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ORIGINAL ARTICLE
Hypertension and Circulatory Control

Septal E/e′ Ratio Is Associated With Cerebral White Matter Hyperintensity Progression in Young-Old Hypertensive Patients

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Background: The incidence of hypertension increases with age, as does that of brain abnormalities associated with cerebral pathologic and functional degeneration. Little is known about the relationship between hypertension-related cardiac changes and cerebral pathologic degeneration. We examined the relationship between left ventricular (LV) diastolic dysfunction and cerebral white matter hyperintensity (WMH) progression in young-old hypertensive patients.

Methods and Results: This single-center prospective longitudinal observational study included 156 individuals aged 65–75 years with well-controlled hypertension, normal LV contraction, and no history of symptomatic heart failure. WMH was quantified on brain magnetic resonance imaging (MRI). The primary outcome was the rate of WMH volume progression between the baseline and follow-up MRI (ΔWMH). Participants were classified into tertiles on the basis of ΔWMH (small, medium, and large ΔWMH). The mean (±SD) age at recruitment was 69.6±2.8 years, and the mean follow-up period was 4.6 years. The ratio of early diastolic mitral inflow velocity to early diastolic septal mitral annulus velocity (septal E/e′) was significantly higher in the large ΔWMH group than in the small and medium ΔWMH groups. On multiple regression analysis, septal E/e′ was significantly positively associated with square-root-transformed ΔWMH (β=0.457, P<0.001).

Conclusions: Septal E/e′ was significantly positively associated with the rate of progression of WMH volume, suggesting that LV diastolic dysfunction is associated with the progression of abnormal brain aging.

Key Words: Abnormal brain aging; Cerebral white matter hyperintensity; Hypertension; Left ventricular diastolic dysfunction; Longitudinal study

Hypertension is a chronic cardiovascular disease that affects the largest number of patients of any disease, with a prevalence that is still rising. Hypertension is also an important cause of death and disability.[1] Hypertension is the risk factor that has been shown to have the strongest association with cerebral white matter hyperintensity (WMH).[2–4] Cerebral WMH on brain magnetic resonance imaging (MRI) is a prevalent aging-related phenomenon that has been implicated in various medical complications.[5–9] Major pathomechanisms underlying WMH progression include chronic hypoperfusion of the brain parenchyma,[10] disruption of the blood-brain barrier,[11] and dysfunction of the perivascular metabolite clearance system,[12] all of which are pathomechanistically related to reduced pulsation of the cerebral arterioles.[13,14]

Previously, our group reported that left ventricular (LV) diastolic dysfunction, even without heart failure (HF), is associated with WMH, which, in turn, has been shown to be closely associated with cognitive decline in elderly patients without ischemic heart disease or stroke.[15] Similarly, Kokubo et al reported that higher night-time systolic blood pressure (BP) levels contribute to greater WMH volumes in older adults with hypertension.[16] However, both these studies were cross-sectional and did not investigate the

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changes in WMH in longitudinal follow-up. Lee et al reported an association between LV diastolic dysfunction and the rate of WMH progression in individuals aged ≥50 years with preserved LV ejection fraction (LVEF).[17] However, so far there is little information about the relationship between WMH progression and cardiac diastolic dysfunction in young-old (age 65–74 years) hypertensive patients.

Thus, we performed what is, to the best of our knowledge, the first longitudinal study on the association between LV diastolic dysfunction and abnormal brain aging, with a focus on the progression of cerebral WMH in young-old hypertensive patients without HF.

Methods

Study Design

This was a single-center prospective longitudinal observational study. The enrollment period was from April 2015 to June 2020. The participants were outpatients aged 65–75 years who were routinely visiting the Department of Cardiology at the National Center for Geriatrics and Gerontology for antihypertensive treatment. Of these patients, those with symptomatic HF, ischemic heart disease, valvular heart disease, atrial fibrillation, stroke, or neurodegenerative disease, as well as those clinically diagnosed with dementia, were excluded. To further exclude patients with a history of myocardial infarction, angina pectoris, and stroke, we used a combination of patient self-declarations, a World Health Organization questionnaire on chest pain,[18] and 12-lead electrocardiography during exercise. The age, sex, height, and weight of each participant were recorded. Blood tests (plasma B-type natriuretic peptide [BNP] concentrations, serum creatinine concentrations, HbA1c, and low-density lipoprotein cholesterol [LDL-C]) and other tests (brain MRI, 24-h ambulatory BP monitoring, carotid duplex ultrasound for measurement of intima-media thickness, brachial-ankle pulse wave velocity, echocardiography, and Mini-Mental State Examination [MMSE]) were performed within 1 month of enrollment.

Patients with hypertension were defined as those already receiving routine antihypertensive treatment; patients with diabetes were defined as those either already receiving routine antidiabetic treatment or with an HbA1c level ≥6.5%. Similarly, patients with hyperlipidemia were defined as those either already receiving routine treatment for hyperlipidemia or with an LDL-C concentration ≥140 mg/dL.

We also excluded patients with an LVEF of ≤50% or an LV end-diastolic volume index of ≥97 mL/m^2 on echocardiography; patients with major brain infarction resulting from major cerebral artery lesions detected on brain MRI; patients with carotid artery stenosis of ≥50% on 2-dimensional and Doppler ultrasonography; and patients with cognitive dysfunction (MMSE score <24).

The study protocol was approved by the Ethics and Conflicts of Interest Committee at the National Center for Geriatrics and Gerontology (Reference no. 1272). The study protocol complied with the Declaration of Helsinki. Written informed consent was obtained from all individuals before their participation in the study.

