Peak exercise stroke volume effects on cognitive impairment in community-dwelling people with preserved ejection fraction

Masamitsu Sugie1,2*, Kazumasa Harada1, Tetsuya Takahashi2,3, Marina Nara2,4, Hisashi Kawai2, Yoshinori Fujiwara2, Joji Ishikawa1, Jun Tanaka1, Teruyuki Koyama5, Hunkyung Kim2, Renpei Sengoku6, Hajime Fujimoto1, Shuichi Obuchi2, Shunei Kyo7 and Hideki Ito8

1Department of Cardiology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan; 2Institute of Gerontology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan; 3Department of Rehabilitation, Juntendo University, Tokyo, Japan; 4Japanese Association for Healthy Life Expectancy, Tokyo, Japan; 5Department of Rehabilitation, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan; 6Department of Neurology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan; 7Department of Cardiac Surgery, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan; 8Department of Diabetes, Metabolism and Endocrinology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan

Abstract

Aims The association of vascular dysfunction and amyloid beta deposition attracted attentions for its relationship with cognitive decline. Previous studies show the correlation between the declined cardiac function and the cognitive impairment. In the present study, we analysed the association between cognitive functions and cardiac parameters in community-dwelling people with preserved ejection fraction without heart failure.

Methods and results Subjects were 108 Japanese community-dwelling middle-aged and older adults with preserved ejection fraction (25 men and 83 women; mean age 74.7 years). Cardiac functional parameters at rest were assessed with B-type natriuretic peptide and echocardiography. The cardiopulmonary exercise test was used to test these parameters during exercise. Cognitive function was assessed with the Japanese version of the Montreal Cognitive Assessment (MoCA-J). Other indices were assessed biochemically, physiologically, and physically. There were significant correlations between MoCA-J score and age (r = −0.388), peak oxygen uptake (VO2, r = 0.201), peak VO2/heart rate (HR, r = 0.243), peak VO2/weight (r = 0.244), peak metabolic equivalents (r = 0.244), usual walking speed (r = −0.200), and the Timed Up and Go test (r = −0.230). Multiple linear regression analysis showed peak VO2/HR was an independent determinant of MoCA-J score after adjusting for potential confounders (β = 0.424). After 6 months of exercise training with 64 subjects, we found that the per cent change of peak VO2/HR was related to the per cent change of MoCA-J score (r = 0.296).

Conclusions These results suggested that peak VO2/HR (an index of stroke volume at peak exercise) might be associated with cognitive impairment based on the vascular cascade hypothesis.

Keywords Community-dwelling people; Cognitive impairment; Cardiac function; Preserved ejection fraction; Vascular cascade; Peak oxygen pulse

Introduction

Mild cognitive impairment (MCI) is associated with increased risk of developing Alzheimer’s disease.1 2 There is a two-hit hypothesis regarding development of Alzheimer’s disease that combines the vascular and amyloid cascade hypotheses. This acknowledges that vascular dysfunction (first hit) is likely to result in amyloid beta deposition (second hit) and ultimately neurodegeneration and cognitive decline.2 Previous studies demonstrated that impaired cerebral blood flow (CBF) or perfusion deficits are present before development of dementia.2 Total CBF is about 20% lower in patients with Alzheimer’s
disease compared with individuals without dementia. Furthermore, increased white matter hyperintensities, which has been associated with cognitive dysfunction, is related to reduced cardiac function through cardiac output (CO) changes during dynamic exercise that effect the changes of middle cerebral artery blood velocity (MCA V<sub>mean</sub>). Therefore, reduced CBF and MCA V<sub>mean</sub> may cause neuronal dysfunction or death.

Interestingly, improvement of cardiac function following cardiac transplantation increased CBF level and improved cognitive function. This suggests that cardiac function affects the vascular cascade hypothesis of cognitive impairment in patients with cardiac disease.

