# 論文要約

Left-atrial volume reduction reflects improvement of cardiac sympathetic nervous function in patients with severe aortic stenosis after transcatheter aortic valve replacement

（左房容積縮小は重症大動脈弁狭窄症患者における経カテーテル的大動脈弁置換術後の心臓交感神経機能改善を反映している）

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## Introduction

Aortic stenosis (AS) is the most common valvular heart disease in the elderly population and increasing morbidity worldwide. Transcatheter aortic valve replacement (TAVR) is an established alternative intervention for surgical aortic valve replacement (SAVR) in inoperable or high-surgical risk patients. Furthermore, TAVR has been increasingly indicated for low-surgical risk patients.

Severe AS impairs cardiac sympathetic nervous (CSN) function because of low cardiac output and left ventricular (LV) pressure overload. TAVR has previously been shown to improve CSN function immediately after the procedure, as evaluated by $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy. It has been reported that poor CSN functional recovery was associated with adverse cardiac events after TAVR.

Severe AS increases LV filling pressure. The continuous exposure to elevated LV filling pressure causes the left atrium (LA) to dilate and become dysfunctional. LA volume reduction and functional recovery induced by TAVR have been shown to be associated with better outcomes after TAVR.

The relationship between these two outcome predictors is unknown. Therefore, we conducted this retrospective observational study to evaluate the correlation between CSN function and LA volume in patients with AS before and after TAVR.

## Methods

We recruited symptomatic patients with severe AS who underwent TAVR at Hiroshima University Hospital between February 2016 and August 2021. Severe AS was defined as (1) an aortic valve area (AVA) < 1.0 $cm^2$ (or AVA indexed by body surface area < 0.6 $cm^2/m^2$) or (2) a resting or inducible peak transaortic velocity > 4.0 m/s or (3) a resting or inducible mean pressure gradient (MPG) > 40 mm Hg. We used MIBG scintigraphy for the assessment of CSN function. Delayed heart-to-mediastinum ratio (dHMR) was calculated semi-automatically using dedicated software (Jetpack, Hitachi), and the change between baseline and 6 months after TAVR was calculated using the following formula: $\Delta dHMR = (post\text{-}procedural\ dHMR) - (baseline\ dHMR)$. In transthoracic echocardiography (TTE), LA volume was measured by the biplane Simpson method and indexed according to the body surface area (LA volume index [LAVI]). We calculated the LAVI reduction rate (ΔLAVI%) between baseline and follow-up echocardiography as follows: $\Delta LAVI\% = ([LAVI_{follow\text{-}up} - LAVI_{baseline}] / LAVI_{baseline}) \times 100$.

All TAVR procedures were conducted via transfemoral approach under general anesthesia using either a balloon-expandable Edwards Sapien XT/Sapien 3 (Edwards Lifesciences, Irvine, CA, USA) or a self-expandable Medtronic CoreValve Evolut R

(Medtronic, Minneapolis, MN, USA) device.

We divided the study patients into 2 groups according to improvement in dHMR defined as ΔdHMR > 0. The correlation between ΔLAVI% and ΔdHMR was assessed by Pearson's method. We performed multiple linear regression analyses using fixed adjustment for age and sex to evaluate the independent association of ΔLAVI% with ΔdHMR; model 1 was performed with covariates that reached $p < 0.05$ in univariate analysis, and model 2 was adjusted by the previously reported variables associated with improvement in the MIBG parameters after TAVR such as baseline estimated glomerular filtration rate (eGFR), clinical frailty scale ≥ 6, baseline AVA, baseline dHMR.

## Results

283 patients underwent TAVR during this period, and 67 underwent MIBG scintigraphy at baseline and 6 months after TAVR. After exclusion, 48 patients treated with TAVR (median age 85 years, IQR 82–88 years; 81% female) were included in the study analyses. Among the 48 patients, 31 (65%) showed improved dHMR after TAVR. There was no significant difference in baseline patient characteristics with or without dHMR improvement: demographic data, symptom, frailty, surgical risk, comorbidities, and medications. The severity of AS was more severe in patients with dHMR improvement (AVA: median 0.58 $cm^2$ [IQR: 0.49–0.72] vs. 0.70 $cm^2$ [0.64–0.90], $p = 0.0270$). Baseline LAVI and dHMR did not differ significantly between the 2 groups.

TAVR improved symptoms and NT-proBNP in both groups. The LV mass index (LVMI), LAVI, and dHMR showed improvement after undergoing TAVR in the dHMR-improved group. Specifically, LVMI decreased from 114.0 $g/m^2$ [98.2–127.1] to 99.0 $g/m^2$ [87.1–110.8] ($p = 0.0016$), LAVI decreased from 47.5 $mL/m^2$ [37.6–55.7] to 36.0 $mL/m^2$ [33.6–52.4] ($p < 0.0001$), and dHMR improved from 2.88 [2.33–3.17] to 3.14 [2.70–3.31] ($p < 0.0001$). However, there was no improvement observed in patients without dHMR improvement.

There was a significant inverse correlation between ΔLAVI% and ΔdHMR ($r = -0.35$, $p = 0.0139$). In multiple linear regression analyses, ΔLAVI% was an independent predictor of ΔdHMR ($\beta = -0.35$, $p = 0.0110$ in model 1; $\beta = -0.32$, $p = 0.0471$ in model 2).

## Discussion

This retrospective observational study revealed that LA volume reduction reflected CSN functional recovery in patients treated with TAVR. To the best of our knowledge, our study is the first to report a relationship between LA volume and CSN function in AS.

We reviewed possible mechanisms to explain our findings. It is well established

that LA volume is related to the severity of left ventricular diastolic dysfunction (LVDD), and it is an essential component of LVDD diagnosis in TTE. LVDD is present in 30%–40% of patients with AS who underwent TAVR and is associated with long-term outcomes after TAVR. Herein, LVDD coexisted in 58% of the study cohort at baseline. It is known that LVDD impairs CSN function. LA volume and CSN function might be interrelated through LVDD coexisting with AS. After TAVR, which contributes to release of aortic obstruction, persistent LVDD represented by LA volume could disturb the recovery of CSN function.

LVMI was reduced after TAVR in patients with dHMR improvement, similar to LAVI. However, the percentage change in LVMI between baseline and 6 months after TAVR (ΔLVMI%) was not correlated with ΔdHMR in trivariate linear regression analysis with fixed adjustment for age and sex ($\beta = -0.08$, $p = 0.5983$). We assume several explanations for why LAVI has a more robust correlation with dHMR than LVMI. First is a timespan after TAVR. It has been reported that LA reverse remodeling after SAVR for severe AS occurred rapidly compared with regression of LV hypertrophy. Their study described that the reduction of LAVI reached a plateau 1 month after SAVR, whereas LVMI was 1 year. Thus, the period of 6 months after TAVR might be too short for evaluating the relationship between LVMI and CSN function. Second is the distribution of autonomic nerves. In the histological study of autopsied hearts without cardiovascular disease, the autonomic nerves, both adrenergic and cholinergic, were more distributed in the atrium compared with the ventricle. This distribution difference might affect the stronger correlation between LA reverse remodeling and recovery of CSN function.

It has been reported that LA reverse remodeling following TAVR is associated with an improved prognosis. Although the mechanism is unknown, it might be related to the CSN improvements reported in this article, but future research is necessary to confirm this hypothesis.

## Conclusion

We found that LA reverse remodeling was correlated with CSN functional recovery after TAVR in patients with symptomatic severe AS. Our results indicated that the ΔLAVI% might be a useful variable reflecting CSN functional improvement after TAVR.