Neuroimaging Studies

Brain MRI was used to quantify WMH volume. A standard series of axial T_1-weighted MRI sequences (repetition time [TR] 485 ms; echo time [TE] 11 ms), T_2-weighted sequences (TR 3,800 ms; TE 93 ms), and fluid-attenuated inversion recovery (FLAIR) sequences (TR 8,000 ms; TE 101 ms; inversion time 2,500 ms; matrix 256×256) were obtained by using a 1.5-T MR system (Avanto; Siemens, Erlangen, Germany). Scans were performed parallel to the anterior commissure-posterior commissure line, with 6-mm slices and an interslice gap of 1.2 mm. MRI data were processed to measure the total volumes of the intracranial space, the parenchyma, ventricles, and WMH by using a fully automatic segmentation program (Software for Neuro-Image Processing in Experimental Research [SNIPER]) developed by the Department of Radiology at Leiden University Medical Center (Leiden, Netherlands). Detailed procedures for MRI post-processing using SNIPER have been described elsewhere.[19]

Echocardiographic Examination

Echocardiography was performed by using an ACUSON SC2000 volume imaging ultrasound system (Siemens Medical Solutions, Tokyo, Japan). All measurements were performed by 2 experienced cardiac sonographers. A 2-dimensional echocardiographic examination was performed by skilled echocardiographers using commercially available echocardiography devices with a 2.5-MHz transducer and a standard multifrequency probe, with comprehensive LV measurements made in the M-mode in the parasternal long-axis view in accordance with a standardized protocol. To determine septal E/e′, pulse-wave tissue Doppler echocardiography was applied to the apical 4-chamber view at the septal mitral annulus. The ratio of early diastolic mitral inflow velocity (E) to early diastolic mitral annulus velocity (e′) of the septum has been identified as a useful index of the existence of LV diastolic dysfunction.[20] Septal E/e′ has been proven to reflect the diastolic LV filling pressure.[21,22] The left atrial maximum volume was calculated by using the biplane disk summation method. We also used e′, the left atrial volume index, and the tricuspid valve regurgitation flow velocity as variables to estimate LV diastolic function. LVEF was also measured.[22] This method of LV diastolic function classification was based on the 2016 recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[23]

Statistical Analysis

Data are presented as the mean±SD, unless stated otherwise. Continuous variables were compared among groups using 1-way analysis of variance followed by Scheffé's test. The Chi-squared test was used to assess the significance of differences between dichotomous variables. Pearson's or Spearman's rank correlation analysis was used to measure correlations between continuous variables and the rate of WMH progression. Variables with $P<0.10$ in correlation analyses were included in subsequent multivariate linear regression analysis by using a backward elimination method. To obtain a normal distribution of the dependent variable, the rate of WMH progression (ΔWMH; mL/year) was square root transformed. Then, to investigate the factors related to ΔWMH, a multivariate analysis was performed after adjustment for age, sex, E/e′, WMH, LDL-C, and total systolic BP, using ΔWMH as an independent variable. To access multicollinearity between variables, the variance inflation factor was measured, with a value of >3.00 indicating significant collinearity. All analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). P values two-tailed was considered statistically significant.

Table 1. Baseline Characteristics in All Patients and According to White Matter Hyperintensity Progression Rate Tertile

