



# Increased arterial velocity pulse index is an independent factor related to skeletal muscle mass reduction and tissue damage in patients with cardiovascular disease

Haruhito Harada<sup>1</sup> · Hisao Ikeda<sup>2</sup> · Yasuhiro Nishiyama<sup>1</sup> · Hiroshi Niiyama<sup>1</sup> · Atsushi Katoh<sup>1</sup> · Hisashi Kai<sup>1</sup>

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## Abstract

Reduced skeletal muscle mass is the most important component of sarcopenia. Aging and chronic diseases, including chronic heart failure, are the causes of reduced skeletal muscle mass. However, little is known about the mechanism of skeletal muscle mass reduction in patients with cardiovascular disease (CVD). The purpose of this study was to assess the associations among skeletal muscle mass reduction, endothelial function, and other markers of advanced vascular damage in CVD patients. This was a retrospective cross-sectional analysis that included 310 inpatients with CVD in our hospital. Flow-mediated vasodilation (FMD) was performed to assess early vascular damage, i.e., endothelial dysfunction. The arterial velocity pulse index (AVI) and arterial pressure volume index (API) were assessed to reveal signs of advanced vascular damage, such as arterial stiffening and increased peripheral resistance. The bioelectrical phase angle (PA), as a marker of tissue damage, and the skeletal muscle index (SMI) were measured. Correlation analyses were performed among these parameters. Sarcopenia was diagnosed in 25.5% of patients according to the Asian Working Group for Sarcopenia criteria. Greater progression of arterial stiffness, shown by a higher AVI, and more severe tissue damage, shown by a narrower PA, were found in individuals with sarcopenia. Stepwise multivariate regression analysis showed that sex, age, PA, hypertension, and AVI were factors independently correlated with SMI. In conclusion, advanced vascular damage, such as increased arterial stiffness and peripheral resistance, might play an important role in the reduction in skeletal muscle mass, possibly through damage to skeletal muscle tissue in CVD patients.

**Keywords** Arterial stiffness · Arteriosclerosis · Cardiovascular disease · Phase angle · Sarcopenia · Skeletal muscle

## Introduction

Loss of skeletal muscle mass, which is one of the essential components of the diagnosis of sarcopenia, progresses with aging and under various chronic pathological conditions, such as inflammation, malignancy, malnutrition, endocrine

disorders, chronic kidney disease (CKD), and chronic heart failure (CHF) [1, 2]. CHF is induced by various cardiovascular diseases (CVDs) and is a common cause of sarcopenia [3, 4]. Sarcopenia decreases quality of life and results in frailty and morbidity [1, 2].

Vascular damage, such as arteriosclerosis and atherosclerosis, is the most common underlying pathogenesis of CVD, especially among the elderly. Vascular endothelial dysfunction detected by flow-mediated vasodilation (FMD) is observed from the early stage of CVD [5]. Arterial stiffening progresses with aging, hypertension, atherosclerosis, and vascular remodeling with smooth muscle cell proliferation and extracellular matrix deposition [6]. In turn, the progression of arterial stiffening induces an increase in central blood pressure, vascular endothelial dysfunction, and injury of the capillary artery, and results in organ damage [6]. Scuteri et al. reported that pulse wave velocity (PWV) was suitable as a marker of arterial stiffness and early vascular aging [7–10].

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✉ Haruhito Harada  
harada\_haruhito@med.kurume-u.ac.jp

<sup>1</sup> Department of Cardiology, Kurume University Medical Center, Kurume, Japan

<sup>2</sup> Department of Physical Therapy, Faculty of Fukuoka Medical Technology, Teikyo University, Omuta, Japan

The arterial velocity pulse index (AVI) and arterial pressure volume index (API) are novel noninvasive methods to assess arterial properties using differential pulse wave analysis. API reflects brachial arterial stiffness [11]. An increase in the AVI indicates increased arterial stiffness from the aorta to the brachial artery and increased resistance of peripheral arteries [12], and the AVI is associated with known risk factors for CVD [13]. Hitsumoto reported the association between AVI and preclinical myocardial damage shown by increasing serum concentrations of cardiac troponin T [14]. These reports suggest that skeletal muscle damage is induced by arterial stiffness and can be evaluated by the bioelectrical phase angle (PA), which is assessed by a bioelectrical impedance assay and is known to be a marker of cell and tissue injury [15].

Little is known about the relationship of vascular damage and tissue damage with the reduction in skeletal muscle mass in patients with CVD. Therefore, we investigated the associations among skeletal muscle mass reduction, endothelial function, and other markers of advanced vascular damage in CVD patients.