Recently, chronic heart failure (HF) with both reduced and preserved ejection fraction (EF) has been associated with a high prevalence of cognitive impairment. Atrial fibrillation is a known risk factor for cognitive decline and dementia due to the attenuated ability to elevate cerebral perfusion during exercise because of the impaired ability to increase CO. Similarly, relationships between cognitive impairment and left ventricle EF, left ventricle stroke volume (SV), and/or CO at rest have been demonstrated in community-dwelling people. In addition, higher peak oxygen uptake (VO<sub>2</sub>), which is known as peak CO during exercise, is associated with better global cognitive function in community-dwelling people.

These previous reports suggest that cardiac function is important in the vascular cascade hypothesis. However, after excluding people with reduced and mid-range EF (<50%), underdiagnosed with chronic HF, atrial fibrillation, and medical treatment, which potentially affect cognitive function, it is unknown if the relationship between cardiac function and cognitive function among community-dwelling people can provide insight into the pathogenesis of cognitive impairment.

The present study aimed to investigate whether cardiac function affects the pathogenesis of cognitive impairment among community-dwelling people with preserved EF (≥50%) after excluding the aforementioned factors, to provide insight into the pathogenesis of cognitive impairment.

**Methods**

**Subjects**

Subjects included 108 community-dwelling people (25 men and 83 women) who lived in the Tokyo metropolitan area. The mean age was 74.7 years (range 52–91 years). None of the subjects were currently hospitalized, but all were receiving outpatient treatment at the Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology. Exclusion criteria were as follows: age younger than 50 years, impaired vision, impaired hearing, musculoskeletal impairments that may interfere with the ability to perform the symptom-limited exercise test, a clinically unstable condition, a diagnosis of reduced and mid-range EF (<50%), moderate to severe cardiac valvular disease (stenosis and/or regurgitation), atrial fibrillation, cerebral infarction, dementia, Alzheimer’s disease, Parkinson’s disease, and treatment with beta-blockers, cilostazol, and donepezil. Potential subjects that habitually performed exercise training were also excluded from the study. Participants’ clinical characteristics are summarized in Table 1.

A 6 month follow-up assessment using methods and procedures similar to those at baseline was conducted with 64 subjects who consented to join an exercise programme and could successfully complete the programme for 6 months.

**Laboratory investigations**

Before entering the study, all subjects had fasting blood samples drawn from a large antecubital vein to determine haemoglobin, haematocrit, serum albumin, creatinine, haemoglobin A1c, and B-type natriuretic peptide (BNP) values. Haemoglobin and haematocrit levels were analysed using Sysmex XE-5000 (Sysmex Corporation, Hyogo, Japan). Serum albumin levels were analysed with the BCP assay (Shino-Test Corporation, Tokyo, Japan), and creatinine levels were analysed with enzyme assays (ShionoTest, Tokyo, Japan). Haemoglobin A1c levels were analysed using high-performance liquid chromatography (G8 Tosoh Corporation, Japan). BNP levels were analysed with the immunoenzymometric assay (E test TOSOH II assay kit, Tosoh Corporation, Japan).

**Brachial-ankle pulse wave velocity measurement**

Subjects were evaluated under quiet resting conditions in the supine position. Their brachial-ankle pulse wave velocity and blood pressure were measured with a vascular testing device (form pulse wave velocity/ABI device; BP-203PREIII, Omron Colin, Kyoto, Japan). Bilateral brachial and ankle arterial pressure waveforms were stored for 10 s with extremity cuffs connected to a plethysmographic sensor and an oscillometric pressure sensor wrapped around the participant’s arms and ankles. We used the mean of the right and left brachial-ankle pulse wave velocity values for the analyses.

