

Vascular Physiology according to Clinical Scenario in Patients with Acute Heart Failure: Evaluation using the Cardio-Ankle Vascular Index

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Increased aortic stiffness may be an important cause of acute heart failure (AHF). Clinical scenario (CS), which classifies the pathophysiology of AHF based on the initial systolic blood pressure (sBP), was proposed to provide the most appropriate therapy for AHF patients. In CS, elevated aortic stiffness, vascular failure, has been considered as a feature of patients categorized as CS1 (sBP > 140 mmHg at initial presentation). However, whether elevated aortic stiffness, vascular failure, is present in such patients has not been fully elucidated. Therefore, we assessed aortic stiffness in AHF patients using the cardio-ankle vascular index (CAVI), which is considered to be independent of instantaneous blood pressure. Sixty-four consecutive AHF patients (mean age, 70.6 ± 12.8 years; 39 men) were classified with CS, based on their initial sBP: CS1: sBP > 140 mmHg (n = 29); CS2: sBP 100-140 mmHg (n = 22); and CS3: sBP < 100 mmHg (n = 13). There were significant group differences in CAVI (CS1 vs. CS2 vs. CS3: 9.7 ± 1.4 vs. 8.4 ± 1.7 vs. 8.3 ± 1.7, $p = 0.006$, analysis of variance). CAVI was significantly higher in CS1 than in CS2 ($p = 0.02$) and CS3 ($p = 0.04$). CAVI did not significantly correlate with sBP at the time of measurement of CAVI ($r = 0.24$ and $p = 0.06$). Aortic stiffness assessed using blood pressure-independent methodology apparently increased in CS1 AHF patients. We conclude that vascular failure is a feature of CS1 AHF initiation.

Keywords: acute heart failure; aortic stiffness; cardio-ankle vascular index; clinical scenario; vascular failure
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Introduction

In the aging society in Japan and Western countries, heart failure has become a major health problem. The mechanisms underlying acute heart failure (AHF) are manifold because this disease results from a complex of structural and functional alterations. Among them, increased aortic stiffness has been proposed as a potential and important non-cardiac factor in the pathogenesis of AHF (Hundley et al. 2001; Cotter et al. 2008; Fallick et al. 2011). Aortic stiffness increases the systolic afterload and worsens ventricular-vascular coupling. The failing heart is particularly sensitive to afterload conditions that are determined by aortic stiffness. Thus, an increase in aortic stiffness might help explain the mechanism of AHF development (Laskey et al. 1985).

Clinical scenario (CS) is a widely accepted tool for AHF management (Mebazaa et al. 2008), especially in Japan. Initial treatment is important to improve AHF prognosis. CS, which classifies the pathophysiology of

AHF based on the initial systolic blood pressure (sBP) at the pre-hospital and early hospital stages, was proposed to provide a flow of initial treatment. Therefore, CS is easy for all health care providers to use. Effective use of this tool leads to an early improvement in symptoms and hemodynamics of AHF because it can rapidly provide the most appropriate therapy for AHF patients. In CS, elevated aortic stiffness-vascular failure has been considered as a feature of patients categorized as CS1 (sBP > 140 mmHg at initial presentation). However, whether aortic stiffness is elevated in such patients has not been fully elucidated.

To date, several parameters have been proposed for quantitatively evaluating atherosclerosis. Among them, brachial-ankle pulse wave velocity (baPWV) has been most frequently used in clinical practice in Japan. However, baPWV essentially depends on blood pressure during measurement and therefore is not a suitable parameter for evaluating arterial stiffness, particularly for patients with changes in blood pressure. In contrast, stiffness parameter β is an index reflecting arterial stiffness with less influence

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of blood pressure. The cardio-ankle vascular index (CAVI) is a new non-invasive aortic stiffness parameter that includes the aorta, femoral artery, and tibial artery by combining two indices: stiffness parameter β and Bramwell-Hill's formula. This index is considered to be independent of instantaneous blood pressure (Hayashi et al. 1980; Shirai et al. 2006). Accordingly, we examined whether the mechanism of decompensation leading to CS1 AHF can be explained by elevated aortic stiffness using CAVI.

