Cardio-Ankle Vascular Index Reflects Impaired Exercise Capacity and Predicts Adverse Prognosis in Patients with Heart Failure

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学位論文

Cardio-Ankle Vascular Index Reflects Impaired Exercise Capacity and Predicts Adverse Prognosis in Patients with Heart Failure

（Cardio-Ankle Vascular Index は心不全患者の運動耐容能低下と不良な予後に関連する）

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論文内容要旨

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学位論文題名	Cardio-Ankle Vascular Index Reflects Impaired Exercise Capacity and Predicts Adverse Prognosis in Patients with Heart Failure （Cardio-Ankle Vascular Index は心不全患者の運動耐容能低下と不良な予後に関連する）

心不全患者における運動耐容能の低下は、不良な予後と関連する。Cardiopulmonary exercise testing (CPX)は運動耐容能を評価する標準的検査であり、心臓リハビリテーションや予後予測に重要である。一方、Cardio-ankle vascular index (CAVI)は動脈硬化の程度を評価し、高い CAVI は冠疾患患者の心血管イベントを予測すると報告されている。しかしながら、心不全患者における CAVI の臨床的意義は明らかではなかった。本研究では、心不全患者における CAVI と運動耐容能の関係および予後予測能について検討した。

CPX と CAVI を実施した心不全入院患者 223 名を解析対象とした。Receiver operating characteristic curve 解析では、CPX で測定した peak VO_2 14 mL/kg/min 以下（運動耐容能低下)に関する CAVI のカットオフ値は 8.9 であった。多変量 Logistic 回帰分析では、CAVI 高値（CAVI ≧ 8.9)は peak VO_2 低下に関する独立した予測因子であった（オッズ比 2.343, P = 0.045)。次にこれらの患者を CAVI に基づいて、低 CAVI 群（CAVI < 8.9, n = 145)と高 CAVI 群（CAVI ≥ 8.9, n = 78)に分類し、両群間の患者特性および退院後の心イベント（心不全入院または心臓死)について比較検討した。高 CAVI 群は低 CAVI 群より年齢が高く（69.0 歳 vs. 58.0 歳、P < 0.001)、body mass index が低値であった（23.0 vs. 24.1、P = 0.013)。退院後の観察期間中（中央値 1,623 日)に、53 件の心不全再入院と 5 件の心臓死を含む 58 件の心イベントが発生した。Kaplan-Meier 解析では、高 CAVI 群では低 CAVI 群に比して退院後の心イベント発生が有意に高率であった（Log-Rank P = 0.004)。多変量 Cox 比例ハザード解析では、高 CAVI は退院後の心イベント発生に関する独立した予測因子であった（ハザード比 1.845、P = 0.035)。

以上より CAVI 高値は心不全患者の運動耐容能低下と関係し、心イベント発生を予測しうる事が示唆された。

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Cardio-Ankle Vascular Index Reflects Impaired Exercise Capacity and Predicts Adverse Prognosis in Patients with Heart Failure

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Abstract

Aims: We aimed to assess the associations of CAVI with exercise capacity in heart failure (HF) patients. In addition, we further examined their prognosis.

Methods: We collected the clinical data of 223 patients who had been hospitalized for decompensated HF and had undergone both CAVI and cardiopulmonary exercise testing.

Results: For the prediction of an impaired peak oxygen uptake (VO2) of < 14 mL/kg/min, receiver-operating characteristic curve demonstrated that the cutoff value of CAVI was 8.9. In the multivariate logistic regression analysis for predicting impaired peak VO2, high CAVI was found to be an independent factor (odds ratio 2.343, P = 0.045). We divided these patients based on CAVI: the low-CAVI group (CAVI < 8.9, n = 145) and the high-CAVI group (CAVI ≥ 8.9, n = 78). Patient characteristics and post-discharge cardiac events were compared between the two groups. The high-CAVI group was older (69.0 vs. 58.0 years old, P < 0.001) and had lower body mass index (23.0 vs. 24.1 kg/m2, P = 0.013). During the post-discharge follow-up period of median 1,623 days, 58 cardiac events occurred. The Kaplan–Meier analysis demonstrated that the cardiac event rate was higher in the high-CAVI group than in the low-CAVI group (log–rank P = 0.004). The multivariate Cox proportional hazard analysis revealed that high CAVI was an independent predictor of cardiac events (hazard ratio 1.845, P = 0.035).

Conclusion: High CAVI is independently associated with impaired exercise capacity and a high cardiac event rate in HF patients.

Key Words: cardio-ankle vascular index, arterial stiffness, cardiopulmonary exercise testing, heart failure, prognosis.

Introduction

Impaired exercise capacity is an independent predictor of poor prognosis in patients with heart failure (HF).(1-3) Cardiopulmonary exercise testing (CPX) is the widely accepted gold-standard approach to assess exercise capacity.(4) However, compared with other exercise tests (6-min walk test, electrocardiography stress testing), CPX is more time-consuming, more expensive, and needs specialized equipment and personnel.(4) Vascular dysfunction (e.g. arterial stiffness, endothelial dysfunction) in HF may contribute to altered ventricular-arterial coupling,(4) and might be associated with impaired exercise capacity.(4, 5) The cardio-ankle vascular index (CAVI) is a measure of arterial stiffness, and is useful to evaluate atherosclerosis, and moreover to predict the prognosis in patients who have multiple risk factors of cardiovascular diseases.(6-9) High CAVI is an independent predictor of cardiovascular events including cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke in patients with acute coronary syndrome.(7)

However, the clinical implication of CAVI in patients with HF is yet unclear, especially in terms of assessing exercise capacity and prognosis. Therefore, we aimed to assess the associations of CAVI with exercise capacity in HF patients. In addition, we further examined their prognosis.

