Exercise Capacity and Frailty Are Associated with Cerebral White Matter Hyperintensity in Older Adults with Cardiovascular Disease

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Summary
Cerebral white matter hyperintensity (WMH) is highly prevalent among older adults. There is little information about the relationship among WMH extent, frailty status, and exercise capacity in older adults with cardiovascular disease (CVD). We assessed the association of WMH with frailty and exercise capacity in CVD patients.

Seventy-eight stable older adults with CVD were evaluated for WMH, the Kihon Checklist (KCL), short physical performance battery score (SPPB), and cardiopulmonary exercise testing. WMH volume was quantified on brain magnetic resonance imaging. Patients were classified into 3 groups (using tertiles of 0.52% and 1.05%) according to WMH as a percentage of intracranial volume (ICV), and their KCL scores and exercise capacities were compared. The 3 WMH/ICV groups were mild (n = 26, 0.26% ± 0.14% of intracranial volume), moderate (n = 26, 0.70% ± 0.15%), and severe (n = 26, 1.75% ± 0.67%). Peak VO2 was 15.2 ± 3.7 mL kg−1 minute−1 (mild group), 12.9 ± 3.5 mL kg−1 min−1 (moderate), and 11.4 ± 2.3 mL kg−1 minute−1 (severe) (mild versus moderate, P = 0.049; mild versus severe, P = 0.001). Multivariate regression analysis showed significant associations of severe WMH/ICV with peak VO2 and SPPB. Cerebral WMH was strongly negatively associated with SPPB and peak VO2. WMH volume may be related to exercise capacity and frailty in stable older adult patients with CVD.

Key words: Cardiopulmonary exercise testing, Cerebral small vessel disease, Physical frailty

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This study was performed with the support of 2019-2021 geriatrics and gerontology research funds sponsored by the Ministry of Health, Labour and Welfare, Japan.

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Received for publication June 7, 2021. Revised and accepted October 1, 2021.

doi: 10.1536/ihj.21-377

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the relationships between WMH and both frailty and exercise capacity in patients with CVD.

**Methods**

**Study population:** Seventy-eight patients aged 65 or more who were hospitalized for CVD in the Department of Cardiology at the National Center for Geriatrics and Gerontology, Obu, Japan, between August 2017 and July 2019 were enrolled in the study.

The inclusion criteria were structural heart disease consisting of coronary artery disease (having experienced angina pectoris or myocardial infarction, with or without a history of revascularization procedures); symptomatic heart failure (non-ischemic cardiomyopathy, ischemia, tachycardia, bradycardia, valvular disease, or hypertension); and other. Non-ischemic cardiomyopathies were defined as ventricular myocardial abnormalities in the absence of coronary artery disease or valvular, pericardial, or congenital heart disease. Tachycardia and bradycardia included atrial, supraventricular arrhythmia and ventricular arrhythmia; sick sinus syndrome; and atrioventricular block in the absence of structural heart disease. Valvular heart disease was diagnosed on the basis of hemodynamic or echocardiographic findings or a history of valvular or congenital cardiac surgery. Hypertension was defined as systolic blood pressure $\geq 140$ mm Hg, diastolic blood pressure $\geq 90$ mm Hg, or a history of treatment for hypertension. Included as “other” were aortic disease, peripheral artery disease, and other vascular diseases. Heart failure was defined as interstitial edema or pulmonary venous congestion on chest X-ray, plus any symptoms (e.g., dyspnea, ankle swelling, peripheral edema, fatigue).

Exclusion criteria were symptomatic stroke or neurodegenerative disorder; pulmonary dysfunction; hepatic dysfunction; end-stage renal dysfunction; malignant tumor prognosis within 1 year after hospitalization or discharge, inability to walk 10 m with or without using auxiliary equipment at discharge; and severe dementia, which was defined as a Mini-Mental State Examination (MMSE) score lower than 18 points. Only patients who were stable after admission were enrolled.