Methods

Study patients

This study included consecutive 64 patients who were admitted to Nagoya City University Hospital because of AHF. Heart failure was diagnosed on the basis of the modified Framingham criteria (McKee et al. 1971). The AHF patients were classified by CS based on the initial sBP (CS1: sBP > 140 mmHg, n = 29; CS2: sBP 100-140 mmHg, n = 22; and CS3: sBP < 100 mmHg, n = 13). Patients with atrial fibrillation or flutter, an artificial pacemaker, a hemodynamically significant valvular disease, a post-prosthetic valve replacement condition, myocarditis, or takotsubo cardiomyopathy were excluded. Patients with peripheral artery disease were also excluded because CAVI cannot be accurately measured if the ankle-brachial pressure index is less than 0.95 (Motobe et al. 2005). Coronary artery disease was defined as positive exercise electrocardiographic changes, abnormal myocardial perfusion scintigraphic findings, and a previous history of coronary revascularization. In those patients, prior myocardial infarction (MI) was diagnosed based on the detection of a localized left ventricular (LV) wall motion abnormality using echocardiography with related electrocardiographic changes. In describing patient characteristics, hypertension was defined as sBP of at least 140 mm Hg and/or diastolic blood pressure of at least 90 mm Hg or being treated with antihypertensive drugs. Diagnostic criteria for diabetes mellitus (DM) followed the report issued by the Japan Diabetes Society (Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus et al. 2010). DM was diagnosed when the fasting blood glucose level was > 126 mg/dL, hemoglobin A1c was > 6.5 %, or when the patient was treated with blood glucose-lowering medicine. Normal-type glycemia is defined as fasting plasma glucose level of < 110 mg/dL. Borderline-type diabetes (neither diabetic nor normal) is defined as fasting plasma glucose level falling between the diabetic and normal range. Hypercholesterolemia is defined as low-density lipoprotein cholesterol level > 140 mg/dL or being treated with cholesterol-lowering medicine. Duration of disease is based on their self-report. All study patients underwent comprehensive echocardiography and CAVI at the time of discharge. Plasma B-type natriuretic peptide (BNP) concentrations were also measured at the same time. All patients provided written informed consent prior to study participation. The study protocol was performed according to the regulations

proposed by the ethical guidelines committee of the Nagoya City University Graduate School of Medical Sciences.

CAVI

CAVI is a new index of the overall stiffness of the artery from the aortic valve to the ankle. CAVI was automatically assessed using a Vasera VS-1000 (Fukuda Denshi, Tokyo, Japan). CAVI was recorded after resting for 5 min with the subject in the supine position. Electrocardiography electrodes were placed on both wrists, and a microphone was placed on the sternum to detect heart sounds. Cuffs were wrapped around both arms and both ankles. Heart-ankle pulse wave velocity (PWV) was calculated by dividing the distance from the aortic valve to the ankle artery with the sum of the difference between the time the pulse waves were transmitted to the brachium and the time the same waves were transmitted to the ankle, and the time difference between the second heart sound on the phonocardiogram and that on the notch of the brachial pulse wave. CAVI is calculated from following equation: $CAVI = a[\rho/PP \times [\ln Ps/Pd] PWV^2] + b$ (a, b, constants; ρ , blood density; PP, pulse pressure; Ps, systolic pressure; and Pd, diastolic pressure). The most noticeable feature of CAVI is its independence from blood pressure at the time of measurement (Hayashi et al. 1980; Shirai et al. 2006), although baPWV depends on blood pressure during measurement (Nye 1964). Thus, CAVI has been thought to be superior to baPWV as a parameter of arterial stiffness (Takaki et al. 2008).

CS

CS is a widely accepted tool for managing AHF on the basis of the initial sBP at the pre-hospital and early hospital stages. The use of CS can rapidly provide the most appropriate therapy for AHF patients. Patients hospitalized for AHF were classified as follows according CS (Mebazaa et al. 2008).