Methods

Subjects and protocol

The patient flow chart is presented in **Figure 1**. This was a prospective observational study of patients who (1) had been both hospitalized at Fukushima Medical University Hospital for decompensated HF and discharged alive between January 2010 and September 2019; and (2) out of the 2,715 HF patients, a total of 497 patients had undergone both CAVI measurement and CPX testing before discharge in a stable condition. Patients with decompensated HF were identified by the current guidelines.(1, 2) Patients with obvious history of peripheral artery disease, those with atrial fibrillation and/or those who were receiving maintenance dialysis throughout the study period were excluded (n = 274). We excluded patients with concurrent peripheral artery disease and atrial fibrillation because it is difficult to accurately measure CAVI in such patients (patients receiving dialysis n = 26 and/or patients with atrial fibrillation n = 208 and/or patients with peripheral artery disease n = 107).(7) Peripheral artery disease was defined as in previous studies.(10, 11) Other co-morbidities were also defined in accordance with our previous studies.(10, 11) We defined reduced ejection fraction (EF) as left ventricular EF (LVEF) < 40%, mid-range EF as 40% ≤ LVEF < 50% and preserved EF ≥ 50%.(1-3) Finally, a total of 223 patients were enrolled. For the prediction of impaired peak VO2, defined as < 14 mL/kg/min,(12) receiver-operating characteristic (ROC) curve demonstrated that the cut-off value of CAVI was 8.9 (**Figure 2**, area under curve 0.67, 95% confidence interval, 0.52–0.69, $P < 0.05$). Next, these patients were divided into two groups based on this cut-off value: the low-CAVI group (CAVI < 8.9, n = 145, 65.0%) and the high-CAVI group (CAVI ≥ 8.9, n = 78, 35.0%). Patient characteristics and post-discharge prognosis were compared between the two groups. The patient characteristics included demographic data at discharge, as well as laboratory data and echocardiographic data, which were obtained within one week prior to discharge when the patient was in a stable condition. We compared post-discharge cardiac events, ischemic events and all-cause mortality.

These patients were followed up until March 2020 for cardiac events as composites of cardiac death or unplanned re-hospitalization for HF treatment, ischemic coronary events and all-cause mortality. For patients that experienced two or more events, only the first event was included in the analysis. Since these patients visited patient's referring hospital monthly or bi-monthly, we were able to follow up on all patients. Status and dates of death were obtained from the patient's medical records. This study conformed to the Declaration of Helsinki(13) and the statement of STROBE (Strengthening the Reporting of Observational studies in Epidemiology).(14) The ethical committee of Fukushima Medical University approved the study protocol. Written informed consent was obtained from all patients.

The measurement of CAVI

We measured CAVI automatically by using VaSera VS-1000 (Fukuda Denshi Co., Ltd., Tokyo, Japan) with the patient in the decubitus position before discharge in a stable condition. We attached cuffs bilaterally to the upper arms and ankles of the patient. We placed electrocardiogram electrodes and a microphone on both wrists and on the sternum, respectively. We analyzed the average CAVI values of both sides.(6-9)

Cardiopulmonary exercise testing

Patients underwent incremental symptom-limited exercise testing before discharge in a stable condition, using an upright cycle ergometer with a ramp protocol (Strength Ergo 8, Fukuda Denshi Co., Ltd., Tokyo, Japan). Breath-by-breath VO_2 was measured during exercise using an Aeromonitor AE-300S (Minato Medical Science Co., Ltd., Osaka, Japan). Breath-by-breath oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured during exercise using an AE-300S respiratory monitor (Minato Medical Science, Co., Ltd.).(15) Peak VO_2 was measured as an average of the last 30 s of exercise, and ventilatory response to exercise (slope of the relationship between ventilation and carbon dioxide production, VE/VCO_2 slope) was calculated as the regression slope relating VE to

CO_2 from the start of exercise until the respiratory compensation point (the time at which ventilation is stimulated by CO_2 output and end-tidal CO_2 tension begins to decrease).(15) We calculated the ventilatory anaerobic threshold using the V-slope method.

Statistical analysis

Normality was confirmed using the Shapiro-Wilk test in each group. Normally distributed variables are presented as mean ± standard deviation, non-normally distributed variables are presented as median (interquartile range), and categorical variables are expressed as counts and percentages. ROC curves for predicting impaired peak VO_2 were plotted using EZR version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).(16) Non-normally distributed variables were compared using the Mann-Whitney U test, and the Fisher's exact test was used for comparisons of categorical variables. If 20% or more cells had expected count less than five, the one-sided Fisher's exact test was adopted. Logistic regression analysis was performed to assess associations between impaired exercise capacity and CAVI, as well as other variables (e.g. age, sex, blood pressure, heart rate, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, cerebral vascular disease, chronic kidney disease, anemia, BNP and LVEF), which are generally thought to be associated with exercise capacity. The occurrence of post-discharge cardiac events, ischemic events and all-cause mortality was compared using the Kaplan-Meier analysis with a log-rank test. We assessed CAVI as a predictor for cardiac events, ischemic coronary events and all-cause mortality using the univariate or multivariate Cox proportional hazard analysis. The threshold for statistical significance was $P < 0.05$. All analyses, except for ROC, were conducted using IBM SPSS Statistics version 26 (IBM, Armonk, NY, USA).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Comparisons of patient characteristics between the low- and high-CAVI groups are shown in **Table 1**. A total of 78 (35.0%) patients belonged to the high-CAVI group. The high-CAVI group was older and showed lower body mass index. Prevalence of hypertension and chronic kidney disease was significantly higher in the high-CAVI group than in the low-CAVI group. In contrast, sex, blood pressure, heart rate, NYHA functional class, other co-morbidities and medications did not differ between the two groups. There were no significant differences regarding BNP levels and LVEF between the two groups.

ROC analysis demonstrated that a CAVI cut-off value of 8.9 predicted impaired exercise capacity (**Figure 2;** area under the curve 0.67, 95% confidence interval, 0.52–0.69, $P < 0.05$). In the multivariate logistic regression analysis for predicting impaired peak VO_2 (**Table 2**), high CAVI was found to be an independent factor (odds ratio 2.343, 95% confidence interval 1.021–5.380, $P = 0.045$).

