Prevalence and Predictors of Atherosclerotic Peripheral Arterial Obstructive Disease in Severe Heart Valve Diseases

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Summary
Despite witnessing an upsurge in heart valve diseases (HVDs), the correlation between HVDs and atherosclerotic peripheral arterial obstructive disease (PAOD) remains unclear. This study aims to investigate the prevalence and predictors of PAOD in HVDs.

In this study, a total of 245 consecutive patients were examined: 153 with severe aortic valve stenosis (AS), 66 with severe primary mitral valve regurgitation (MR), and 26 with severe pure native aortic valve regurgitation (AR). All patients underwent ultrasound scan of the carotid artery to ascertain the presence of internal carotid artery stenosis (ICAS). ICAS was defined as a peak systolic velocity $\geq 125$ cm/second and/or $\geq 50\%$ reduction in diameter. In addition, we measured the ankle-brachial index in each leg using a volume plethysmograph. A result of $\leq 0.9$ was considered lower extremity artery disease (LEAD).

The presence of ICAS was statistically more frequent in patients with severe AS than in patients with severe MR and AR (11.1% versus 1.5% versus 3.8%; $P = 0.038$). LEAD was present in patients with severe AS (17.6%) and MR (10.6%) but not in patients with severe AR ($P = 0.037$). The multivariate analysis revealed that the presence of severe AS (OR, 5.6 [1.3-24.9]; $P = 0.023$) was an independent predictor for ICAS, while history of coronary artery disease (OR, 4.8 [2.2-10.5]; $P < 0.001$) was an independent predictor for LEAD.

The prevalence of PAOD varies depending on each valvular disease. Individual screening should be considered on the basis of atherosclerotic risk factors, especially for patients with severe AS.

Key words: Aortic valve stenosis, Mitral valve regurgitation, Aortic valve regurgitation, Internal carotid artery stenosis, Lower extremity artery disease, Coronary artery disease

The advent of an aging society in recent years has led to an upsurge in patients with heart valve diseases (HVDs). The annual report by The Japanese Association for Thoracic Surgery revealed that the number of operations for valvular heart disease increased by 73.8% in the last 10 years. In addition, transcatheter aortic valve implantation (TAVI) and mitral valve intervention have become the leading treatments for high-risk operable or inoperable patients. Assumedly, the number of patients requiring the invasive treatment for valvular heart disease will increase in the future.

Aortic valve stenosis (AS) is primarily caused by a congenitally abnormal aortic valve, rheumatic heart disease, and degenerative process. Previous studies have related degenerative aortic valve disease, which is an inevitable consequence of aging, to atherosclerosis. Indeed, some studies have reported that prevalence of concomitant coronary artery disease (CAD) is around 50% and increases with age. In addition, concomitant CAD with severe AS has been proven to be associated with short- and long-term mortality. However, the correlation between severe AS and atherosclerotic peripheral arterial obstructive disease (PAOD) remains unclear.

Mitral valve regurgitation (MR) is the second leading valve disease after AS and is classified as either primary MR, due to mitral leaflet pathological abnormality, or secondary MR, due to left ventricular and/or left atrial remodeling. In particular, secondary MR complicates the course of 13%-50% of the acute myocardial infarctions. Conversely, the relationship between primary severe MR and arteriosclerosis disease, including PAOD, remains unknown.

Aortic valve regurgitation (AR) is the third leading valvular heart disease. In the developed countries, most common etiology of AR is either congenital (bicuspid aortic valve) or degenerative disease as pure native aortic valve disease. Although the incidence of severe pure native AR increases with age, the correlation between severe pure native AR and PAOD warrants further investigation.