	Total (n=156)	ΔWMH tertile		
		Small (n=52)	Medium (n=52)	Large (n=52)
Age (years)	69.6±2.8	69.6±3.0	69.1±2.6	70.0±2.9
Male sex	72 (46.7)	27 (51.9)	25 (48.1)	20 (38.5)
BMI (kg/m²)	23.7±3.3	23.5±2.9	24.1±3.8	23.4±3.2
MMSE score	28.4±1.7	28.8±1.4	28.4±1.6	28.1±2.0
Diabetes	30 (19.2)	6 (11.5)	11 (21.2)	13 (25.0)
Dyslipidemia	93 (59.6)	30 (57.7)	27 (51.9)	36 (69.2)
Drug therapy				
ACEI/ARB	101 (64.7)	33 (63.5)	35 (67.3)	33 (63.5)
CCB	102 (65.4)	34 (65.4)	31 (59.6)	37 (71.2)
β-blocker	49 (31.4)	15 (28.8)	19 (36.5)	15 (28.8)
Diuretic	33 (21.2)	11 (21.2)	14 (26.9)	8 (15.4)
Spironolactone	6 (3.8)	2 (3.8)	3 (5.8)	1 (1.9)
Statin	89 (67.4)	27 (51.9)	30 (57.7)	32 (61.5)
No. antihypertensive medications 1/2/3/4	66/56/24/10	24/18/6/4	23/14/10/5	19/23/7/2
Brain MRI				
Baseline WMH (mL)	5.43±6.86	2.83±2.7	3.77±4.2	9.69±9.5*,†
Median [IQR]	2.96 [1.42–6.35]	1.79 [1.01–3.57]	2.55 [1.27–4.86]	6.22 [4.12–11.80]
WMH volume change (mL)	2.71±3.70	0.16±0.15	1.43±0.56*	6.52±4.26*,†
Median [IQR]	1.40 [0.29–3.54]	0.12 [0.03–0.29]	1.40 [0.90–1.87]	5.49 [3.48–8.04]
WMH progression rate (mL/year)	0.60±0.82	0.04±0.03	0.31±0.12*	1.45±0.93*,†
Median [IQR]	0.31 [0.07–0.79]	0.03 [0.06–0.07]	0.31 [0.20–0.41]	1.17 [0.78–1.74]
Square root ΔWMH (mL/year)	0.62±0.46	0.16±0.10	0.55±0.11*	1.16±0.34*,†
Median [IQR]	0.55 [0.26–0.89]	0.17 [0.08–0.26]	0.55 [0.45–0.64]	1.08 [0.88–1.32]
24-h ABPM data				
Total SBP (mmHg)	129.4±11.9	127.1±12.4	130.1±11.8	131.1±11.5
Total DBP (mmHg)	76.1±6.6	75.4±7.2	76.7±6.6	76.2±5.9
Daytime SBP (mmHg)	131.0±17.8	128.3±18.9	131.2±21.3	133.6±11.6
Daytime DBP (mmHg)	77.9±8.8	78.0±7.3	77.8±12.0	78.0±6.3
Night-time SBP (mmHg)	118.6±14.6	115.3±13.7	119.9±13.3	120.8±16.2
Night-time DBP (mmHg)	68.8±7.9	67.4±7.7	69.6±8.3	69.3±7.6
Laboratory measurements				
BNP (pg/mL)	25.4±24.5	23.2±20.7	26.1±27.4	26.8±25.2
eGFR (mL/min/1.73 m²)	68.5±14.3	67.7±14.2	69.1±15.1	68.6±13.8
HbA1c (%)	6.0±0.7	5.9±0.8	6.0±0.7	5.9±0.6
LDL-C (mg/dL)	109.6±20.6	110.6±17.0	113.3±21.3	104.9±22.4
Echocardiographic data				
LVEF (%)	66.3±4.5	66.4±4.3	66.4±4.6	66.1±4.7
Septal E/e′	10.6±2.5	9.3±1.57	9.9±2.56	12.5±1.95*,†
e′ (cm/s)	6.5±1.6	7.1±1.5	7.0±1.7	5.5±1.0*,†
TR flow (cm/s)	220.0±37.5	225.7±26.5	210.0±52.5	224.3±25.6
LAVI (mL/m²)	25.5±4.6	25.8±4.9	25.1±4.2	25.6±4.9
E/A	0.80±0.19	0.78±0.18	0.80±0.19	0.81±0.20
DT (ms)	0.24±0.07	0.24±0.07	0.24±0.08	0.24±0.06
RWT	0.41±0.05	0.41±0.05	0.42±0.05	0.41±0.05
Total LVMI (g/m²)	83.2±17.8	83.9±16.3	81.5±17.9	84.1±19.3
Carotid artery ultrasound				
IMT (mm)	1.1±0.4	1.0±0.3	1.2±0.5	1.2±0.4
Pulse wave velocity				
baPWV (m/s)	1,741±294	1,724±321	1,726±290	1,772±271

Small: (0.16×10^{-3}–0.12 mL/year), Medium: (0.13–0.53 mL/year), Large (0.54–4.91 mL/year) ΔWMH groups (tertiles), respectively. Unless indicated otherwise, data are given as the mean±SD or n (%). *P<0.05 compared with small ΔWMH; †P<0.05 compared with medium ΔWMH. A, atrial filling velocity; ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; DBP, diastolic blood pressure; DT, deceleration time; E, early diastolic mitral inflow velocity; e′, early diastolic mitral annular tissue velocity; eGFR, estimated glomerular filtration rate; IMT, intima-media thickness; IQR, interquartile range; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; RWT, relative wall thickness; SBP, systolic blood pressure; TR, tricuspid regurgitation; WMH, cerebral white matter hyperintensity; ΔWMH, rate of progression of WMH.

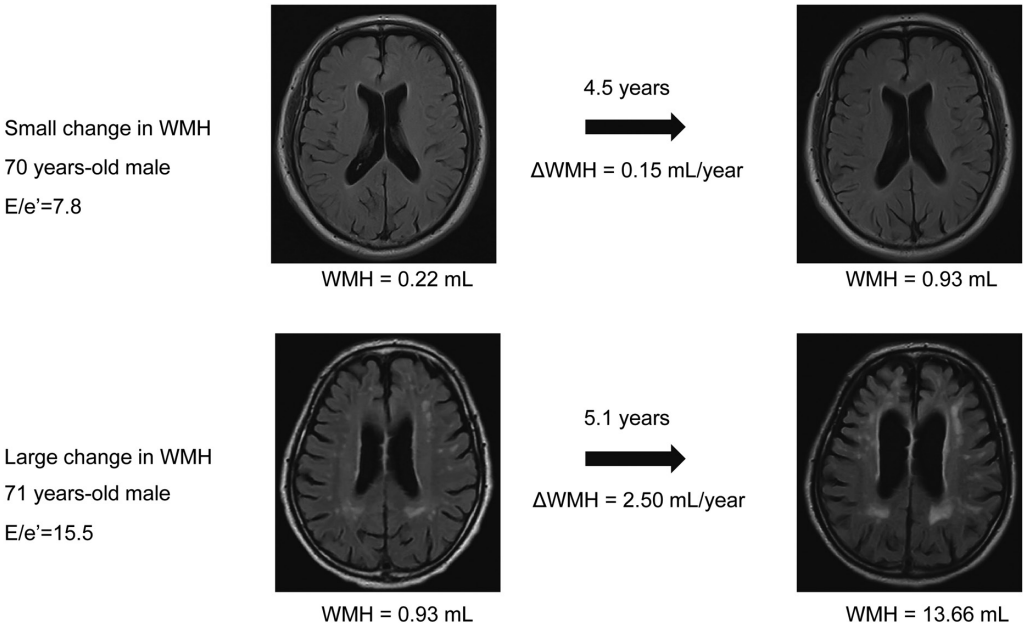

Figure 1. Representative magnetic resonance images of white matter hyperintensity (WMH) showing small (**Top**) and large (**Bottom**) changes in WMH.

