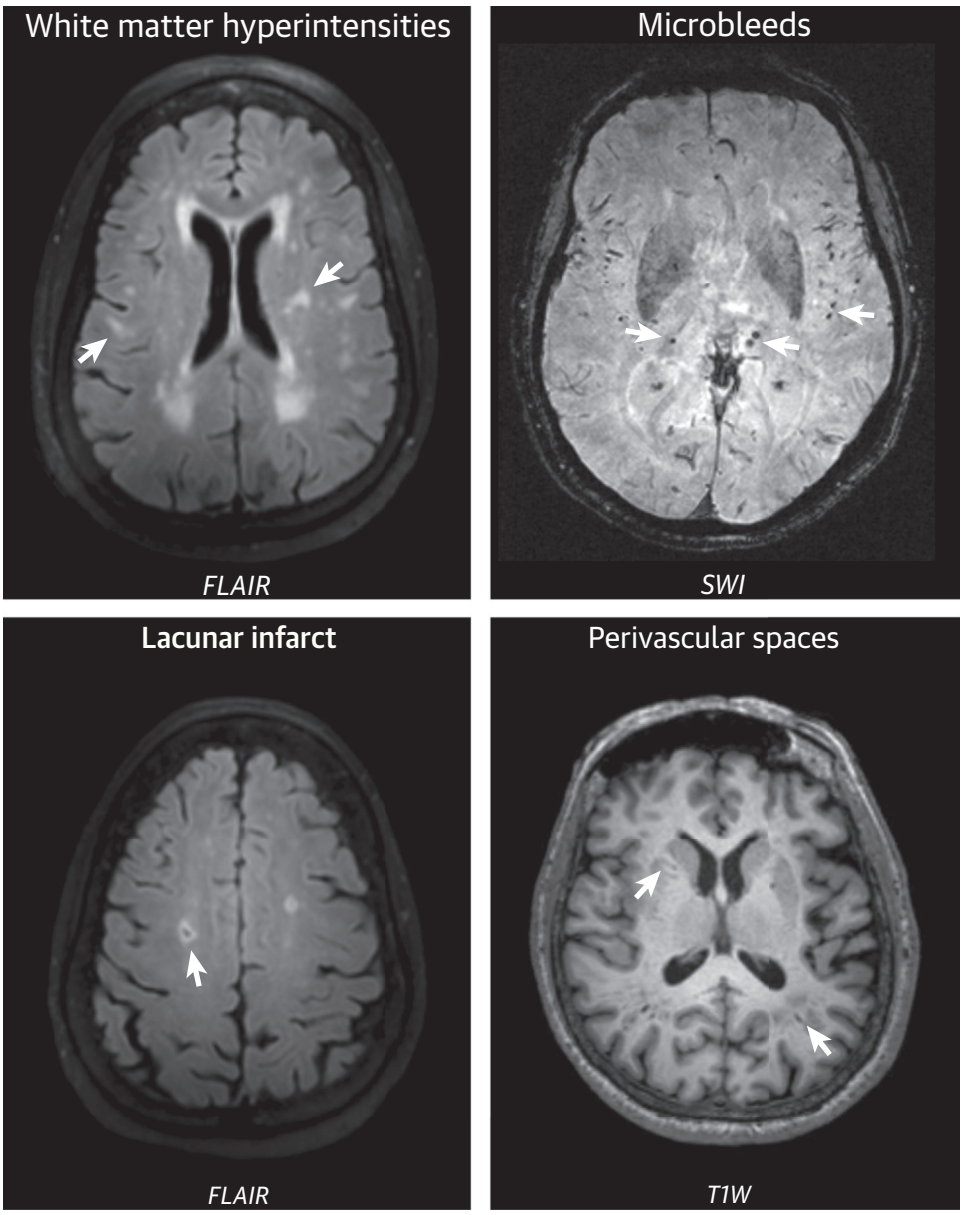
basal ganglia) (14). To minimize variation in the rating, all brain MRI markers of CSVD were scored by 1 neuroradiologist with 13 years of experience in CSVD imaging (J.B.), blinded to all patient data and following internationally accepted STRIVE (STandards for ReportIng Vascular changes on nEuroimaging) criteria and the standardized Staals classification (14,15).