Apparently, carotid ultrasound findings (intima-media thickness [IMT], carotid plaque score, and carotid steno-
sis) are associated with an increased risk of cardiovascular events. In addition, these parameters have been used as makers for perioperative risk stratification of cardiac surgery. Lower extremity artery disease (LEAD) is atherosclerosis that causes narrowing or occlusion of the lower extremity arteries, which reduces the blood flow. It is diagnosed by calculating the ankle-brachial index (ABI), which is the ratio of the systolic blood pressure at the ankle and in the arm. Lower ABI (≤ 0.9) is significantly related to cardiovascular mortality regardless of the presence of symptoms.

In patients with HVDs, the role of carotid artery ultrasound and measurement of ABI is not only to detect PAOD but also to determine whether the treatment strategy for severe HVDs is affected by the presence of PAOD. Hence, this study aims to investigate the prevalence and the predictors of atherosclerotic PAOD in severe HVDs (severe AS, severe primary MR, and severe pure native AR).

Methods

Study population: Between June 2009 and March 2017, we retrospectively examined consecutive patients with severe HVDs (severe AS, severe primary MR, and severe pure native AR) diagnosed by echocardiography according to the guidelines of ASE in Teikyo University Hospital.

All patients who underwent echocardiography, carotid artery ultrasound scanning, and ABI evaluation within 3 months were enrolled in this study. The exclusion criteria in this study were as follows: patients who were < 40 years old, undergoing hemodialysis, with history of infective endocarditis, and with history of intervention therapy for carotid artery and/or for LEAD. In addition, patients with poorly visualized carotid artery were also excluded from this study.

Clinical data: We assessed the clinical data from electronic medical records after obtaining approval from the Institutional Review Board of our hospital (Teikyo 17-076). In addition, the medical information of all patients was collected, such as age, gender, and cardiovascular risk factors (e.g., hypertension, diabetes mellitus, cigarette smoking, and dyslipidemia), along with history of intervention therapy for carotid artery and/or for LEAD. In addition, patients with poorly visualized carotid artery were also excluded from this study.

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Echocardiographic measurements: In this study, we enrolled patients with severe AS, severe primary MR, and severe pure native AR. Severe HVDs were diagnosed on the basis of physical examination and transthoracic echocardiography using the PHILIPS IE33 or EPIC E7. For the quantification of AS, we measured the trans-aortic peak velocity, the maximum and mean trans-aortic pressure gradient, and the aortic valve area using the continuity equation based on the guidelines of ASE. In addition, the left ventricular stroke volume index was evaluated using the following formula: LVOTVTI × LVOTarea/body surface area. We considered stroke volume index < 35 mL/m² as low flow. Severe AS was defined as trans-aortic peak velocity ≥ 4 m/second and/or a mean aortic valve gradient ≥ 40 mmHg. We also included the low-flow severe AS (aortic valve area ≤ 1.0 cm²).

We used the measurement of the narrowest width of the proximal regurgitant jet (vena contracta) and PISA methods to quantitate the severity of MR. Severe MR was defined as a vena contracta width > 0.7 cm or regurgitant volume ≥ 60 mL/beat or regurgitant fraction ≥ 50% or effective orifice area ≥ 0.40 cm². Of note, only primary severe MR was included in this study.

For the quantification of AR, vena contracta was measured by color Doppler from the parasternal long-axis view. We calculated the AR volume based on the comparison of the measurement of the aortic stroke volume at the LVOT with the mitral or pulmonic stroke volume. Severe AR was defined as a vena contracta width > 0.6 cm or regurgitant volume ≥ 60 mL/beat or regurgitant fraction ≥ 50%. In this study, we included only pure severe native AR.