During the post-discharge follow-up period (median 1,623 days), 58 cardiac events including 53 worsening HF and 5 cardiac deaths, 11 ischemic coronary events and 39 all-cause deaths occurred. The Kaplan-Meier analysis showed that cardiac event rates and all-cause mortality were higher in the high-CAVI group than in the low-CAVI group (**Figure 3**; cardiac event rates, log-rank $P = 0.004$; **Figure 5**; all-cause mortality, log-rank $P = 0.015$), however ischemic coronary events did not differ between the high-CAVI and the low-CAVI group (**Figure 4**; log-rank $P = 0.822$). In the multivariate Cox proportional hazard analysis (**Table 3**), we considered possible confounding factors, which differed between the groups (i.e. age, sex, body mass index, hypertension and chronic kidney disease), and high CAVI was found to be an independent predictor of cardiac events (hazard ratio 1.845, 95% confidence interval 1.044–3.261, $P = 0.035$). In contrast, high CAVI did not fully predict ischemic coronary events and all-cause mortality in the multivariate Cox proportional hazard analysis (**Tables 4 and 5**). Furthermore, in the subgroup analysis for predicting cardiac events (**Table 6**), there was no significant interactions between prognostic impact of CAVI and both sex ($P = 0.704$), age ($P = 0.291$), and LVEF ($P = 0.279$).

Discussion

The present study, to the best of our knowledge, was the first to report that (A) high CAVI (≥ 8.9) was independently associated with impaired peak VO_2 (< 14 mL/kg/min), and (B) high CAVI independently predicted the cardiac events in patients with HF.

There was weak association between CAVI and exercise capacity in the present study. Concordant with our data, it has recently been reported that CAVI was associated with 6-min walk test, and indicated that arterial stiffness may relate to partly exercise capacity.(17) Regarding arterial stiffness and impaired exercise capacity in HF patients, abnormal ventricular-arterial coupling may be caused by vascular dysfunction in HF.(4) Because of arterial stiffness and an impaired peripheral vasodilatory response to exercise, the timing and amplitude of the reflected pulse wave are changed, and as a result the pulsatile load arriving at the heart during late systole increases.(4, 18) After that, the myocardial workload during exercise increases and contributes to functional exercise intolerance.(4) Arterial stiffening and abnormal vasorelaxation during exercise elevate filling pressure and impair cardiac output reserve in HF patients, and contribute to exercise intolerance.(4, 5, 19) Vascular dysfunction also decreases the O_2 delivery to the skeletal muscle at the start of exercise, and the skeletal muscle uses anaerobic energy.(4, 20) The decrease of the finite energy sources needed to maintain exercise at latter exercise stages contributes to exercise intolerance.(4, 20) In addition, CAVI was reportedly to be an independent risk factor for frailty,(21) which is associated with adverse outcome in HF patients.(22, 23) Arterial hemodynamic dysfunction may have a predictive effect on reduction in muscle mass, and the reduction results in a decrease in body mass, grip strength, and walking speed.(21) Muscle blood flow decreases were partly related to the degree of atherosclerosis.(24) Therefore, atherosclerosis and arterial stiffness were risk factors for frailty.(21) (25)

Especially, in patients with HFpEF, arterial stiffness is increased and is correlated with decreased exercise capacity.(5, 26-29) Arterial stiffening and impaired arterial vasodilator reserve with exercise are important in the pathophysiology of HFpEF that is independent of hypertension and mean blood pressure alone.(5) A reduction in pulsatile arterial afterload improves functional capacity measured by the 6-min walk test.(4, 30) The impairment oxygen delivery and extraction in tissue is considered a important determinant of exercise tolerance.(4, 31, 32)

In the present study, CAVI was an independent predictor of impaired peak VO_2, after adjustment for important factors including age, blood pressure and LVEF. Thus, CAVI may be a useful marker for impaired exercise capacity, especially in HF patients who have difficulty undergoing CPX testing and other exercise tests.

There are stronger relationships between arterial stiffness and HF, because decreases in arterial wall compliance increase cardiac afterload and exacerbate HF.(8) Meguro et.al. reported that the high brachial-ankle pulse wave velocity (BaPWV) group had a lower event-free survival rate than the low BaPWV group, so elevated arterial stiffness is a risk factor for rehospitalization or cardiac death of HF patients.(33) On the other hand, PWV has a weak point; it is known to depend on blood pressure at the time of measurement, whereas CAVI is independent of blood pressure.(6) Consistent with our results that the cut-off value of CAVI was 8.9, a recent review of vascular function has suggested that CAVI ≥ 9.0 is a marker of vascular failure.(9) Additionally, it has been reported that CAVI ≥ 9.0 predicted higher cardiovascular events in diabetic patients.(34) On the other hand, the associations between changes of CAVI and prognosis have not yet been examined.(35) A prospective, large-scale, and longitudinal study with repeated measurement of CAVI in high cardiovascular risk patients, the Coupling registry, has been under way.(35) The study may provide useful information on the significance of both baseline CAVI and changes in CAVI over time as indicators of cardiovascular prognosis.(35)

Our study has several strengths. For example, to the best of our knowledge, the present study is the first to show associations between increased CAVI and impaired exercise as well as adverse prognosis in HF patients, taking into consideration a multifaceted background and exercise capacity within a given population. Second, we were able to follow up on all patients.