NEUROPSYCHOLOGICAL TESTING. Participants underwent an extensive and standardized cognitive test battery based on the Dutch Parelsnoer Initiative (16), providing cognitive functioning in the following 4 major cognitive domains: memory, language, attention-psychomotor speed, and executive functioning. Cognitive test scores were transformed to *z*-scores with control participants as the reference and were corrected for age, sex, and years of education. Cognitive impairment was defined as *z*-score lower than -1.5 in ≥1 cognitive domain.

STATISTICAL METHODS. Continuous variables are presented as mean ± SD or median (interquartile range) as appropriate. Logistic regression analyses were performed to investigate the relations of hypertensive exposure markers with presence of CSVD and with cognitive impairment. All analyses concerning CSVD were adjusted for age, sex, and cardiac index; all analyses concerning cognitive impairment were adjusted for cardiac index (of note, cognitive test scores were calculated with correction for age, sex, and education). Odds ratios (ORs) for aortic PWV are reported per 1-m/s increment; for LVMi, per 10-g/m^2 increment; and for LV mass-to-volume ratio, per 0.10-g/ml increment. Two-sided p values of <0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics, version 22 (IBM, Armonk, NY).

Effect modification by patient group (HF, VCI, COD, or control) was assessed by interaction terms

FIGURE 1 **Examples of Cerebral Small Vessel Disease Visualized by Brain MRI**



The arrows indicate examples of white matter hyperintensities, microbleeds, lacunar infarct, and perivascular spaces as shown by brain MRI. FLAIR = fluid attenuation inversion recovery; MRI = magnetic resonance imaging; SWI = susceptibility-weighted imaging; T1W = T1 weighted.

for each analysis. Results are reported stratified in the case of significant effect modification ($p < 0.10$); otherwise, results are reported based on pooled data.

Causal mediation analysis was performed in R, version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) using Mediation Package, version 4.4.7 to assess whether the presence of CSVD mediates the relation between hypertensive exposure markers and cognitive impairment. Logistic regression models were used to regress the mediator (presence of CSVD; dichotomous) on X (hypertensive exposure markers; continuous) and to regress Y (cognitive impairment; dichotomous) on mediator and X. Mediation analyses were repeated, allowing for an interaction between X and the mediator.

TABLE 2 Prevalence of Cerebral Small Vessel Disease and Cognitive Impairment

	All Participants (N = 558)	HF (n = 162)	VCI (n = 160)	COD (n = 108)	Control Participants (n = 128)
Brain magnetic resonance					
Cerebral small vessel disease	351 (68.7)	87 (58.4)	132 (89.2)	75 (82.4)	57 (46.3)
White matter hyperintensities (Fazekas >1)	188 (36.9)	42 (28.4)	100 (67.6)	25 (27.8)	21 (17.1)
Microbleeds	130 (25.4)	35 (23.5)	55 (37.2)	21 (23.1)	19 (15.4)
Lacunar infarcts	181 (35.4)	42 (28.2)	74 (50.0)	53 (58.2)	12 (9.8)
Perivascular spaces	146 (28.6)	35 (23.5)	61 (41.2)	27 (29.7)	23 (18.7)
Cognitive impairment					
≥1 Cognitive domain impaired	149 (26.9)	28 (17.6)	72 (45.0)	38 (35.5)	11 (8.6)
≥1 Cognitive domain impaired with presence of cerebral small vessel disease	114 (22.4)	17 (11.6)	60 (40.5)	28 (30.8)	9 (7.3)
Memory impaired	92 (16.6)	16 (10.0)	55 (34.4)	19 (17.8)	2 (1.6)
Language impaired	26 (4.7)	5 (3.1)	16 (10.0)	4 (3.7)	1 (0.8)
Attention/speed impaired	71 (12.8)	8 (5.0)	36 (22.5)	22 (20.6)	5 (3.9)
Executive function impaired	32 (5.8)	4 (2.5)	20 (12.5)	5 (4.7)	3 (2.3)

Values are n (%).
Abbreviations as in Table 1.

RESULTS

Participants were, on average, 67.8 ± 8.8 years of age, and 35.8% of participants were female. Table 1 shows detailed characteristics for the total study population and per patient group.

Cardiovascular MRI data were available in 529 (94.6%) participants and brain MRI data in 558 (99.8%) participants. Examples of CSVD by brain MRI are shown in Figure 1. CSVD was detected in 68.7% of participants and cognitive impairment in ≥1 domain in 26.9% of participants (Table 2, Central Illustration).