## Materials and methods

### Study design and patients

This was a retrospective cross-sectional study. A total of 310 consecutive CVD patients who were admitted to our hospital between April 2013 and December 2015 were retrospectively enrolled. Patients who had undergone pacemaker implantation were excluded from this study because a bioelectrical impedance assay is contraindicated. Patients with malignancy were also excluded because a narrow PA is documented in the context of various cancers [16–19]. Written informed consent was obtained from all patients, and the study was approved by the Ethics Committee of Kurume University.

### Diagnosis of sarcopenia

Sarcopenia was diagnosed according to the diagnostic algorithm recommended by the Asian Working Group for Sarcopenia guidelines in 2014 [20]. Sarcopenia was defined as a low skeletal muscle index (SMI) ( $<7.0 \text{ kg/m}^2$  in males;  $<5.7 \text{ kg/m}^2$  in females) associated with either low handgrip strength ( $<26 \text{ kgf}$  in males;  $<18 \text{ kgf}$  in females) or low gait speed ( $<0.8 \text{ m/s}$ ). Nonsarcopenia was diagnosed when subjects had a normal SMI ( $\geq 7.0 \text{ kg/m}^2$  in males;  $\geq 5.7 \text{ kg/m}^2$  in females) or when they had normal handgrip strength ( $\geq 26 \text{ kgf}$  in males;  $\geq 18 \text{ kgf}$  in females) and normal gait speed ( $\geq 0.8 \text{ m/s}$ ). The age criterion of more than 65 years old was not adopted for sarcopenia diagnosis in this study

because age is a possible confounding factor of disease-related sarcopenia; hence, CVD patients younger than 65 years old were included.

### Muscle mass measurements

Muscle mass was measured by the bioelectrical impedance assay using the InBody S10 body composition analyzer (Biospace, Tokyo, Japan). This system applies electricity at frequencies of 1, 5, 50, 250, and 500 kHz and 1 MHz through the body. Whole-body impedance was measured using an ipsilateral foot–hand electrical pathway. Bioelectrical impedance assay measurements were performed after 8 h of no exercise, 4 h of fasting, and voiding of the bladder [21]. Edematous patients were examined after edema had improved. Appendicular muscle mass was calculated as the sum of the muscle mass of the arms and legs. Absolute appendicular muscle mass was converted to the SMI by dividing the value by the square of the height in meters ( $\text{kg/m}^2$ ).

### Muscle strength measurements

Muscle strength was assessed based on handgrip strength using a Smedley hand dynamometer MY-2080 (Matsumiya Ikaseiki Seisakusho Co. Ltd, Tokyo, Japan). One test was performed for each hand, and the result from the stronger hand was used for sarcopenia diagnosis.

### Physical performance measurements

Physical performance was assessed based on usual gait speed. A previous technique reported by Tanimoto et al. [22] was modified for this purpose. Patients were asked to walk straight ahead for 12 m at their usual speed for the measurement of 10-m-walk time. The walking speed reached a steady speed within the first 2 m. Gait speed ( $\text{m/s}$ ) was calculated by dividing the distance covered (10 m) by the 10-m-walk time (s).

### Bioelectrical PA measurement

The bioelectrical PA was measured by the bioelectrical impedance assay using the InBody S10 body composition analyzer (Biospace). To measure the maximum PA, electricity at a frequency of 50 kHz was applied through the body. Whole-body impedance and reactance were measured using an ipsilateral right hand–trunk–right foot electrical pathway. PA was calculated using the following equation:  $\text{PA (degrees)} = \arcsin (\text{reactance/impedance}) \times 180/\pi$ . The PA is  $0^\circ$  if the circuit is a pure electrolytic solution and  $90^\circ$  if the circuit is a system of pure cell membranes with no fluid [15]. Therefore, the presence of tissue damage is suggested when the PA value is reduced.

## AVI measurement

The AVI was measured using a commercially available instrument (PASSESA AVI-1500; Shisei Datum, Tokyo, Japan) after at least 4 h of fasting in a quiet room with the temperature maintained at 20–25 °C. As Hitsumoto et al. described previously [14, 23], the AVI has the characteristics of a pulse wave pattern at higher cuff pressures compared with systolic blood pressure. The first peak of the differentiated waveform between pulse wave and time (Vf) and the absolute value of the bottom of the valley of the differentiated waveforms between pulse wave and time (Vr) were automatically measured, and then the AVI was calculated as  $20 \times (Vr/Vf)$ . Because Vr represents the reflected pulse wave, the AVI increases as the wave reflections increase. Thus, AVI is an assessment of arterial stiffness from the aorta to the muscular artery, systemic hemodynamics, and functional changes in peripheral resistance vessels [12]. The validity and reliability of the AVI measured using this method have been confirmed by Sasaki-Nakashima et al. [24].

