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Transcatheter aortic valve implantation improves cognitive function associated with increased cerebral blood flow in elderly patients with severe aortic stenosis

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Short running title: Evidence for improved cognitive function after TAVI

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Abstract

Aim: The aim of this study was to examine the mechanisms of cognitive impairment and reversibility in elderly patients with severe aortic stenosis (AS) after transcatheter aortic valve implantation (TAVI) with a special reference to cerebral blood flow (CBF).

Methods and results: We examined 15 elderly patients with severe AS (mean age 83.2±4.5 years, 12 female) who underwent TAVI. Before and 3 months after TAVI, we evaluated cognitive function with the Logical Memory II (LM II), cardiac output (CO) with echocardiography, and CBF with ^{99m}Tc single-photon emission computed tomography (SPECT). LM II score and CO were significantly increased after TAVI compared with baseline ($P<0.01$ for LM II, $P<0.005$ for CO). Notably, CBF in the local regions, including that in the right hippocampus, was significantly increased after TAVI ($P<0.005$ at each voxel). The patients with increased CO after TAVI also showed significantly increased CBF in the right hippocampus compared with those without it ($P<0.01$). Importantly, CBF in the right hippocampus were positively correlated with LM II scores ($P<0.05$).

Conclusions**:** These results provide the first evidence that TAVI may improve cognitive functions associated with increased cerebral perfusion especially in the hippocampus in elderly patients with severe AS.

Classification: aortic stenosis, TAVI, Chronic heart failure

Condensed abstract

Before and 3 months after transcatheter aortic valve implantation (TAVI), we measured cerebral blood flow (CBF) with ^{99m}Tc single-photon emission computed tomography, cardiac output (CO) with echocardiography, and cognitive functions with Logical Memory II (LM II), in 15 elderly patients with severe aortic stenosis (AS). Local CBF, CO, and LM II were significantly improved at 3 months after TAVI compared with baseline. Importantly, there were significant correlations among them, especially in the hippocampus. These results provide the first evidence that TAVI may improve cognitive functions associated with increased cerebral perfusion especially in the hippocampus in elderly patients with severe AS.

Abbreviations

AS = aortic stenosis

CBF = cerebral blood flow

CO = cardiac output

DW-MRI = diffusion-weighted magnetic resonance imaging

eNOS = endothelial nitric oxide synthase

GDS = geriatric depression scale

LM II = Logical Memory II

MCI = mild cognitive impairment

MMSE = Mini Mental State Examination

MoCA = Montreal Cognitive Assessment

NYHA = New York Heart Association

SPECT = single-photon emission computed tomography

TAVI = transcatheter aortic valve implantation

Introduction

Severe aortic valve stenosis (AS) is the most common valvular heart disease in the elderly in the Western countries and Asia that gradually progresses valve calcification and eventually causes heart failure.[1,2] The interaction between the heart and the brain is important in the elderly with multiple co-morbidities,[3] because the two important organ systems share many pathophysiological mechanisms.[3] Indeed, cognitive impairment is frequently noted in patients with AS.[4,5,6] Although severe AS is conventionally treated with surgical aortic valve replacement, the less invasive transcatheter aortic valve implantation (TAVI) has been developed for such elderly frail patients at high surgical risks.[7]

Previous studies examined cognitive functions and diffusion-weighted magnetic resonance imaging (DW-MRI) in patients with severe AS who underwent TAVI.[4,8] Notably, recent studies have demonstrated that some patients with severe AS showed improved cognitive functions after TAVI.[5,9] However, detailed mechanisms for the improvement after TAVI remain to be examined. Notably, cerebral perfusion has been regarded as an important pathophysiological factor of the heart and brain interactions.[3] We and others previously demonstrated that brain perfusion single-photon emission computed tomography (SPECT) is a useful imaging technique to evaluate regional cerebral perfusion and its relevance to cognitive impairment or stress cardiomyopathy.[10,11]

In the present study, we thus tested our hypothesis that TAVI increases CBF associated with increased cardiac output (CO) with a resultant improvement of cognitive functions in elderly patients with severe AS, using brain perfusion SPECT imaging before and 3 months after TAVI.

Methods

The present study protocol was approved by the ethics committee of the Tohoku University Graduate School of Medicine (No. 2018-1-329) and was performed in compliance with the Declaration of Helsinki (UMIN000034203).