**Study protocol:** After appropriate medical therapy, a physical examination, laboratory measurements, cardiopulmonary exercise testing (CPX), the Kihon Checklist (KCL) questionnaire, timed up-and-go (TUG) test, and short physical performance battery (SPPB) were performed within 3 days of study enrollment. All patients were in a stable condition at the time of testing. KCL scores, TUG, SPPB, and CPX were compared among patient groups with different degrees of WMH. The study protocol complied with the Declaration of Helsinki, and written informed consent was obtained from each subject. The ethics review board of the National Center for Geriatrics and Gerontology, Japan, approved the study (approval no. 1090).

**Neuroimaging studies:** Patients underwent 1.5-T brain MRI (Siemens Avanto, Munich, Germany) with T1- and T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. The protocol for brain MRI has been described in detail elsewhere. Individual intracranial volume (ICV) and WMH volume were quantified by using the Software for Neuro-Image Processing in Experimental Research (SNIPER) segmentation application. The procedures used for SNIPER have been described in detail elsewhere. In the analyses, individual WMH volume was divided by the ICV to minimize the bias for each individual head size (WMH/ICV, %). Moreover, patients were classified into 3 groups according to the tertiles of WMH/ICV, because there is no consensus on an appropriate cutoff value for older adult populations. The 3 WMH groups were mild ($n = 26, 0.26\% \pm 0.14\%$ of intracranial volume), moderate ($n = 26, 0.70\% \pm 0.15\%$), and severe ($n = 26, 1.75\% \pm 0.67\%$) (Figure 1).

**KCL:** The KCL was developed by the Japanese Ministry of Health, Labour and Welfare to identify older persons in need of care; it is a reliable tool for predicting general frailty in older adults. The KCL is a 25-item self-administered questionnaire. It comprises 7 categories of questions that assess instrumental activities of daily living,
physical function, nutritional status, oral function, social activities of daily living, cognitive function, and depressive mood. Each domain is rated on a pass (0) / fail (1) basis, and the sum of all indices ranges from 0 (no frailty) to 25 (severe frailty); a higher score indicates worse functioning. The KCL is thus a comprehensive evaluation tool that examines the social, psychological, and physical aspects of frailty. A KCL score of 0 to 3 is classified as robust, 4 to 7 as pre-frail, and ≥ 8 as frail.

**CPX procedure:** Each patient underwent CPX, at a progressively increasing work rate, to maximum tolerance on a cycle ergometer. The test protocol was conducted in accordance with the recommendations of the American Thoracic Society and American College of Chest Physicians. The oxygen and carbon dioxide sensors were calibrated before each test with known oxygen, nitrogen, and carbon dioxide concentrations. Test termination criteria were patient request, volitional fatigue, ventricular tachycardia, or ≥ 2 mm horizontal or downsloping ST-segment depression during exercise. A qualified exercise physiologist conducted each test under a physician’s supervision. A 12-lead electrocardiogram was monitored continuously, and blood pressure was measured every minute during exercise and throughout the 5-minute recovery period. Respiratory gas exchange variables, including VO2, VCO2, and minute ventilation (VE), were acquired continuously throughout the test. An Oxycon Pro ergospirometer (CareFusion; San Diego, CA, USA); gas-exchange data were obtained breath-by-breath. Peak VO2 and peak respiratory exchange ratio were determined as the highest 30-second average values obtained during the final stage of the test. The ratio of the increase in VO2 to the increase in work rate (WR) \( \frac{\Delta V\text{O}_2}{\Delta W\text{R}} \) was calculated by least-squares linear regression from the data recorded between 30 s after the start of the incremental exercise and 30 s before the end of the exercise.

**Statistical analysis:** Data are presented as the mean ± standard deviation, unless otherwise stated. Comparison of continuous variables among groups was performed by one-way analysis of variance followed by Scheffé’s test. The chi-squared test was used to assess the significance of differences between dichotomous variables. Univariate linear regression analysis of the relationship between various parameters and WMH/ICV was used to assess the relationships between WMH/IV and clinical variables. To investigate the factors related to WMH/ICV, a stepwise multivariate analysis was performed after adjustment for age, body mass index, peak work rate, peak VO2, ratio of early mitral inflow velocity to early diastolic mitral annulus velocity (E/e’), TUG test results, KCL score, and SPPB score, by using WMH/ICV as an independent variable. To investigate the CPX result or frailty parameters and potential confounders were assessed with a multivariate linear regression model. All analyses were performed with the SPSS 17.0 software package (SPSS; Chicago, IL, USA). A P-value of < 0.05 was considered statistically significant.

