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Original Article

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Clinical Significance of Arterial Velocity Pulse Index in Patients With Stage B Heart Failure With Preserved Ejection Fraction

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Abstract

Background: In clinical settings, the arterial velocity pulse index (AVI) is explored as a novel marker of atherosclerosis using pulse wave analysis; however, data regarding the correlations between AVI and heart failure (HF) are limited. This study aimed to elucidate the clinical significance of AVI in patients with stage B HF with preserved ejection fraction (HFpEF).

Methods: In this cross-sectional study, 345 patients with stage B HFpEF (no symptoms despite evidence of cardiac structural or functional impairment, and left ventricular ejection fraction which is estimated by echocardiography ≥ 50%) were enrolled. Patients with a history of HF hospitalization were excluded. The AVI was measured using a commercial device, and associations between AVI and various clinical parameters were examined.

Results: Significant correlations between AVI and various clinical parameters, such as E/e' as a maker of left ventricular diastolic function ($r = 0.35$; $P < 0.001$), high-sensitivity cardiac troponin T levels as a marker of myocardial injury ($r = 0.47$; $P < 0.001$), reactive oxygen metabolite levels as an oxidative stress marker ($r = 0.31$; $P < 0.001$), urinary albumin concentration as a marker of kidney function ($r = 0.34$; $P < 0.001$) and calf circumference as a marker of muscle mass volume ($r = -0.42$; $P < 0.001$) were observed. Furthermore, multiple regression analyses revealed that these clinical parameters were selected as independent variables when AVI was used as a subordinate factor.

Conclusions: This study shows that AVI might be a determining factor for prognosis in patients with stage B HFpEF. Nevertheless, further comprehensive prospective studies, including intervention therapies, are warranted to validate the findings of this study.

Keywords: Arterial velocity pulse index; Heart failure with preserved ejection fraction; Stage B; Left ventricular diastolic function; High-sensitivity cardiac troponin T; Oxidative stress; Sarcopenia

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Introduction

In recent years, extended life expectancy or lifestyle changes have markedly contributed to the elevated incidence of heart failure (HF) worldwide. Contrarily, there have been remarkable advancements with multiple therapeutic agents of proven benefit in HF with reduced ejection fraction; HF with preserved ejection fraction (HFpEF) lacks evidence-based therapies [1, 2]. In addition, epidemiological studies have reported that patients with HF with a history of HF hospitalization exhibit poor prognosis because of rehospitalization owing to HF worsening, cardiovascular diseases, or other adverse events [3, 4]. Thus, it is imperative to investigate the novel diagnosis and therapy for HFpEF before the prevalence of HF hospitalization or symptoms of HF such as dyspnea or edema.

The arterial velocity pulse index (AVI), a novel marker of atherosclerosis, uses oscillometric cuffs to measure pulse waveforms [5]. Increments in AVI depict the enhancement of reflected waves resulting from atherosclerosis or other parameters. In addition, several clinical studies reported the clinical efficacy of AVI as a cardiovascular risk factor [6-8]. Conversely, some studies reported that physiological markers of atherosclerosis, such as pulse wave velocity, cardio-ankle vascular index, augmentation index (AIx) and flow-mediated dilation, correlated with the pathogenesis or prognosis of HF [9-12]. Nevertheless, data regarding the correlations between AVI and HF, including HFpEF, are limited. Hence, this cross-sectional study aimed to elucidate the clinical significance of AVI in patients with stage B HFpEF.

Materials and Methods

Patients

This cross-sectional study was performed at the Hitsumoto Medical Clinic in Yamaguchi, Japan, between December 2015 and November 2018. A total of 345 patients with stage B HFpEF (no symptoms despite evidence of cardiac structural or functional impairment, and left ventricular ejection fraction which is estimated by echocardiography ≥ 50%) were enrolled. Stage B HF was defined based on the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart

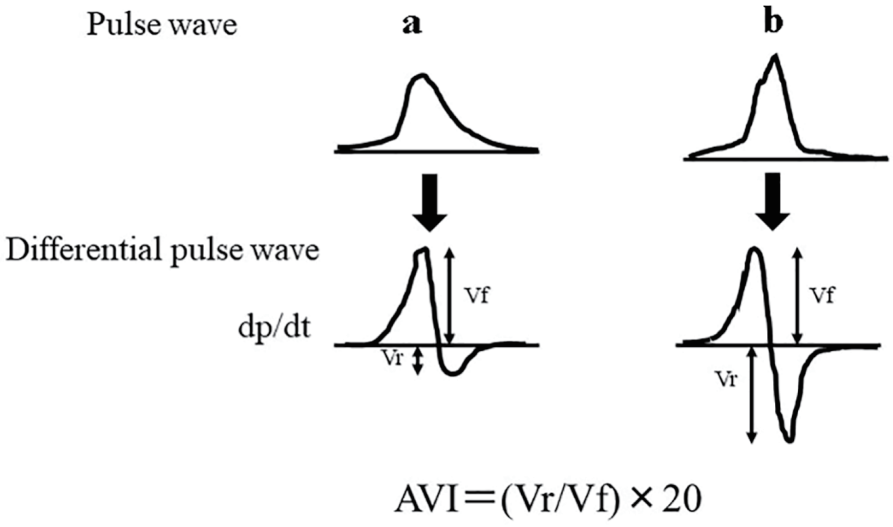

Figure 1. The measurement concept of the AVI. AVI has the characteristics of a pulse wave pattern at higher cuff pressures than the systolic blood pressure. We measured two variables automatically, i.e. Vf (the first peak of the differential of the waveform with respect to time) and Vr (the absolute value of the bottom of the valley of the differential of the waveform with respect to time), and AVI was automatically calculated as 20 × (Vr/Vf). (a) Pulse wave pattern of low AVI levels. (b) Pulse wave pattern of high AVI levels. AVI: arterial velocity pulse index.

Failure in Adults [13]. Of note, patients with a history of HF hospitalization were excluded from the study. Patients comprised 121 males (35.0%) and 224 females (65.0%), with the mean age of 74 ± 7 years (mean ± standard deviation). This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as the Helsinki Declaration. The study protocol was approved by the Institutional Review Board of the Hitsumoto Medical Clinic (approval number: 2015-11).

AVI measurement

The AVI was measured using a commercially available instrument (PASSESA AVI-1500; Shisei Datum, Tokyo, Japan) in the sitting position as previously described [5]. All measurements were performed when participants were in a quiet room (temperature, 20 - 25 °C). Figure 1 shows the measurement concept of AVI. Of note, AVI has the characteristics of a pulse wave pattern at higher cuff pressures than the systolic blood pressure. We measured two variables automatically, i.e. Vf (the first peak of the differential of the waveform with respect to time) and Vr (the absolute value of the bottom of the valley of the differential of the waveform with respect to time), and AVI was automatically calculated as 20 × (Vr/Vf). Although the systolic waveform rapidly increases and decreases in response to reflected arterial waves, the initial waveform is not affected by the reflected arterial waves. Vf indicates the initial waveform, while Vr indicates the subsequent (weaker) waveform affected by reflected arterial waves. As the wave reflections become stronger, AVI increases in parallel with an increase in Vr. Prior studies have established the validity and reliability of AVI measured using this method [14, 15].

Assessment of clinical parameters

Various clinical parameters such as physical measurement, traditional cardiovascular risk factor, history of ischemic heart disease, blood glucose-related parameters, echocardiographic findings, kidney function, brain natriuretic peptide (BNP) levels, high-sensitivity cardiac troponin T (hs-cTnT) levels and oxidative stress were evaluated. Obesity was defined using the body mass index (BMI), evaluated as the weight (kg) divided by the squared height (m^2). Calf circumferance was mesured as a surrogate marker of muscle mass volume [16]. Current smoking was defined as smoking, at least, one cigarette per day over the previous 28 days. In addition, history of ischemic heart disease was defined as patients with a history of myocardial infarction and/or angiography-proven significant stenosis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or those taking antihypertensive medications. Dyslipidemia was defined as low-density lipoprotein cholesterol levels ≥ 140 mg/dL, high-density lipoprotein cholesterol levels ≤ 40 mg/dL, triglyceride levels ≥ 150 mg/dL, or based on ongoing treatment for dyslipidemia. We defined diabetes mellitus as having fasting blood glucose levels of ≥ 126 mg/dL or hemoglobin A1c levels of ≥ 6.5%, which is estimated by the National Glycohemoglobin Standardization Program, or taking of antidiabetic treatment. We measured glucose and insulin levels using the glucose oxidase method and an enzyme immunoassay, respectively. To measure insulin resistance, HOMA-IR was calculated using the following equation [17]: HOMA-IR = fasting glucose concentration (mg/dL) × fasting insulin concentration (μg/