Study Patients

From January 2017 to September 2018, we examined consecutive 57 patients with severe AS at our Tohoku University Hospital as candidates for TAVI. Inclusion criteria were 1) heart failure with New York Heart Association functional class (NYHA) II to III symptoms, and 2) patient consent to receive cognitive function tests for at least 1 hour. Exclusion criteria were 1) acute decompensated heart failure and heart failure with NYHA IV symptoms, 2) refusal cognitive tests, and 3) insufficient quality of ^{99m}Tc SPECT. Based on these criteria, we excluded 35 patients in advance, including acute decompensated heart failure and heart failure with NYHA IV symptoms in 15, and refusal of receiving cognitive function tests for at least 1 hour in 20. Thus, we initially included 22 patients, in whom 7 were then excluded because of drop out owing to refusal of follow-up cognitive tests (n=2), and insufficient quality of ^{99m}Tc SPECT (n=5). Finally, we enrolled 15 patients in the present study with a special reference to the association of cerebral blood flow (CBF) and cognitive functions (**Supplementary Figure 1**). Before and 3 months after TAVI, we measured cognitive functions with the Logical Memory II (LM II),[12] and Mini Mental State Examination (MMSE),[13] geriatric depression scale (GDS),[14] CO with echocardiography, and CBF with ^{99m}Tc SPECT.

The baseline, TAVI procedure, and follow-up data were all collected in a dedicated database. The details of TAVI procedure are mentioned in the **Supplementary Materials**.

Echocardiography

The details of Echocardiography are mentioned in the **Supplementary Materials**.

CBF Image Acquirement and Pre-processing

CBF can be measured by not only SPECT but also MRI.[15.16] Since we and others previously demonstrated that SPECT is a useful imaging technique to evaluate regional cerebral perfusion and its relevance to cognitive impairment or stress cardiomyopathy,[10,11] we selected SPECT for measuring CBF. H.Suzuki, who was blinded to the results of the imaging studies before and 3 months after TAVI, analyzed and reported SPECT scans. ^{99m}Tc-SPECT CBF images were acquired with a dual-head gamma camera (Symbia E, Siemens, Erlangen, Germany). The following CBF image pre-processing and analyses were performed using SPM 12.[17] First, before CBF image analysis, we co-registered CBF images at 3 months to their corresponding baseline images. Second, the baseline and co-registered CBF images were normalized to the standard Montreal Neurological Institute space, using the SPECT template available in SPM 12. Finally, the normalized images were smoothed with an isotropic Gaussian kernel by convolving a 12 mm full width at half maximum to produce CBF maps. These pre-processing steps were described in details in our previous reports.[16,18]

Assessment of Cognitive Functions

A standardized cognitive assessment with the LM II, MMSE, and GDS was performed by a single experienced stuff blinded to the results of the imaging studies before and 3 months after TAVI. LM subtest of the Wechsler Memory Scale-Revised is internationally used as an operational definition to identify individuals with mild cognitive impairment (MCI). In particular, LM II (30-min delayed test of prose recall) is an indicator to discriminate between healthy older adults and individuals with very mild cognitive impairment.[12] MMSE is widely used screening tool for cognitive impairment.[13] GDS is a screening instrument for late-life depression that demonstrates good accuracy.[14] In addition, GDS is based mainly on behavioral and cognitive aspects of depression and was not heavily weighted toward somatic complaints.[14] Thus, GDS is supposed to reliably differentiate depressed from non-depressed elderly suffering from physical illness.

Statistical Analysis:

Continuous variables are presented as mean±standard deviation (SD). Normality was assessed using the Shapiro-Wilk test. Continuous variables were compared by Wilcoxon signed rank test. Statistical analysis was performed with the use of JMP pro 14 at a significance threshold of $P<0.05$ except for voxel-wise CBF analyses.

We explored which brozirain areas showed CBF changes after TAVI by conducting a voxel-wise comparison between CBF maps before and 3 months after TAVI at an exploratory significance threshold of $P<0.005$. CBF within the areas, which changed after TAVI, were calculated and then were used for a paired t test between baseline and 3 months. A repeated measures linear mixed-model analysis was performed to evaluate changes in CBF and those in cognitive function tests. The details of the SPECT image pre-processing and analysis are mentioned in the **Supplementary Materials**.