**Results**

**Baseline characteristics:** The baseline clinical characteristics of the patients and a comparison among the mild, moderate, and severe WMH groups are shown in Table I. The study enrolled 78 consecutive older adult patients with CVD (44 male (56%); mean age ± SD, 80.1 ± 7.7 years). At the time of enrollment, all patients were stable and on optimal pharmacological therapy according to current CVD or heart failure treatment guidelines. The mean (25th, 75th percentile) plasma brain natriuretic peptide (BNP) level after stabilization was 181 (34, 260) pg/mL, and the mean LV ejection fraction was 56.7% ± 14.2%. The KCL results revealed that 53.8% of the patients had frailty (mean KCL score for all patients, 8.7 ± 5.8).

**Comparison among mild, moderate, and severe WMH:** Although there were no significant differences in underlying disease and medication use among the 3 groups, patients in the severe WMH group were significantly older than those in the mild or moderate group. Similarly, the frequency of a history of heart failure was significantly higher in the severe WMH group than in the mild group (Table I, Figure 2). With the exception of E/e’ (significantly lower in the severe group than in the mild group) there were no significant differences in echocardiography data among the 3 groups. On laboratory measurement, plasma BNP levels after CVD stabilization and estimated glomerular filtration rate were comparable in the 3 groups.

Although there were no significant differences in the MMSE scores, peak VO2 was 15.2 ± 3.7 mL kg⁻¹ minute⁻¹ in the mild WMH group, 12.9 ± 3.5 mL kg⁻¹ minute⁻¹ in the moderate group, and 11.4 ± 2.3 mL kg⁻¹ minute⁻¹ in the severe group (mild versus moderate, \( P = 0.049 \); mild versus severe, \( P = 0.001 \)) (Table I, Figure 2). The KCL score was 6.6 ± 4.7 in the mild WMH group, 8.4 ± 6.0 in the moderate group, and 11.6 ± 5.6 in the severe group (mild versus severe, \( P = 0.008 \)). The TUG score was significantly worse in the severe WMH groups than in the mild WMH group (mild versus severe, \( P < 0.001 \)). Similarly, the SPPB score was significantly worse in the severe WMH group than in the mild or moderate group (mild versus severe, \( P = 0.001 \); moderate versus severe, \( P = 0.009 \)). After adjustment for age and gender, there were no significant differences in KCL or TUG scores among the 3 groups. However, SPPB was significantly worse in the moderate WMH group than in the mild WMH group (\( P = 0.041 \)), and it tended to be worse in the severe WMH group than in the moderate WMH group (\( P = 0.058 \)) (data not shown).