The present study has several limitations. First, since CAVI measurement is inappropriate for patients with concurrent peripheral artery disease and atrial fibrillation, which are sometimes complicated with HF, CAVI is not necessarily indicated for all HF patients. Second, the results of the current study may not represent the general population, as this was a prospective cohort study of a single center with a relatively small number of patients. We considered several confounding factors and performed multivariate Cox proportional hazard analysis, but we cannot exclude all residual confounding factors, and we might not completely adjust for the effects of the differences in the backgrounds between the groups. Third, in the present study we considered the variables during hospitalization for decompensated HF, but we did not analyze the changes in medical parameters (e.g. CAVI) throughout the clinical course and post-discharge treatment. Fourth, although we encouraged CAVI and CPX in hospitalized patients, attending physicians could not perform these measurements in all patients for various reasons (e.g. patient refusal, medical reasons, timing of hospital discharge). Thus, potential selection bias in these measurements possibly existed. Fifth, the present study was a cross-sectional and prospective observational study, therefore we could not fully explain the causal relationships and mechanisms of increased CAVI on impaired exercise capacity and worse prognosis. Therefore, the present results should be considered preliminary, and further studies analyzing larger population are required.

Conclusion

High CAVI is independently associated with impaired exercise capacity, and leads to a high cardiac event rate in HF patients.

Conflict of Interest

Akiomi Yoshihisa and Tomofumi Misaka belong to the Department of Advanced Cardiac Therapeutics, which is supported by Fukuda-Denshi CO, Ltd. Tetsuro Yokokawa belong to the Department of Pulmonary Hypertension, which is supported by ACTELION PHARMA Co, Ltd. These company are not associated with the contents of the current study.

Author Contributions

Koichiro Watanabe: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Visualization. Akiomi Yoshihisa: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Supervision, Project administration, Funding acquisition. Yu Sato: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Visualization. Yu Hotsuki: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Fumiya Anzai: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Yasuhiro Ichijo: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Yusuke Kimishima: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Tetsuro Yokokawa: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Tomofumi Misaka: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Takamasa Sato: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Takashi Kaneshiro: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Masayoshi Oikawa: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Atsushi Kobayashi: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Review & Editing. Yasuchika Takeishi: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Supervision, Project administration.

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FIGURE LEGENDS

Figure 1.

Patient flow chart. CAVI, cardio-ankle vascular index; VO_2, oxygen uptake.

Figure 2.

Receiver-operating characteristic curve for the prediction of impaired peak oxygen uptake (VO_2) by cardio-ankle vascular index (CAVI). The cut-off value of CAVI was 8.9. Area under curve was 0.67 and 95% confidence interval were 0.52-0.69 ($P < 0.05$).

Figure 3.

Kaplan-Meier analysis for cardiac event in high [cardio-ankle vascular index (CAVI) ≥ 8.9] and low CAVI (CAVI < 8.9) groups. Event rates were analyzed by a log-rank test.

Figure 4.

Kaplan-Meier analysis for ischemic event in high [cardio-ankle vascular index (CAVI) ≥ 8.9] and low CAVI (CAVI < 8.9) groups. Event rates were analyzed by a log-rank test.

Figure 5.

Kaplan-Meier analysis for all-cause mortality in high [cardio-ankle vascular index (CAVI) ≥ 8.9] and low CAVI (CAVI < 8.9) groups. Event rates were analyzed by a log-rank test.

Table 1. Baseline patient characteristics

	Low CAVI (CAVI < 8.9, n = 145)	**High CAVI (CAVI ≥ 8.9, n = 78)**	**P value**
CAVI	7.31 (6.50–8.00)	9.62 (9.36–10.14)	< 0.001
Demographic data			
Age (years old)	58.0 (46.0–65.0)	69.0 (61.0–74.0)	< 0.001
Male sex (n, %)	112 (77.2)	66 (84.6)	0.191
Body mass index (kg/m^2)	24.1 (22.2–28.1)	23.0 (21.4–26.3)	0.013
Systolic blood pressure (mmHg)	122.5 (108.0–143.0)	130.0 (115.0–151.5)	0.094
Diastolic blood pressure (mmHg)	71.5 (61.0–86.0)	77.0 (62.0–91.0)	0.436
Heart rate (/min)	78.0 (65.0–96.0)	73.0 (62.0–89.5)	0.140
NYHA functional class III or IV (n, %)	1 (0.7)	1 (1.3)	0.578
Ischemic etiology (n, %)	41 (32.5)	29 (44.6)	0.070
Reduced/mid-range/preserved EF (n, %)	48 (38.4)/ 24 (19.2)/ 53 (42.4)	19 (29.7)/ 14 (21.9)/ 31 (48.8)	0.496
Co-morbidities			
Hypertension (n, %)	99 (68.3)	64 (82.1)	0.019
Diabetes mellitus (n, %)	60 (41.4)	41 (52.6)	0.072
Dyslipidemia (n, %)	116 (80.0)	68 (87.2)	0.122
Coronary artery disease (n, %)	51 (35.2)	35 (44.9)	0.101
Cerebral vascular disease (n, %)	17 (11.7)	9 (11.5)	0.577
Chronic kidney disease (n, %)	48 (34.3)	37 (54.4)	0.005
Anemia (n, %)	31 (22.5)	23 (33.3)	0.067
Medications			
β blockers (n, %)	126 (86.9)	68 (87.2)	0.565
ACEIs/ARBs (n, %)	117 (80.7)	67 (85.9)	0.216
Loop diuretics (n, %)	84 (57.9)	49 (62.8)	0.286
Inotropic agents (n, %)	16 (11.0)	12 (15.4)	0.233
Calcium blockers (n, %)	40 (27.6)	28 (35.9)	0.129
Antiplatelet agents (n, %)	71 (49.0)	31 (60.3)	0.070
Anticoagulants (n, %)	68 (46.9)	35 (44.9)	0.441
Laboratory data			

BNP (pg/mL)	151.6 (43.8–509.4)	207.4 (72.5–431.3)	0.326
Echocardiographic data			
LVEF (%)	45.0 (31.9–60.4)	46.0 (36.9–63.0)	0.250
Cardiopulmonary exercise testing			
Peak VO_2 (mL/kg/min)	17.3 (14.4–21.1)	14.6 (12.8–17.7)	< 0.001
VE-VCO_2 slope	30.8 (26.7–34.0)	32.7 (29.1–39.8)	< 0.001

CAVI, cardio-ankle vascular index; NYHA, New York Heart Association; EF, ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; VO_2, oxygen uptake; VE-VCO_2, ventilatory equivalent versus carbon dioxide output.