Results

Patients Characteristics

Clinical characteristics of the included and excluded patients are shown in **Supplementary Tables 1 and 2**. There were no significant differences in the results of cognitive function tests at the baseline between the included and excluded patients. In the present study, the mean age was 83.2±4.5 years old, and 80% were female. On the basis of a cut-off of <24 points of MMSE, 5 patients (33.3%) were considered cognitively impaired, whereas no patients were diagnosed as having dementia that required the treatment with acetylcholine esterase inhibitors. No patients had luminal narrowing > 25% in the carotid arteries, although we did not evaluate the status of the posterior artery.

Procedural Characteristics and Clinical Outcome

The procedural characteristics and clinical outcomes are shown in **Table 1**. No patients needed implantation of a second valve or showed myocardial infarction or cardiovascular death at 30 days after TAVI. Notably, no patients showed clinical symptoms or sings for transient ischemic attack or stroke after TAVI. In addition, CO was also significantly increased at 3 months after TAVI compared with baseline (baseline, 4.03±0.88 vs. 3 months, 5.10±1.14 L/min, P=0.0045).

Changes in Cognitive Functions after TAVI

At baseline, the mean scores of LM II, MMSE and GDS were 8.7±1.5, 24.6±1.3, and 4.3±1.1, respectively. LM II was significantly improved at 3 months after TAVI compared with baseline (baseline, 8.7±6.0 vs. 3 months, 13.8±8.1, P<0.01). In contrast, there were no significant differences in MMSE or GDS during the study period (MMSE, baseline, 24.6±1.3 vs. 3 months, 25.2±1.5, P=0.42; GDS, baseline, 4.3±1.1 vs. 3 months 4.2±0.9, P=1.0) (**Figure 1**). Among 5 patients (one-third of patients of the present study) with cognitive impairment at baseline, 3 showed that Logical Memory II was improved at 3 months after TAVI. In these 3 patients with MMSE scores 23, 18 and 13 at baseline, Logical Memory II scores increased at 3 months after TAVI from 6 to 12, 4 to 6, and 0 to 5, respectively.

Changes in Cerebral Blood Flow after TAVI

There were no significant differences in the whole CBF during the study period (baseline, 39.3±1.0 vs. 3 months, 39.2±1.0 ml/100g/min, P=0.76). However, CBF in specific regions were significantly increased after TAVI compared with baseline (baseline, 51.2±1.0 vs. 3 months, 53.3±1.0 ml/100g/min, P<0.001) (**Figure 2A-F**). All 5 patients with cognitive impairment at baseline showed that CBF increased at 3 months after TAVI. Indeed, in these 5 patients with MMSE scores 23, 20, 18, 18 and 13 at baseline, CBF (ml/100g/min) increased at 3 months after TAVI from 54.9 to 56.1, 48.3 to 50.6, 50.6 to 52.4, 53.6 to 56.3, and 51.0 to 53.3, respectively. This correlation between right hippocampal CBF and LM II scores was supported by the result from repeated measures linear mixed-model analysis (P=0.017)

(**Figure 2G**). Moreover, the patients with increased CO after TAVI had significantly increased CBF in the right hippocampus compared with those without it (with increased CO, 1.06±0.07 vs. without, 0.94±0.04, for changes in CBF in the right hippocampus after TAVI, $P<0.01$) (**Figure 2H**). Importantly, there was no significant difference in blood pressure during the study period (systolic blood pressure, baseline, 120.6±15.4 vs. 3 months, 121.6±14.4, $P=0.57$; diastolic blood pressure, baseline, 62.9±12.4 vs. 3 months 64.9±9.2, $P=0.63$).

Discussion

The major findings of the present study were that (1) LM II was significantly improved after TAVI, (2) CBF in the local regions, including the right hippocampus, was significantly increased at 3 months after TAVI, (3) increase in CO was associated with that in CBF in the right hippocampus, and (4) CBF in the right hippocampus was positively correlated with LM II. To the best of our knowledge, this is the first study that demonstrates that TAVI may improve cognitive functions associated with increased cerebral perfusion especially in the hippocampus in elderly patients with severe AS.