CS1: dyspnea and/or congestion with sBP of > 140 mmHg; CS2: dyspnea and/or congestion with sBP of 100-140 mmHg; CS3: dyspnea and/or congestion with sBP of < 100 mmHg; CS4: dyspnea and/or congestion with signs of acute coronary syndrome; and CS5: isolated right ventricular failure. In this study, patients with acute coronary syndrome (CS4) and pulmonary hypertension (CS5) were excluded.

Statistical analysis

SPSS statistical software (version 23.0, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous variables are presented as mean \pm standard deviation (SD) for normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. Categorical variables are summarized as the frequency (%). For the comparison of two groups, continuous variables were compared by unpaired Student's t-tests for normally distributed variables and Mann-Whitney

U-tests for non-normally distributed variables. Variables in more than two groups were evaluated using analysis of variance (ANOVA) with Bonferroni adjustment for normally distributed variables and Kruskal-Wallis test for non-normally distributed variables. Differences in prevalence between two groups were compared using the Chi-square test. Differences in prevalence among three groups were also compared using the Ryan's test. Relationships between two variables were evaluated by univariate linear regression analysis. The independence of the association between variables was tested using multiple regression analysis. Analysis of covariance (ANCOVA) was performed to compare CAVI among the three groups using age, body mass index (BMI), estimated glomerular filtration rate (eGFR), and pulse pressure at the time of measurement of CAVI (PP) as multiple covariates. Differences with $p < 0.05$ were considered statistically significant.

Results

There were significant differences in CAVI among the three groups (CS1 vs. CS2 vs. CS3: 9.7 ± 1.4 vs. 8.4 ± 1.7 vs. 8.3 ± 1.7 , $p = 0.006$, ANOVA). CAVI was significantly higher in CS1 than in CS2 ($p = 0.02$) and CS3 ($p = 0.04$); in contrast, no significant differences were detected in CAVI between CS2 and CS3 ($p = 0.99$) (Fig. 1). Patient clinical characteristics are presented in Table 1. No significant differences were found in patient sex, age, height, weight, and BMI among the three groups. The left ventricular ejection fraction (LVEF) at the time of discharge, as well as on admission, was not significantly different among the three groups. Patients were divided into two groups based on their LVEF on admission: those with LVEF $\geq 50\%$ (HF

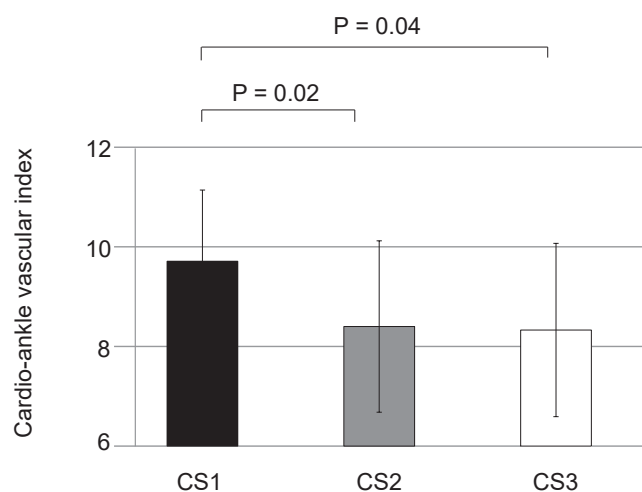


Fig. 1. Comparison of cardio-ankle vascular index (CAVI) among CS groups.

CAVI was significantly different among the three groups (CS1 vs. CS2 vs. CS3: 9.7 ± 1.4 vs. 8.4 ± 1.7 vs. 8.3 ± 1.7 , $p = 0.006$, ANOVA). CAVI was significantly higher in CS1 than in CS2 ($p = 0.02$) and CS3 ($p = 0.04$); however, no significant difference was detected in CAVI between CS2 and CS3 ($p = 0.99$). The mean and standard deviation are shown.