Table 2. Logistic regression analysis for predicting impaired peak VO_2

	Univariate		**Multivariate**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
High CAVI (≥ 8.9)	2.697 (1.481–4.911)	0.001	2.343 (1.021–5.380)	0.045
Age	1.037 (1.012–1.063)	0.003	1.009 (0.977–1.043)	0.584
Male sex	0.224 (0.113–0.446)	< 0.001	0.120 (0.049–0.292)	< 0.001
Body mass index	1.004 (0.942–1.071)	0.899		
Systolic BP	1.001 (0.991–1.011)	0.864		
Diastolic BP	1.005 (0.992–1.018)	0.469		
Heart rate	1.009 (0.995–1.023)	0.210		
Hypertension	2.477 (1.166–5.261)	0.018	2.245 (0.850–5.926)	0.103
Diabetes mellitus	1.194 (0.668–2.137)	0.550		
Dyslipidemia	1.030 (0.478–2.217)	0.940		
Coronary artery disease	1.623 (0.901–2.925)	0.107		
Cerebral vascular disease	0.719 (0.275–1.882)	0.502		
Chronic kidney disease	3.043 (1.627–5.692)	<0.001	2.137 (0.973–4.694)	0.059
Anemia	2.697 (1.400–5.198)	0.003	1.795 (0.797–4.046)	0.158
log BNP	1.993 (1.162–3.419)	0.012	1.913 (0.989–3.700)	0.054
LVEF	0.999 (0.979–1.020)	0.953		

OR, odds ratio; CI, confidence interval; CAVI, cardio-ankle vascular index; BP, blood pressure; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

Table 3. Cox proportional hazard model for cardiac events

	Univariate		Multivariate	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
High CAVI (≥ 8.9)	2.090 (1.248–3.500)	0.005	2.090 (1.248–3.500)	0.005
Age (older vs. younger)	1.520 (0.894–2.585)	0.122		
Male sex	0.771 (0.423–1.408)	0.397		
Body mass index	0.994 (0.933–1.059)	0.858		
Hypertension	1.195 (0.644–2.217)	0.572		
Chronic kidney disease	1.600 (0.933–2.744)	0.088		

HR, hazard ratio; CI, confidence interval; CAVI, cardio-ankle vascular index.

Table 4. Cox proportional hazard model for ischemic coronary events

	Univariate		Multivariate	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
High CAVI (≥ 8.9)	1.152 (0.336–3.945)	0.822		
Age	1.061 (1.000–1.126)	0.049		
Male sex	0.600 (0.159–2.266)	0.451		
Body mass index	1.065 (0.948–1.196)	0.290		
Hypertension	31.818 (0.095–10611.11)	0.243		
Chronic kidney disease	1.134 (0.318–4.046)	0.846		

HR, hazard ratio; CI, confidence interval; CAVI, cardio-ankle vascular index.

Table 5. Cox proportional hazard model for all-cause mortality

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
High CAVI (≥ 8.9)	2.145 (1.142–4.027)	0.018	1.802 (0.912–3.561)	0.090
Age	1.027 (1.000–1.055)	0.051	1.018 (0.989–1.048)	0.227
Male sex	1.140 (0.503–2.583)	0.754		
Body mass index	0.921 (0.840–1.010)	0.081		
Hypertension	1.377 (0.607–3.125)	0.445		
Chronic kidney disease	1.612 (0.843–3.081)	0.149		

HR, hazard ratio; CI, confidence interval; CAVI, cardio-ankle vascular index.

Table 6. Cox proportional hazard model for cardiac events: the impact of high CAVI (Sub-group analysis)

Factor	Subgroup	n	HR (95% CI)	P value	Interaction P value
Total			**2.090 (1.248–3.500)**	**0.005**	
Sex	Male	178	2.057 (1.138–3.719)	0.017	0.704
	Female	45	2.491 (0.854–7.268)	0.095	
Age	Older (≥ median 61 years)	116	1.802 (0.905–3.586)	0.094	0.291
	Younger (< median 60 years)	107	2.908 (1.133–7.466)	0.026	
LVEF	Reduced and mid-range EF	105	1.934 (1.036–3.608)	0.038	0.279
	Preserved EF	84	3.572 (1.196–10.672)	0.023	

HR, hazard ratio; CI, confidence interval; CAVI, cardio-ankle vascular index; LVEF, left ventricular ejection fraction; EF, ejection fraction.

Supplementary Table 1. Baseline patient characteristics based on age (n = 223)

	Younger age **(age < 61, n = 107)**	**Older age** **(age ≥ 61, n = 116)**	**P value**
CAVI	7.25 (6.43–8.05)	9.04 (7.87–9.70)	<0.001
High CAVI	15 (14.0)	63 (54.3)	<0.001
Demographic data			
Age (years old)	50.0 (41.5–57.0)	70.0 (65.0–75.0)	<0.001
Male sex (n, %)	86 (80.4)	92 (79.3)	0.488
Body mass index (kg/m^2)	25.4 (22.0–28.9)	23.2 (21.5–25.3)	0.001
Systolic blood pressure (mmHg)	124.0 (109.5–146.0)	127.0 (109.5–144.5)	0.780
Diastolic blood pressure (mmHg)	79.0 (64.0–91.5)	68.0 (60.0–80.0)	0.005
Heart rate (/min)	85.0 (68.0–97.5)	72.0 (61.0–88.0)	0.002
NYHA functional class Ⅲ or Ⅳ (n, %)	1 (0.9)	1 (0.9)	0.731
Ischemic etiology (n, %)	28 (30.8)	42 (42.0)	0.072
Reduced/mid-range/preserved EF (n, %)	37 (39.8)/ 20 (21.5)/ 36 (38.7)	30 (31.3)/ 18 (18.8)/ 48 (50.0)	0.286
Co-morbidities			
Hypertension (n, %)	71 (66.4)	92 (79.3)	0.021
Diabetes mellitus (n, %)	51 (47.7)	50 (43.1)	0.494
Dyslipidemia (n, %)	85 (79.4)	99 (85.3)	0.163
Coronary artery disease (n, %)	38 (35.5)	48 (41.4)	0.223
Cerebral vascular disease (n, %)	7 (6.5)	19 (16.4)	0.018
Chronic kidney disease (n, %)	33 (33.0)	52 (48.1)	0.019
Anemia (n, %)	17 (17.0)	37 (34.6)	0.003
Medications			
β blockers (n, %)	91 (85.0)	103 (88.8)	0.264
ACEIs/ARBs (n, %)	86 (80.4)	98 (84.5)	0.264
Loop diuretics (n, %)	62 (57.9)	71 (61.2)	0.620
Inotropic agents (n, %)	12 (11.2)	16 (13.8)	0.354
Calcium blockers (n, %)	27 (25.2)	41 (35.3)	0.067
Antiplatelet agents (n, %)	49 (45.8)	69 (59.5)	0.041
Anticoagulants (n, %)	50 (46.7)	53 (45.7)	0.876