Changes in Cognitive Functions after TAVI

In the current practice guidelines, management of cognitive impairment needs to be improved, as proven therapeutic options are still lacking.[3] Although the number of patients with cognitive impairment and heart failure has been rapidly increasing in Western countries and Asia,[1,19] heart failure-associated cognitive impairment may be underestimated. Indeed, in the present study, 5 patients (33.3%) had actually cognitive impairment (MMSE<24). A recent study also demonstrated that 22~39% patients with severe AS had impaired cognitive functions at baseline.[5,6] In the present study, although there were no significant differences in MMSE or GDS at 3 months after TAVI, LM II was significantly improved at 3 months after TAVI. Recent studies examined the global cognitive functions after TAVI, using

MMSE and the Montreal Cognitive Assessment (MoCA).[5,20,21] The MMSE, originally developed to screen for Alzheimer dementia, is currently widely used to assess post-stroke cognitive impairment,[22] although MMSE has been shown to lack sensitivity in the detection of very mild cognitive impairment.[22]

More recently, the MoCA has been developed to detect mild cognitive impairment with high sensitively, which consists of 7 cognitive domains, including orientation, attention, short-term memory, naming, visuospatial, language, and abstract reasoning.[5] LM II was specialized to diagnose very mild cognitive impairment and episode memory.[12] In the present study, we used LM II instead of the MoCA for the following reasons. First, in a recent study, mean total MoCA score, especially short-term memory of the MoCA, was improved after TAVI.[5] Second, there was a significant improvement in the Immediate Recall Memory Test, with a trend toward improved Delayed Recall Memory Test.[9] Third, LM II is a quantifiable neuropsychological test.[12] Taken together, it is possible that TAVI improves cognitive functions, especially LM II (episode memory), in the present study. In the present study, we had to exclude many patients and eventually analyzed a relatively small number of patients, whose mean age was 83.2±4.5 years old. A recent study has demonstrated that the risk and age of patients undergoing TAVI have been become lower.[23] Thus, it is remains to be elucidated whether TAVI improves cognitive function in younger patients with severe AS. Future studies with a large number of patients are needed to perform a multivariable analysis to adjust for possible factors contributing to the changes at follow-up.

Roles of Increased Cerebral Blood Flow

Recent studies showed that TAVI improves cognitive functions,[5,9,24] and there were several hypotheses regarding the mechanisms of cognitive improvement after TAVI.[24-26] First, improvement of CBF due to improved CO after TAVI may contribute to the improvement of cognitive functions. Second, alleviation of physical symptoms and subsequent improvement in functional status may contribute to the improvement of cognitive functions. However, detailed mechanisms of the improvement of cognitive functions after TAVI remain to be examined.

Accelerated cognitive decline may result from chronic low cerebral perfusion in the long-term course of heart disease as a pathophysiological consequence between the heart and brain interactions.[3] In the present study, TAVI significantly improved CO, local CBF especially in the right hippocampus, and LM II scores. Importantly, CO was associated with CBF in the right hippocampus, with a positive correlation with LM II scores. Thus, we were able to elucidate that TAVI increases CO and cerebral perfusion (especially that in the hippocampus) associated with improved cognitive functions, probably through the heart-brain interaction in the elderly patients with severe AS.

Notably, we have recently demonstrated that whole-brain low-intensity pulsed ultrasound therapy markedly ameliorates cognitive impairment associated with improved CBF in mouse models of dementia, in which endothelial nitric oxide synthase (eNOS) activation plays a central role.[27] It is conceivable that increased CBF caused by upregulated eNOS may also be involved in the beneficial effects of TAVI.

Importance of Hippocampus for Cognition

In the present study, although the whole CBF was not significantly increased, local CBF, especially that in the right hippocampus, was significantly increased after TAVI. Notably, we recently demonstrated that patients with chronic heart failure frequently have cognitive impairment, where the hippocampus blood flow is significantly decreased.[16] A possible mechanism of cognitive impairment in chronic heart failure is abnormality of the hippocampus, which is the important brain area for memory.[28] Moreover, the hippocampus is one of the brain regions most vulnerable to cerebral hypoxia.[29,30] Importantly, patients with obstructive sleep apnea who underwent continuous positive airway pressure had improved cognitive function associated with improved gray matter volume in the hippocampus but not in the whole brain.[31] It is possible that the hippocampus is one of the watersheds and may be the first area where CBF reduction or improvement occurs. In the present study, although the whole CBF was not significantly increased, local CBF, including that in the hippocampus, was significantly increased after TAVI. Notably, in the present study, CBF in the local regions, not only in the right but also in the left hippocampus, was significantly increased after TAVI. The lack of statistical association between the left hippocampal blood flow and Logical Memory II scores may be due to the small sample size. Thus, it is possible that hemodynamic improvement by TAVI increases the perfusion in these regions, although the effect of cerebral hypoxia on brain abnormality in patients with severe AS remains to be elucidated.