with preserved EF; HFpEF) and those with LVEF $< 50\%$ (HF with reduced EF; HFrEF). The number of patients in each group was as follows. (HFpEF vs. HFrEF: CS1: 8 vs. 21; CS2: 5 vs. 11; CS3: 3 vs. 10; $p = 0.91$). Plasma BNP concentrations also did not differ among the groups. There were no significant differences in heart rate among the three groups. sBP at the time of measurement of CAVI (Ps) was significantly different among the groups (CS1 vs. CS2 vs. CS3: 139.4 ± 19.3 vs. 129.2 ± 14.1 vs. 105.4 ± 10.3 mmHg, $p < 0.001$, ANOVA). Ps was significantly higher in CS1 ($p < 0.001$) and CS2 ($p < 0.001$) than in CS3 and was not significantly different between CS1 and CS2 ($p = 0.09$). Diastolic blood pressure at the time of measurement of CAVI (Pd) was also significantly different among the groups (CS1 vs. CS2 vs. CS3: 79.0 ± 10.3 vs. 79.6 ± 9.6 vs. 64.9 ± 7.0 mmHg, $p < 0.001$, ANOVA). Pd was significantly higher in CS1 ($p < 0.001$) and CS2 ($p < 0.001$) than in CS3 and was not significantly different between CS1 and CS2 ($p = 0.99$). There were significant group differences in pulse pressure at the time of measurement of CAVI (PP) (CS1 vs. CS2 vs. CS3: 60.4 ± 15.5 vs. 49.5 ± 15.7 vs. 40.5 ± 8.8 mmHg, $p < 0.001$, ANOVA). PP was significantly higher in CS1 than in CS2 ($p = 0.03$) and CS3 ($p < 0.001$) and was not significantly different between CS2 and CS3 ($p = 0.23$). The prevalence of hypertension was also higher in CS1 (65.5%) and CS2 (63.6%) than in CS3 (7.7%) ($p < 0.001$). The prevalence of a history of heart failure was not significantly different among the three groups. The prevalence of hypercholesterolemia, coronary artery disease, and smoking history, which can have an impact on CAVI, was not significantly different among the three groups. The prevalence of DM or borderline-type diabetes, which can also have an impact on CAVI, was not significantly different among the three groups (CS1 vs. CS2 vs. CS3: 34.5 vs. 27.3 vs. 7.7%, $p = 0.19$). Thus, the impact of DM/borderline-type diabetes on increased CAVI in CS1 could be excluded. All patients with DM in this study had type 2 diabetes. No use of insulin was observed. Hemoglobin A1c (HbA1c) was significantly higher in patients with DM/borderline-type diabetes than in those without DM/borderline-type diabetes (6.7 ± 1.0 vs. $5.7 \pm 0.4\%$, $p < 0.001$). Although CAVI did not differ between patients with and without DM/borderline-type diabetes (9.1 ± 1.5 vs. 8.8 ± 1.9 , $p = 0.54$); patients with DM/borderline-type diabetes showed a high tendency in CAVI. Eighteen patients were first diagnosed with DM/borderline-type diabetes when hospitalized for AHF (53% of total DM/borderline-type diabetes). The median duration of DM/borderline-type diabetes in the remaining 16 patients was 4.5 years. In such patients, CAVI had no relationship with the disease duration ($r = 0.43$, $p = 0.10$). The eGFR did not differ among the groups. CAVI could also be affected by cardiac medicines. Angiotensin-converting enzyme inhibitors (ACEs/

Table 1. Comparisons of clinical characteristics among the three groups.