Laboratory data			
BNP (pg/mL)	139.5 (40.5–548.0)	177.2 (67.3–431.4)	0.382
Echocardiographic data			
LVEF (%)	44.9 (33.1–58.0)	49.8 (35.6–61.0)	0.198
Cardiopulmonary exercise testing			
Peak VO_2 (mL/kg/min)	17.2 (14.3–21.4)	15.4 (12.8–18.5)	0.001
VE-VCO_2 slope	30.3 (26.6–33.0)	33.1 (29.3–38.3)	<0.001

CAVI, cardio-ankle vascular index; NYHA, New York Heart Association; EF, ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; VO_2, oxygen uptake; VE-VCO_2, ventilatory equivalent versus carbon dioxide output.

Supplementary Table 2. Baseline patient characteristics: patients with older age (n=116)

	Low CAVI (CAVI < 8.9, n = 53)	High CAVI (CAVI ≥ 8.9, n = 63)	P value
CAVI	7.78 (7.15–8.38)	9.68 (9.30–10.32)	<0.001
Demographic data			
Male sex (n, %)	40 (75.5)	52 (82.5)	0.240
Body mass index (kg/m^2)	23.5 (22.4–25.3)	22.7 (21.1–25.3)	0.181
Systolic blood pressure (mmHg)	127.0 (109.0–138.0)	130.0 (110.5–150.0)	0.309
Diastolic blood pressure (mmHg)	68.0 (60.0–77.0)	70.0 (60.0–88.0)	0.200
Heart rate (/min)	72.0 (61.0–87.0)	72.0 (62.0–89.0)	0.684
NYHA functional class Ⅲ or Ⅳ (n, %)	0 (0.0)	1 (1.6)	0.543
Ischemic etiology (n, %)	20 (42.6)	22 (41.5)	0.539
Reduced/mid-range/preserved EF (n, %)	15 (33.3)/ 9 (20.0)/ 21 (46.7)	15 (29.4)/ 9 (17.6)/ 27 (52.9)	0.828
Co-morbidities			
Hypertension (n, %)	41 (77.4)	51 (81.0)	0.402
Diabetes mellitus (n, %)	19 (35.8)	31 (49.2)	0.104
Dyslipidemia (n, %)	44 (83.0)	55 (87.3)	0.348
Coronary artery disease (n, %)	23 (43.4)	25 (39.7)	0.414
Cerebral vascular disease (n, %)	10 (18.9)	9 (14.3)	0.339
Chronic kidney disease (n, %)	21 (39.6)	31 (56.4)	0.061
Anemia (n, %)	18 (35.3)	19 (33.9)	0.522
Medications			
β blockers (n, %)	48 (90.6)	55 (87.3)	0.401
ACEIs/ARBs (n, %)	43 (81.1)	55 (87.3)	0.255
Loop diuretics (n, %)	31 (58.5)	40 (63.5)	0.359
Inotropic agents (n, %)	6 (11.3)	10 (15.9)	0.333
Calcium blockers (n, %)	17 (32.1)	24 (38.1)	0.316
Antiplatelet agents (n, %)	32 (60.4)	37 (58.7)	0.504
Anticoagulants (n, %)	26 (49.1)	27 (42.9)	0.315
Laboratory data			
BNP (pg/mL)	158.8 (46.5–431.5)	234.2 (94.8–431.3)	0.163

Echocardiographic data			
LVEF (%)	45.7 (34.1–61.3)	50.3 (38.1–60.8)	0.680
Cardiopulmonary exercise testing			
Peak VO_2 (mL/kg/min)	15.9 (13.9–19.4)	14.6 (12.6–17.7)	0.110
VE-VCO_2 slope	32.9 (28.9–36.3)	33.2 (30.0–39.9)	0.121

CAVI, cardio-ankle vascular index; NYHA, New York Heart Association; EF, ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; VO_2, oxygen uptake; VE-VCO_2, ventilatory equivalent versus carbon dioxide output.