Study Limitations

Several limitations should be mentioned for the present study. First, this study was a single-center study with a relatively small number of patients. Fragility index value of 1 for our study indicated that an outcome change in a single patient would make the difference in the main outcome non-significant. Thus, future studies with a large number of patients are needed to perform a multivariable analysis to adjust for possible factors contributing to the changes at follow-up. Second, the present study focused on the abnormality of the hippocampus blood flow based on our previous study in rats.[30] However, substantial anatomical differences including the prefrontal cortex may exist between rats and humans. Third, there was a lack of control AS patients (without TAVI), although it is ethically and practically difficult to recruit such patients. Fourth, although we performed the commonly used tests for cognitive functions as previously reported,[5,9,12~14] we were unable to exclude a possible involvement of the learning effect. Future studies are needed to elucidate this effect. Fifth, the present study did not verify the cerebral structure and the CBF measurement using other modalities such as MRI. However, as mentioned above, we and others already demonstrated that brain perfusion SPECT imaging is useful for solid assessment of quantitative cerebral perfusion and its relevance to cognitive impairment.[10,11]

Conclusions

In the present study, we were able to demonstrate for the first time that TAVI may improve cognitive functions associated with increased cerebral perfusion especially in the hippocampus in elderly patients with severe AS.

Impact on daily practice

Recent studies suggest cognitive decline may result from chronic low cerebral perfusion in the long-term course of heart disease as a pathophysiological consequence between the heart and brain interactions. Based on the present study, TAVI may improve cognitive functions associated with increased cerebral perfusion especially in the hippocampus in elderly patients with severe AS.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Figure Legends

Figure 1. Changes in Cognitive Functions after TAVI in Patients with Severe AS

A. Logical Memory II (LM II) score was significantly improved at 3 months after transcatheter aortic valve implantation (TAVI) compared with baseline.

B, C. There were no significant differences in Mini Mental State Examination (MMSE) or geriatric depression scale (GDS) at 3 months after TAVI compared with baseline.

n.s, not significant.

Figure 2. Changes in Regional Cerebral Blood Flow after TAVI and Their Associations with Cognitive and Cardiac Functions

Glass brain representations showing TAVI-induced regional cerebral blood flow changes (black areas) from the coronal (**A**), axial (**B**), and sagittal (**C**) views ($P<0.005$ at each voxel). The coronal (**D**) and axial (**E**) slices including the right hippocampus are also presented. The green arrowheads indicate the right hippocampus.

F. Local CBF was significantly increased after TAVI compared with baseline (baseline, 51.2±1.0 vs. 3 months, 53.3±1.0 ml/100g/min, W 60.0, $P<0.0001$).

G. Linear mixed effect model showed that CBF in the right hippocampus were positively correlated with LM II scores.

H. The patients with increased cardiac output (CO) after TAVI was significantly increased CBF in the right hippocampus compared with those without it.

TAVI, transcatheter aortic valve implantation; CBF, cerebral blood flow; CO, cardiac output; LM II, Logical memory II.

Table 1. Procedural Characteristics and Clinical Outcomes of the Study Population

	Patients (n=15)
Procedural characteristics	
Approach	
Transfemoral	14 (93)
Subclavian	1 (7)
Transapical	0
Valve type	
Edwards SAPIEN 3	6 (40)
Medtronic Corevalve or EvolutR	9 (60)
Need for second valve	0 (0)
Clinical outcomes: 30 days	
Stroke	0 (0)
Myocardial infarction	0 (0)
Major or life-threatening bleeding	1 (7)
New-onset atrial fibrillation	1 (7)
New pacemaker implantation	1 (7)
Acute kidney injury stage 2 or 3	0 (0)
Major vascular complication	1 (7)
Echocardiographic characteristics	
Peak velocity at discharge, m/s	2.28±0.45
Mean transprosthetic gradient at discharge, mmHg	10.8±4.6
Aortic valve area at discharge, cm^2	1.73±0.29
Cardiac output, l/min	5.10±1.14
Moderate or severe aortic regurgitation at discharge	0 (0)
Clinical outcomes: from 30 days to 3 months	
Stroke	0 (0)
Myocardial infarction	0 (0)
Major or life-threatening bleeding	0 (0)
New-onset atrial fibrillation	0 (0)

Categorical variables are expressed as n (%) and continuous variables as mean±SD.