**Echocardiography**

All subjects underwent transthoracic echocardiography using an echocardiograph equipped with a broadband transducer (Vivid E9®, GE Healthcare, Tokyo, Japan). Measurements for the left ventricle were obtained from the parasternal long-axis...
Table 1 Participant characteristics

| Characteristic                          | Male [n (%)] | Age [years; mean (range)] | Body mass index, kg/m² [mean (range)] | MOC-A-J score [mean (range)] | Mild cognitive impairment [n (%)] |
|----------------------------------------|--------------|---------------------------|---------------------------------------|-----------------------------|----------------------------------|
|                                        | 25 (23.1)    | 74.7 (52–91)              | 22.7 (16.3–28.2)                      | 24.7 (16–30)                | 63 (58.3)                        |
| Type of illness [n (%)]                |              |                           |                                       |                             |                                  |
| Hypertension                           |              |                           |                                       |                             |                                  |
| Dyslipidemia                           |              |                           |                                       |                             |                                  |
| Diabetes mellitus                      |              |                           |                                       |                             |                                  |
| Chronic kidney disease                 |              |                           |                                       |                             |                                  |
| Coronary artery disease                |              |                           |                                       |                             |                                  |
| Post cardiac surgery                   |              |                           |                                       |                             |                                  |
| Cancer                                 |              |                           |                                       |                             |                                  |
| Sarcopenia                             |              |                           |                                       |                             | 19 (17.6)                        |
| Biomarker [mean (range)]               |              |                           |                                       |                             |                                  |
| Haemoglobin, g/dL                      | 12.9 (7.9–15.5) |                           |                                       |                             |                                  |
| Haematocrit, %                         | 38.7 (24.4–46.3) |                           |                                       |                             |                                  |
| Serum albumin, g/dL                    | 3.98 (2.6–4.8) |                           |                                       |                             |                                  |
| Creatinine, mg/dL                      | 0.81 (0.5–2.3) |                           |                                       |                             |                                  |
| Haemoglobin A1c, %                     | 6.12 (4.6–9.6) |                           |                                       |                             |                                  |
| B-type natriuretic peptide (pg)        | 42.4 (6.0–203.4) |                           |                                       |                             |                                  |
| Echocardiography [mean (range)]        |              |                           |                                       |                             |                                  |
| Ejection fraction, %                   | 67.7 (50.0–80.0) |                           |                                       |                             |                                  |
| Stroke volume, mL/bpm                  | 65.9 (35.0–106.0) |                           |                                       |                             |                                  |
| Cardiac output, L/min                  | 4.47 (2.6–7.3) |                           |                                       |                             |                                  |
| Rest HR (bpm)                          | 68.6 (42.0–95.0) |                           |                                       |                             |                                  |
| Cardiopulmonary exercise test [mean (range)] | 990.0 (343–1695) |                           |                                       |                             |                                  |
| Peak VO₂, mL/min                       |                           |                           |                                       |                             |                                  |
| Peak VO₂/hour rate, mL/bpm             |                           |                           |                                       |                             |                                  |
| Peak VO₂/weight, mL/min/kg             |                           |                           |                                       |                             |                                  |
| Peak metabolic equivalents             |                           |                           |                                       |                             |                                  |
| Peak heart rate, bpm                   |                           |                           |                                       |                             |                                  |
| Peak systolic blood pressure, mmHg     |                           |                           |                                       |                             |                                  |
| Physiological Assessment [mean (range)] |                           |                           |                                       |                             |                                  |
| Skeletal muscle mass index, kg/m²      | 6.20 (4.35–8.08) |                           |                                       |                             |                                  |
| Male                                   | 6.99 (5.1–8.1) |                           |                                       |                             |                                  |
| Female                                 | 5.94 (4.4–8.1) |                           |                                       |                             |                                  |
| Brachial-ankle pulse wave velocity, cm/min | 1742 (1086–3004) |                           |                                       |                             |                                  |
| Physical Assessment [mean (range)]     |              |                           |                                       |                             |                                  |
| Hand grip strength, kg                 | 20.0 (8–41)   |                           |                                       |                             |                                  |
| Male                                   | 27.7 (14–41)  |                           |                                       |                             |                                  |
| Female                                 | 17.7 (8–27)   |                           |                                       |                             |                                  |
| Usual walking speed, m/s               | 1.01 (0.4–1.5) |                           |                                       |                             |                                  |
| Timed Up and Go test, s               | 8.03 (4.8–23.1) |                           |                                       |                             |                                  |
| Drugs [n (%)]                          |              |                           |                                       |                             |                                  |
| Calcium blocker                        | 39 (36.1)     |                           |                                       |                             |                                  |
| Angiotensin-converting enzyme inhibitor | 6 (5.6)       |                           |                                       |                             |                                  |
| Angiotensin II receptor blocker         | 29 (26.9)     |                           |                                       |                             |                                  |
| Statin                                 | 25 (23.1)     |                           |                                       |                             |                                  |
| Insulin                                | 4 (3.7)       |                           |                                       |                             |                                  |
| Sulfonlureas                           | 1 (0.9)       |                           |                                       |                             |                                  |
| Biguanides                             | 9 (8.3)       |                           |                                       |                             |                                  |
| Thiazolidinediones                     | 1 (0.9)       |                           |                                       |                             |                                  |
| Alpha-glucosidase inhibitors           | 5 (4.6)       |                           |                                       |                             |                                  |
| Dipeptidyl peptide-4                  | 9 (8.3)       |                           |                                       |                             |                                  |
| Prednisolone                           | 3 (2.8)       |                           |                                       |                             |                                  |
| Aspirin                                | 14 (13)       |                           |                                       |                             |                                  |