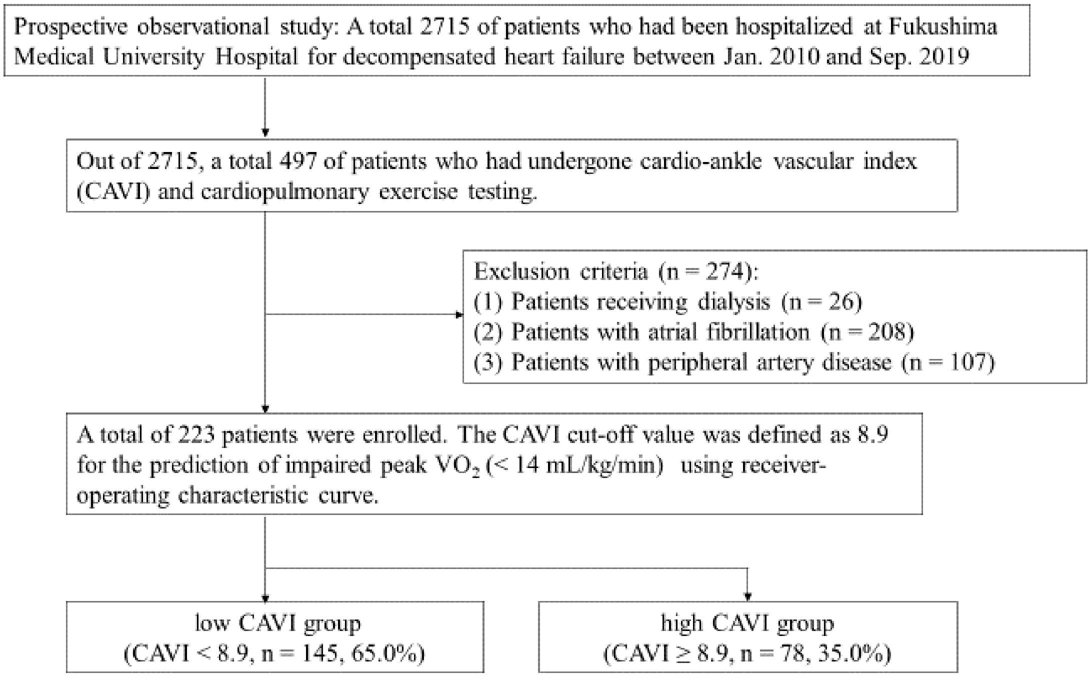
Supplementary Table 3. Baseline patient characteristics: patients with younger age (n = 107)

	Low CAVI (CAVI < 8.9, n = 92)	High CAVI (CAVI ≥ 8.9, n = 15)	P value
CAVI	7.11 (6.15–7.73)	9.56 (9.49–9.79)	<0.001
Demographic data			
Male sex (n, %)	72 (78.3)	14 (93.3)	0.155
Body mass index (kg/m^2)	25.4 (22.0–29.0)	24.6 (22.9–27.2)	0.650
Systolic blood pressure (mmHg)	122.0 (107.5–144.0)	134.0 (119.0–152.0)	0.114
Diastolic blood pressure (mmHg)	75.5 (62.0–91.0)	87.0 (79.0–104.0)	0.069
Heart rate (/min)	85.0 (68.5–100.5)	79.0 (66.5–88.0)	0.260
NYHA functional class Ⅲ or Ⅳ (n, %)	1 (1.1)	0 (0.0)	0.860
Ischemic etiology (n, %)	21 (26.6)	7 (58.3)	0.033
Reduced/mid-range/preserved EF (n, %)	33 (41.3)/ 15 (18.8)/ 32 (40.0)	4 (30.8)/ 5 (38.5)/ 4 (30.8)	0.276
Co-morbidities			
Hypertension (n, %)	58 (63.0)	13 (86.7)	0.061
Diabetes mellitus (n, %)	41 (44.6)	10 (66.7)	0.095
Dyslipidemia (n, %)	72 (78.3)	13 (86.7)	0.361
Coronary artery disease (n, %)	21 (26.6)	7 (58.3)	0.033
Cerebral vascular disease (n, %)	7 (7.6)	0 (0.0)	0.336
Chronic kidney disease (n, %)	27 (31.0)	6 (46.2)	0.219
Anemia (n, %)	13 (14.9)	4 (30.8)	0.153
Medications			
β blockers (n, %)	78 (84.8)	13 (86.7)	0.604
ACEIs/ARBs (n, %)	74 (80.4)	12 (80.0)	0.602
Loop diuretics (n, %)	53 (57.6)	9 (60.0)	0.547
Inotropic agents (n, %)	10 (10.9)	2 (13.3)	0.528
Calcium blockers (n, %)	23 (25.0)	4 (26.7)	0.557
Antiplatelet agents (n, %)	39 (42.4)	10 (66.7)	0.071
Anticoagulants (n, %)	42 (45.7)	8 (53.3)	0.391
Laboratory data			
BNP (pg/mL)	144.0 (42.1–548.0)	93.5 (29.0–404.1)	0.443

Echocardiographic data			
LVEF (%)	44.9 (31.6–59.1)	46.0 (36.9–50.0)	0.682
Cardiopulmonary exercise testing			
Peak VO_2 (mL/kg/min)	18.0 (14.5–22.4)	14.7 (13.4–16.5)	0.035
VE-VCO_2 slope	30.0 (26.5–33.1)	30.5 (27.6–32.8)	0.353

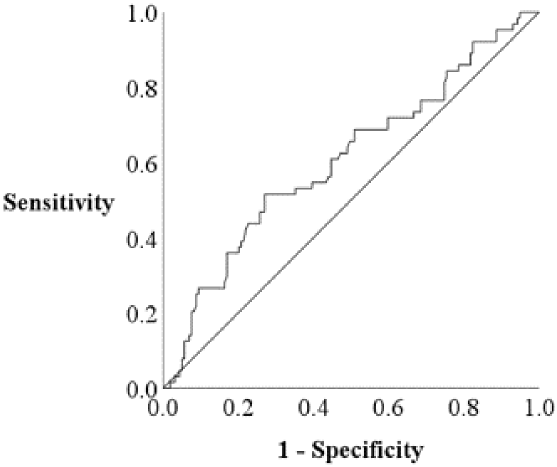
CAVI, cardio-ankle vascular index; NYHA, New York Heart Association; EF, ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; VO_2, oxygen uptake; VE-VCO_2, ventilatory equivalent versus carbon dioxide output.

Figure 1.