HYPERTENSIVE EXPOSURE MARKERS IN RELATION TO BRAIN OUTCOME. Aortic PWV was associated with CSVD (OR: 1.17; 95% confidence interval [CI]: 1.05 to 1.30; p = 0.003) in patients with HF, VCI, and COD but not in control participants (Table 3). LVMi was associated with CSVD in all patient groups, although the relation was more prominent in patients with COD (OR: 5.69; 95% CI: 1.63 to 19.87; p = 0.006) compared to patients with HF, patients with VCI, and control participants (OR: 1.30; 95% CI: 1.05 to 1.62; p = 0.017). LV mass-to-volume ratio was significantly associated with CSVD in all participants (OR: 1.81; 95% CI: 1.46 to 2.24; p < 0.001).

Aortic PWV (OR: 1.07; 95% CI: 1.02 to 1.13; p = 0.009) and LV mass-to-volume ratio (OR: 1.27; 95% CI: 1.07 to 1.51; p = 0.007) were associated with cognitive impairment in ≥1 domain among all participants, whereas LVMi was not.

Relations of hypertensive exposure markers with CSVD and cognitive impairment showed no important change after additional correction for systolic BP. Correction for medical history of hypertension did not affect the relation of LVMi with CSVD in patients with COD (OR: 5.77; 95% CI: 1.63 to 20.39; p = 0.007) but attenuated the association of LVMi with CSVD in patients with HF, patients with VCI, and control participants (OR: 1.22; 95% CI: 0.99 to 1.50; p = 0.062). Relations of aortic PWV and LV mass-to-volume ratio with CSVD and with cognitive impairment were not affected by correction for medical history of hypertension.

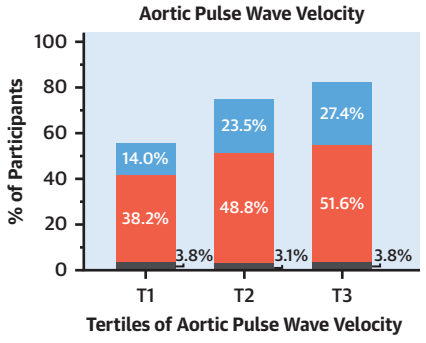
MEDIATION BY CSVD. Causal mediation analysis showed significant mediation by presence of CSVD for all 3 hypertensive exposure markers in relation to cognitive impairment (Central Illustration and Supplemental Table 1). In the relation between aortic PWV and cognitive impairment, 44.6% of the total effect was attributable to mediation by the presence of CSVD (p = 0.004). The mediation effect was 89.5% (p = 0.022) for LVMi and 59.0% (p < 0.001) for LV mass-to-volume ratio in their respective relations with cognitive impairment. Conclusions did not change when the possible interaction between hypertensive exposure markers and CSVD was taken into account.

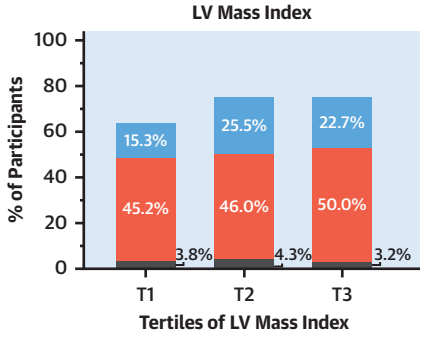
DISCUSSION

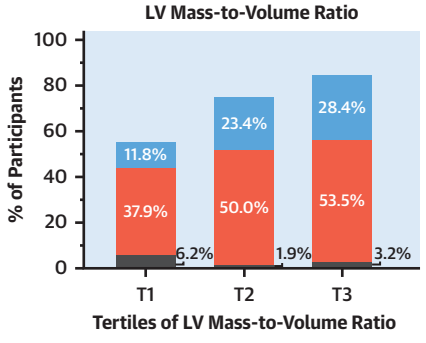
The main findings of this study are that hypertensive exposure markers by cardiovascular MRI are associated with presence of CSVD by brain MRI and with cognitive impairment in ≥1 domain and that the presence of CSVD is a significant mediator in the relation between hypertensive exposure and cognitive impairment. Aortic PWV, LVMi, and LV mass-to-volume ratio were all associated with CSVD—aortic

CENTRAL ILLUSTRATION **Hypertensive Exposure Markers by Cardiovascular Magentic Resonance Imaging in Relation to Cerebral Small Vessel Disease and Cognitive Impairment**