Carotid ultrasound: The IMT and the presence of carotid plaque and carotid stenosis were evaluated using high-resolution B-mode ultrasound (Aplio XG; Toshiba Medical, Tokyo, Japan). The carotid ultrasound scan protocol requires the visualization of the near and far wall of the right and left common carotid arteries, the internal carotid artery, and the bifurcation. In addition, we evaluated the maximum IMT of the common carotid artery (CCA-IMT). Carotid plaque was defined as a focal region with hyperechogenicity and percutaneous or surgical coronary artery revascularization. We defined the cardiovascular risk factors as follows: arterial hypertension, systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg in, at least, two measurements or blood pressure requiring medical therapy during index hospitalization or antihypertensive medication before echo examination; dyslipidemia was defined as total cholesterol ≥ 220 mg/dL (5.0 mmol/L), low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL (3.2 mmol/L), high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL during index hospitalization, or previously diagnosed and/or on lipid-lowering therapy; diabetes mellitus, fasting venous plasma glucose ≥ 126 mg/dL (7.0 mmol/L) confirmed by repeated testing or casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during index hospitalization or diagnosed previously; and smoking, self-reported regular smoking habit. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) < 60 mL/minute per 1.73 m².

Ankle-brachial pressure index: After placing the patients in the supine position for more than 5 minutes, we recorded the blood pressure using an automated waveform analyzer (Colin VP-2000; Colin Medical Instruments Corp., Komaki, Japan). All recordings were collected while patients were receiving their regular medication. We used the left and right ABIs and the lower value of the ABI for data analysis. A result of ≤ 0.9 was considered...
ICAS: Carotid ultrasound finding and the prevalence of cerebral infarction. Data are expressed as medians with interquartile ranges.

**Results**

**Patient characteristics:** During the study period, there were 496 patients with severe AS, 198 with severe primary MR, and 26 with severe pure native AR diagnosed by echocardiography. Of these patients, 153 patients with severe AS, 66 with severe primary MR, and 26 with severe pure native AR who underwent carotid artery ultrasound scanning and ABI evaluation within 3 months were consisted in the study population. Bicuspid aortic valve disease was included in both AS and AR groups. There were no patients with two types of severe HVDs. Table I summarizes the baseline characteristics of the study population. Patients with severe AS were older than the remaining patients. With regard to traditional risk factors, diabetes and dyslipidemia were significantly more frequent in patients with severe AS.

**Carotid ultrasound finding and the prevalence of ICAS:** The CCA-IMT and the carotid plaque score were significantly higher in patients with severe AS than in patients with severe MR and AR (Figure 1A and B). The presence of carotid plaque was statistically more frequent in patients with severe AS than in patients with severe MR and AR (96.8% versus 85.1% versus 73.1%; \( P < 0.001 \)). Ultrasonography revealed that ICAS was present in 17 patients (10.9%) with severe AS, one (1.5%) with severe MR, and one (3.9%) with severe AR. In addition, ICAS was statistically more frequent in patients with severe AS than in the remaining patients (\( P = 0.038 \)).

**ABI and the prevalence of LEAD:** In this study, the ABI was significantly lower in patients with severe AS than in patients with severe MR and AR (Figure 2). In addition, the prevalence of LEAD in patients with severe AS, MR, and AR was 18.0%, 10.6%, and 0%, respectively. LEAD was statistically more frequent in patients with severe AS than in the remaining patients (\( P = 0.037 \)).

**Predictor of ICAS in patients with HVDs:** Table II shows the univariate and multivariate analyses of potential predictors of ICAS. Significant univariate correlates of ICAS included age \( \geq 75 \) years, history of CAD, and presence of severe AS. The multivariate logistic regression models identified the presence of severe AS as the only independent predictor of ICAS (OR, 5.6 [1.3-24.9]; \( P = 0.023 \)).

**Predictor of LEAD in patients with HVDs:** Table III shows the univariate and multivariate analyses of potential predictors of LEAD. Significant univariate correlates of LEAD included age \( \geq 75 \) years, dyslipidemia, history of CAD, and presence of severe AS. The multivariate logistic regression models identified history of CAD as the only independent predictor of LEAD (OR, 4.8 [2.2-10.5]; \( P < 0.001 \)).