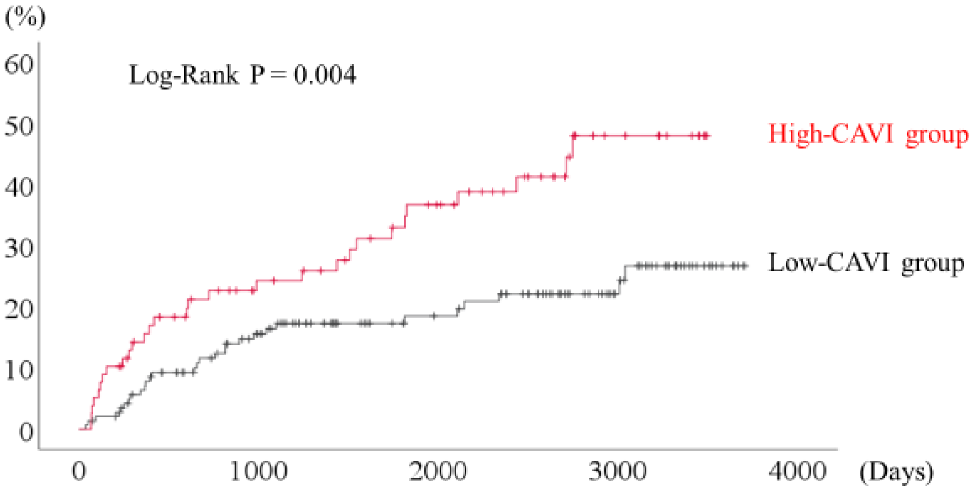
Patient flow chart. CAVI, cardio-ankle vascular index; VO_2, oxygen uptake.

Figure 2.



Receiver-operating characteristic curve for the prediction of impaired peak oxygen uptake (VO_2) by cardio-ankle vascular index (CAVI). The cut-off value of CAVI was 8.9. Area under curve was 0.67 and 95% confidence interval were 0.52-0.69 ($P < 0.05$).

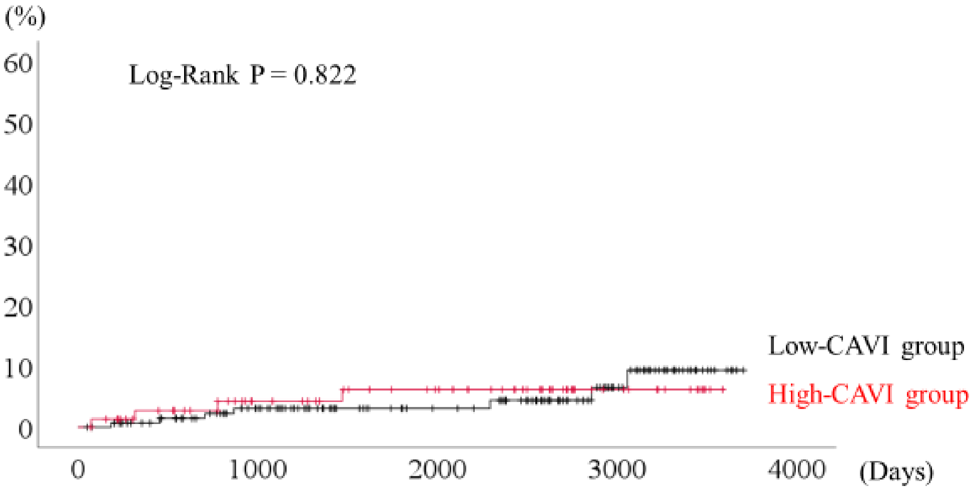
Figure 3.



Number at risk					
High-CAVI group	78	47	32	10	0
Low-CAVI group	145	101	68	35	0

Kaplan-Meier analysis for cardiac event in high [cardio-ankle vascular index (CAVI) ≥ 8.9] and low CAVI (CAVI < 8.9) groups. Event rates were analyzed by a log-rank test.

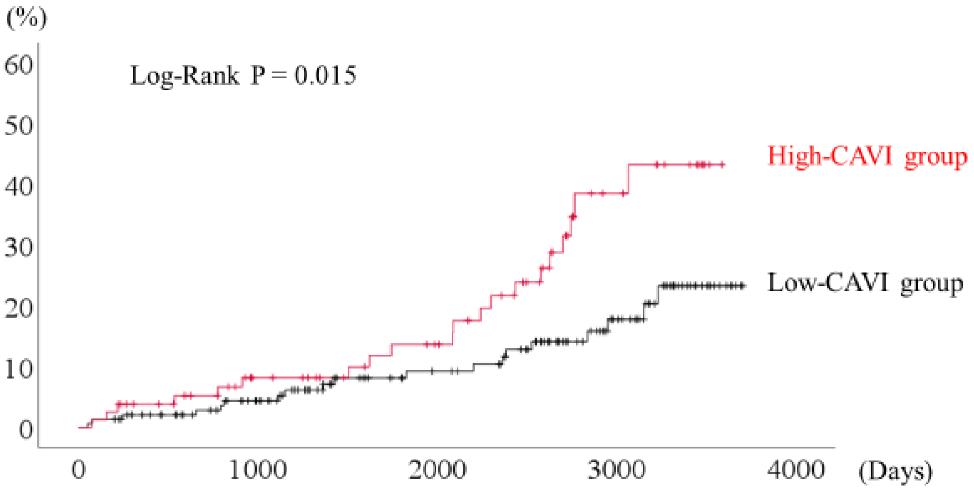
Figure 4.



Number at risk					
High-CAVI group	78	54	42	13	0
Low-CAVI group	145	110	75	34	0

Kaplan-Meier analysis for ischemic event in high [cardio-ankle vascular index (CAVI) ≥ 8.9] and low CAVI (CAVI < 8.9) groups. Event rates were analyzed by a log-rank test.

Figure 5.



Number at risk					
High-CAVI group	78	56	44	13	0
Low-CAVI group	145	114	80	38	0

Kaplan-Meier analysis for all-cause mortality in high [cardio-ankle vascular index (CAVI) ≥ 8.9] and low CAVI (CAVI < 8.9) groups. Event rates were analyzed by a log-rank test.