Results

Baseline Clinical Characteristics

Baseline clinical characteristics for all patients, as well as for the small (0.16×10^{-3}–0.12 mL/year), medium (0.13–0.53 mL/year), and large (0.54–4.91 mL/year) ΔWMH groups (tertiles) separately, are presented in **Table 1**. There were significant differences in the change in WMH volume from baseline among the ΔWMH tertiles, with that in the large ΔWMH group being significantly larger than in the small or medium ΔWMH groups. The study enrolled 156 consecutive young-old patients (age 65–75 years) with hypertension (72 [46.7%] men; mean age 69.6±2.8 years), and the mean follow-up period was 4.6±1.1 years. The mean plasma BNP concentration was 25.4±24.5 pg/mL, mean LVEF was 66.3±4.5%, and the mean total systolic BP by 24-h ambulatory BP monitoring was 129.4±11.9 mmHg. Representative magnetic resonance images of changes in WMH in 2 patients are shown in **Figure 1**; the upper and lower panels are representative of small and large increases in WMH, respectively.

Comparisons Among Small, Medium, and Large ΔWMH Groups

Age, sex, body mass index, and MMSE score were comparable among the 3 groups. Antihypertensive medication use, BP, and laboratory measurements (including BNP, intima-media thickness, and brachial-ankle pulse wave velocity) were also comparable among the 3 groups (**Table 1**). On echocardiography, with the exception of E/e′ and e′, there were no significant differences among the 3 groups. E/e′ was significantly higher and e′ was significantly lower in the large ΔWMH group than in the small and medium ΔWMH groups (both P<0.05; **Table 1**; **Figure 2**). There were no significant differences among the 3 groups in the other parameters.

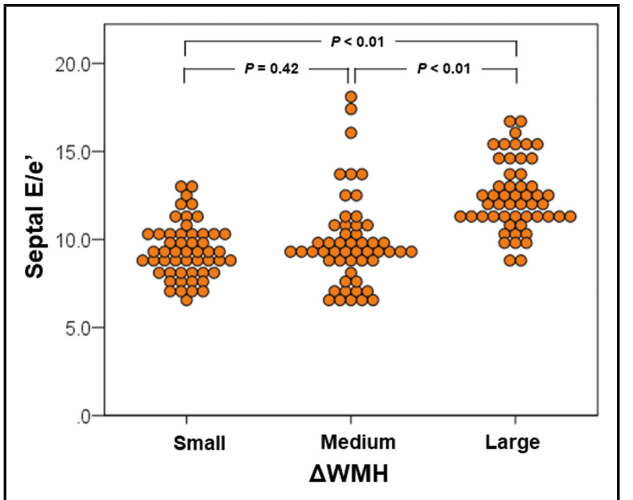

Figure 2. Septal E/e′ according to ΔWMH tertile {small (0.16×10^{-3}–0.12 mL/year), medium (0.13–0.53 mL/year), and large (0.54–4.91 mL/year)} of the white matter hyperintensity progression rate. E, early diastolic mitral inflow velocity; e′, early diastolic mitral annular tissue velocity.

Rate of Increase in Cerebral WMH Volume

Correlation analyses revealed that the rate of WMH progression was significantly correlated with baseline WMH volume and E/e′ (**Table 2**). In the subsequent multivariate linear regression analysis, E/e′ was significantly associated with the square-root-transformed WMH progression rate (β=0.457; 95% confidence interval 0.063–0.108; P<0.001) after adjustment for age, sex, LDL-C, and total systolic BP

Table 2. Correlations Between Clinical Variables and White Matter Hyperintensity Progression Rate

	r	P value
Age	0.065	0.417
Male sex	−0.122	0.122
BMI	−0.021	0.790
MMSE	−0.141	0.125
Baseline WMH volume	0.500*	<0.001*
Total SBP	0.132*	0.098*
Total DBP	0.056	0.489
BNP	0.056	0.485
eGFR	−0.007	0.930
HbA1c	−0.020	0.803
LDL-C	−0.141*	0.080*
LVEF	−0.019	0.216
Septal E/e′	0.584*	<0.001*
TR flow	0.045	0.580
LAVI	−0.026	0.749
E/A	0.065	0.420
DT	−0.008	0.918
RWT	−0.030	0.121
Total LVMI	−0.026	0.749
IMT	0.097	0.230
baPWV	0.068	0.400

*Significant associations. Abbreviations as in Table 1.

(**Table 3**). We plotted the association between the square-root-transformed WMH progression rate and E/e′ (**Figure 3A**) and baseline WMH (**Figure 3B**).

Discussion

The main finding of the present study is that LV diastolic dysfunction is associated with the rate of WMH volume progression in young-old patients with hypertension. To the best of our knowledge, this is the first study to show a significant association between the WMH progression rate and LV diastolic dysfunction in this group of patients. Importantly, our results were obtained from analyses in a strictly defined sample of young-old patients aged between 65 and 75 years with hypertension and without HF in whom we evaluated WMH volume using MRI. Notably, the association remained significant after adjustment for age, sex, LDL-C, and total systolic BP, which, in accordance with previous studies,[4–6] we recognized as conventional cerebrovascular risk factors in our present longitudinal study. Considering this background, there may be a mechanism that connects WMH progression over a long period of time and the progression of LV diastolic dysfunction in young-old patients with hypertension. Further prospective investigations are required to clarify this point.