## API measurement

The API was measured using a commercially available instrument (PASSESA AVI-1500; Shisei Datum, Tokyo, Japan) after at least 4 h of fasting in a quiet room with the temperature maintained at 20–25 °C. As Komine and Sueta described previously [11, 23], the API reflects the characteristics of arterial stiffness of the brachial artery using the time series of occlusive-cuff pressure and the amplitudes of pulse oscillations measured based on local slopes of the curve between the decreasing cuff pressure and the corresponding arterial pressure volume. Details of the API measurement were described by Komine et al. [11].

## FMD measurement

FMD was measured using a commercially available, high-resolution, ultrasound device equipped with a 10-MHz linear array transducer (UNEXEF18G system; UNEX Corporation, Nagoya, Japan) after at least 4 h of fasting in a quiet room with the temperature maintained at 20–25 °C, as previously described by Kanahara et al. [25]. After baseline diameter measurement, the right forearm was clamped with a pressure of 250 mmHg, which was maintained for 5 min to create an ischemic condition in the arm. The alteration of artery diameter was continuously monitored from 30 s before pressure release to 3 min thereafter. FMD was calculated using the following formula:  $\text{FMD (\%)} = [(\text{diameter of the maximum dilatation after releasing the ischemic condition} - \text{baseline diameter}) / \text{baseline diameter}] \times 100$ .

## Updated Charlson's age-comorbidity index (CACI)

To compare background characteristics between non-sarcopenia and sarcopenia, the updated CACI [26] was adopted. The updated CACI is composed of 17 scored comorbidities, such as age, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease (COPD), connective-tissue disease, peptic ulcer disease, diabetes mellitus, moderate to severe CKD, hemiplegia, leukemia, malignant lymphoma, solid tumor, liver disease, and AIDS. We referred to the following site <https://www.mdcalc.com/charlson-comorbidity-index-cci>.

## Statistical analysis

Clinical data on admission were collected from hospital charts and databases. Statistical analysis was performed using Ekuseru-Toukei 2012 software (Social Survey Research Information Co., Ltd, Tokyo, Japan). Numerical data are expressed as the means  $\pm$  standard deviations or as medians with 95% confidence intervals. Student's *t* test and the Mann–Whitney *U*-test were used to compare the two groups, as appropriate. Proportional data were analyzed using the chi-squared test or Fisher's exact test. Single regression analysis was performed to assess the relationships between the SMI or PA and each of the other variables. Categorical variables were converted to dummy variables before the analysis. The following baseline variables were used for single regression analysis: age, sex, FMD, AVI, API, pulse pressure, PA, SMI, hypertension, diabetes mellitus, and dyslipidemia (comorbidities associated with atherosclerosis progression). Stepwise multivariate regression analysis was performed to identify independent correlation factors among the variables with a significance level of  $p < 0.05$  in the comparison between sarcopenia and nonsarcopenia groups and  $p < 0.1$  in the single regression analysis for SMI. Partial correlation analysis was performed among FMD, AVI, API, PA, SMI, age, sex, updated CACI, systolic and diastolic blood pressure, pulse pressure, hypertension, diabetes mellitus, liver dysfunction, CKD, COPD, connective-tissue disease, and seven kinds of medication (including ARB/ACE inhibitors, calcium-channel blockers,  $\beta$ -blockers, isosorbide dinitrate/nicorandil, diuretics, statin, and oral antidiabetic agents/insulin). Statistical significance was considered at the level of  $p < 0.05$ .

## Results

### Baseline characteristics and demographics

Among the 310 CVD patients, the mean age was 72 years (age range: 18–98 years), and 179 were males. As shown in

Table 1, sarcopenia was diagnosed in 79 of 310 study patients (25.5%). The SMI was significantly smaller in sarcopenic patients than in nonsarcopenic patients, as were handgrip

strength and gait speed. Sarcopenia was more common in older subjects, female subjects, and participants with a lower BMI. Diastolic blood pressure, but not systolic blood pressure,

