Prevalence, Clinical Profile, and In-Hospital Outcomes of Sleep-Disordered Breathing in Patients Undergoing Transcatheter Aortic Valve Implantation in Japan

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Background: The prevalence, patient profile, and outcomes of sleep-disordered breathing (SDB) in aortic stenosis (AS) remain unknown, especially in East Asia.

Methods and Results: One hundred and eighty-one AS patients undergoing transcatheter aortic valve implantation (TAVI) were enrolled. Sixty-one patients (33.7%) had SDB, and lower stroke volume index was an independent determinant of SDB. Incidence of in-hospital stroke after TAVI was higher in the SDB group.

Conclusions: SDB is associated with left ventricular systolic dysfunction in Japanese AS patients referred for TAVI. SDB was highly associated with the incidence of stroke as a procedural complication.

Key Words: Aortic stenosis; Sleep-disordered breathing; Transcatheter aortic valve implantation

Aortic stenosis (AS) is recognized as progressive aortic valve narrowing with left ventricular (LV) pressure overload and concentric remodeling, leading to a decrease in cardiac output and heart failure (HF). Sleep-disordered breathing (SDB) is highly prevalent, but remains underrecognized as a comorbidity in patients with HF, which contributes to increased mortality. Furthermore, treatment of SDB had the potential to minimize postoperative morbidity and mortality, as shown in several observational studies. Transcatheter aortic valve implantation (TAVI) is a safer alternative to open heart surgery in elderly patients and has become a popular therapeutic choice for AS management. There is accumulating evidence regarding the prevalence and clinical importance of SDB in AS patients referred for TAVI in Western countries. For instance, according to reports from 2 centers in Germany, 43–61% of AS patients had SDB, as assessed on polygraphy (apnea-hypopnea index [AHI] >15). Furthermore, SDB prevalence was independent of LV systolic function. Data on real-world prevalence, patient profile, and outcomes of SDB in AS patients, however, are still limited. In particular, data from East Asian countries, which have the lowest prevalence of obesity worldwide, are lacking. Therefore, the aim of this study was to evaluate the real-world prevalence, clinical profile, and in-hospital outcomes of SDB in AS patients undergoing TAVI in Japan.

Methods

We evaluated 181 patients with severe AS referred for TAVI with a balloon-expandable valve (SAPIEN XT, Edwards Lifesciences, CA, USA) at Keio University Hospital between January 2014 and February 2016. Inclusion criteria for TAVI were as follows: (1) New York Heart Association functional class ≥II; and (2) mean gradient >40 mmHg, jet velocity >4.0 m/s, or aortic valve area <1.0 cm² (or effective orifice area index <0.6 cm²/m²). Patients who refused to participate and those with severe dementia, delirium, or other conditions that made it difficult to complete pulse oximetry were excluded. Incidence and pre-stroke volume index was an independent determinant of SDB. Incidence of in-hospital stroke after TAVI was higher in the SDB group.
Statistical Analysis

Normally distributed data are expressed as mean±SD, non-parametric data as median (IQR), and categorical data as absolute values and percentages. Independent continuous variables were compared using Mann-Whitney U-test, and categorical variables, with Pearson’s chi-squared test. P<0.05 was considered statistically significant. Multiple logistic regression analysis was performed to identify the independent determinants of SDB in this cohort. Logistic regression modeling was carried out by adjusting for clinically relevant variables, and the factors that were significantly different between the SDB and control groups (P<0.01) were included in the multivariate analysis (i.e., age, gender, obesity, prior myocardial infarction (MI), and stroke volume index (SVI)). Data were analyzed using Pearson’s correlation, Mann-Whitney U-test, and chi-squared test with SPSS version 24.0 (SPSS, Chicago, IL, USA). P<0.05 was considered statistically significant.

Results

Median patient age and BMI was 85 years (IQR, 82–87 years) and 21.8 kg/m² (IQR, 19.4–24.4 kg/m²), respectively; 58 patients (32%) were male. Median 3%ODI was 10.61 (IQR, 6.11–19.14). One hundred and fifty patients (82.9%)
had 3%ODI ≥5; 61 (33.7%) had 3%ODI ≥15; and 14 (7.7%) had 3%ODI ≥30. A comparison between the patients with 3%ODI ≥15 (SDB group) and those with 3%ODI <15 (control group) is given in Table 1. The SDB group had higher BMI and more history of MI than the control group. Notably, age, sex, prevalence of coronary risk factors, calcification of aortic valve and coronary artery, frailty, and MMSE did not differ between the 2 groups. C-reactive protein (CRP) and B-type natriuretic peptide did not differ between the 2 groups. SVI and LV ejection fraction (LVEF) were lower in the SDB group (Table 2). 3%ODI correlated negatively with SVI (r=−0.20, P=0.007) and tended to correlate with LVEF (r=−0.13, P=0.07). On multivariate logistic regression analysis adjusted for age, gender, obesity, and previous MI, lower SVI was an independent determinant of SDB in this cohort (Table 3).