HR, heart rate; MoCA-J, Japanese version of the Montreal Cognitive Assessment; peak VO₂, peak oxygen uptake.

and apical four-chamber views, in accordance with standard criteria. Left ventricular EF, SV, and CO were automatically calculated with the modified Simpson rule in the apical two-chamber and four-chamber views. We excluded the reduced and mid-range EF (<50%), according to the guideline of European Society of Cardiology (2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF). 

Cardiopulmonary exercise test

All subjects underwent a symptom-limited bicycle ergometer cardiopulmonary exercise test (CPET) using an upright, electromagnetically braked cycle ergometer (Aerobike Strength Ergo-8, Mitsubishi Electronic, Tokyo, Japan), a metabolic analyser (Aeromonitor AE-310S, Minato Medical Science, Osaka, Japan), and an electrocardiogram (Stress test system ML-9000, Fukuda Denshi, Tokyo, Japan). The exercise test began with a 3 min rest on the ergometer followed by a 4 min warm-up at 0 W and 60 rpm. The load was then increased incrementally by 15 W per minute during the exercise test. All CPET parameters were measured from the beginning of the initial rest on the cycle ergometer until the end of the exercise session.

The CPET was terminated on the subject’s request, if abnormal physiological responses occurred or if a subject was unable to continue to perform the pedalling exercise correctly. VO₂, carbon dioxide output (VCO₂), minute ventilation, tidal volume, and frequency of respiration were smoothed with an 8-breath moving average. Peak VO₂ was defined as the highest VO₂ value obtained during the last minute of the CPET. Peak W was defined as the power at the measured peak VO₂. VO₂/hour rate (HR) (oxygen pulse) was calculated by dividing the moving average VO₂ by the HR. When the respiratory exchange ratio (VCO₂/VO₂) was less than 1.0 at peak exercise, the test was considered insufficient because of the subject’s poor effort and those peak exercise data were not used in the analyses.

Skeletal muscle mass index and body mass index

Appendicular skeletal muscle mass was measured using total body dual-energy X-ray absorptiometry (Lunar iDXA, GE Healthcare, Tokyo, Japan). The sum of the muscle mass of the four limbs was considered the appendicular skeletal muscle mass. The skeletal muscle mass index was calculated as appendicular skeletal muscle mass divided by the height in metres squared (kg/m²). Body mass index was calculated as body weight divided by height in metres squared (kg/m²).