mL)/405. The standard technique for echocardiography was performed using HI VISION Avius (Hitachi Medical Corporation, Tokyo, Japan), and valvular heart disease was diagnosed on the basis of the Japanese Circulation Society guidelines (Guidelines for the Clinical Application of Echocardiography (JCS 2010)). Valvular heart disease comprised aortic or mitral valve disease (aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation). Using echocardiography, left ventricular wall thickness, left ventricular extended period diameter, left ventricular ejection fraction, left atrial dimension and E/e' were measured. The estimated glomerular filtration rate (eGFR) was evaluated using the adjusted Modification of Diet in the Renal Disease Study equation, which was proposed by the working group of the Japanese Chronic Kidney Disease Initiative [18]. The urinary albumin concentration was measured using a commercial kit (Siemens/Bayer DCA 2000+ analyzer; Siemens Healthineers, Tokyo, Japan). Moreover, we measured BNP levels using a commercial kit (SHIONOSPOT Reader; Shionogi & Co., Osaka, Japan) and hs-cTnT levels using a commercial kit (Roche Diagnostics, Basel, Switzerland) [19]. As an oxidative stress maker *in vivo* [20], the reactive oxygen metabolites (d-ROMs) test was performed using a commercial kit (Diacron, Grosseto, Italy).

Statistical analysis

In this study, data were analyzed using MedCalc for Windows (version 14.8.1; MedCalc Software, Ostend, Belgium) and StatView J5.0 (HULINKS, Tokyo, Japan). Data are presented as mean ± standard deviation. The correlation coefficient was estimated by Spearman rank order correlation analysis. In addition, the multivariate analysis was conducted by multiple regression analysis. The receiver-operating characteristic (ROC) curves were constructed, and the maximum Youden index [21] was used to determine the optimal AVI cutoff levels for determining high E/e', high hs-cTnT and low calf circumference. Furthermore, we considered $P < 0.05$ as statistically significant.

Results

Table 1 summarizes the patients' characteristics. The mean AVI levels were 30 ± 7 (range: 14 - 54). The distribution of AVI exhibited nearly normal distribution. Table 2 presents the correlations between AVI and various clinical parameters. In addition, age, presence of diabetes mellitus, fasting blood glucose levels, left ventricular wall thickness, E/e', urinary albumin concentration, BNP, hs-cTnT and d-ROMs test exhibited significantly positive correlation with AVI. However, male gender, body height, BMI, pulse rate, eGFR, renin-angiotensin system inhibitor use and statin use exhibited significantly negative correlation with AVI. Table 3 summarizes the results of a multiple regression analysis with AVI as a subordinate factor. Explanatory factors were selected by examining multicollinearity among the variables or by conducting a stepwise method, and nine factors were selected. Of those nine factors, seven factors (E/e', hs-cTnT, calf circumference, urinary albumin concentration, body height, d-ROM test and pulse rate) were identified as independent variables when AVI was used as a subordinate factor. Figure 2 shows the ROC curve analysis for the detection of high E/e' of > 15, high hs-cTnT of ≥ 0.014 ng/mL and low calf circumference (< 34 cm in males and < 33 cm in females) based on previous studies. The maximum

Table 1. Patient Characteristics

n (male/female)	345 (121/224)
Age (years)	74 ± 7
Body height (cm)	155 ± 10
Body mass index (kg/m2)	22.8 ± 3.8
Calf circumference (cm)	32.5 ± 3.0
Current smoker, n (%)	56 (16)
Ischemic heart disease, n (%)	85 (25)
Hypertension, n (%)	256 (74)
Systolic blood pressure (mm Hg)	143 ± 22
Diastolic blood pressure (mm Hg)	82 ± 10
Pulse rate (/min)	70 ± 11
Dyslipidemia, n (%)	227 (66)
Diabetes mellitus, n (%)	124 (36)
Fasting blood glucose (mg/dL)	109 ± 28
HOMA-IR	2.1 ± 1.7
Hemoglobin A1c (%)	6.2 ± 1.0
Heart valvular disease, n (%)	269 (78)
IVSTd (mm)	9.8 ± 1.7
LVDd (mm)	50.4 ± 3.6
LVEF (%)	67.7 ± 8.7
LAD (mm)	42.6 ± 5.6
E/e'	10.5 ± 3.3
eGFR (mL/min/1.73 m^2)	49.9 ± 18.9
Log-urinary albumin (mg/g Cr)	1.8 ± 0.5
Log-BNP (pg/mL)	2.0 ± 0.3
Log-hs-cTnT (ng/mL)	-2.0 ± 0.3
d-ROMs test (U. CARR)	304 ± 113
AVI	30 ± 7
Medication	
RAS inhibitor, n (%)	217 (63)
β blocker, n (%)	71 (21)
Diuretics, n (%)	70 (20)
Statin, n (%)	130 (38)

Continuous values are mean ± SD. HOMA-IR: homeostasis assessment insulin resistance; IVSTd: interventricular septal thickness at end-diastole; LVDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial dimension; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-cTnT: high-sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites; AVI: arterial velocity pulse index; RAS: renin-angiotensin system.