**Table 1** Baseline characteristics and demographics

|                                           | Total                | Nonsarcopenia       | Sarcopenia          | <i>p</i> value |
|-------------------------------------------|----------------------|---------------------|---------------------|----------------|
| <i>N</i> (%)                              | 310                  | 231 (74.5)          | 79 (25.5)           | –              |
| Age, years                                | 72 ± 12              | 69 ± 13             | 78 ± 8              | <0.0001        |
| Female, <i>N</i> (%)                      | 131                  | 81 (35.1)           | 50 (63.3)           | <0.0001        |
| Height, cm                                | 157.5 ± 10.8         | 160.2 ± 9.8         | 149.6 ± 9.7         | <0.0001        |
| Weight, kg                                | 62.0 ± 15.7          | 66.8 ± 14.6         | 47.9 ± 9.0          | <0.0001        |
| Body mass index, kg/m <sup>2</sup>        | 24.7 ± 4.3           | 25.9 ± 4.3          | 21.4 ± 3.0          | <0.0001        |
| Diagnostic component for sarcopenia       |                      |                     |                     |                |
| Skeletal muscle index, kg/m <sup>2</sup>  | 6.78 ± 1.42          | 7.33 ± 1.10         | 5.18 ± 0.95         | <0.0001        |
| Handgrip strength, kgf                    | 23.6 ± 13.4          | 28.1 ± 13.2         | 13.8 ± 7.2          | <0.0001        |
| Gait speed, m/s                           | 1.05 ± 0.38          | 1.18 ± 0.36         | 0.79 ± 0.30         | <0.0001        |
| Systolic blood pressure, mmHg             | 125 ± 21             | 125 ± 21            | 123 ± 22            | 0.3764         |
| Diastolic blood pressure, mmHg            | 68 ± 13              | 70 ± 14             | 65 ± 13             | 0.0039         |
| Basic parameter                           |                      |                     |                     |                |
| Hemoglobin, g/dl                          | 12.6 ± 2.2           | 13.1 ± 2.2          | 11.4 ± 1.7          | <0.0001        |
| Serum albumin, g/dl                       | 4.1 ± 0.5            | 4.2 ± 0.5           | 3.9 ± 0.4           | <0.0001        |
| Total cholesterol, mg/dl                  | 172 ± 38             | 174 ± 41            | 167 ± 31            | 0.1156         |
| eGFR, ml/min/1.73 m <sup>2</sup>          | 62 ± 22              | 64 ± 21             | 56 ± 25             | 0.0095         |
| Hs-CRP, ng/ml, median (95% CI, <i>N</i> ) | 1025 (881–1600, 172) | 921 (748–1250, 126) | 1920 (915–6450, 46) | 0.0457         |
| Cardiovascular disease, <i>N</i> (%)      |                      |                     |                     |                |
| Chronic heart failure, AHA/ACC stage C&D  | 60                   | 37 (16.0)           | 23 (29.1)           | 0.01361        |
| Coronary artery disease (including CABG)  | 147                  | 115 (49.8)          | 32 (40.5)           | 0.19170        |
| Hypertensive heart disease                | 16                   | 12 (5.2)            | 4 (5.1)             | 1.00000        |
| Cardiomyopathy (including secondary)      | 21                   | 17 (7.4)            | 4 (5.1)             | 0.60938        |
| Valvular heart disease                    | 19                   | 13 (5.6)            | 6 (7.6)             | 0.58744        |
| Arrhythmia (excluding PMI)                | 48                   | 32 (13.9)           | 16 (20.3)           | 0.20684        |
| Peripheral artery disease                 | 13                   | 9 (3.9)             | 4 (5.1)             | 0.74533        |
| Cardiovascular surgery (excluding CABG)   | 1                    | 0 (0.0)             | 1 (1.3)             | 0.25484        |
| Aortic disease                            | 6                    | 3 (1.3)             | 3 (3.8)             | 0.17525        |
| Others                                    | 39                   | 30 (13.0)           | 9 (11.4)            | 0.84496        |
| Comorbidity, <i>N</i> (%)                 |                      |                     |                     |                |
| Hypertension                              | 195                  | 153 (66.2)          | 42 (53.2)           | 0.04336        |
| Diabetes mellitus                         | 112                  | 92 (39.8)           | 20 (25.3)           | 0.02146        |
| Dyslipidemia                              | 126                  | 103 (44.6)          | 23 (29.1)           | 0.01706        |
| Hyperuricemia                             | 27                   | 22 (9.5)            | 5 (6.3)             | 0.49184        |
| Obesity                                   | 32                   | 31 (13.4)           | 1 (1.3)             | 0.00098        |
| Chronic kidney disease                    | 46                   | 24 (10.4)           | 22 (27.8)           | 0.00039        |
| Stroke                                    | 27                   | 22 (9.5)            | 5 (6.3)             | 0.49184        |
| Liver dysfunction                         | 19                   | 16 (6.9)            | 3 (3.8)             | 0.42110        |
| Chronic obstructive pulmonary disease     | 12                   | 9 (3.9)             | 3 (3.8)             | 1.00000        |
| Connective-tissue disease                 | 18                   | 9 (3.9)             | 9 (11.4)            | 0.01867        |
| Update Charlson's age-comorbidity index   | 3.5 ± 1.8            | 3.2 ± 1.7           | 4.5 ± 1.5           | <0.0001        |
| Medications, <i>N</i> (%)                 |                      |                     |                     |                |
| ARB/ACE inhibitors                        | 164                  | 119 (51.5)          | 45 (57.0)           | 0.60184        |
| Calcium-channel blockers                  | 106                  | 82 (35.5)           | 24 (30.4)           | 0.49230        |
| β-blockers                                | 116                  | 82 (35.5)           | 34 (43.0)           | 0.28124        |
| Isosorbide dinitrate/Nicorandil           | 71                   | 48(20.8)            | 23(29.1)            | 0.16210        |
| Diuretics                                 | 77                   | 49 (21.2)           | 28 (35.4)           | 0.01549        |
| Statins                                   | 124                  | 95 (41.1)           | 29 (36.7)           | 0.50904        |
| Oral antidiabetic agents/insulin          | 60                   | 48 (20.8)           | 12 (15.2)           | 0.32447        |