Exacerbation of Cerebral WMH

Increased WMH volume is associated with complex aging factors, such as atherosclerosis,[24] dementia,[25] decreased skeletal muscle mass,[26] frailty,[27] albuminuria,[28] and cardiac dysfunction.[15] In a previous cross-sectional study, our group reported that the echocardiographic index E/e′ was associated with WMH volume.[15] In the present longitudinal study, we found that septal E/e′ was strongly associated with the rate of WMH progression, whereas LVEF was not. In addition, we showed that septal E/e′ was associated with the rate of WMH volume progression, as was baseline WMH volume. Furthermore, we showed that baseline WMH volume was associated with the progression rate in young-old hypertensive patients. As shown by the multivariate analysis, LV diastolic dysfunction was strongly associated with WMH exacerbation, even when hypertension and hypercholesterolemia were considered.[17] Therefore, it seems reasonable that the existence of LV diastolic dysfunction may be related to WMH exacerbation.

Patient Characteristics

Our ambulatory patients were all hypertensive and aged 65–75 years (mean age 69.6 years; mean MMSE score 28.4). Lee et al reported an association between LV diastolic dysfunction and the WMH progression rate.[17] However, eligible patients in that study were those participating in a health checkup program; only 64.8% had hypertension, including atrial fibrillation, and the subjects were not checked for dementia using tests such as the MMSE.[17] In addition, the BP parameters obtained at the initial visit and at approximately 12-month intervals thereafter were averaged.[17] Thus, the present study differs to the study of Lee et al,[17] which assessed BP without ambulatory BP measurement. Baseline WMH volume remained an independent factor in the present study, suggesting that a relatively large WMH volume was associated with potentially faster WMH progression, even in patients with hypertension who are only young-old.

Cardiac Function and WMH Progression

Because the heart primarily generates the pulsation of the

Table 3. Multiple Regression Analysis for White Matter Hyperintensity Progression Rate

	Unstandardized coefficients	Standardized coefficients		95% CI for B		Collinearity statistics
	B	β	P value	Lower bound	Upper bound	VIF
Age	0.008	0.050	0.384	−0.010	0.026	1.012
Sex	−0.032	−0.035	0.559	−0.141	0.077	1.110
Septal E/e′	0.086	0.457	<0.001	0.063	0.108	1.186
Baseline WMH	0.028	0.410	<0.001	0.020	0.036	1.120
LDL-C	−0.002	−0.098	0.097	−0.004	0.001	1.076
Total SBP	−0.001	−0.015	0.793	−0.005	0.004	1.061

Analysis of variance (ANOVA) P<0.05, adjusted R^2=0.505. CI, confidence interval; VIF, variance inflation factor. Other abbreviations as in Table 1.

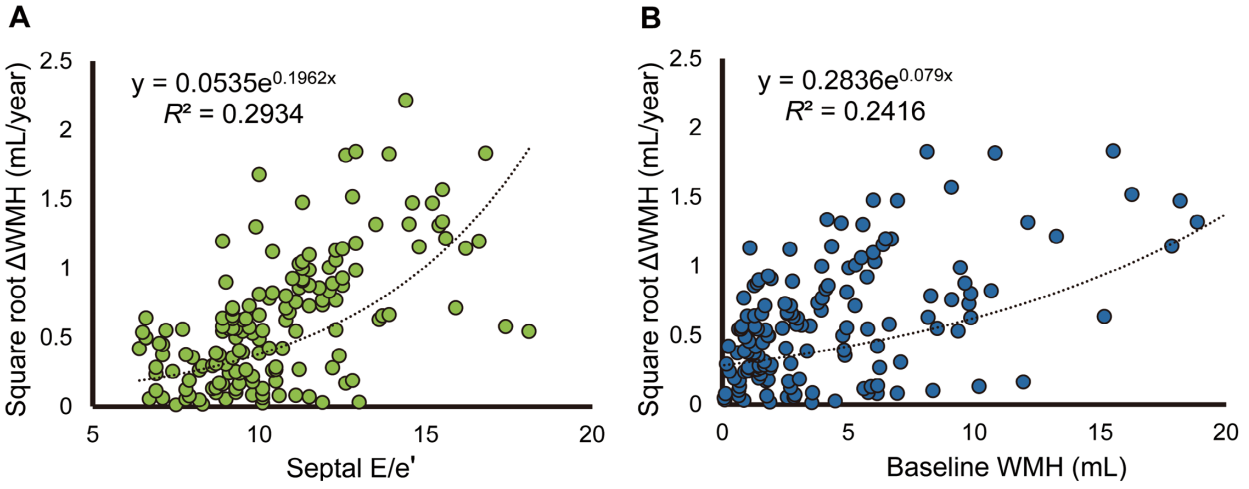

Figure 3. Relationships between the square root of the white matter hyperintensity progression rate (ΔWMH) and (**A**) septal E/e′ and (**B**) baseline white matter hyperintensity (WMH). Dotted lines are exponential curves. E, early diastolic mitral inflow velocity; e′, early diastolic mitral annular tissue velocity.