Characteristic	CS1	CS2	CS3	<i>P</i>
Number	29	22	13	
Male/female	15/14	15/7	9/4	0.39
Age (years)	70.6 ± 13.2	71.1 ± 13.0	69.6 ± 11.4	0.95
Height (cm)	157.9 ± 9.6	159.4 ± 11.0	161.2 ± 8.0	0.60
Weight (kg)	53.9 ± 12.2	54.5 ± 14.5	50.1 ± 7.7	0.34
Body mass index (kg/m ²)	21.4 ± 3.2	22.0 ± 3.9	19.2 ± 2.2	0.06
LVEF (%) on admission	40.1 ± 16.1	38.5 ± 13.7	37.0 ± 18.5	0.52
LVEF (%) at discharge	46.2 ± 16.1	42.4 ± 16.5	37.3 ± 15.1	0.24
Heart rate (beats/min)	66.7 ± 11.0	71.1 ± 16.0	74.7 ± 15.0	0.20
Ps (mm Hg)	139.4 ± 19.3*	129.2 ± 14.1*	105.4 ± 10.3	< 0.001
Pd (mm Hg)	79.0 ± 10.3*	79.6 ± 9.6*	64.9 ± 7.0	< 0.001
PP (mm Hg)	60.4 ± 15.5*†	49.5 ± 15.7*	40.5 ± 8.8	< 0.001
Total cholesterol (mg/dL)	178.9 ± 39.4	172.1 ± 37.9	168.6 ± 42.7	0.70
Triglycerides (mg/dL)	132.4 ± 59.2	113.1 ± 73.6	104.4 ± 49.7	0.36
HDL cholesterol (mg/dL)	48.3 ± 15.8	49.1 ± 15.6	52.4 ± 22.8	0.78
LDL cholesterol (mg/dL)	105.0 ± 33.3	102.1 ± 34.4	96.0 ± 40.5	0.76
Glucose (mg/dL)	112.0 ± 48.4	114.0 ± 37.4	112.8 ± 32.7	0.99
Hemoglobin A1c (%)	6.5 ± 1.1	6.2 ± 0.6	5.9 ± 1.0	0.25
eGFR (mL/min/1.73m ²)	49.1 ± 19.3	58.2 ± 10.1	58.7 ± 14.5	0.07
Hemoglobin (g/dL)	12.7 ± 2.3	13.1 ± 2.5	12.6 ± 1.8	0.77
BNP (pg/mL)	159.0 [IQR, 111.4-368.6]	298.0 [IQR, 82.6-395.5]	392.0 [IQR, 212.2-834.1]	0.10
Hypertension (%)	19 (65.5)*	14 (63.6)*	1 (7.7)	0.001
Hypercholesterolemia (%)	19 (65.5)	11 (50.0)	6 (46.2)	0.39
Diabetes mellitus (%)	14 (48.3)	10 (45.5)	4 (30.8)	0.56
Borderline type diabetes (%)	2 (6.9)	1 (4.5)	3 (23.1)	0.40
Coronary artery disease (%)	9 (31.0)	6 (27.3)	5 (38.5)	0.79
Prior MI (%)	8 (27.6)	6 (27.3)	3 (7.7)	0.95
Smoking history (%)	13 (44.8)	10 (45.5)	4 (46.2)	0.65
Prior heart failure (%)	7 (24.1)	3 (13.6)	6 (46.2)	0.10

LVEF, left ventricular ejection fraction; Ps, systolic pressure at the time of measurement of CAVI; Pd, diastolic pressure at the time of measurement of CAVI; PP, pulse pressure at the time of measurement of CAVI; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; MI, myocardial infarction.

**P* < 0.01 vs. CS3. †*P* < 0.05 vs. CS2.

Data represent mean ± standard deviation. Values in parentheses are percentage.

BNP is represented median and interquartile range (IQR).

angiotensin receptor blockers (ARBs) are known to have an effect on reduction of CAVI (Kinouchi et al. 2010). However, reflecting the prevalence of a history of heart

failure of each group, the use of ACEs/ARBs did not differ among the groups. In addition, other medications did not differ among the three groups (Table 2). Table 3 shows the

Table 2. Comparisons of medications.

Medications	CS1	CS2	CS3	<i>P</i>
Loop diuretics (%)	21 (72.4)	17 (77.3)	8 (61.5)	0.60
Statins (%)	19 (65.5)	10 (45.5)	5 (38.5)	0.18
Antiplatelets (%)	13 (44.8)	6 (27.3)	5 (38.5)	0.44
ACEIs / ARBs (%)	23 (79.3)	20 (90.9)	8 (61.5)	0.11
β-blockers (%)	19 (65.5)	13 (59.1)	8 (61.5)	0.89
CCBs (%)	9 (31.0)	5 (22.7)	0 (0)	0.08

Values in parentheses are percentage.