Figure 1

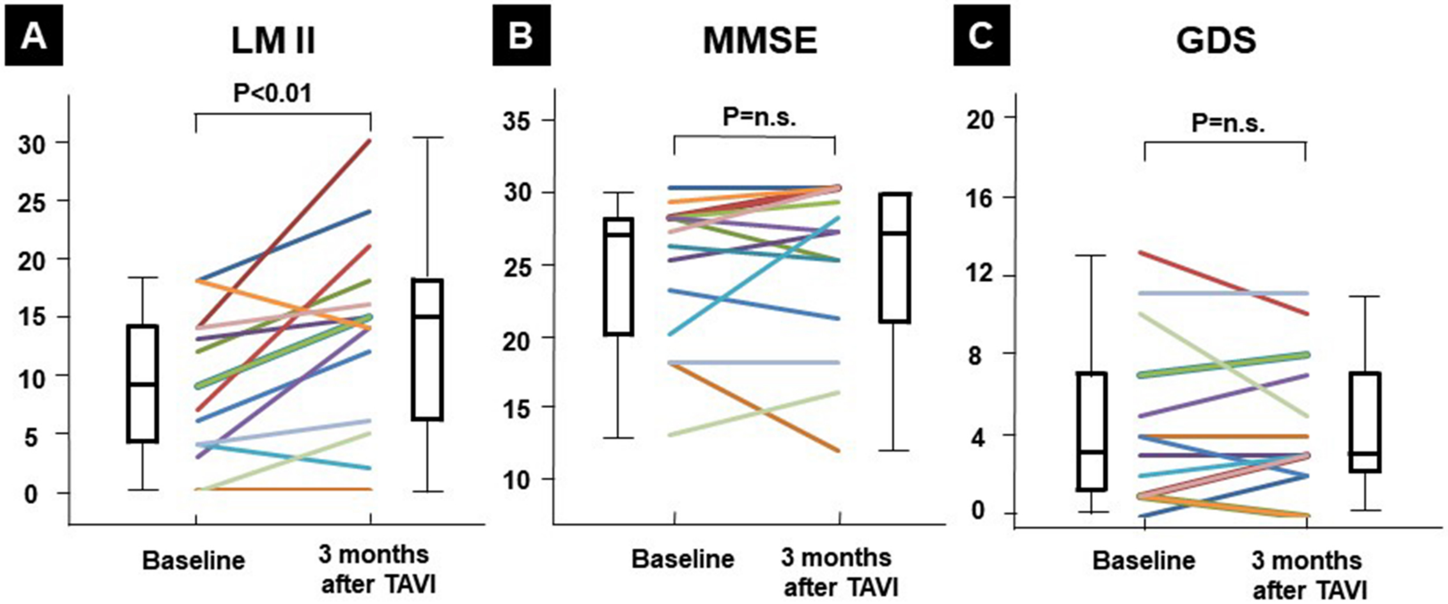
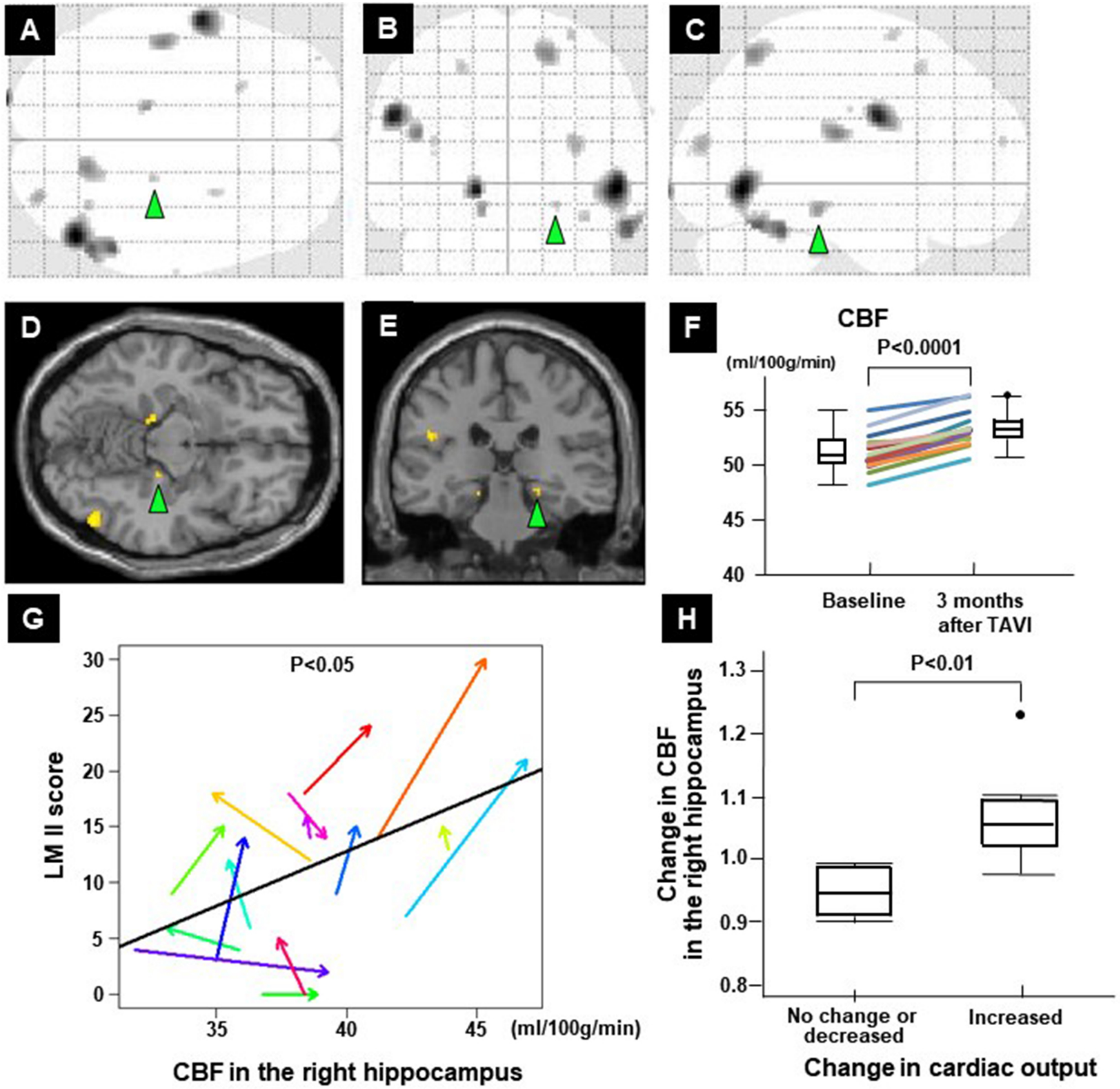