Increasing Rates of Cerebral Small Vessel Disease and Cognitive Impairment with Increase in Hypertensive Exposure Markers

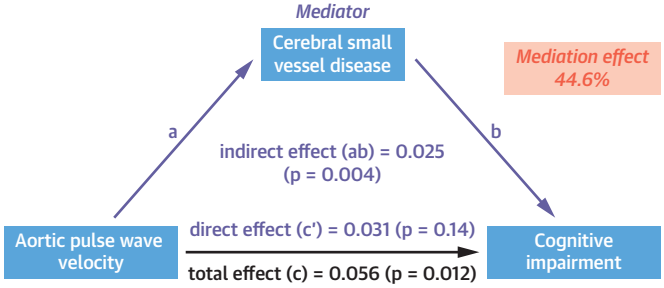


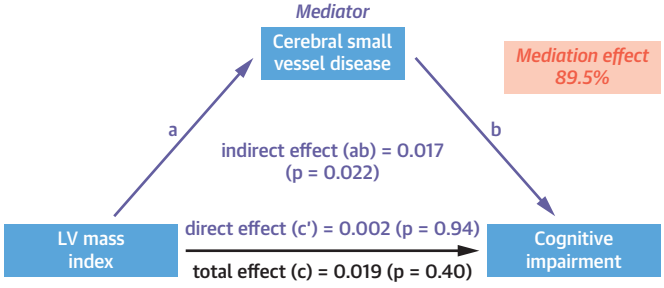


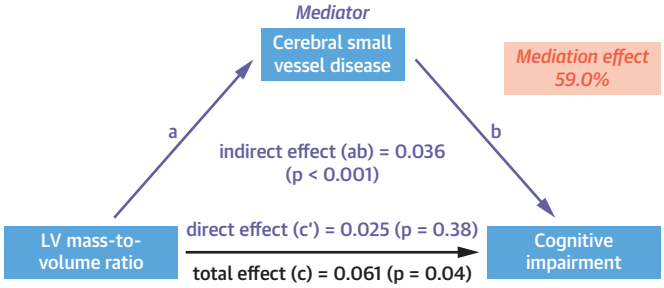


Cognitive Impairment with Cerebral Small Vessel Disease
Cerebral Small Vessel Disease Only
Cognitive Impairment Only

Significant Mediation by Cerebral Small Vessel Disease in the Relation Between Hypertensive Exposure Markers and Cognitive Impairment







Amier, R.P. et al. J Am Coll Cardiol Img. 2020;■(■):■-■.

The distribution of cerebral small vessel disease and cognitive impairment are shown for each hypertensive exposure marker. Causal mediation analysis is shown for cerebral small vessel disease as a mediator in the relation between hypertensive exposure markers and cognitive impairment. (Effects are risk differences resulting from change in hypertensive exposure marker from the 25th to 75th percentile). The mediation effect is the indirect effect expressed as a percentage of the total effect, that is, the proportion of the relation between the independent and dependent variables attributable to mediation. LV = left ventricular.

TABLE 3 Relations of Hypertensive Exposure Markers With Cerebral Small Vessel Disease and Cognitive Impairment

	Cerebral Small Vessel Disease			Cognitive Impairment		
	Stratification	OR (95% CI)	p Value	Stratification	OR (95% CI)	p Value
Aortic pulse wave velocity	Patients	1.17 (1.05–1.30)*†	0.003	–	1.07 (1.02–1.13)*†	0.009
	Control participants	0.94 (0.82–1.07)	0.33			
LV mass index	HF, VCI, control participants	1.30 (1.05–1.62)*	0.017	Patients	1.00 (0.98–1.01)	0.78
	COD	5.69 (1.63–19.87)*†	0.006	Control participants	0.49 (0.19–1.23)	0.13
LV mass-to-volume ratio	–	1.81 (1.46–2.24)*†	<0.001	–	1.27 (1.07–1.51)*†	0.007
Systolic blood pressure	–	1.01 (1.00–1.03)	0.012	–	1.00 (0.99–1.01)	0.477
Medical history of hypertension	–	3.28 (2.15–5.02)	<0.001	–	1.57 (1.04–2.38)	0.031

Cerebral small vessel disease is corrected for age, sex, and cardiac index; cognitive impairment is corrected for age, sex, education, and cardiac index. Results are reported as stratified or pooled according to interaction terms for patient group (see Statistical Methods). *Remained significant after additional correction for systolic blood pressure. †Remained significant after additional correction for medical history of hypertension.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