**Correlation between WMH and various parameters:** The results of univariate linear regression analyses of the relationships between various parameters and WMH are listed in Table II. Linear regression analysis showed a significant negative correlation between WMH/ICV and peak VO2 (\( r = -0.344, P = 0.004 \)) and a significant positive correlation between WMH/ICV and KCL score (\( r = 0.276, P = 0.021 \)). A stepwise multivariate analysis revealed that SPPB was an independent factor for WMH/ICV (\( \beta = -0.12 \) (95% CI -0.18 to -0.061, \( P < 0.001 \)). We performed a multivariate regression analysis of peak VO2, VE/VCO2 slope, KCL score, and SPPB score with age, gender, body mass index, category of WMH/ICV, log BNP, and MMSE score as explanatory variables (Table II).
|                  | Mild (n = 26) | Moderate (n = 26) | Severe (n = 26) |
|------------------|---------------|-------------------|-----------------|
| **Age (years)**  | 75.3 ± 7.1    | 80.0 ± 6.7 *      | 84.8 ± 6.4 *†   |
| **Male (%)**     | 61.5          | 57.7              | 50.0            |
| **BMI (kg m⁻²)** | 23.1 ± 4.5    | 23.5 ± 4.4        | 21.0 ± 3.6      |
| **WML/ICV (%)**  | 0.26 ± 0.14   | 0.70 ± 0.15 *     | 1.75 ± 0.67 *†  |
| **Atrial fibrillation (%)** | 28.0          | 42.3              | 16.0            |
| **Smoking (%)**  | 11.5          | 3.8               | 7.7             |
| **History of heart failure (%)** | 11.5          | 19.2              | 34.6 *          |
| **ACC/AHA stage B/C/D heart failure** | 17/9/0        | 9/17/0            | 6/18/2 *        |
| **Heart failure (%)** | 76            | 76                | 80              |
| **Non-ischemic cardiomyopathy** | 15            | 4                 | 8               |
| **Ischemic heart disease** | 31            | 21                | 21              |
| **Hypertensive** | 10            | 13                | 8               |
| **Tachycardia-induced** | 8             | 20                | 12              |
| **Valvular disease** | 8             | 10                | 23              |
| **Bradycardia**  | 4             | 8                 | 8               |
| **Post PCI, CABG (%)** | 12            | 7                 | 12              |
| **Other (%)**    | 12            | 17                | 8               |
| **Medications**  |               |                   |                 |
| **Diuretic (%)** | 38.5          | 44.0              | 60.0            |
| **Tolvaptan**    | 3.8           | 20.0              | 16.0            |
| **ACE-I/ARB (%)**| 69.2          | 52.0              | 55.0            |
| **Beta blocker (%)** | 42.3          | 28.0              | 24.0            |
| **Antiplatelet (%)** | 50.0          | 38.4              | 44.0            |
| **Anticoagulant (%)** | 34.6          | 44.0              | 20.0            |
| **Spironolactone (%)** | 15.4          | 28.0              | 12.0            |
| **CPX data**     |               |                   |                 |
| **RER**          | 1.12 ± 0.07   | 1.12 ± 0.06       | 1.10 ± 0.06     |
| **Peak WR (W)**  | 67.2 ± 29.5   | 47.9 ± 28.1 *     | 34.7 ± 21.6 *   |
| **Resting HR (bpm)** | 76 ± 16       | 72 ± 13           | 73 ± 12         |
| **Peak HR (bpm)** | 126 ± 20      | 109 ± 18 *        | 108 ± 17 *      |
| **Peak VO₂ (kg (mL minute⁻¹ kg⁻¹))** | 15.2 ± 3.7    | 12.9 ± 3.5 *      | 11.4 ± 2.3 *    |
| **VE/VCO₂ slope** | 33.2 ± 9.5    | 39.4 ± 16.4       | 37.1 ± 7.0      |
| **ΔVO₂/ΔWR**     | 8.7 ± 3.0     | 7.0 ± 3.4         | 5.7 ± 4.3 *     |
| **RCP**          | 133 ± 20      | 136 ± 25          | 138 ± 26        |
| **Peak SBP (bpm)** | 190 ± 29      | 178 ± 42          | 186 ± 36        |
| **Echocardiography** |             |                   |                 |
| **LVEF (%)**     | 57.7 ± 13.9   | 59.9 ± 12.3       | 52.5 ± 15.9     |
| **LAD (cm)**     | 4.0 ± 0.8     | 4.1 ± 0.6         | 3.8 ± 0.5       |
| **E/e'**         | 14.6 ± 7.5    | 15.5 ± 5.2        | 19.5 ± 7.7 *    |
| **Cardiac output (L minute⁻¹)** | 4.1 ± 1.1     | 3.7 ± 1.3         | 3.5 ± 0.9       |
| **Laboratory data** |             |                   |                 |
| **Hb (mg dL⁻¹)** | 12.7 ± 1.6    | 12.4 ± 2.1        | 11.7 ± 1.4      |
| **TP (g dL⁻¹)**  | 7.0 ± 0.6     | 13.2 ± 32.3       | 6.7 ± 0.6       |
| **Alb (g dL⁻¹)** | 3.9 ± 0.5     | 3.8 ± 0.5         | 3.5 ± 0.4 *     |
| **Tchol (mg dL⁻¹)** | 172.3 ± 35.3  | 166.0 ± 26.3      | 176.0 ± 33.6    |
| **CRP (mg dL⁻¹)** | 0.8 ± 2.2     | 1.1 ± 1.7         | 0.6 ± 1.1       |
| **HbA1c (%)**    | 6.1 ± 0.7     | 6.1 ± 0.5         | 6.4 ± 0.8 *     |
| **BNP on admission (pg mL⁻¹)** | 355 ± 996     | 303 ± 259         | 507 ± 467       |
| **BNP after stable (pg mL⁻¹)** | 145 ± 150     | 205 ± 295         | 192 ± 139       |
| **eGFR (mL minute⁻¹ 1.73 m⁻²)** | 57.1 ± 16.0    | 53.7 ± 24.1       | 47.1 ± 25.9     |
| **SPPB**         | 10.6 ± 1.4    | 9.6 ± 3.0         | 7.3 ± 3.3 *†    |
| **TUG**          | 9.7 ± 3.1     | 14.9 ± 12.3       | 16.4 ± 6.7 *    |
| **KCL**          | 6.6 ± 4.7     | 8.4 ± 6.0         | 11.6 ± 5.6 *    |
| **MMSE**         | 27.6 ± 3.5    | 25.5 ± 5.9        | 25.1 ± 4.1      |