cerebral small arteries, previous studies have investigated the link between cardiac hemodynamics and the brain's degenerative processes. Reduced cardiac output, increased LV mass index, and raised right atrial pressure have been shown to be associated with the development of dementia, compromised white matter microstructure, and increased WMH volume, respectively.[29–31] However, E/e′ may have some advantages as an indicator because it is an easily measured and widely used echocardiographic marker that is associated with long-term cerebral WMH progression.[21,32]

Notably, in the present study we found that an elevated E/e′, as well as a large baseline WMH volume, seemed to be associated with a faster rate of WMH progression. As the E/e′ value increased, the rate of increase in WMH tended to accelerate (**Figure 3A**). Given that cerebral WMH in patients with LV dysfunction has a long-term progressive course, the E/e′ value and baseline WMH both seemed to affect WMH progression. The association between E/e′ and cerebral WMH progression may be supported by similarities in the mechanisms underlying LV diastolic dysfunction and reduced cerebral arteriolar compliance. First, a common dysregulated remodeling process underlies both LV diastolic dysfunction and cerebral arteriolar stiffness, including chronic changes in the amount, properties, and cross-linking of the extracellular matrix, resulting in increased passive tension in those systems.[33–38] Second, chronic subclinical tissue inflammation in both systems induces increased vascular permeability and activates inflammatory cascades, resulting in fibrosis and degeneration of the myocardium and the brain parenchyma.[5,35,39] Third, sustained activation of the sympathetic and renin-angiotensin-aldosterone systems induces chronic elevation in tone and endothelial dysfunction of both myocardial and cerebral arterioles,[36] resulting in decreased reactivity to nitric oxide.[40]

BP and WMH Progression

The fundamental goal of hypertension treatment is to reduce the total risk of cardiovascular, cerebrovascular, renal, and vascular complications and death.[7] However, even with good BP control, many patients still have different degrees of target organ damage and adverse cardiovascular and cerebrovascular events. In the present study, the mean total systolic BP among patients was 129.4 mmHg, suggesting that, in many of them, hypertension was well controlled by the use of appropriate combinations of antihypertension agents. BP has an effect on the development of WMH.[41,42] Wartolowska et al[41] showed that WMH was strongly associated with current and past elevated BP in subjects aged 40–69 years. In another study from our group, higher night-time systolic BP levels were found to contribute to greater WMH volumes in older adult hypertensive patients.[16] Surprisingly, dementia (as determined by the MMSE) and total systolic BP were each comparable among our groups, regardless of the WMH progression rate. However, we must be careful in interpreting these results because patients with severe dementia and brain infarction were excluded from this study.

Hypertension is possibly the most powerful modifiable risk factor for the development of HF.[43] It is well accepted that there are deterioration pathways common to WMH and HF with preserved EF.[44,45] Therefore, appropriate treatment to prevent hypertension may be the key to preventing WMH exacerbation. A further detailed and prospective analysis is required to determine whether this is indeed the case.

Clinical Implications

Septal E/e′ was an independent factor in the rate of WMH volume progression, even after adjustment for age, sex, LDL-C, and systolic BP, which are known to be related to WMH volume. In the present study, we showed that LV diastolic dysfunction contributed to WMH deterioration. Consequently, slowing the progression of LV diastolic dysfunction is likely to be important,[46] not only for preventing HF, but also for minimizing WMH exacerbation. For example, hypertension, obesity, diabetes, and chronic kidney disease induce and accelerate LV diastolic dysfunc-

tion.[45,47] Therefore, appropriate treatment of these diseases could prevent both WMH exacerbation and HF with preserved EF.

Study Limitations

Our study has a number of limitations. This was a single-center study with a small sample size. With respect to evaluating changes in cognitive function in patients with hypertension, neither the size of the sample nor the time period was sufficient. Moreover, we did not assess repeated measures over time or investigate the incidence of cardiac events in enrolled patients. The possibility that the population that developed major cardiovascular events or whose medical conditions had deteriorated substantially may have been prevented from undergoing follow-up MRIs could be a potential source of selection bias. Methodological limitations of measuring E/e′ or the rate of WMH volume progression should also be addressed. First, we used the septal e′ value rather than the average of septal and lateral e′ values to measure E/e′. This may explain, in part, the high frequency of E/e′ elevation in the study and indicates the need for careful interpretation of the study results.[22] More precise assessment of LV diastolic function is required to uncover pathophysiological findings of WMH.

Second, although the magnetic field strength was harmonized, sequence harmonization between different scanners and matching of the MRI machines between baseline and follow-up were not performed, and this may have reduced data reproducibility. Further prospective community-based studies with a standardized evaluation and follow-up protocol may help resolve these issues. From this perspective, further studies are needed.

Conclusions

The existence of LV diastolic dysfunction was significantly associated with the rate of WMH volume progression, suggesting that hypertension is a potential risk factor for WMH deterioration. The rate of WMH volume progression may be related to LV diastolic dysfunction and baseline WMH volume in young-old patients with hypertension.

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Disclosures

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Author Contributions

K.N., A.H., T.K., M.K., T.M., H.A., and A.S. supervised the research and prepared the text. N.O., T. Sugimoto, and T. Sakurai evaluated WMH. K.N., A.H., T.K., M.K., and A.S. evaluated the patients. All authors reviewed the text and agree with the paper's publication.

IRB Information

This study was approved by the Ethics and Conflicts of Interest Committee of the National Center for Geriatric and Gerontology (Reference no. 1272).