*p* value comparison between nonsarcopenia and sarcopenia, ACC American College of Cardiology, ACE angiotensin converting enzyme, AHA American Heart Association, ARB angiotensin II receptor blocker, CABG coronary artery bypass grafting, CI confidential interval, eGFR estimated glomerular filtration rate, Hs-CRP high sensitive c-reactive protein, PMI pacemaker implantation

**Table 2** Vascular and tissue damages

|                                    | Total <i>N</i> = 310 | Nonsarcopenia<br><i>N</i> = 231 (74.5) | Sarcopenia<br><i>N</i> = 79 (25.5) | <i>p</i> value |
|------------------------------------|----------------------|----------------------------------------|------------------------------------|----------------|
| Vascular damages                   |                      |                                        |                                    |                |
| Arterial velocity pulse index      | 24.8 ± 8.0           | 23.4 ± 7.4                             | 28.7 ± 8.6                         | <0.0001        |
| Flow-mediated vasodilation, (%)    | 4.65 ± 2.18          | 4.84 ± 2.28                            | 4.08 ± 1.75                        | 0.0023         |
| Arterial pressure volume index     | 28.1 ± 9.2           | 28.0 ± 9.6                             | 28.3 ± 8.2                         | 0.8236         |
| Pulse pressure, (mmHg)             | 56 ± 19              | 56 ± 20                                | 58 ± 18                            | 0.2610         |
| Tissue damage                      |                      |                                        |                                    |                |
| Bioelectrical phase angle, degrees | 4.48 ± 1.35          | 4.80 ± 1.29                            | 3.57 ± 1.09                        | <0.0001        |

*p* value: comparison between nonsarcopenia and sarcopenia

was significantly lower in sarcopenic patients than in non-sarcopenic patients. Hemoglobin, albumin, and eGFR were lower and hs-CRP was higher in the sarcopenia group than in the nonsarcopenia group. Total cholesterol was similar between the sarcopenia and nonsarcopenia groups. Symptomatic heart failure (AHA/ACC stage C and D) was more common in sarcopenic patients than in nonsarcopenic patients, whereas no significant difference was found in the prevalence of other CVDs between the two groups. The prevalence of CKD was higher in sarcopenic patients than in nonsarcopenic patients. Sarcopenic patients had a lower prevalence of hypertension, diabetes mellitus, dyslipidemia, and obesity than nonsarcopenic patients. The prevalence of connective-tissue disease (17 rheumatoid arthritis and one CREST syndrome) was significantly higher in sarcopenic patients. No significant difference was found in liver dysfunction or COPD. The updated CACI was significantly higher in sarcopenic patients than in nonsarcopenic patients. Higher use of diuretics was found in sarcopenic patients than in nonsarcopenic patients.

### Vascular and tissue damage

AVI, a marker of vascular stiffness, was significantly higher in sarcopenic patients than in nonsarcopenic patients. On the other hand, FMD, a marker of vascular endothelial function, was lower in sarcopenic patients than in nonsarcopenic patients. Sarcopenic patients showed a narrower PA, an indicator of tissue damage, than nonsarcopenic patients (Table 2). No significant differences in API or pulse pressure were found between sarcopenic and nonsarcopenic patients.

### Relationships among atherosclerotic markers, SMI, and tissue damage

As shown in Fig. 1a, b, the AVI had modest negative associations with the SMI ( $r = -0.4089$ ,  $p < 0.0001$ ) and PA ( $r = -0.3990$ ,  $p < 0.0001$ ). There were weak positive associations of FMD with the SMI ( $r = 0.1703$ ,  $p < 0.005$ ) and PA ( $r = 0.2310$ ,  $p < 0.0001$ ) (Fig. 1c, d). In addition,

the PA showed a modest positive association with SMI ( $r = 0.4937$ ,  $p < 0.0001$ ) (Fig. 1e).