**Clinical outcome and PAOD:** In this study, the prevalence of PAOD was 15.9% in 245 patients. Patients with both ICAS and LEAD were 2.9%, all of whom were patients with severe AS. Of the 245 study patients, 225 underwent invasive treatment (aortic valve replacement, 63; TAVI, 79; mitral valve plasty, 45; mitral valve replacement, 15; and aortic valve replacement, 23). Among 225 patients, no patients with ICAS had carotid artery intervention and cerebral infarction during the perioperative phase. However, we experienced only one patient in this study with severe AS who had cerebral infarction.

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During the perioperative phase, we performed coronary revascularization (concomitant coronary artery bypass grafting or percutaneous coronary intervention before and after TAVI) for 25 patients (11.1%). No significant difference was observed in the coronary revascularization rate among HVDs: 17 patients (12%) in severe AS, seven (11.7%) in severe MR, and one (4.3%) in severe AR. Table IV shows both univariate and multivariate analyses of potential predictors of coronary revascularization during the perioperative phase. The presence of PAOD was not an independent predictor for coronary revascularization.

**Discussion**

This study demonstrated the prevalence and identified predictor of PAOD in patients with severe HVDs (AS, primary MR, and pure native AR). The results revealed that ICAS was present in 7.8% and LEAD in 13.9% of study patients. Severe AS was a significant predictor of both ICAS and LEAD.

**ICAS:** Almost all patients with ICAS had severe AS. In this study, ICAS was determined in 11.1% of patients with severe AS, whereas previous studies have reported...
that ICAS was present in 12%-33% of severe AS patients.\textsuperscript{23-27} The relatively low prevalence of ICAS in this study could be attributed to the difference in the patients' background, such as gender and race. Condado, et al. reported that approximately 20% of 996 patients with TAVR or SAVR had ICAS. The proportion of females in their

**Table II.** Predictor of ICAS in Patients with Severe HVDs

| Variables                  | Univariate OR (95% CI) | P value | Multivariate OR (95% CI) | P value |
|----------------------------|------------------------|---------|--------------------------|---------|
| Age ≥ 75 years             | 5.4 (1.2-24.0)         | 0.026   | 5.6 (1.3-24.9)           | 0.023   |
| Male gender                | 1.5 (0.6-3.9)          | 0.373   | 1.5 (0.6-3.9)            | 0.373   |
| Hypertension               | 2.7 (0.6-11.9)         | 0.199   | 2.7 (0.6-11.9)           | 0.199   |
| Diabetes                   | 1.1 (0.4-3.3)          | 0.813   | 1.1 (0.4-3.3)            | 0.813   |
| Dyslipidemia               | 2.0 (0.8-5.3)          | 0.157   | 2.0 (0.8-5.3)            | 0.157   |
| Smoking                    | 1.7 (0.7-4.4)          | 0.265   | 1.7 (0.7-4.4)            | 0.265   |
| CKD                        | 0.9 (0.4-2.4)          | 0.880   | 0.9 (0.4-2.4)            | 0.880   |
| History of CAD             | 2.5 (0.9-7.1)          | 0.079   | 2.5 (0.9-7.1)            | 0.079   |
| History of CI              | 0.9 (0.2-4.3)          | 0.094   | 0.9 (0.2-4.3)            | 0.094   |
| Presence of severe AS      | 5.6 (1.3-24.9)         | 0.023   | 5.6 (1.3-24.9)           | 0.023   |

ICAS indicates internal carotid artery stenosis; OR, odds ratio; 95% CI, 95 percentile confidence interval; CKD, chronic kidney disease; CAD, coronary artery disease; CI, cerebral infarction; and AS, aortic valve stenosis