Table 2. AVI and Various Clinical Parameters

	r	P value
Sex (female = 0, male = 1)	-0.16	0.002
Age	0.18	< 0.001
Body height	-0.20	< 0.001
Body mass index	-0.18	< 0.001
Calf circumference	-0.42	< 0.001
Current smoker (no = 0, yes = 1)	0.10	0.072
Ischemic heart disease (no = 0, yes = 1)	0.08	0.160
Hypertension (no = 0, yes = 1)	0.02	0.684
Systolic blood pressure	0.03	0.539
Diastolic blood pressure	0.02	0.730
Pulse rate	-0.20	< 0.001
Dyslipidemia (no = 0, yes = 1)	0.09	0.078
Diabetes mellitus (no = 0, yes = 1)	0.17	0.002
Fasting blood glucose	0.14	0.009
HOMA-IR	0.04	0.481
Hemoglobin A1c	0.09	0.105
Heart valvular disease	0.08	0.153
IVSTd	0.11	0.043
LVDd	0.05	0.401
LVEF	0.03	0.614
LAD	0.07	0.183
E/e'	0.35	< 0.001
eGFR	-0.12	0.024
Log-urinary albumin	0.34	< 0.001
Log-BNP	0.23	< 0.001
Log-hs-cTnT	0.47	< 0.001
d-ROMs test	0.31	< 0.001
RAS inhibitor (no = 0, yes = 1)	-0.11	0.034
β blocker (no = 0, yes = 1)	0.08	0.095
Diuretics (no = 0, yes = 1)	0.03	0.527
Statin (no = 0, yes = 1)	-0.11	0.044

r expressed correlation coefficient. HOMA-IR: homeostasis assessment insulin resistance; IVSTd: interventricular septal thickness at end-diastole; LVDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial dimension; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-cTnT: high sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites; RAS: renin-angiotensin system.

Youden's index suggested that AVI of > 30 was the optimal cutoff point to determine the high E/e', high hs-cTnT and low calf circumference.

Discussion

Previous studies demonstrated a significant correlation between the arterial reflection wave and body height or pulse rate [22, 23]. Likewise, this study demonstrated that the body height and pulse rate were selected as the independent variables for AVI as a subordinate factor, suggesting that AVI depicts features of the arterial reflection wave. Conversely, E/e' as a maker of left ventricular diastolic function, hs-cTnT levels as a marker of myocardial injury, urinary albumin cancentration as a marker of kidney function, d-ROMs tests as an oxidative stress marker and calf circumference as a marker of muscle mass volume were selected as independent variables for AVI as a subordinate factor.

Table 3. Multiple Regression Analysis for AVI

Explanatory factor	β	P value
E/e'	0.29	< 0.001
Log-hs-cTnT	0.27	< 0.001
Calf circumference	-0.26	< 0.001
Log-urinary albumin	0.16	< 0.001
Body height	-0.12	0.005
d-ROMs test	0.11	0.022
Pulse rate	-0.10	0.024
Sex (male)	-0.07	0.125
Log-BNP	0.06	0.189

R^2 = 0.41. AVI: arterial velocity pulse index; hs-cTnT: high-sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites; BNP: brain natriuretic peptide; β: standardized regression coefficient; R^2: coefficient of determination.