### Independent factors associated with SMI reduction

AVI, FMD, PA, age, male sex, hypertension, diabetes mellitus, and dyslipidemia were used as variables in the multivariate regression analysis for SMI because they met the selection criteria based on the comparison between sarcopenia and nonsarcopenia and single regression analyses for SMI. Stepwise multivariate regression analysis showed that male sex, age, PA, hypertension, and AVI were independent factors associated with the SMI in CVD patients, although FMD, diabetes mellitus, and dyslipidemia were not associated with the SMI (Table 3).

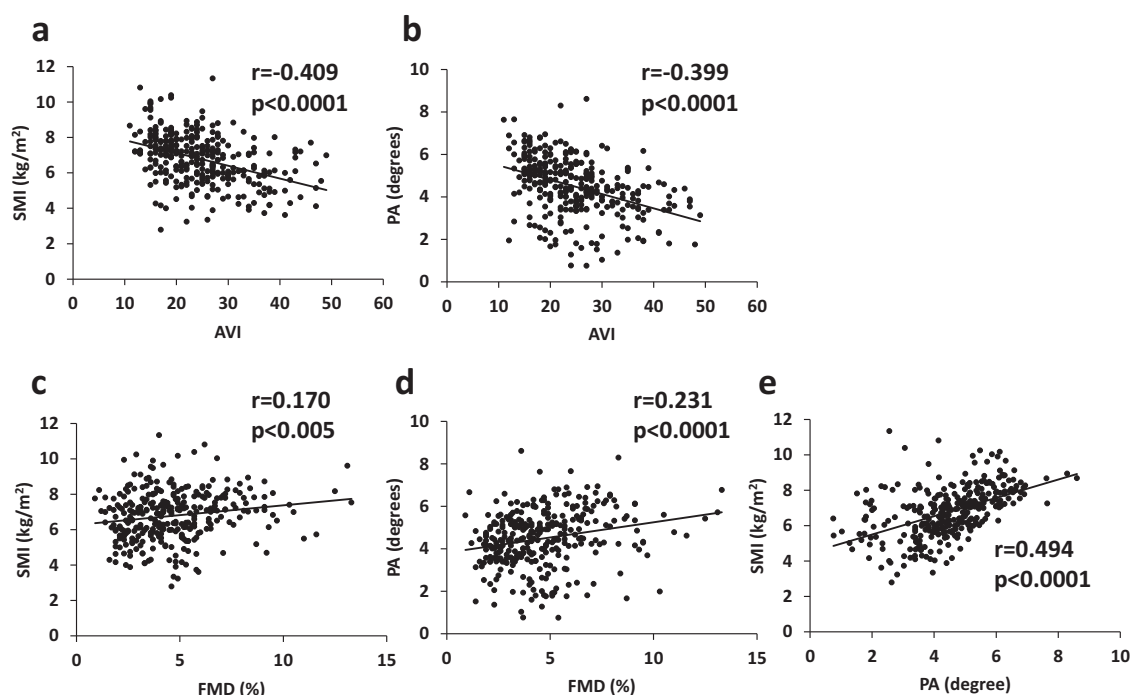
### Sex differences

Whether sex affects the association of the AVI with a reduced SMI and a narrow PA was assessed (Table 4). In both the male and female subgroups, the AVI was negatively associated with the SMI and PA, and the SMI was positively associated with the PA in CVD patients. However, FMD was not associated with SMI reduction in either sex, whereas FMD had a weak association with PA in males.

### Partial correlation analysis among FMD, AVI, PA, and SMI adjusted by comorbidity and drugs

Each pair of correlations among FMD, AVI, PA, and SMI was examined by partial correlation analysis adjusted for API, age, sex, updated CACI, systolic and diastolic blood pressure, pulse pressure, hypertension, diabetes mellitus, liver dysfunction, CKD, COPD, and connective-tissue disease. A significant correlation was found between SMI and AVI and between SMI and PA but not between AVI and PA (Supplement Table 1). In addition, a partial correlation was found among each pair of FMD, AVI, PA, and SMI adjusted for seven kinds of medication, as shown in





**Fig. 1** Single regression analyses among flow-mediated vasodilation (FMD), arterial velocity pulse index (AVI), bioelectrical phase angle (PA), and skeletal muscle index (SMI)

Table 1; however, the relationship between FMD and SMI was not significant (Supplement Table 2).