ACEIs, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blocker; CCBs, calcium channel blocker.

Table 3. Results of univariate regression analysis for the CAVI.

Variable	Univariate	
	Correlation coefficient	<i>P</i>
Age (years)	0.41	0.001
Height (cm)	-0.01	0.94
Weight (kg)	-0.23	0.07
Body mass index (kg/m ²)	-0.33	0.01
Heart rate (beats/min)	-0.04	0.97
Ps (mm Hg)	0.24	0.06
Pd (mm Hg)	0.16	0.20
PP (mm Hg)	0.19	0.13
LV ejection fraction (%)	-0.15	0.24
eGFR (mL/min/1.73m ²)	-0.48	< 0.001
Glucose (mg/dL)	0.02	0.87
Hemoglobin A1c (%)	0.10	0.45

Abbreviations as in Table 1.

results of CAVI univariate regression analyses. CAVI was significantly correlated with age ($r = 0.41$, $p = 0.001$), BMI ($r = -0.33$, $p = 0.01$), and eGFR ($r = -0.48$, $p < 0.001$). However, CAVI did not significantly correlate with Ps ($r = 0.24$, $p = 0.06$), Pd ($r = 0.16$, $p = 0.20$), or PP ($r = 0.19$, $r = 0.13$). CAVI also did not significantly correlate with plasma glucose levels ($r = 0.02$, $p = 0.87$) or HbA1c ($r = 0.10$, $r = 0.45$). Multiple regression analysis was also performed to examine the factors that influenced CAVI, including CS and the factors that have correlation with CAVI in univariate regression analysis, such as age, BMI, and eGFR. In that

analysis, CS1 [$\beta = 0.33$, 95% confidence interval (CI) = 0.40-1.86, $p = 0.003$] was selected as the determinant for CAVI. In another model including CS2 or CS3 but not CS1, neither CS2 ($\beta = -0.14$, 95% CI = -1.39-0.23, $p = 0.16$) nor CS3 ($\beta = -0.22$, 95% CI = -1.89-0.01, $p = 0.06$) were selected as the determinant for CAVI (Table 4). Furthermore, CAVI also significantly differed among three groups in ANCOVA adjusted for age, BMI, PP, and eGFR [$F(2, 57) = 5.76$, $p = 0.005$]. These findings indicate that increased aortic stiffness is a feature of CS1 AHF but not of CS2 AHF or CS3 AHF.

Table 4. Results of multivariate regression analysis for the CAVI.

Variable	Coefficient			Coefficient			Coefficient		
	β	95% CI	<i>P</i>	β	95% CI	<i>P</i>	β	95% CI	<i>P</i>
Age (years)	0.17	-0.01-0.06	0.20	0.16	-0.02-0.06	0.27	0.08	-0.03-0.05	0.55
Body mass index (kg/m ²)	-0.23	-0.23- -0.003	0.045	-0.17	-0.21-0.04	0.17	-0.30	-0.28- -0.02	0.02
eGFR (mL/min/1.73m ²)	-0.27	-0.06- -0.003	0.03	-0.35	-0.06- -0.01	0.008	-0.37	-0.07- -0.01	0.004
CS1	0.33	0.40-1.86	0.003						
CS2				-0.14	-1.39-0.23	0.16			
CS3							-0.22	-1.89-0.01	0.06

CI, confidence interval; Other abbreviations as in Table 1.

Discussion

This is the first study to report the association between CS and aortic stiffness. The main finding of this study was increased aortic stiffness-vascular failure was demonstrated in patients with CS1 AHF. Aortic stiffness evaluated using blood pressure-independent methodology, CAVI, is the key for understanding the pathophysiology of AHF patients categorized as CS1.