Left ventricular diastolic dysfunction plays a vital role in the HFpEF pathogenesis, and left ventricular diastolic dysfunction is reportedly caused by not only heart condition, such as left ventricular hypertrophy or myocardial fibrosis, but also arterial dysfunction [24, 25]. In addition, some clinical studies reported that the augmentation index as a representative marker of the arterial reflection wave exhibited a significant correlation with parameters of left ventricular diastolic dysfunction [26, 27]. Hence, significant correlations between AVI and E/e' in this study considered the significance of an increase in the arterial reflection wave, which is caused by various factors, including atherosclerosis for the diastolic function of stage B HFpEF. Meanwhile, hs-cTnT is used as a biomarker to assess the degree of myocardial injury in the clinical setting. Moreover, several studies have suggested the clinical efficacy of hs-cTnT as a prognostic value such as the incidence of all-cause mortality or rehospitalization for HF in patients with HFpEF [28]. Hence, the significant correlation between AVI and hs-cTnT in this study could be interpreted that an increase in the arterial reflection wave caused myocardial damage; furthermore, AVI could provide prognosis in patients with stage B HFpEF.

Having a target value of AVI to prevent adverse cardiovascular events in patients with stage B HFpEF is beneficial. This study attempts to decide cutoff levels of AVI for detecting high E/e' of > 15 or high hs-cTnT of ≥ 0.014 ng/mL, which reportedly correlate with diastolic dysfunction, HF hospitalization and cardiovascular risk [29-31]. The ROC curve analysis for

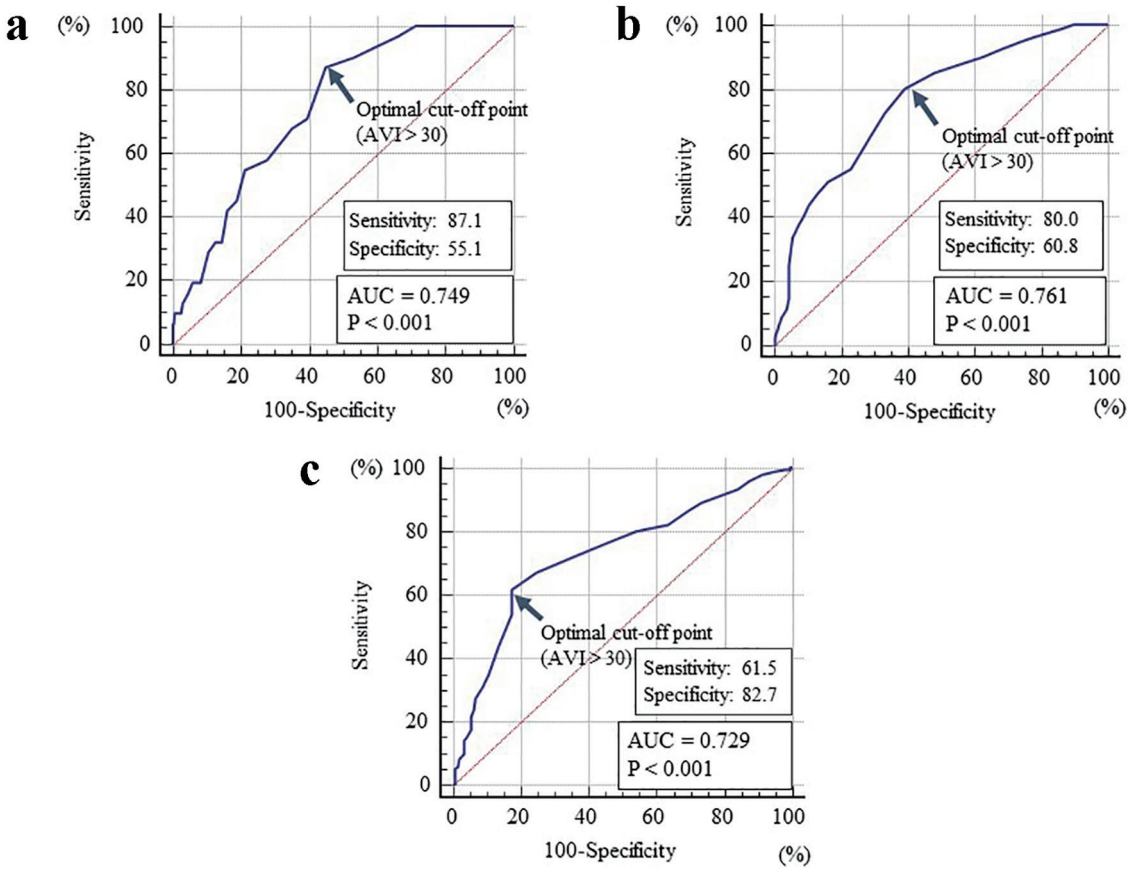

Figure 2. The cutoff value of the AVI for determining high E/e', high hs-cTnT and low calf circumference. (a) High E/e' of > 15; (b) high hs-cTnT of ≥ 0.014 ng/mL; (c) low calf circumference of < 34 cm in males and < 33 cm in females. AVI: arterial velocity pulse index; hs-cTnT: high-sensitivity cardiac troponin T; AUC: area under the curve.