References

1. NCD Risk Factor Collaboration. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: A pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* 2021; **398:** 957–980, doi:10.1016/S0140-6736(21)01330-1.
2. Wiseman RM, Saxby BK, Burton EJ, Barber R, Ford GA, O'Brien JT. Hippocampal atrophy, whole brain volume, and white matter lesions in older hypertensive subjects. *Neurology* 2004; **63:** 1892–1897, doi:10.1212/01.wnl.0000144280.59178.78.
3. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology* 2011; **77:** 461–468, doi:10.1212/WNL.0b013e318227b227.
4. Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, et al. Stroke risk profile predicts white matter hyperintensity volume: The Framingham Study. *Stroke* 2004; **35:** 1857–1861, doi:10.1161/01.STR.0000135226.53499.85.
5. Pantoni L. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010; **9:** 689–701, doi:10.1016/S1474-4422(10)70104-6.
6. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: The Cardiovascular Health Study. *Stroke* 2005; **36:** 56–61, doi:10.1161/01.STR.0000149625.99732.69.
7. Cacciatore F, Abete P, Ferrara N, Calabrese C, Napoli C, Maggi S, et al. Congestive heart failure and cognitive impairment in an older population. Osservatorio Geriatrico Campano Study Group. *J Am Geriatr Soc* 1998; **46:** 1343–1348, doi:10.1111/j.1532-5415.1998.tb05999.x.
8. Almeida OP, Flicker L. The mind of a failing heart: A systematic review of the association between congestive heart failure and cognitive functioning. *Intern Med J* 2001; **31:** 290–295, doi:10.1046/j.1445-5994.2001.00067.x.
9. Tilvis RS, Kahonen-Vare MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. *J Gerontol A Biol Sci Med Sci* 2004; **59:** 268–274, doi:10.1093/gerona/59.3.m268.
10. Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke* 2001; **32:** 2530–2533, doi:10.1161/hs1101.098360.
11. Massaro AR, Dutra AP, Almeida DR, Diniz RV, Malheiros SM. Transcranial Doppler assessment of cerebral blood flow: Effect of cardiac transplantation. *Neurology* 2006; **66:** 124–126, doi:10.1212/01.wnl.0000191397.57244.91.
12. Vogels RL, van der Flier WM, van Harten B, Gouw AA, Scheltens P, Schroeder-Tanka JM, et al. Brain magnetic resonance imaging abnormalities in patients with heart failure. *Eur J Heart Fail* 2007; **9:** 1003–1009, doi:10.1016/j.ejheart.2007.07.006.
13. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: A pathoanatomical study. *Ann Neurol* 1986; **19:** 253–262, doi:10.1002/ana.410190306.
14. De Groot JC, De Leeuw FE, Oudkerk M, Van Gijn J, Hofman A, Jolles J, et al. Periventricular cerebral white matter lesions predict rate of cognitive decline. *Ann Neurol* 2002; **52:** 335–341, doi:10.1002/ana.10294.
15. Shimizu A, Sakurai T, Mitsui T, Miyagi M, Nomoto K, Kokubo M, et al. Left ventricular diastolic dysfunction is associated with cerebral white matter lesions (leukoaraiosis) in elderly patients without ischemic heart disease and stroke. *Geriatr Gerontol Int* 2014; **14**(Suppl 2)**:** 71–76, doi:10.1111/ggi.12261.
16. Kokubo M, Shimizu A, Mitsui T, Miyagi M, Nomoto K, Murohara T, et al. Impact of night-time blood pressure on cerebral white matter hyperintensity in elderly hypertensive patients. *Geriatr Gerontol Int* 2015; **15**(Suppl 1)**:** 59–65, doi:10.1111/ggi.12662.
17. Lee WJ, Jung KH, Ryu YJ, Lee ST, Park KI, Chu K, et al. Echocardiographic index E/e′ in association with cerebral white matter hyperintensity progression. *PLoS One* 2020; **15:** e0236473, doi:10.1371/journal.pone.0236473.
18. Cook DG, Shaper AG, MacFarlane PW. Using the WHO (Rose) angina questionnaire in cardiovascular epidemiology. *Int J Epidemiol* 1989; **18:** 607–613, doi:10.1093/ije/18.3.607.
19. Admiraal-Behloul F, van den Heuvel DM, Olofsen H, van Osch MJ, van der Grond J, van Buchem MA, et al. Fully automatic