Aortic stiffness and CS1 AHF

As arterial stiffness increases, PWV along the aorta increases, such that the reflected pulse wave arrives earlier at the ascending aorta and augments the late-systolic ascending aortic pressure waveform (O'Rourke and Mancina 1999). These changes cause an increase in the systolic load, which also deteriorates LV relaxation (Abhayaratna et al. 2006; Ikonomidis et al. 2008; Weber et al. 2008; Fukuta et al. 2010). Thus, increased aortic stiffness has been recognized as an important non-cardiac factor in the pathogenesis of AHF (Hundley et al. 2001; Cotter et al. 2008; Fallick et al. 2011). CS1 is characterized by aortic stiffness-vascular failure, with AHF developing when the intrinsic activated sympathetic nerve system causes a reduction in venous compliance and an increase in arterial resistance. A reduction in large venous compliance leads to an increase in venous return, resulting in an increased preload. On the arterial side, increased arterial resistance causes an increase in afterload. As a result, there is a shift of volume from capacitance vessels into the systemic circulation, increasing the effective circulatory volume and causing pulmonary congestion along with an acute elevation of filling pressure that parallels the increase in blood pressure (Kawaguchi et al. 2003; Gheorghide et al. 2006). In patients with increased aortic stiffness, even a slight increase in afterload could lead to the provocation of a major hemodynamic change, potentially progressively deteriorating heart failure (Laskey et al. 1985). In addition, blood pressure variability is a feature of hypertension in the

elderly (Aronow and Ahn 1994). Blood pressure variability is a well-established predictor of future cardiovascular events, including heart failure, both in the general population (Mitchell et al. 2010) and in individuals with hypertension (Laurent et al. 2003). The relationship between blood pressure variability and aortic stiffness has been reported in patients with hypertension (Schillaci et al. 2012). Given these findings, increased aortic stiffness shown in this study is deeply involved in the mechanism of CS1 AHF accompanied with the acute blood pressure change.

Blood pressure and CAVI

CAVI was significantly higher only in CS1 AHF than in the other groups. It was reported that CAVI is independent of instantaneous blood pressure (Shirai et al. 2006). Although Ps was significantly different among the groups, there was no significant relationship between CAVI and Ps in this study. Thus, CAVI was not affected by Ps. Previous studies have reported that CAVI is influenced by various factors, such as hypertension (Masugata et al. 2009), dyslipidemia (Soska et al. 2012), DM (Ibata et al. 2008), coronary artery disease (Nakamura et al. 2008), decreased eGFR (Kubozono et al. 2009), and smoking history (Kubozono et al. 2011). In the present study, the prevalence of hypertension was significantly different among the groups; in contrast, other factors that affect CAVI did not differ among the groups. However, elevated CAVI was not necessarily consistent with the higher prevalence of hypertension; the higher prevalence of hypertension was observed in CS1 and CS2 but not in CS3, though CAVI was only higher in CS1. On the other hand, PP was different in CS1 and CS2. Pulse pressure is a surrogate measure for increased proximal aortic stiffness (Mitchell et al. 2003) which can be evaluated using CAVI. Although no significant relationship between CAVI and PP was found in our study, there is a report that shows the relationship between CAVI and PP in patients with hypertension (Okura et al. 2007). Thus, increased CAVI in patients with CS1

AHF is related to continuous high blood pressure, hypertension, and increased pulse pressure, which have a close relationship with increased aortic stiffness. In multiple regression analysis, including CS and the factors that have a correlation with CAVI, CS1 was only selected as a determinant for CAVI. CAVI was also significantly different among CS groups in ANCOVA adjusted for age, BMI, eGFR, and PP. Therefore, increased aortic stiffness-vascular failure, is a feature of patients categorized as CS1.

Cardiac function and CAVI

No significant difference was found in LVEF among the three groups. Plasma BNP concentration also did not differ among the groups. Noguchi et al. (2011) investigated the relationship between CAVI and cardiac function. In that report, no significant difference was found in CAVI between patients with hypertension and preserved LVEF and those with reduced LVEF. Thus, CAVI is not affected by cardiac function. In fact, LVEF had no relationship with CAVI in this study. To that point, the results of the present study are consistent with that prior report. In addition, no significant group difference was found in the prevalence of prior heart failure in this study. This finding indicates that aortic stiffness was already advanced at the time of the first onset of CS1 AHF.