WMH indicates white matter hyperintensity; BMI, body mass index; WHM/ICV, white matter hyperintensity as a percentage of intracranial volume; ACC, American College of Cardiology; AHA, American Heart Association; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; PCI, percutaneous coronary intervention; CABG, coronary arterial bypass graft; CPX, cardiopulmonary exercise testing; RER, respiratory exchange ratio; WR, work rate; HR, heart rate; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; LAD, left atrium dimension, E/e’, ratio of early transmitral flow velocity to early diastolic mitral annular velocity; Hb, hemoglobin; TP, total protein; Alb,Albumin; Tchol, total cholesterol; CRP, C-reactive protein; HbA1c, glycated hemoglobin; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; SPPB, short physical performance battery; TUG, timed up-and-go test; KCL, Kihon checklist; J-CHS, Japanese version of the Cardiovascular Health Study; and MMSE, Mini-Mental State Examination. *P < 0.05 versus mild; †P < 0.05 versus moderate.
Exercise capacity and cerebral WMH in CVD

Figure 2. Comparison of exercise capacity (peak VO₂), frailty (KCL score), and balance (TUG and SPPB) among the 3 WMH/ICV groups (mild, moderate, and severe). VO₂ indicates O₂ uptake; KCL, Kihon checklist; TUG, timed up-and-go test; and SPPB, short physical performance battery.

Table II. Correlation Between WMH/ICV and Clinical Variables

| Clinical variable | WMH/ICV | r    | P     |
|-------------------|---------|------|-------|
| Age (years)       |         | 0.467| < 0.001|
| BMI (kg m⁻²)      |         | -0.254| 0.025|
| Peak WR (W)       |         | -0.368| 0.002|
| Peak VO₂ kg⁻¹ (mL minute⁻¹ kg⁻¹) | | -0.344| 0.004|
| VE/VCO₂ slope     |         | 0.084| 0.498|
| LVEF (%)          |         | -0.175| 0.131|
| E/e               |         | 0.264| 0.042|
| Alb (g dL⁻¹)      |         | -0.303| 0.008|
| BUN (mg dL⁻¹)     |         | 0.152| 0.193|
| Cr (mg dL⁻¹)      |         | 0.106| 0.364|
| T.chol (mg dL⁻¹)  |         | 0.089| 0.448|
| Fe (μg dL⁻¹)      |         | -0.172| 0.151|
| CRP (mg dL⁻¹)     |         | -0.040| 0.676|
| Log BNP (pg mL⁻¹) after stabilization | | 0.251| 0.048|
| MMSE              |         | -0.314| 0.008|
| SPPB              |         | -0.423| < 0.001|
| TUG               |         | 0.275| 0.026|
| KCL               |         | 0.276| 0.021|

WMH/ICV indicates white matter hyperintensity as a percentage of intracranial volume; BUN, blood urea nitrogen; and Cr, creatinine; for other abbreviations see Table I.

Discussion

Our main finding was the clear association of WMH with frailty and with exercise capacity in older adults with CVD. To the best of our knowledge, this is the first study to show an association between WMH and exercise capacity in these patients. Importantly, our results were obtained from analyses of older adult patients (average 80.1 years) with CVD in whom we evaluated exercise capacity by using CPX. Notably, peak VO₂ was strongly associated with WMH in these patients. Considering this background, there might be a mechanism that connects WMH and exercise capacity. Further prospective investigations are required to clarify this point.