segmentation of white matter hyperintensities in MR images of the elderly. *Neuroimage* 2005; **28:** 607–617, doi:10.1016/j.neuroimage.2005.06.061.
20. Sharp AS, Tapp RJ, Thom SA, Francis DP, Hughes AD, Stanton AV, et al. Tissue Doppler E/E′ ratio is a powerful predictor of primary cardiac events in a hypertensive population: An ASCOT substudy. *Eur Heart J* 2010; **31:** 747–752, doi:10.1093/eurheartj/ehp498.
21. Arques S, Roux E, Luccioni R. Current clinical applications of spectral tissue Doppler echocardiography (E/E′ ratio) as a non-invasive surrogate for left ventricular diastolic pressures in the diagnosis of heart failure with preserved left ventricular systolic function. *Cardiovasc Ultrasound* 2007; **5:** 16, doi:10.1186/1476-7120-5-16.
22. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. *Circulation* 2000; **102:** 1788–1794, doi:10.1161/01.cir.102.15.1788.
23. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016; **17:** 1321–1360, doi:10.1093/ehjci/jew082.
24. Bots ML, van Swieten JC, Breteler MM, de Jong PT, van Gijn J, Hofman A, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. *Lancet* 1993; **341:** 1232–1237, doi:10.1016/0140-6736(93)91144-b.
25. Desmond DW. Cognition and white matter lesions. *Cerebrovasc Dis* 2002; **13**(Suppl 2)**:** 53–57, doi:10.1159/000049151.
26. Wakefield DB, Moscufo N, Guttmann CR, Kuchel GA, Kaplan RF, Pearlson G, et al. White matter hyperintensities predict functional decline in voiding, mobility, and cognition in older adults. *J Am Geriatr Soc* 2010; **58:** 275–281, doi:10.1111/j.1532-5415.2009.02699.x.
27. Hirashiki A, Shimizu A, Suzuki N, Nomoto K, Kokubo M, Sugimoto T, et al. Exercise capacity and frailty are associated with cerebral white matter hyperintensity in older adults with cardiovascular disease. *Int Heart J* 2022; **63:** 77–84, doi:10.1536/ihj.21-377.
28. Yamasaki K, Hata J, Furuta Y, Hirabayashi N, Ohara T, Yoshida D, et al. Association of albuminuria with white matter hyperintensities volume on brain magnetic resonance imaging in elderly Japanese: The Hisayama Study. *Circ J* 2020; **84:** 935–942, doi:10.1253/circj.CJ-19-1069.
29. Jefferson AL, Beiser AS, Himali JJ, Seshadri S, O'Donnell CJ, Manning WJ, et al. Low cardiac index is associated with incident dementia and Alzheimer disease: The Framingham Heart Study. *Circulation* 2015; **131:** 1333–1339, doi:10.1161/CIRCULATIONAHA.114.012438.
30. Lee WJ, Jung KH, Ryu YJ, Kim JM, Lee ST, Chu K, et al. Association of cardiac hemodynamic factors with severity of white matter hyperintensities in chronic valvular heart disease. *JAMA Neurol* 2018; **75:** 80–87, doi:10.1001/jamaneurol.2017.2853.
31. Moore EE, Liu D, Pechman KR, Terry JG, Nair S, Cambronero FE, et al. Increased left ventricular mass index is associated with compromised white matter microstructure among older adults. *J Am Heart Assoc* 2018; **7:** e009041, doi:10.1161/JAHA.118.009041.
32. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: A consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; **28:** 2539–2550, doi:10.1093/eurheartj/ehm037.
33. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, 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:** 2672–2713, doi:10.1161/STR.0b013e3182299496.
34. Baumbach GL, Heistad DD. Remodeling of cerebral arterioles in chronic hypertension. *Hypertension* 1989; **13:** 968–972, doi:10.1161/01.hyp.13.6.968.
35. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2014; **11:** 507–515, doi:10.1038/nrcardio.2014.83.
36. Sciarretta S, Paneni F, Palano F, Chin D, Tocci G, Rubattu S, et al. Role of the renin-angiotensin-aldosterone system and inflammatory processes in the development and progression of diastolic dysfunction. *Clin Sci (Lond)* 2009; **116:** 467–477, doi:10.1042/CS20080390.
37. Rosenberg GA, Sullivan N, Esiri MM. White matter damage is associated with matrix metalloproteinases in vascular dementia. *Stroke* 2001; **32:** 1162–1168, doi:10.1161/01.str.32.5.1162.
38. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left atrial structure and function, and left ventricular diastolic dysfunction: JACC state-of-the-art review. *J Am Coll Cardiol* 2019; **73:** 1961–1977, doi:10.1016/j.jacc.2019.01.059.
39. Wardlaw JM, Doubal FN, Valdes-Hernandez M, Wang X, Chappell FM, Shuler K, et al. Blood-brain barrier permeability and long-term clinical and imaging outcomes in cerebral small vessel disease. *Stroke* 2013; **44:** 525–527, doi:10.1161/STROKEAHA.112.669994.
40. Iliff JJ, Wang M, Zeppenfeld DM, Venkataraman A, Plog BA, Liao Y, et al. Cerebral arterial pulsation drives paravascular CSF–interstitial fluid exchange in the murine brain. *J Neurosci* 2013; **33:** 18190–18199, doi:10.1523/JNEUROSCI.1592-13.2013.
41. Wartolowska KA, Webb AJS. Midlife blood pressure is associated with the severity of white matter hyperintensities: Analysis of the UK Biobank cohort study. *Eur Heart J* 2021; **42:** 750–757, doi:10.1093/eurheartj/ehaa756.
42. Kim JS, Lee S, Suh SW, Bae JB, Han JH, Byun S, et al. Association of low blood pressure with white matter hyperintensities in elderly individuals with controlled hypertension. *J Stroke* 2020; **22:** 99–107, doi:10.5853/jos.2019.01844.
43. Di Palo KE, Barone NJ. Hypertension and heart failure: Prevention, targets, and treatment. *Heart Fail Clin* 2020; **16:** 99–106, doi:10.1016/j.hfc.2019.09.001.
44. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. *BMJ* 2010; **341:** c3666, doi:10.1136/bmj.c3666.
45. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; **355:** 260–269, doi:10.1056/NEJMoa051530.
46. Oeun B, Hikoso S, Nakatani D, Mizuno H, Suna S, Kitamura T, et al. Prognostic impact of echocardiographic diastolic dysfunction on outcomes in patients with heart failure with preserved ejection fraction: Insights from the PURSUIT-HFpEF Registry. *Circ J* 2021; **86:** 23–33, doi:10.1253/circj.CJ-21-0300.
47. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC Jr, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011; **306:** 856–863, doi:10.1001/jama.2011.1201.