**Table III.** Predictor of LEAD in Patients with Severe HVDs

| Variables                  | Univariate OR (95% CI) | P value | Multivariate OR (95% CI) | P value |
|----------------------------|------------------------|---------|--------------------------|---------|
| Age ≥ 75 years             | 2.5 (1.1-6.1)          | 0.039   | 4.7 (2.1-10.5)           | <0.001  |
| Male gender                | 0.9 (0.4-1.9)          | 0.854   | 1.1 (0.4-3.4)            | 0.889   |
| Hypertension               | 1.0 (0.4-2.7)          | 0.931   | 4.7 (2.1-10.5)           | <0.001  |
| Diabetes                   | 1.7 (0.8-3.6)          | 0.208   | 4.7 (2.1-10.5)           | <0.001  |
| Dyslipidemia               | 2.0 (0.9-4.1)          | 0.077   | 4.7 (2.1-10.5)           | <0.001  |
| Smoking                    | 1.0 (0.2-2.1)          | 0.977   | 4.7 (2.1-10.5)           | <0.001  |
| CKD                        | 1.1 (0.5-2.2)          | 0.840   | 4.7 (2.1-10.5)           | <0.001  |
| History of CAD             | 4.7 (2.1-10.5)         | <0.001  | 4.7 (2.1-10.5)           | <0.001  |
| History of CI              | 1.1 (0.4-3.4)          | 0.889   | 4.7 (2.1-10.5)           | <0.001  |
| Presence of severe AS      | 2.6 (1.1-6.2)          | 0.035   | 4.7 (2.1-10.5)           | <0.001  |

LEAD indicates lower extremity artery disease; OR, odds ratio; 95% CI, 95 percentile confidence interval; CKD, chronic kidney disease; CAD, coronary artery disease; CI, cerebral infarction; and AS, aortic valve stenosis

**Table IV.** Predictor of Coronary Revascularization During the Perioperative Phase in Patients with Severe HVDs

| Variables                  | Univariate OR (95% CI) | P value | Multivariate OR (95% CI) | P value |
|----------------------------|------------------------|---------|--------------------------|---------|
| Age ≥ 75 years             | 1.2 (0.5-2.8)          | 0.630   | 4.1 (1.6-10.7)           | 0.004   |
| Male gender                | 3.1 (1.3-7.6)          | 0.012   | 4.1 (1.6-10.7)           | 0.004   |
| Hypertension               | 3.8 (0.9-16.8)         | 0.075   | 4.1 (1.6-10.7)           | 0.004   |
| Diabetes                   | 3.2 (1.4-7.7)          | 0.008   | 4.1 (1.6-10.7)           | 0.004   |
| Dyslipidemia               | 5.3 (1.9-14.7)         | 0.001   | 4.6 (1.6-13.4)           | 0.005   |
| Smoking                    | 3.0 (1.3-7.0)          | 0.012   | 4.6 (1.6-13.4)           | 0.005   |
| CKD                        | 1.1 (0.5-2.5)          | 0.850   | 4.6 (1.6-13.4)           | 0.005   |
| History of CAD             | 4.8 (2.0-11.7)         | <0.001  | 4.6 (1.6-13.4)           | 0.005   |
| History of CI              | 1.1 (0.4-3.4)          | 0.889   | 4.6 (1.6-13.4)           | 0.005   |
| Presence of severe AS      | 1.3 (0.5-3.1)          | 0.592   | 4.6 (1.6-13.4)           | 0.005   |
| Presence of ICAS           | 2.5 (0.8-8.4)          | 0.129   | 4.6 (1.6-13.4)           | 0.005   |
| Presence of LEAD           | 1.8 (0.6-5.1)          | 0.303   | 4.6 (1.6-13.4)           | 0.005   |
| Presence of PAOD (ICAS and/or ICAS) | 1.8 (0.7-4.7) | 0.209   | 4.6 (1.6-13.4)           | 0.005   |

CAD indicates coronary artery disease; OR, odds ratio; 95% CI, 95 percentile confidence interval; CKD, chronic kidney disease; CI, cerebral infarction; AS, aortic valve stenosis; ICAS, internal carotid artery stenosis; LEAD, lower extremity artery disease; and PAOD, peripheral arterial obstructive disease
study population was less than 50%. However, in our study, the number of female patients was significantly high (69.2%), which is almost the same rate as other reports for Japanese patients with severe AS. Rockman revealed that Asian females have a significantly decreased prevalence of ICAS than Caucasian males. Our study also found that the prevalence of ICAS was 16.7% for male patients only. The incidence of ICAS in Japanese male with severe AS seems almost the same as that in Western with severe AS.