The comparison of in-hospital clinical outcomes between the SDB and control groups is given in Table 4. The SDB group had a higher incidence of stroke as a procedural complication (6.6% vs. 0%, P=0.012). Of the 4 patients

### Table 2. Laboratory and Echocardiography Parameters vs. SDB Status

| Echocardiography variables | SDB group 3%ODI ≥15 (n=61) | Control group 3%ODI <15 (n=120) | P-value |
|----------------------------|-------------------------------|----------------------------------|---------|
| LVDd (cm)                  | 4.5 (4.1–4.9)                 | 4.3 (4.0–4.7)                    | 0.112   |
| LVDs (cm)                  | 2.8 (2.5–3.3)                 | 2.6 (2.3–3.0)                    | 0.012   |
| LVEF (%)                   | 64.8 (58.5–71.2)              | 70.4 (63.0–75.0)                 | 0.019   |
| LVMI (g/m²)                | 137 (114–165)                 | 131 (111–168)                    | 0.348   |
| Peak velocity (m/s)        | 4.4±0.7                       | 4.6±0.8                         | 0.156   |
| MAG (mmHg)                 | 41.5 (32.5–54.0)              | 46.0 (36.0–61.0)                 | 0.171   |
| AVA index (cm²/m²)         | 0.42 (0.36–0.49)              | 0.46 (0.39–0.53)                 | 0.162   |
| SVI (mL/m²)                | 42.6 (36.2–49.6)              | 47.7 (40.3–54.7)                 | 0.005   |
| Left atrial diameter (cm)  | 4.3 (3.5–4.8)                 | 4.2 (3.8–4.8)                    | 0.963   |
| ePAP (mmHg)                | 32.0 (24.5–36.0)              | 32.0 (26.0–40.0)                 | 0.359   |

Laboratory data

| BNP (pg/mL)                | 217 (120–511)                 | 202 (99–368)                     | 0.821   |
| Hemoglobin (g/dL)          | 11.4±1.5                      | 11.3±1.5                        | 0.909   |
| eGFR (mL/min/1.73m²)       | 49 (40–58)                    | 51 (36–62)                      | 0.668   |
| CRP (mg/dL)                | 0.04 (0.02–0.21)              | 0.08 (0.03–0.29)                 | 0.399   |

Data given as mean±SD or median (IQR). AVA, aortic valve area; BNP, B-type natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MAG, mean aortic gradient; ODI, oxygen desaturation index; ePAP, systolic pulmonary artery pressure; SDB, sleep-disordered breathing; SVI, stroke volume index.

### Table 3. Multivariate Indicators of SDB

| OR  | 95% CI       | P-value |
|-----|--------------|---------|
| Age (years) | 1.07 | 0.99–1.15 | 0.090   |
| Male     | 1.57 | 0.79–3.11 | 0.202   |
| Obesity (BMI ≥25 kg/m²) | 1.52 | 0.68–3.40 | 0.308   |
| Previous MI | 4.85 | 0.89–26.52 | 0.069   |
| SVI (mL/m²) | 0.97 | 0.94–1.00 | 0.047   |

Abbreviations as in Tables 1,2.

### Table 4. In-Hospital Clinical Outcomes vs. SDB Status

| Clinical outcomes | SDB group 3%ODI ≥15 (n=61) | Control group 3%ODI <15 (n=120) | P-value |
|-------------------|-----------------------------|----------------------------------|---------|
| All-cause death   | 0 (0)                       | 3 (2.5)                          | 0.289   |
| Cardiac death     | 0 (0)                       | 1 (0.8)                          | 0.663   |
| Periprocedural MI | 1 (1.6)                     | 1 (0.8)                          | 0.562   |
| Stroke            | 4 (6.6)                     | 0 (0)                            | 0.012   |
| Major bleeding    | 2 (3.3)                     | 2 (1.7)                          | 0.414   |
| Acute kidney injury | 1 (1.6)                 | 3 (2.5)                          | 0.586   |
| New PM implantation | 5 (8.2)                | 5 (4.2)                          | 0.207   |

Data given as n (%). PM, pacemaker. Other abbreviations as in Table 1.
who had stroke, 3 patients had ischemic stroke, which occurred on postoperative day 0, 2 and 5; 1 patient had hemorrhagic stroke on postoperative day 14. Other outcomes, however, did not differ between the 2 groups.

