Cardio-Ankle Vascular Index and Heart Failure Hospitalization in Patients With Aortic Stenosis Following Transcatheter Aortic Valve Implantation

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Background: The cardio-ankle vascular index (CAVI) is associated with the severity of vascular stiffness and heart failure (HF). However, little is known about CAVI in aortic stenosis (AS) patients, probably because of the difficulty of accurately measuring CAVI in these patients owing to their slow-rising pulse. In this study, we investigated the prevalence and prognostic impact of abnormally elevated CAVI measured after transcatheter aortic valve implantation (TAVI).

Methods and Results: Among patients with AS who underwent TAVI, those with bilateral peripheral artery disease, atrial fibrillation, and systolic HF were excluded. The effect of post-TAVI elevated CAVI (defined as ≥9.0) on HF readmission after the index discharge was investigated. In all, 149 patients (mean ± SD age 84.8 ± 5.6 years, 24.2% men, mean ± SD post-TAVI CAVI 9.6 ± 1.4) were included in the study. There was no significant difference in baseline characteristics between groups with and without elevated CAVI, except for lower high-density lipoprotein cholesterol (HDL-C) and a higher prevalence of HF history in the group with elevated CAVI (P<0.05 for both). Post-TAVI elevated CAVI (n=102) was associated with lower freedom from HF recurrence during the observational period (89.1% vs. 100%; median 726 days [interquartile range 329–1,104 days]; P<0.05). Moreover, CAVI was an independent predictor of HF occurrence (hazard ratio 1.62; 95% confidence interval 1.07–2.46; P=0.022).

Conclusions: Elevated CAVI was associated with HF occurrence before and after TAVI.

Key Words: Aortic stenosis; Cardio-ankle vascular index; Heart failure with preserved ejection fraction

The survival of patients with AS has improved considerably owing to the development of transcatheter aortic valve implantation (TAVI). Of note, recent studies indicate that TAVI can be used even in intermediate- and low-risk elderly cohorts with favorable results. However, the occurrence of heart failure after TAVI remains an unsolved issue. Several risk factors for the occurrence of heart failure after TAVI have been reported, including atrial fibrillation, left ventricular ejection fraction (LVEF), ischemic heart disease, and pulmonary hypertension, but the effect of vascular stiffness remains unknown.

CAVI is calculated by measuring brachial-ankle pulse wave velocity. Patients with AS have a slow-rising pulse, making CAVI measurement challenging. Following TAVI, this issue is resolved and CAVI can be measured correctly. CAVI measured immediately after TAVI would be similar to that measured just before TAVI. In the pres-
ent study, we investigated the effect of post-TAVI CAVI on heart failure occurrence after the index discharge.

**Methods**

**Subjects and Study Design**

Consecutive patients with symptomatic severe AS, which was defined as an aortic valve area <1.0 cm$^2$ and peak velocity thorough the aortic valve >4.0 m/s, who finally received TAVI were prospectively enrolled in this study. Patients with reduced LVEF (<50%), bilateral peripheral artery disease, or atrial fibrillation were excluded from the study, given the effects of these conditions on CAVI.

In addition, post-TAVI data from patients who underwent an alternative approach or had major comorbidities, including death, cardiac tamponade, disabling stroke, severe infection, and moderate or greater aortic regurgitation, were excluded given their effects on heart failure events.

CAVI examinations were performed 1–2 weeks after TAVI. Patient cohorts were stratified into 2 groups (i.e., high and low CAVI groups) using a cut-off CAVI value of 9.0 according to the manufacturer’s instructions. The effect of CAVI on the incidence of heart failure readmission after TAVI was investigated.

Informed consent was obtained from all participants before they were enrolled in the study. This study was approved by the Ethics Committee of the University of Toyama (Reference no. 28-404).

**TAVI**

Patient selection for TAVI was determined by a heart team, which comprised cardiologists, cardiovascular surgeons, and anesthesiologists, according to the indications of the PARTNER trial. All patients received balloon-expandable valves (Sapien XT or Sapien 3; Edwards Lifesciences, Irvine, CA, USA) or self-expandable valves (Corevalve or Evolut R; Medtronic, Minneapolis, MN, USA) via a transfemoral approach under general anesthesia.

**Transthoracic Echocardiography**

Transthoracic echocardiography was performed 2 days before TAVI and 1–2 weeks after TAVI. Standard M-mode, 2-dimensional, Doppler, and tissue Doppler studies were performed using standard techniques. The aortic valve area was calculated using a continuity equation.

**CAVI Measurement**

CAVI was measured using a commercial device (Vasera; Fukuda Denshi, Tokyo, Japan) according to previously described methods. Briefly, the brachial and ankle pulse waves were determined using inflatable cuffs, with the pressure maintained between 30 and 50 mmHg to ensure that the cuff pressure had minimal effect on systemic hemodynamics. Blood and pulse pressures were determined simultaneously, with the patient lying supine for 10 min in a quiet room.