Physical performance evaluation

For the Timed Up and Go (TUG) test, subjects were instructed to stand up from a chair, walk forward to a 3 m marker, turn, walk back to the chair, and sit down again as fast as possible. The time was recorded in seconds. Two trials were conducted per person, with the shorter time used in the analyses.
Walking speed is an established indicator of overall gait performance. To test usual walking speed, we asked subjects to walk along a straight 11 m walkway on a flat floor once, at their usual speed. Walking speed was measured over a 5 m distance between markers placed 3 and 8 m from the start of the walkway. Two trials were conducted per person, with the shorter time used in the analyses.

Hand grip strength is a valid indicator of overall muscle strength and is a useful indicator of upper extremity strength. Handgrip strength was assessed two times on each hand alternately using a Smedley-type hand dynamometer (JAMAR, Sammons Preston Rolyan, IL, USA). The highest value of two trials was used in the analyses.

For each subject, all physical performance parameters were assessed by trained research assistants.

Assessment of cognitive function

Cognitive function was assessed using with the Japanese version of the Montreal Cognitive Assessment (MoCA-J). It is traditionally used in clinical settings to detect cognitive impairment in older adults with MCI or early dementia. MoCA-J scores range from 0 to 30, with higher scores indicating better cognitive performance. The MoCA-J was selected a priori as the study’s main cognitive test, given it has greater sensitivity in detecting MCI in community-dwelling people than the Mini-Mental State Examination. Trained research assistants assessed each subject’s cognitive functioning using the MoCA-J.

Exercise training programme

Each exercise session included warm-up, cool down, and flexibility exercises. In addition, each session comprised 30 min of submaximal aerobic exercise with cycling training at 50–70% of the peak VO₂ and 15 min of submaximal resistance training (knee extension, hip abduction, rowing, and leg press) at 50–70% of one repetition maximum. Subjects underwent one exercise session 2 days per week over a 6-month period. Training was performed according to the American Heart Association’s guidelines.

Statistical analyses

Sample size of 108 patients was calculated for 95% power, \( \alpha = 0.05, \beta = 0.05 \), and anticipated effect size = 0.25 using sample size software (G*Power 3.1.9.2. Germany).

Spearman’s correlation analysis was performed to examine the relationships between MoCA-J score and biochemical parameters, physiological assessment, cardiac functional parameters of echocardiography, CPET, and physical functional assessments. Multiple linear regression analyses to predict MoCA-J score were adjusted for age, sex, peak VO₂/HR, TUG, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, and sarcopenia. We used paired t-tests to compare the indices [MoCA-J score, peak VO₂, peak VO₂/HR, peak VO₂/weight, peak metabolic equivalents (METs), peak HR, usual walking speed, and TUG] between baseline and after the 6 month exercise training programme. Pearson’s correlation analysis was performed to examine the relationship between the per cent change of MoCA-J score and the per cent change of peak VO₂, peak VO₂/HR, peak VO₂/weight, peak METs, peak HR, usual walking speed, and TUG. All statistical analyses were performed using SPSS Version 22 (IBM Japan, Tokyo, Japan). The significance level was set at \( P < 0.05 \) for all tests.

Ethical considerations

This study was approved by the Ethics Committee of the Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology (authorization number: 240301) and conforms with the principles outlined in the Declaration of Helsinki. All participants gave their written informed consent before data collection.

Results

Table 2 shows the results of the univariate correlation analyses. The MoCA-J score showed significant positive correlations with peak VO₂, peak VO₂/HR, peak VO₂/weight, and peak METs and significant negative correlations with age, usual walking speed, and TUG. Table 3 shows the results of multiple linear regression analysis to predict MoCA-J score at baseline. Peak VO₂/HR was an independent determinant of MoCA-J score (\( B = 0.424, P < 0.01 \)), even after adjustment for potential confounders (age, peakVO₂/HR, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, and sarcopenia), sex (\( B = 1.920, P < 0.05 \)), and TUG (\( B = -0.228, P < 0.05 \)). Table 4 shows the results of the comparison of the indices between baseline and after 6 months of exercise training. Peak VO₂, peak VO₂/HR, peak VO₂/weight, peak METs, TUG, and MoCA-J scores were significantly improved after exercise training, whereas peak HR and usual walking speed were not.