AVI as high of > 30 suggested an optimal cutoff point for differentiating both high E/e' and hs-cTnT. Although the specificity is relatively low, this study indicates that the incidence of cardiovascular events, including initial HF hospitalization, in patients with stage B HFpEF could be prevented by maintaining AVI of ≤ 30 in daily practice.

The urinary albumin concentration is a maker of not only kidney function but also systemic endothelial function [32]. Moreover, studies reported the significance of endothelial dysfunction in the HFpEF pathogenesis [33-35]. Contrarily, the PROMIS-HFpEF study demonstrated that a high incidence of coronary microvascular dysfunction in HFpEF correlates with systemic endothelial dysfunction, including urinary albumin concentration, and the authors deduced that microvascular dysfunction might be a promising therapeutic target in HFpEF [35]. Hence, an independent correlation between AVI and urinary albumin concentration suggested that AVI could signify not only systemic endothelial function but also coronary microvascular function; consequently, it is a useful target factor to prevent cardiovascular adverse events in patients with stage B HFpEF.

Some studies suggested close correlations between oxidative stress and HFpEF [36, 37]. In addition, oxidative stress is reportedly affected by an increase in the arterial reflection wave [38, 39]. Likewise, this study suggested a significant correlation between the d-ROMs test as a marker of oxidative stress and AVI. Contrarily, medications, such as renin-angiotensin system inhibitor and statins, exhibited antioxidative stress efficacy. In addition, several clinical studies reported that these medications exhibited positive effects on the arterial reflection wave [40, 41]. In this study, the renin-angiotensin system inhibitor and statin use exhibited significantly negative correlations with AVI in the univariate analysis, although these medications were not selected as variables for the multivariate analysis. Corroborating the literature, this study suggested that anti-oxidant medications, such as renin-angiotensin system inhibitor or statin, should be considered for patients with high AVI.

In recent years, several clinical studies have highlighted the significance of sarcopenia in the HFpEF pathogenesis [42]. In addition, other clinical studies reported that sarcopenia could be affected by an increase in the arterial reflection wave [43, 44]. However, Kawakami et al reported that the calf circumference positively correlated with the appendicular skeletal muscle mass and skeletal muscle index, and could be used as a surrogate marker of the muscle mass for

diagnosing sarcopenia [16]. Hence, an independent correlation between AVI and calf circumference could suggest that sarcopenia affected an increase in the arterial reflection wave; this caused increased left ventricular afterload, which, in turn, caused adverse cardiac events in patients with stage B HFpEF. Similarly, Kawakami et al reported that the cutoff values of calf circumference for predicting sarcopenia were < 34 cm in males and < 33 cm in females in the Japanese population. Conversely, AVI of > 30 cm was the optimal cutoff level for determining the low calf circumference, which was elucidated by Kawakami's report. Moreover, AVI of > 30 cm suggested a definitive value to determine the high E/e' or high hs-cTnT in this study. However, studies suggested that exercise training exhibited augmented calf circumference values [45]. Although racial differences should be considered, the findings of this and previous studies suggested that we should aggressively perform intervention therapy by exercise training to target the calf circumference as ≥ 34 cm in males and ≥ 33 cm in females, resulting in the prevention of adverse cardiovascular events by decline of AVI levels in patients with stage B HFpEF.

Limitations

This study has several limitations. First, the medical treatments for HF and/or traditional cardiovascular risk factors could have affected the study results. Second, the calf circumference was measured as a surrogate marker of the muscle mass volume in this study. Nevertheless, calf circumference is a simple parameter of the muscle mass volume. Thus, further studies using accurate methods, such as computed tomography or dual-energy X-ray absorptiometry, are needed to elucidate the correlation between AVI and muscle mass volume. Finally, this was a single-center, cross-sectional study, and the sample size was relatively small. Hence, additional prospective studies, including investigations of interventional therapies, are warranted to elucidate the clinical significance of AVI in patients with stage B HFpEF.

Conclusions

This study suggests that AVI could be a determining factor for prognosis in patients with stage B HFpEF. Nevertheless, further prospective studies, including intervention therapies, are warranted to validate the results of this study.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

All patients provided informed consent.

Author Contributions

The author was involved in preparing the study design as well as acquisition, analysis and interpretation of data.

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