PWV only in patients with cardiovascular disease and LVMi and LV mass-to-volume ratio in all participants. Both aortic PWV and LV mass-to-volume ratio were also associated with cognitive impairment in all participants. The relations of hypertensive exposure markers with poorer brain health largely persisted after correction for either systolic BP or medical history of hypertension. These findings indicate that the impact of hypertension on brain structure and function is not an on/off phenomenon but, rather, a sliding scale, where an increasing extent of hypertensive exposure (i.e., severity and/or duration of hypertension) is related to higher rates of CSVD and cognitive impairment. Moreover, although no temporal relations can be assumed from this cross-sectional study, causal mediation analysis supports the hypothesis that hypertensive exposure may lead to CSVD, which, in turn, may lead to cognitive impairment.

Compared to previous studies, important strengths of our study are the assessment of multiple hypertensive exposure markers; use of optimal imaging modalities for both cardiovascular remodeling and vascular brain injury assessment; high-resolution brain MRI, allowing more sensitive detection of CSVD; and comprehensive assessment of cognitive functioning. Our results are largely in line with those of previous studies. LVMi by echocardiography or cardiovascular MRI has been linked to declining white matter microstructural integrity, white matter hyperintensities, poorer cognitive functioning, and incident dementia (17–21). LV mass-to-volume ratio was included in 1 previous study and was related to poorer cognitive functioning and incident dementia in a geriatric population (20). To our knowledge, no other data are yet available on LV-mass-to-volume ratio in relation to vascular brain injury. Aortic PWV by cardiovascular MRI has been linked to white matter hyperintensities and, in patients with hypertension, to lacunar infarcts as well (22–24). Vascular applanation tonometry-based measures of global PWV (carotid-femoral or brachial-ankle) have repeatedly been linked to white matter hyperintensities and lower cognitive performance in the general population, elderly individuals, and patients with hypertension (25–30). Carotid-femoral PWV also indicated higher a risk of conversion to dementia in elderly patients with mild cognitive impairment, during a mean follow-up of 4.5 years (31).

Although LVMi and LV mass-to-volume ratio are both thought to reflect cardiac remodeling in response to hypertension, LVMi was not related to cognitive impairment, and the relation with CSVD was less robust (i.e., independent of medical history of hypertension only in patients with COD). One previous study in elderly cardiac outpatients found no significant relation of LVMi with cognitive performance, and other studies have reported conflicting results on whether this relation was independent of BP (19–21,32). LVMi is a structural parameter, whereas LV mass-to-volume ratio is a geometric parameter indicating an increase in LV mass relative to LV dimensions. Because the total amount of myocardium will also increase with general cardiac enlargement for reasons unrelated to hypertensive exposure, LVMi may become less specific for hypertensive exposure in populations with higher rates of manifest cardiovascular disease. LV mass-to-volume ratio can, however, indicate relative hypertrophy even in dilated LVs and may therefore be more suited for application in a clinical setting.

Increasing evidence is showing that the impact of hypertension on the brain is broader than previously recognized and involves subclinical repetitive microinjuries that may contribute to cognitive

impairment over time (33,34). Whether specific patient populations with higher cardiovascular disease burden could benefit from more intensive BP management (e.g., <120 mm Hg target systolic BP) is yet to be determined, although the ACCORD (Action to Control Cardiovascular Risk in Diabetes), SPRINT (Systolic Blood Pressure Intervention Trial), and INFINITY (Intensive Versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline In the Elderly) trials have shown promising effects on reducing the progression of vascular brain injury, with varying effects on cognitive functioning (35–39). The results of our study also suggest that chronicity of inadequate BP control may be an important factor in the relation between hypertension and poorer brain health.

Clinical awareness of the vascular vulnerability of the brain may be warranted, especially in elderly patients and those with high cardiovascular disease burden. When cerebral homeostatic mechanisms are compromised, regulating BP may become a delicate balance of reducing potential harm by increased pressure/pulsatility while preventing episodes of low-grade ischemia. This increasing complexity within individual patients will likely require multidisciplinary approaches for optimal evaluation and management, in which cardiovascular imaging markers may contribute to more accurate detection of those most vulnerable to vascular brain injury and cognitive impairment attributable to hypertension.