For the longitudinal analysis, univariate correlations between the per cent change of MoCA-J score and the per cent change of the indices that improved after the 6 month exercise programme are shown in Table 2. The per cent change of MoCA-J score had a significant positive correlation with peak VO₂/HR (\( r = 0.296, P < 0.05 \)).

880 M. Sugie et al.

ESCHF 2018; 5: 877–884
DOI: 10.1002/ehf2.12311
Table 2: Correlation coefficient between MoCA-J and related factors at baseline and between %change of MoCA-J and %change of related factors after 6 months

| Related factors                        | Correlation coefficient | P-value |
|---------------------------------------|-------------------------|---------|
| Baseline (vs. MoCA-J)                 |                         |         |
| Age                                   | −0.388                  | <0.001  |
| Body mass index, kg/m²                 | −0.049                  | n.s.    |
| Haematocrit, %                        | 0.009                   | n.s.    |
| Serum albumin, g/dL                   | 0.169                   | n.s.    |
| Creatinine, mg/dL                     | −0.129                  | n.s.    |
| Haemoglobin A1c, %                    | 0.105                   | n.s.    |
| B-type natriuretic peptide (pg)       | −0.087                  | n.s.    |
| Brachial-ankle pulse wave velocity, cm/min | −0.188                  | n.s.    |
| Stroke volume, ml/bpm                 | 0.190                   | n.s.    |
| Cardiac output, L/min                 | 0.086                   | n.s.    |
| Ejection fraction, %                  | −0.013                  | n.s.    |
| Rest heart rate, bpm                  | −0.251                  | <0.01   |
| Peak VO₂, L/min                       | 0.201                   | <0.05   |
| Peak VO₂/heart rate, ml/bpm           | 0.243                   | <0.05   |
| Peak VO₂/weight, ml/min/kg            | 0.244                   | <0.05   |
| Peak metabolic equivalents            | 0.244                   | <0.05   |
| Peak heart rate, bpm                  | 0.081                   | n.s.    |
| Peak systolic blood pressure, mmHg    | −0.011                  | n.s.    |
| Skeletal muscle mass index, kg/m²     | −0.041                  | n.s.    |
| Hand grip strength, kg                | 0.130                   | n.s.    |
| Usual walking speed, s                | −0.200                  | <0.05   |
| Timed Up and Go test, s               | −0.230                  | <0.05   |
| After 6 months (vs. %change of MoCA-J) |                        |         |
| %Change of peak VO₂                   | 0.072                   | n.s.    |
| %Change of peak VO₂/heart rate        | 0.296                   | <0.05   |
| %Change of peak VO₂/weight            | 0.159                   | n.s.    |
| %Change of peak heart rate            | −1.700                  | n.s.    |
| %Change of peak metabolic equivalents | 0.071                   | n.s.    |
| %Change of usual walking speed        | 0.142                   | n.s.    |
| %Change of Timed Up and Go test       | −0.124                  | n.s.    |

MoCA-J, Japanese version of the Montreal Cognitive Assessment; n.s., not significant; peak VO₂, peak oxygen uptake. P-values were calculated using Spearman’s correlation analyses in baseline. P-values were calculated using Pearson’s analyses in after 6 month analyses.

Discussion

Our study using data from unselected outpatients with preserved EF without HF in a Japanese geriatric clinic found that 58.3% of subjects presented cognitive impairment that fulfilled criteria for MCI (Table 1). This MCI prevalence rate was similar to a previous report in older community residents in Japan (64.1%).

It is known that there are relationships between cognitive impairment and TUG test performance,22 aortic pulse wave velocity23 left ventricle EF,14 left ventricle SV, CO,15 and peak VO₂. Furthermore, a relationship between cognitive impairment and sarcopenia was recently identified.25 This study showed that peak VO₂/HR (i.e. cardiac function during exercise) was more important in the pathophysiology of cognitive impairment among community-dwelling outpatients with preserved EF than the factors listed previously. However, this study found that although positive, the relationship between peak VO₂/HR and cognitive function was relatively weak, because this study excluded subjects with potentially low peak VO₂/HR, such as those with reduced and mid-range EF (<50%), chronic HF, and atrial fibrillation.