Discussion

Despite the clinical significance of SDB in HF, screening for SDB is not generally performed in AS patients in clinical practice. To our knowledge, this is the largest study to date investigating SDB in patients with AS. On pulse oximetry, 33.7% of severe AS patients had SDB (equivalent to AHI ≥20). Polygraphy or PSG needs to be used for the diagnosis of SDB as well as a firm distinction between obstructive and central apnea. Referral to these sleep studies, however, is often hesitated because of its physical and economic burden, especially in the very elderly population, which might affect the results due to selection bias. Naturally, patients eligible for TAVI are elderly. Therefore, we chose pulse oximetry in this study because of its simplicity and validity. Because the current diagnostic process using PSG can identify only a limited proportion of patients with SDB from a large number of AS patients, more patients could benefit from the diagnosis and treatment of SDB on nocturnal pulse oximetry screening as a readily available and inexpensive screening tool.

The present cohort consisted of super-elderly patients (median age, 85 years [IQR, 82–87 years]). In a cross-sectional study involving 741 men aged >20 years, the prevalence of SDB (AHI >10) increased monotonically with age (20–44 years, 3.2%; 45–64 years, 11.8%; 65–100 years, 23.9%). Although the previous data in super-elderly patients are sparse, the high prevalence of SDB in the present cohort could partly be explained by the advanced age of these patients. SDB is also well known to be associated with the prevalence of coronary risk factors, cardiovascular comorbidity, and cognitive dysfunction in young or middle-aged patients. In the present study, however, there was no association between SDB and hypertension, diabetes, dyslipidemia, atrial fibrillation, or cognitive dysfunction, although the SDB group did have a higher prevalence of MI. Notably, several downstream consequences of SDB (e.g., inflammation [serum CRP] and calcification of arteries) also did not differ between the SDB and control groups in this cohort, contrasting with previous studies. This suggests that the association between SDB and these pathogeneses may decline in super-elderly AS patients who had more confounding factors, in contrast to young or middle-aged patients.

Lower SVI was an independent determinant of SDB in Japanese AS patients, which is consistent with previous studies reporting an association between SDB and worse LV function. In a prospective observational study, ODI was significantly correlated with LVEF in patients with obstructive-type SDB. Both obstructive and central types of SDB are associated with cyclical activation of the sympathetic nervous system and periodic hypoxemia, which may accelerate cardiac deterioration.

Whether SDB could become a potential therapeutic target to improve short- and long-term clinical outcomes of TAVI patients is also an intriguing question that needs to be better understood, due to the improved prognosis in AS patients attributable to TAVI. SDB increases the risk of perioperative complications and should be recognized and managed throughout this period. In the present study there was a higher incidence of stroke (ischemic and hemorrhagic) as a procedural complication in AS patients referred for TAVI. Interestingly, in a previous meta-analysis, SDB was common in stroke patients irrespective of the type of stroke, and there are numerous possible reasons for this association (i.e., acute hemodynamic changes during episodes of apnea, vascular endothelial dysfunction, increased hypertension, decreased cerebral blood flow, hypercoagulability, cyclical activation of the sympathetic nervous system, and atherosclerosis). Further randomized controlled trials or prospective studies involving a larger number of subjects and a background-matched cohort are required to elucidate whether SDB could be a therapeutic target to improve clinical outcome.

Study Limitations

This study had several limitations. First, the number of enrolled patients was small; therefore, the statistical power might not be sufficient to detect any negative outcomes. Second, PSG is preferred over pulse oximetry in terms of accurate determination of the severity and type of SDB (obstructive or central type) and the exact total sleep duration. Additionally, to convincingly compare the prevalence of SDB in Japan with that in Western countries, future studies using the same modality (i.e., polygraphy) are warranted. Third, the effect of AS on the hemodynamics (e.g., poor peripheral perfusion) might also affect the value of pulse oximetry. Thus, a validation study with simultaneous evaluation of pulse oximetry and PSG is warranted in AS patients. Fourth, to the best of our knowledge, because there have been no previous studies on SDB in super-elderly patients equivalent to the present one, we cannot clearly distinguish the effect of AS from that of aging. To convincingly answer this question, a future study evaluating the change of SDB severity after TAVI could be helpful. Thus, if SDB severity is attenuated by TAVI, AS and its hemodynamics could affect the occurrence of SDB.

Conclusions

SDB was highly prevalent and associated with LV systolic dysfunction and a higher incidence of stroke as a procedural complication in Japanese AS patients referred for TAVI. Although it remains uncertain as to whether SDB could become a potential therapeutic target, pulse oximetry could be at least a useful tool to estimate the risk of procedural complications.

Disclosures

K.H. is proctor for Edwards Lifesciences. The other authors declare no conflicts of interest.

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