## Discussion

The present study demonstrated that CVD patients with sarcopenia had lower SMI, lower PA, higher AVI, and decreased FMD than those without sarcopenia. In CVD patients, the AVI was negatively correlated with the SMI and PA, and FMD was weakly correlated with the SMI and PA. Furthermore, the PA had a positive association with the SMI. Stepwise multivariate regression analysis (Table 3) and partial correlation analysis adjusted for age, sex, and comorbidity (Supplement Table 1) showed that independent factors associated with the SMI in CVD patients were male sex, age, PA, and AVI but not FMD.

The AVI is a novel indicator of arterial stiffness from the aorta to the muscular artery and peripheral resistance [12–14, 23, 24]. In the present study, SMI reduction was associated with AVI independent of other significant factors, such as male sex, age, hypertension, and PA (Table 3). There are several possible mechanisms by which increased arterial stiffness induces SMI reduction. First, arterial stiffening is considered to induce peripheral organ damage through hemodynamic effects. The aorta and the elastic arteries with normal vascular compliance buffer the transmission of the impact of pulse pressure to the peripheral

**Table 3** Stepwise multivariate regression analysis for SMI

|              | Standard error | $\beta$ | <i>p</i> value |
|--------------|----------------|---------|----------------|
| Male         | 0.1280         | 0.4541  | <0.0001        |
| Age          | 0.0056         | −0.2075 | <0.0001        |
| Phase angle  | 0.0523         | 0.1779  | <0.0001        |
| Hypertension | 0.1185         | 0.1381  | <0.0001        |
| AVI          | 0.0082         | −0.0956 | 0.0415         |

Age, male sex, FMD, AVI, PA, hypertension, diabetes mellitus, and hyperlipidemia were used as the variables for stepwise multivariate regression analysis for SMI. There was no significant correlation with FMD, diabetes mellitus, and dyslipidemia

AVI arterial velocity pulse index,  $\beta$  standardized partial regression coefficient, FMD flow-mediated vasodilation, SMI skeletal muscle index

arteries and arterioles, which results in the protection of microvascular circulation in the peripheral organs. However, when vascular compliance is decreased with aortic stiffening, the impact of pulse pressure is not attenuated and arrives at the peripheral arteries and arterioles. The enhanced impact of pulse pressure decreases microvascular circulation and induces organ damage [6]. In addition, the increased hemodynamic impact of arterial stiffening is considered to trigger systemic atherothrombotic events [27]. Second, the increase in vascular stiffness is a characteristic of early vascular aging and induces vascular remodeling associated with decreased elastin and increased collagen

**Table 4** Single regression analysis of each marker by sex

| Whole subjects,<br><i>N</i> = 310 |                | PA      | SMI     | Male, <i>N</i> = 179 |                | PA      | SMI     | Female, <i>N</i> = 131 |                | PA      | SMI     |
|-----------------------------------|----------------|---------|---------|----------------------|----------------|---------|---------|------------------------|----------------|---------|---------|
| AVI                               | <i>P</i> value | <0.0001 | <0.0001 | AVI                  | <i>P</i> value | <0.0001 | <0.0001 | AVI                    | <i>P</i> value | 0.0032  | 0.0135  |
|                                   | <i>r</i> value | −0.3990 | −0.4089 |                      | <i>r</i> value | −0.3617 | −0.3194 |                        | <i>r</i> value | −0.2554 | −0.2155 |
| FMD                               | <i>P</i> value | <0.0001 | 0.0026  | FMD                  | <i>P</i> value | 0.0007  | 0.0510  | FMD                    | <i>P</i> value | 0.3003  | 0.5441  |
|                                   | <i>r</i> value | 0.2310  | 0.1703  |                      | <i>r</i> value | 0.2525  | 0.1461  |                        | <i>r</i> value | 0.0912  | 0.0535  |
| PA                                | <i>P</i> value | –       | <0.0001 | PA                   | <i>P</i> value | –       | <0.0001 | PA                     | <i>P</i> value | –       | <0.0001 |
|                                   | <i>r</i> value |         | 0.4937  |                      | <i>r</i> value |         | 0.3443  |                        | <i>r</i> value |         | 0.3924  |

AVI arterial velocity pulse index, FMD flow-mediated vasodilation, PA bioelectrical phase angle, *r* correlation coefficient, SMI skeletal muscle index

contents [7, 8]. Arterial stiffening enhances hypertension, and vascular remodeling impairs oxygen diffusion and nutrient supply to peripheral organs [7]. Taken together, these results suggest that the increase in arterial stiffness induced skeletal muscle damage and consequently reduced skeletal muscle mass in CVD patients. Previous reports suggested a correlation between appendicular muscle mass and both brachial–ankle PWV and the ankle–brachial index [28, 29]. However, it should be noted that in contrast to APIs reflecting brachial arterial stiffness, AVIs represent not only arterial stiffness from the aorta to the brachial artery but also other factors, such as peripheral arterial resistance [12, 23, 30]. Peripheral resistance is increased by the remodeling of small arteries and arterioles characterized by medial smooth muscle cell proliferation and extracellular matrix deposition, as well as increased vascular tone. The combination of these advanced vascular damages detected by AVI may play a role in skeletal damage and skeletal muscle mass reduction in CVD patients.