Previously, higher VO₂ max was reported to be associated with better global cognitive function and better performance in the domains of memory, executive function, and motor skill in middle-aged and older adults.17 Another report indicated that cardiorespiratory fitness (i.e. peak VO₂) was associated with better performance on cognitive function tests and higher volumes of several regions of grey matter.24 Additionally, Reiter et al. assessed the association between cortical atrophy (a biomarker of Alzheimer’s disease) and an exercise intervention in an MCI group and a healthy older adults group and reported that with cardiorespiratory fitness, improved peak VO₂ was positively correlated with cortical thickness in both groups.26

Peak VO₂ is generally calculated using the Fick principle: Peak VO₂ = SV × HR × AVO₂diff (arterial-venous oxygen difference). Peak VO₂ is strongly correlated with peak CO; therefore, peak VO₂ is considered an index of CO. Similarly, peak VO₂/HR is strongly correlated with peak SV; meaning peak VO₂/HR is considered an index of SV. In addition, it was previously reported that peak AVO₂diff did not change after exercise training in either young or older adults.28

Based on these previous reports, our results suggest that SV at peak exercise with one cardiac contraction (i.e. peak VO₂/HR) rather than peak HR is an important factor among the components of peak VO₂. Therefore, although previous studies reported the effectiveness of peak VO₂ in cognitive function, such as those with reduced and mid-range EF (≤50%), chronic HF, and atrial fibrillation.

Table 3: Multiple linear regression analysis for predicting MoCA-J score (baseline)

| B              | β     | P-value | LCI  | UCI  |
|----------------|-------|---------|------|------|
| Peak VO₂/HR    | 0.424 | 0.303   | <0.01| 0.124| 0.724|
| Timed Up and Go test | −0.228| −0.214  | <0.01| −0.426| −0.030|
| Age            | −0.073| −0.19   | n.s. | −0.147| 0.000|
| Sex            | 1.920 | 0.263   | <0.05| 0.421| 3.419|

MoCA-J, Japanese version of the Montreal Cognitive Assessment; peak VO₂/HR, peak oxygen uptake/heart rate; n.s., not significant. Adjusted for (rest heart rate, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, and sarcopenia) conventional risk factors in addition to peak VO₂/HR, LCI; lower 95% confidence intervals, UCI; upper 95% confidence intervals.

ESC Heart Failure 2018; 5: 877–884
DOI: 10.1002/ehf2.12311
function, peak VO₂/HR may be a contributor. Furthermore, this suggests that peak VO₂/HR may be important in vascular dysfunction cascade through CBF and MCA V\(_{\text{mean}}\) mechanisms among community-dwelling people with preserved EF. In addition, recent reports\(^{29,30}\) suggest the strong relationship between CBF and cognitive functions. This also supported our results. This study also showed that only the percent change of peak VO₂/HR had a positive correlation with the percent change of MoCA-J score after the 6 month exercise programme (Table 2). This may also indicate that peak VO₂/HR affects both improvement and decline in cognitive function.

Interestingly, Saito et al. reported in the review about ‘Alzheimer’s disease malignant cycle’ that impaired arterial pulsation, which could be an exacerbation factor of cerebral amyloid angiopathy, which results in arteriolosclerosis (hypoperfusion); furthermore, hypoperfusion induces β-amyloid overproduction and elimination failure.\(^{31}\)

Based on these reports, the relation between percent change of peak VO₂/HR and MoCA-J score might be a phenotype of the relation between the SV with one cardiac contraction during exercise (i.e. peak VO₂/HR), which might relate with arterial pulsation and β-amyloid metabolism.