STUDY LIMITATIONS. The cross-sectional nature of our study allows the investigation of only associations.

The Heart-Brain Connection Study included several patient populations with specific manifestations of cardiovascular disease and was not specifically designed to investigate hypertension. Therefore, possible effect modification by patient group was checked for in each analysis to ensure that associations were similar across all groups before pooling data and to ensure that associations were not driven by 1 specific patient group. Finally, although none of our participants had a medical history of hypertrophic cardiomyopathy, aortic valve stenosis, sarcoidosis, or amyloidosis, it should be noted that considering LVMi and LV mass-to-volume ratio as markers of hypertensive exposure is only appropriate in absence of a primary cardiac cause of hypertrophy.

CONCLUSIONS

The extent of hypertensive exposure assessed by cardiovascular MRI is associated with higher rates of CSVD and cognitive impairment in patients with cardiovascular disease and control individuals. A substantial proportion of the relation between hypertensive exposure markers and cognitive impairment may be attributable to the presence of CSVD, as suggested by causal mediation analysis. These findings also suggest that cardiovascular imaging markers of hypertensive exposure may be useful to detect those most vulnerable to vascular brain injury and cognitive impairment related to hypertension.

AUTHOR RELATIONSHIP WITH INDUSTRY

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Hypertensive disease involves subclinical, repetitive cerebrovascular microinjuries that may cause cognitive impairment over time.

COMPETENCY IN PATIENT CARE: Clinical awareness of vascular vulnerability of the brain is warranted, especially in elderly patients and in those with high cardiovascular disease burden.

TRANSLATIONAL OUTLOOK 1: When cerebral homeostatic mechanisms are compromised by the presence of cerebral small vessel disease, regulating blood pressure may become a delicate balance of reducing further harm by high blood pressure while preventing episodes of low-grade ischemia.

TRANSLATIONAL OUTLOOK 2: Longitudinal cohort studies should investigate the temporal relations of vascular brain injury and cognitive impairment to further investigate the complex causal mechanisms.

REFERENCES

1. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke 2011;42:2672–713.

2. Gardener H, Wright CB, Rundek T, Sacco RL. Brain health and shared risk factors for dementia and stroke. Nat Rev Neurol 2015;11:651–7.

3. Mensah GA, Wei GS, Sorlie PD, et al. Decline in cardiovascular mortality: possible causes and implications. Circ Res 2017;120:366–80.

4. Mok V, Kim JS. Prevention and management of cerebral small vessel disease. J Stroke 2015;17:111–22.

5. Suzuki H, Gao H, Bai W, et al. Abnormal brain white matter microstructure is associated with both pre-hypertension and hypertension. PLoS One 2017;12:e0187600.

6. McGrath ER, Beiser AS, DeCarli C, et al. Blood pressure from mid- to late life and risk of incident dementia. Neurology 2017;89:2447–54.

7. Power MC, Tingle JV, Reid RI, et al. Midlife and late-life vascular risk factors and white matter microstructural integrity: the Atherosclerosis Risk in Communities neurocognitive study. J Am Heart Assoc 2017;6:e005608.

8. Caplan LR. Lacunar infarction and small vessel disease: pathology and pathophysiology. J Stroke 2015;17:2–6.

9. Shi Y, Wardlaw JM. Update on cerebral small vessel disease: a dynamic whole-brain disease. Stroke Vasc Neurol 2016;1:83–92.

10. de Roos A, van der Grond J, Mitchell G, Westenberg J. Magnetic resonance imaging of cardiovascular function and the brain: is dementia a cardiovascular-driven disease? Circulation 2017;135:2178–95.

11. Hooghiemstra AM, Bertens AS, Leeuwis AE, et al. The missing link in the pathophysiology of vascular cognitive impairment: design of the Heart-Brain Study. Cerebrovasc Dis Extra 2017;7:140–52.

12. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

13. World Health Organization. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation. Geneva, Switzerland: World Health Organization; 2008.

14. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. Neurology 2014;83:1228–34.

15. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–38.

16. Aalten P, Ramakers IH, Biessels GJ, et al. The Dutch Parelsnoer Institute—neurodegenerative diseases; methods, design and baseline results. BMC Neurol 2014;14:254.

17. Moore EE, Liu D, Pechman KR, et al. Increased left ventricular mass index is associated with compromised white matter microstructure among older adults. J Am Heart Assoc 2018;7:e009041.