While the prevalence of ICAS in patients with primary MR and pure native AR has not been previously evaluated, this study demonstrated that only a few patients with severe MR and AR had ICAS. The rate of male patients with severe MR and AR was higher than the rate of male patients with AS; however, those males were younger. Perhaps, this might be one of the reasons for the low prevalence of ICAS in patients with MR and AR.

The presence of severe AS was the only significant independent predictor for ICAS, which was not surprising because severe AS correlated not only with the degenerative process but also with the systemic atherosclerotic process. Although routine screening of ICAS for patients with MR and AR might be unnecessary, screening focusing on patients with severe AS should be considered.

**LEAD:** We observed a statistically significant difference among patients with AS, MR, and AR for the presence of LEAD. The prevalence of LEAD in patients with severe AS was 18.0%. Only a few studies reported the prevalence of PAOD for patients with AS. Sinning, et al. demonstrated that 25.1% of patients had LEAD in the German real-world TAVI Registry, which presented a higher rate compared to the prevalence of LEAD in our study, perhaps due to the methodology used in that study. They defined LEAD as follows: claudication, history of peripheral arterial surgery or angioplasty, ABI < 0.9, or stenoses ≥ 50% of the iliofemoral axis. The patients with history of intervention therapy for LEAD were excluded in our study.

The only independent predictor of LEAD in multivariate analyses was the history of CAD. Previous studies have demonstrated that the ankle-brachial pressure index significantly correlates with the presence and severity of CAD. LEAD is prevalent in patients with CAD. Routine screening of LEAD for all patients with HVDs is controversial. Hence, an individual screening based on atherosclerotic risk factors, especially history of CAD, should be considered.

**Clinical impact of screening PAOD:** This study revealed that PAOD was common in patients with severe AS but rare in patients with severe AR. The number of operations for aortic valve disease is more than double than that for other valve diseases. Thus, an individual screening based on atherosclerotic risk factors for PAOD in patients with severe AS should be considered. Previous studies have denied any significant relationship between coexisting ICAS and the risk of perioperative stroke for patients undergoing both surgical aortic valve replacement and TAVI. Moreover, perioperative stroke after surgical procedures could be attributed to several causes other than ICAS. Thus, controversy exists about the indication of screening for ICAS in HVDs. However, patients with asymptomatic ICAS are at high risk of myocardial infarction. Patients with severe AS and coexisting LEAD were also reported to have high cardiovascular mortality. At the time that severe AS has been newly diagnosed, as well as preoperative phase, screening PAOD might be useful in identifying patients at high risk of cardiovascular event, in whom optimal medical treatment would significantly reduce this risk.

**Limitations:** This is a single-center, retrospective study with a relatively small sample size, especially that of the AR patients’ group. In addition, the rate of cerebrovascular events in this study was low compared to that in previous studies.

In this study, only patients who performed both carotid artery ultrasound scanning and ABI evaluation were included. In almost all cases, the purpose of these examinations was perioperative risk assessment for invasive treatment. Therefore, patients who were accidentally found and/or were not scheduled for invasive treatment were not included. Hence, there may be a selection bias. However, to the best of our knowledge, this is the first study to investigate the correlation between PAOD and HVDs (AS, primary MR, and pure native AR). This study demonstrated that the prevalence of PAOD was different among the three groups. Further studies are warranted to evaluate the clinical impact of coexisting PAOD in all the patients with HVDs for long-term prognosis.

**Conclusions**

The prevalence of PAOD varies depending on each valvular disease. Hence, an individual screening based on atherosclerotic risk factors, especially for patients with severe AS, should be considered.

**Disclosure**

**Conflicts of interest:** The authors declare that there is no conflict of interest.

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