A
LM II
P<0.01
30
25
20
15
10
5
0
Baseline
3 months
after TAVI
B
MMSE
P=n.s.
35
30
25
20
15
10
Baseline
3 months
after TAVI
C
GDS
P=n.s.
20
16
12
8
4
0
Baseline
3 months
after TAVI

Figure 2


A
B
C
D
E
F
CBF
(ml/100g/min)
P<0.0001
55
50
45
40
Baseline
3 months after TAVI
G
P<0.05
LM II score
30
25
20
15
10
5
0
35
40
45
(ml/100g/min)
CBF in the right hippocampus
H
P<0.01
Change in CBF in the right hippocampus
1.3
1.2
1.1
1.0
0.9
0.8
No change or decreased
Increased
Change in cardiac output

Supplementary materials

Supplementary methods

TAVI procedure

In accordance with the Japanese Circulation Society guidelines, our heart team, including cardiologists, at least 2 cardiac surgeons, and anesthesiologists, determined the indication and approach of TAVI procedure, and the type of transcatheter valve used. (Guidelines for catheter intervention for congenital heart disease and structural heart disease (JCS 2014) http://www.j-circ.or.jp/guideline/pdf/JCS2014_nakanishi_h.pdf)

Periprocedural events were defined according to the Valve Academic Research Consortium (VARC)-2 criteria. (Kappetein AP, et al. *J Am Coll Cardiol.* 2012;60:1438-54.)