This study showed that peak VO₂/HR is important in the pathophysiology of cognitive impairment compared with any other cognitive-related potential factors (usual walking speed, TUG, aortic pulse wave velocity, and sarcopenia) among community-dwelling older adults with preserved EF. Recently, a high prevalence of cognitive impairment was reported in patients with chronic HF (both HF with reduced and preserved EF).\(^{11}\) Interestingly, we found that peak VO₂/HR is related to skeletal muscle mass index, which is an important factor in sarcopenia,\(^{32}\) and hypothesized that the decline of peak VO₂/HR with decreased skeletal muscle mass in sarcopenia is a phenotype of HF with preserved EF.\(^{32}\) Therefore, multiple linear regression analysis to predict MoCA-J score (cognitive impairment) showed that peak VO₂/HR is a determinant factor after adjusting for potential confounders (including sarcopenia) among the community-dwelling people with preserved EF (without HF).

In present study, the evaluations using SV, CO, and brain scan were not carried out to confirm or rule out amyloid angiopathy or other brain pathology such as extensive vascular leukoencephalopathy. In addition to the adequate control group for the exercise programme, further analyses such as CBF and/or MCA V\(_{\text{mean}}\) are necessary to support our results.

In conclusion, peak VO₂/HR (an index of SV at peak exercise) is important for cognitive function among community-dwelling people with preserved EF, which may be related to the vascular cascade hypothesis, and this result is useful to understand the mechanism of cognitive function not only community-dwelling people but also among HF with reduced and preserved EF.

### Acknowledgements

The exercise training programme was offered to all participants with the cooperation of the stuff of Health Management Services, Inc. We thank Bonnie Lynch, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript. We thank Shogo Endo, PhD, from Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology for giving academic support to revise this manuscript.

### Conflict of interest

None declared.

### Funding

This study had no sponsor.

---

### Table 4 Comparison of the indices between baseline and after 6 month exercise training

|                  | Baseline (\(n = 64\)) | After 6 months (\(n = 64\)) | \(P\)-value |
|------------------|------------------------|-------------------------------|-------------|
| MoCA-J score     | 25.1 ± 2.8             | 26.6 ± 2.7                    | <0.001      |
| Peak VO₂, mL/min | 1033.9 ± 266.3         | 1103.6 ± 337.2                | <0.05       |
| Peak VO₂/heart rate, mL/bpm | 8.1 ± 2.1             | 8.5 ± 2.1                     | <0.001      |
| Peak VO₂/weight, mL/min/kg | 18.4 ± 4.2             | 19.8 ± 4.9                    | <0.01       |
| Peak metabolic equivalents | 5.27 ± 1.2             | 5.64 ± 1.4                    | <0.01       |
| Peak heart rate, bpm | 128 ± 19               | 131 ± 20                      | n.s.        |
| Usual walking speed, m/s | 4.85 ± 1.2             | 4.7 ± 1.3                     | <0.01       |
| Timed Up and Go test, s | 7.4 ± 1.9             | 7.2 ± 1.9                     | <0.05       |

MoCA-J, Japanese version of the Montreal Cognitive Assessment; peak VO₂, peak oxygen uptake; n.s., not significant. \(P\)-values were calculated using paired t-tests analyses.
29. Ogoh S. Relationship between cognitive function and regulation of cerebral blood flow. *The Journal of Physiological Sciences: JPS* 2017; 67: 345–351.

30. Toth P, Tarantini S, Csiszar A, Ungvari Z. Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. *Am J Physiol Heart Circ Physiol* 2017; 312: H1–H20.

31. Saito S, Ihara M. New therapeutic approaches for Alzheimer’s disease and cerebral amyloid angiopathy. *Front Aging Neurosci* 2014; 6: 290.

32. Sugie M, Harada K, Takahashi T, Nara M, Ishikawa J, Koyama T, Kim H, Tanaka J, Fujimoto H, Obuchi S, von Haehling S, Kyo S, Ito H. Relationship between skeletal muscle mass and cardiac function during exercise in community-dwelling older adults. *ESC Heart Failure* 2017; 4: 409–416.