CPX is a useful and reliable tool for assessing exercise capacity and therapeutic effect. Peak VO₂ and VE/VCO₂ slope in particular are known to be prognostic markers of chronic heart failure. To the best of our knowledge, there have been no previous investigations of the relationships between exercise capacity as assessed by CPX and WMH as assessed by MRI in patients with CVD. WMH/ICV was significantly correlated with peak WR or peak VO₂, but not with VE/VCO₂ slope (Table II). In addition, peak VO₂ but not VE/VCO₂ slope was independently associated with severe WMH after adjustment for age, gender, BMI, and MMSE (Table III). The reason for the difference in the associations between these two major CPX parameters and severe WMH remains unclear. Further investigations are needed in this regard.

Although we know of no previous data on the rela-
Table III. Multivariate Regression Models for CPX and Frailty Parameters

| Parameter | Coefficient | SE | Beta | P   | Coefficient | SE | Beta | P   | Coefficient | SE | Beta | P   | Coefficient | SE | Beta | P   |
|-----------|-------------|----|------|-----|-------------|----|------|-----|-------------|----|------|-----|-------------|----|------|-----|
| Peak VO₂ | -0.08       | 0.05| -0.18| 0.118| 0.211       | 0.173| -0.06| 0.05| -0.05       | 0.14| 0.08| 0.20  | 0.073       | 0.14| 0.08 | 0.20 |
| VE/VCO₂  | 0.118       | 0.24| -0.46| 0.663| -0.31       | 0.223| -0.25| 0.14| -0.05       | 0.234| 0.031| 0.002 | 0.002       | 0.234| 0.031| 0.02 |
| SPPB      | -0.31       | 0.08| -0.33| 0.002| -0.07       | 0.031| 0.005| 0.04 | -0.05       | 0.005| 0.005| 0.005 | 0.005       | 0.005| 0.005| 0.01|
| Age (years) | -0.14     | 0.05| -0.27| 0.08 | -0.07       | 0.031| 0.005| 0.04 | -0.05       | 0.005| 0.005| 0.005 | 0.005       | 0.005| 0.005| 0.01|
| Gender    | 0.22        | 0.18| 0.16 | 0.12 | 0.27       | 0.123| 0.015| 0.001| 0.03        | 0.003| 0.034| 0.034 | 0.034       | 0.034| 0.034| 0.03|
| BMI (kg/m²) | -0.14     | 0.08| -0.27| 0.08 | -0.07       | 0.031| 0.005| 0.005| -0.05       | 0.005| 0.005| 0.005 | 0.005       | 0.005| 0.005| 0.01|
| WMH       | -0.118      | 0.173| -0.06| 0.05 | -0.05       | 0.203| 0.002| 0.002| 0.02        | 0.002| 0.034| 0.034 | 0.034       | 0.034| 0.034| 0.03|
| MMSE      | 0.22        | 0.18| 0.16 | 0.12 | 0.27       | 0.123| 0.015| 0.001| 0.03        | 0.003| 0.034| 0.034 | 0.034       | 0.034| 0.034| 0.03|

CPX indicates cardiopulmonary exercise testing; SE, standard error; WMH, white matter hyperintensity; for other abbreviations see Table I.

relationships between CPX parameters and WMH, there have been several reports of the association between frailty and WMH. Moon, et al.24) reported that baseline WMH volume was significantly associated with decline in SPPB performance in dementia-free older adults with memory complaints. However, these data were not obtained in older adults with CVD. Baseline WMH was associated with frailty as assessed by KCL or SPPB scoring in our cross-sectional study. After a stepwise multivariate analysis was performed, SPPB was an independent factor associated with WMH/ICV in older adults with CVD. SPPB consists of gait, strength, and balance analyses and is used as a comprehensive assessment of lower limb function.27) It has been utilized in multiple studies that have consistently confirmed its validity for predicting the incidence of disability, hospital admission, and all-cause mortality.28) Our results suggested that WMH is linked with lower limb dysfunction in older adults with CVD.