18. Haring B, Omidpanah A, Suchy-Dicey AM, et al. Left ventricular mass, brain magnetic resonance imaging, and cognitive performance: results from the Strong Heart Study. Hypertension 2017;70:964–71.

19. Scuteri A, Coluccia R, Castello L, Nevola E, Brancati AM, Volpe M. Left ventricular mass increase is associated with cognitive decline and dementia in the elderly independently of blood pressure. Eur Heart J 2009;30:1525–9.

20. Moazzami K, Ostovaneh MR, Ambale Venkatesh B, et al. Left ventricular hypertrophy and remodeling and risk of cognitive impairment and dementia: MESA (Multi-Ethnic Study of Atherosclerosis). Hypertension 2018;71:429–36.

21. Elias MF, Sullivan LM, Elias PK, et al. Left ventricular mass, blood pressure, and lowered cognitive performance in the Framingham offspring. Hypertension 2007;49:439–45.

22. Brandts A, van Elderen SG, Westenberg JJ, et al. Association of aortic arch pulse wave velocity with left ventricular mass and lacunar brain infarcts in hypertensive patients: assessment with MR imaging. Radiology 2009;253:681–8.

23. Sala M, van den Berg-Huysmans A, van der Grond J, et al. Aortic arch stiffness is associated with incipient brain injury in patients with hypertension. Am J Hypertens 2016;29:705–12.

24. King KS, Chen KX, Hulsey KM, et al. White matter hyperintensities: use of aortic arch pulse wave velocity to predict volume independent of other cardiovascular risk factors. Radiology 2013;267:709–17.

25. Hughes TM, Wagenknecht LE, Craft S, et al. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET study. Neurology 2018;90:e1248–56.

26. Rosano C, Watson N, Chang Y, et al. Aortic pulse wave velocity predicts focal white matter hyperintensities in a biracial cohort of older adults. Hypertension 2013;61:160–5.

27. Triantafyllidi H, Tzortzis S, Lekakis J, et al. Association of target organ damage with three arterial stiffness indexes according to blood pressure dipping status in untreated hypertensive patients. Am J Hypertens 2010;23:1265–72.

28. Cui C, Sekikawa A, Kuller LH, et al. Aortic stiffness is associated with increased risk of incident dementia in older adults. J Alzheimers Dis 2018;66:297–306.

29. Muela HC, Costa-Hong VA, Yassuda MS, et al. Hypertension severity is associated with impaired cognitive performance. J Am Heart Assoc 2017;6:e004579.

30. Iulita MF, Noriega de la Colina A, Girouard H. Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? J Neurochem 2018;144:527–48.

31. Rouch L, Cestac P, Sallerin B, et al. Pulse wave velocity is associated with greater risk of dementia in mild cognitive impairment patients. Hypertension 2018;72:1109–16.

32. Eggermont LHP, Aly MFA, Vuijk PJ, et al. Cardiac function and cognition in older community-dwelling cardiac patients. Psychogeriatrics 2017;17:356–63.

33. Liao D, Cooper L, Cai J, et al. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control. The ARIC Study. Atherosclerosis Risk in Communities study. Stroke 1996;27:2262–70.

34. Basile AM, Pantoni L, Pracucci G, et al. Age, hypertension, and lacunar stroke are the major determinants of the severity of age-related white matter changes. The LADIS (Leukoaraiosis and Disability in the Elderly) study. Cerebrovasc Dis 2006;21:315–22.

35. de Havenon A, Majersik JJ, Tirschwell DL, McNally JS, Stoddard G, Rost NS. Blood pressure, glycemic control, and white matter hyperintensity progression in type 2 diabetics. Neurology 2019;92:e1168–75.

36. Sprint Mind Investigators for the SPRINT Research Group, Nasrallah IM, Pajewski NM, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. JAMA 2019;322:524–34.

37. White WB, Wakefield DB, Moscufo N, et al. Effects of intensive versus standard ambulatory blood pressure control on cerebrovascular outcomes in older people (INFINITY). Circulation 2019;140:1626–35.

38. Sprint Mind Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA 2019;321:553–61.

39. Williamson JD, Launer LJ, Bryan RN, et al. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. JAMA Intern Med 2014;174:324–33.

KEY WORDS cognition, left ventricular mass, left ventricular mass-to-volume ratio, pulse wave velocity, vascular brain injury

APPENDIX For a supplemental table, please see the online version of this paper.