DM and CAVI

Diabetes patients accounted for 50% of the participants of this study. As mentioned above, DM and borderline-type diabetes have a significant influence on CAVI (Ibata et al. 2008). However, the prevalence of DM/borderline-type diabetes did not differ among the three groups. A previous study also reported that CAVI was significantly higher in DM patients with hypertension as compared with healthy controls and patients with “only” hypertension (Wang et al. 2013). In this study, the prevalence of hypertension patients with DM/borderline-type diabetes also did not differ among the three groups. Thus, the impact of DM/borderline-type diabetes on CAVI was similar among the three groups. The positive correlation of CAVI with plasmatic glucose level or HbA1c was not confirmed in this study. Ibata et al. (2013) reported that elevated CAVI have a close association with HbA1c and improvement of DM control has a significant correlation with improvement of CAVI. In that report (Ibata et al. 2013), HbA1c was as follows: DM patients vs. non-DM patients, 9.6 ± 2.3 vs. $5.3 \pm 0.3\%$. Thus, HbA1c levels of our patients did not match with those of that study. The difference between HbA1c in these two studies might have resulted in the overall differences. The duration of DM also did not correlate with CAVI. However, the duration of DM was confirmed in only 43% of DM patients in this study. Therefore, the number of cases was too low to examine the association between CAVI and DM duration. The proportion of DM/borderline-type diabetes was similar among the three groups in this study. Thus, the impact of DM or borderline-type diabetes is unlikely to be the reason

for increased CAVI in only CS1.

Clinical implication

Large epidemiological registries, including the Acute Decompensated Heart Failure Syndromes (ATTEND) registry (Sato et al. 2013) in our country, have shown that among AHF patients, 60-70% have hypertension, 30% have DM, and 25% have dyslipidemia (Sakata and Shimokawa 2013). These data suggest that few patients with heart failure do not have underlying atherosclerotic disease. Thus, in clinical settings, evaluating aortic stiffness using CAVI is useful for finding out high-risk patients of CS1 heart failure in patients with accumulated risk of atherosclerosis. In patients with hypertension and increased pulse pressure, in particular, strict interventions, such as blood pressure control, might help prevent the onset of new CS1 AHF. Another large Japanese study, Japanese Cardiac Registry of Heart Failure in Cardiology (JCAR-CARD) (Hamaguchi et al. 2011), reported that hypertension is an important factor associated with readmission for heart failure, as with infectious diseases, arrhythmias, and myocardial ischemia. Thus, blood pressure is an important therapeutic target that can potentially reduce readmissions due to heart failure.

Study limitations

This study had several limitations. First, this was a cross-sectional study conducted at a single institution that included a limited number of patients. Thus, selection bias could occur, and the result should be carefully interpreted. Second, we obtained CAVI at the time of discharge, but not in an ultra-acute phase, such as just after hospitalization. It is realistically difficult to measure CAVI in such phases because of the inability to take a supine position. Some cases have received intravenous continuous infusions, such as vasodilators, or catecholamine in such phases. In those cases, it was not suitable to measure CAVI that requires a blood pressure measurement in the limb. Therefore, CAVI was uniformly measured at the time of discharge to match the conditions. However, CAVI is not affected by blood pressure at the time of measurement. Thus, we believe that CAVI was measured at the appropriate timing. Finally, CAVI has been measured under the cardiac medication, which may influence CAVI. The improvement of CAVI by medication has been reported in the course of 6 months or 1 year (Kurata et al. 2008; Sasaki et al. 2009; Kinouchi et al. 2010). Accordingly, the influences of medication are mild if they were started after hospitalization. In addition, the prevalence of cardiac medication did not differ among the groups. Thus, cardiac medications would have a similar influence on CAVI among the groups in this study. Although a prospective study with a larger number of patients should be conducted to confirm the present findings, including the verification of the relationship between aortic stiffness and prognosis, we believe that the current findings are important for understanding the

pathophysiology of patients with CS1 AHF.

Conclusion

Increased aortic stiffness, vascular failure, is demonstrated in patients with CS1 AHF. Vascular failure is an important factor in AHF initiation and in particular in CS1.

Conflict of Interest

The authors declare no conflict of interest.

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