WMH also contributes to the development of atrophy patterns in brain regions related to dementia.29) Here, we did not find a significant association between WMH severity and cognitive decline in the MMSE in the 3 group comparisons, although WMH/ICV was significantly associated with MMSE in the linear and multivariate regression analyses. In our sample population there was, therefore, at least in part, a mild association between WMH and cognitive function.

Blood pressure has an impact on the development of WMH.27,28) Kim, et al.28) reported that low systolic blood pressure was associated with a relatively large volume of periventricular WMH in elderly individuals with controlled hypertension (mean age 73.8 years). In contrast, Wartolowska, et al.27) showed that WMH was strongly associated with current and past elevated blood pressure in subjects aged 40 to 69 years (especially in those under the age of 50). Our study did not show an association between WMH and blood pressure. We speculated that one of the main reasons for this discrepancy might have been a difference in the patient population. In our study, 77% of the patients had heart failure, and the average age of our CVD patients was 80.1 years. Further investigations are required to clarify the relationship between blood pressure and WMH, especially in older patients with CVD, including refractory heart failure.

Worldwide, CVD is the leading cause of morbidity and mortality, with age being the primary risk factor.9) In the aging population, the prognostic determinants of longevity include frailty, health status, disability, and cognition. However, these constructs are seldom measured and factored into clinical decision-making or evaluation of the prognosis of these at-risk older adults. Considering the common effects of LV dysfunction on systemic perfusion, the relationships between brain abnormalities and LV dysfunction might therefore be expected to be the same systemic relationships.27) Shimizu, et al.30) from our group have reported that LV diastolic dysfunction is associated with WMH. We found here that LV ejection fraction was not associated with WMH, whereas E/e' appeared to be associated with it, in accordance with our previous study.30) On the basis of a previous study in CVD patients,30) considering that LV diastolic dysfunction itself reduces systemic perfusion in the same manner as does LV systolic dysfunction, systemic hypoperfusion as a result of the progression of LV diastolic dysfunction might impair the autoregulation of cerebral blood flow, disrupt cerebral perfusion, and cause WMH development and progression.
Disorders of the small blood vessels in the ischemic heart and brain are considered to be closely linked because of similarities between these organs in terms of hemodynamics and the development of atherosclerosis. Moreover, increased night-time systolic blood pressure levels contribute to increased WMH volumes in older adult hypertensive patients. WMH volume is associated with complex aging factors, such as atherosclerosis, dementia, decreased skeletal muscle strength, and cardiac dysfunction, thereby leading to the progression of frailty and balance loss in older adults with CVD. These associations, taken together, indicate that WMH volume is associated with complex aging factors, such as atherosclerosis, dementia, decreased skeletal muscle strength, and cardiac dysfunction, thereby leading to the progression of frailty and balance loss in older adults with CVD. The progression of exercise intolerance in these patients is likely related to not only cardiac dysfunction but also cerebral small vessel disease. The most important, but difficult to answer, question is how frailty is associated with WMH development and progression. Preventive strategies that reduce the odds of developing CVD and WMH could decrease the incidence, or delay the onset, of dementia. Further detailed and prospective analysis is required to settle this matter.

Our study has a number of limitations. It was a single-center study with a small sample size. Moreover, we did not assess repeated measures over time or investigate the incidence of cardiac events in enrolled patients. Of note, not all older adult CVD patients can undertake CPX or frailty assessments, because a certain amount of physical ability is required.

Conclusion

Frailty status as determined by the SPPB test was significantly positively associated, and peak VO2 was significantly negatively associated, with WMH percentage volume in stable older adult patients with CVD. WMH volume may be related to exercise capacity and frailty in stable older adult patients with CVD.

Acknowledgments

This study was performed with the support of 2019-2021 geriatrics and gerontology research funds sponsored by the Ministry of Health, Labour and Welfare, Japan. The authors are indebted to the staff of the National Center for Geriatrics and Gerontology, Obu, Japan, and particularly to Kimiko Hori (physiologist technician) and Ikue Ueda (occupational therapist). In addition, we thank Saeko Omura of the Center for performing the technical analysis of WMH by MRI.

Disclosure

Conflicts of interest: There are no conflicts of interest to declare.

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