Bilateral CAVI values were averaged in general. Patients with bilateral peripheral artery disease with an ankle-brachial index <0.9 were excluded. For those with unilateral disease, CAVI values obtained from the healthy leg were used.

**Statistical Analysis**

Continuous variables are expressed as the mean±SD or median and interquartile range (IQR) depending on their distribution and were compared between groups using unpaired t-tests or the Mann-Whitney U test, as appropriate. Categorical variables are expressed as numbers and percentages and were compared between the 2 groups.
were included in the study (Figure 1).

Patients’ baseline characteristics are summarized in Table 1. The mean age was 84.7 years and 24% of patients were male. Mean CAVI was 9.64 ± 1.36 and 102 (68.5%) patients were assigned to the high CAVI group, defined as CAVI ≥ 9.0.

There were no statistically significant differences in baseline characteristics between the high and low CAVI groups, except for the higher prevalence of former heart failure admission and lower HDL-C levels in the high CAVI group (P<0.05 for both).

Post-TAVI Clinical Data
Clinical data following TAVI are summarized in Table 2. There were no statistically significant differences in post-TAVI data, except for a lower LVEF in the high CAVI group (P<0.01).

There were also no significant differences between the low and high CAVI groups in the rates of periprocedural complications, such as vascular complications (4.2% vs. 3.9%, respectively), bleeding requiring transfusion (23.4% vs. 26.5%, respectively), acute kidney injury (6.4% vs.
Clinical Implication of CAVI in AS Patients

Effect of CAVI on the Primary Endpoint

During the observation period (median 726 days; IQR 326–1,104 days) after the index discharge, 11 patients (7.4%) were readmitted for heart failure. Of note, no patients in the low CAVI group experienced heart failure readmission. Freedom from heart failure readmissions was significantly lower in the high CAVI group (89.1% vs. 100%; P<0.05; Figure 2). Overall, 11 (7.4%) patients died, and there was no significant difference between the low and high CAVI groups in freedom from all-cause death (2.1% vs. 9.8%, respectively; P=0.10).

After adjusting for the estimated glomerular filtration rate, which was another significant variable in the univariate analyses, the hazard ratio for CAVI to predict heart failure readmissions was 1.62 (95% confidence interval 1.07–2.46; P=0.022; Table 3).

Renal function impairment was significantly greater and CAVI values were significantly higher in patients with heart failure readmissions after TAVI (Table 4).

Discussion

In this study we investigated the association between CAVI

| Table 2. Patient Characteristics After TAVI |
|--------------------------------------------|
| **High CAVI** (n=102) | **Low CAVI** (n=47) |
|------------------------|---------------------|
| CAVI 10.3±1.1 | 8.2±0.6** |
| Hemoglobin (g/dL) 10.2±1.6 | 10.2±1.1 |
| Serum albumin (g/dL) 3.4±0.5 | 3.4±0.4 |
| Serum creatinine (mg/dL) 0.94±0.41 | 0.98±0.48 |
| eGFR (mL/min/1.73m²) 52±19 | 52±20 |
| Plasma BNP (pg/mL) 81 [52–155] | 75 [38–114] |
| Aortic valve area (cm²) 1.4±0.3 | 1.5±0.3 |
| Maximum velocity across the aortic valve (m/s) 2.1±0.5 | 2.1±0.5 |
| Left ventricular ejection fraction (%) 65.4±11.5 | 69.0±7.4** |
| Left ventricular mass (g) 179.7±55.6 | 178.2±55.3 |
| Left ventricular mass index (g/m²) 127.4±36.4 | 127.1±38.4 |
| Septal wall thickness (mm) 10.8±2.1 | 10.6±1.8 |
| Posterior wall thickness (mm) 10.8±1.7 | 10.8±1.3 |
| E (cm/s) 80.0±28.0 | 82.6±25.1 |
| A (cm/s) 109.6±28.1 | 11.5±28.7 |
| E/A ratio 0.8±0.4 | 0.8±0.5 |
| Lateral E' (cm/s) 5.3±1.7 | 5.7±1.9 |
| Septal E' (cm/s) 4.2±1.1 | 4.3±1.2 |
| E/E' ratio 17.8±6.3 | 18.2±7.2 |
| Left atrium diameter (mm) 41.7±8.7 | 42.5±7.9 |
| TVR flow pressure gradient (mmHg) 23.7±7.5 | 23.0±7.1 |

Data are presented as the mean±SD or median [interquartile range]. *P<0.05, **P<0.01 compared with the high CAVI group. A, peak late diastolic filling velocity; E, peak early diastolic filling velocity; E’, peak early diastolic mitral annular velocity; TVR, tricuspid valve regurgitation. Other abbreviations as in Table 1.