FMD was significantly lower in sarcopenic patients than in nonsarcopenic patients (Table 2). Aging-dependent decreases in the production of nitric oxide and suppression of the mTOR complex are candidate factors involved in the manifestation of sarcopenia [31]. Reduced NO bioavailability was suggested by the endogenous inhibitor, asymmetric dimethylarginine (ADMA), in patients with CKD [32]. Endothelial dysfunction might be induced by endogenous inhibitors, such as ADMA, because CKD is a common morbidity of sarcopenia. Previous reports have shown that endothelial dysfunction induces hypoperfusion, resulting in organ dysfunction in the brain and muscle [32, 33]. However, it was unexpected that FMD was not a significant factor involved in SMI reduction in CVD patients (Table 3). The reason was unknown in this study. In addition, it was unexpected that the simple markers related to the aorta, muscular artery, pulse pressure, and API were not associated with sarcopenia and/or SMI. This finding suggested that AVI is not dependent simply on the increased stiffness of the aorta or brachial artery. The AVI is

determined by multiple factors, including the comprehensive stiffness from the aorta to the muscular artery, systemic hemodynamics, and peripheral artery resistance. In CVD patients, it is possible that skeletal muscle damage and reduction would be related to more advanced vascular changes, accompanied by vascular stiffening or vascular remodeling, but not to early vascular damage, such as endothelial dysfunction.

Another important finding of this study was that a narrow PA was associated with SMI reduction in CVD patients. To the best of our knowledge, this is the first report that a narrow PA is associated with both skeletal muscle mass loss and aortic stiffness. Previous studies have shown that a narrow PA was correlated with SMI reduction and was an independent risk factor for frailty and mortality in elderly individuals [15, 34, 35]. Another study demonstrated that a narrower PA was associated with markers of malnutrition and atherosclerosis in patients on peritoneal dialysis [36]. In addition, chronic inflammation and malnutrition are involved in the pathogenesis of SMI reduction [37]. Thus, one of the possible explanations may be that a narrow PA would reflect the skeletal muscle damage induced by chronic inflammation and/or malnutrition resulting from arterial stiffness in CVD patients. This issue should be addressed in a future study.

A previous study reported that sarcopenic obesity is commonly found in the community-dwelling older population [38, 39]. However, this was not the case with our present study, which included only CVD patients and showed a higher prevalence of CHF in sarcopenic patients. Sarcopenic patients were older and had a lower BMI and a lower prevalence of hypertension, diabetes mellitus, dyslipidemia, and obesity than nonsarcopenic patients, as shown in Table 1. This finding may be attributable to cardiac cachexia in CHF patients, especially in elderly patients.

Aging is strongly associated with arterial stiffness and sarcopenia. However, AVI was a significant marker for detecting sarcopenia even after adjustment for age (Supplement Table 3). Therefore, it is suggested that the

reduction of vascular stiffening factors (e.g., hypertension, diabetes mellitus, hyperlipidemia) beginning in adolescence is necessary to prevent sarcopenia.

## Limitations

Because this was a cross-sectional analysis, the longitudinal changes in the associations among vascular damage markers, PA, and SMI were not assessed. Second, at present, AVI is not the gold-standard method for evaluating arterial stiffness. However, it has been reported that AVI is correlated with other established markers of arterial stiffness, such as the cardio-ankle vascular index [12, 13]. Next, significant associations were found between AVI and PA and height, weight, and BMI (Supplement Table 4). These findings were consistent with a previous report showing that AVI is negatively associated with height and BMI [14]. According to the measurement principles of AVI and PA, height and body weight may have an impact on the associations of AVI and PA with SMI as confounding factors. To solve this issue, further detailed study is awaited. Finally, the number of patients studied in this study was small. Therefore, a large-scale study is needed to draw stronger conclusions in the future.

## Conclusion

Among CVD patients, skeletal muscle mass reduction was associated with the AVI independent of age and sex. In addition, skeletal muscle mass reduction was correlated with a tissue damage marker, PA. These findings suggest that advanced vascular damage, including arterial stiffening and increased peripheral resistance, rather than endothelial dysfunction, might play a role in skeletal muscle reduction, possibly through skeletal muscle damage in CVD patients.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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