Figure 2. Freedom from heart failure readmissions following transcatheter aortic valve implantation stratified by cardio-ankle vascular index (CAVI) levels. CHF, chronic heart failure.
aged >80 years was 9.8±1.3,\textsuperscript{20} which is comparable to that in the present cohort. Patients with AS may not necessarily have considerably higher CAVI than those without AS. The prevalence of atherosclerosis risk factors was comparable between the low and high CAVI groups. The pathophysiology of AS progression involves endothelial dysfunction, immune cell infiltration, myofibroblast and osteoblast differentiation, and, subsequently, calcification of the aortic valve, all of which seem to be different from the pathophysiology of atherosclerosis.\textsuperscript{4,5} The severity of AS and the progression of vascular stiffness may not necessarily be dependent on each other.

One possible explanation for the high CAVI in some patients is the high-density lipoprotein cholesterol (HDL-
C level. HDL-C is associated with anti-inflammation and stabilization of endothelial function, as well as improvements in diastolic function in patients with diastolic dysfunction.\textsuperscript{21,22} In the present cohort, the low HDL-C may have contributed to the progression of vascular stiffness and incremental CAVI levels.

**Vascular Stiffness and Diastolic Dysfunction**
In patients without AS, vascular stiffness is associated with diastolic dysfunction.\textsuperscript{23} In the present cohort, almost all patients had diastolic dysfunction, defined as an E/e’ ratio >14, an E’ value at the lateral wall <10 cm/s, and an E’ value at the septal wall <7 cm/s.\textsuperscript{24} These values did not differ significantly regardless of CAVI values: the progression of diastolic dysfunction in AS patients would predominantly come from the stenotic aortic valve, rather than incremental vascular stiffness.

**Prognostic Impact of Vascular Stiffness Following TAVI**
High CAVI was an independent predictor of heart failure readmissions following TAVI. In addition, the prevalence of previous heart failure hospitalizations was higher among patients with high CAVI. In patients with HfPeF, a cohort that may have similar physiology to the present cohort following TAVI, high CAVI was an independent predictor of heart failure recurrence.\textsuperscript{25}

Following TAVI, patients with low CAVI had a greater LVEF. Although further studies are warranted, low CAVI, indicating low vascular stiffness, may allow further cardiac reverse remodeling via lesser afterload on the left ventricle. Taking all these findings in consideration, following TAVI, persistently elevated vascular stiffness may increase afterload on the left ventricle and disturb cardiac unloading/reverse remodeling, resulting in heart failure recurrence. Among the patients with heart failure recurrence, one patient experienced de novo atrial fibrillation. Atrial fibrillation is strongly associated with the development of heart failure. The persistently elevated vascular stiffness may have also triggered anatomical and electrical remodeling in the atrium, resulting in the progression of left heart impairment.\textsuperscript{26}

Given our findings, CAVI may be a useful marker to risk stratify patients who undergo TAVI. Those with higher CAVI should be carefully monitored to prevent worsening heart failure.

**Interventions for Vascular Stiffness Following TAVI**
Thus far, there are no established therapeutic or prophylactic strategies to improve clinical outcomes following TAVI by interventions targeting vascular stiffness. A sodium-glucose cotransporter 2 inhibitor, which was recently demonstrated to improve clinical outcomes in patients with HfPeF, may be a potential therapeutic tool because of its diuretic and renoprotective effects.\textsuperscript{28} The medication may further improve vascular stiffness and endothelial function.\textsuperscript{29} Such novel medications may ameliorate vascular stiffness and further improve clinical outcomes in patients undergoing TAVI.

**Study Limitations**
This study has several limitations that should be considered. First, the sample size was moderate. Second, we restricted variables included in the multivariable analysis given such a small number of events. Third, there may be any other uninvestigated confounders. Given that CAVI is independent of hemodynamics, we assumed post-TAVI CAVI was a unique fixed variable in each patient. Fourth, trends in CAVI during the observation period remain uninvestigated. Fifth, we excluded patients with bilateral peripheral artery diseases, atrial fibrillation, and heart failure with reduced ejection fraction given the effects of these conditions on CAVI. The applicability of our findings to these excluded cohorts remains unknown. Sixth, some patients were lost follow-up. Finally, the association between CAVI and flow-mediated dilation was not investigated.

**Conclusions**
Among patients with severe AS, an elevated CAVI was associated with worsening heart failure before and after TAVI.

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**Disclosures**
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**IRB Information**
This study was approved by the Ethics Committee, University of Toyama (Reference no. 28-404).

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