Echocardiography

Before and 3 months after TAVI, echocardiography studies were performed by experienced sonographers blinded to the results of the cognitive tests and the imaging studies. Measurements were made from an average of 3 cardiac cycles in sinus rhythm and 3 to 5 cycles in atrial fibrillation. Assessment of the native AV and the bioprosthesis were made according to the original Valve Academic Research Consortium (VARC-1), American Society of Echocardiography, and European Association of Echocardiography. (Kappetein AP, et al. *J Am Coll Cardiol.* 2012;60:1438-54.; Zamorano JL, et al. *Eur Heart J.* 2011;32:2189-214.) Measurements of CO and left ventricular ejection fraction were performed according to the guidelines. (Baumgartner H, et al. *J Am Soc Echocardiogr*. 2009;22:1-23.) Carotid ultrasonography studies were performed by experienced sonographers who were blinded to the results of the cognitive tests and the imaging studies before TAVI.

SPECT image pre-processing and analysis

The SPECT image pre-processing and analysis consists of the 6 steps as follows;(1) co-registering CBF images at 3 months after TAVI to their corresponding baseline images before TAVI, (2) normalizing these images to the standard Montreal Neurological Institute space, (3) smoothing the normalized images, (4) comparing these pre-processed baseline images with those at 3 months after TAVI, (5) calculating CBF within the brain regions derived from the step (4) and (6) testing an association of contrasts for cognitive test scores with those for CBF of (5). Since all these 6 steps do not require any arbitrary interventions from the analyst, there was no inter- and intra-observer variabilities.

Supplementary Table

Supplementary Table 1. Clinical characteristics of the included patients and excluded patients

	Include Patients (n=15)	Exclude Patients (n=7)	P value
Age, years	83.2±4.5	84.0±6.1	0.41
Female, n (%)	12 (80)	6 (86)	0.74
Body mass index, kg/m^2	22.8±2.2	21.4±2.1	0.19
Handedness - right-handed, n(%)	15 (100)	7 (100)	-
Hypertension, n (%)	14 (93)	6 (86)	0.57
Diabetes mellitus, n (%)	4 (27)	1 (14)	0.51
Dyslipidemia, n (%)	12 (80)	5 (71)	0.66
Atrial fibrillation, n (%)	5 (33)	1 (14)	0.33
New York Heart Association functional			
Class II, n (%)	12 (80)	4 (57)	0.27
Class III, n (%)	3 (20)	3 (43)	0.27
Coronary artery disease, n (%)	3 (20)	4 (57)	0.086
Previous myocardial infarction, n (%)	0 (0)	1 (14)	0.12
Previous stroke/transient ischemic attack, n (%)	4 (26.7)	0 (0)	0.063
Peripheral vascular disease, n (%)	2 (13)	1 (14)	0.95
Chronic obstructive pulmonary disease, n (%)	0 (0)	3 (43)	0.0048
Chronic kidney disease, n (%)	10 (67)	5 (71)	0.82
STS-PROM, %	6.7±3.1	8.7±3.7	0.19
MMSE < 24	5 (33)	5 (71)	0.21
Echocardiographic characteristics			
Left ventricular ejection fraction, %	66.8±13.7	62.6±10.8	0.31
Peak velocity, m/s	4.62±0.74	4.98±0.98	0.50
Aortic mean gradient, mmHg	50.5±17.4	58.7±23.5	0.50
Aortic valve area, cm^2	0.71±0.15	0.66±0.26	0.42
Cardiac output, l/min	4.03±0.88	3.59±1.28	0.31
Medical treatments, n (%)			

ACE-I or ARB, n (%)	9 (60)	7 (100)	0.018
Beta-blocker, n (%)	3 (20)	4 (57)	0.086
CCB, n (%)	8 (53)	3 (43)	0.64
Diuretic, n (%)	7 (47)	6 (86)	0.069
Statin, n (%)	10 (67)	2 (29)	0.092
Acetylcholine esterase inhibitors, n (%)	0 (0)	0 (0)	-
Cognitive function tests			
Mini Mental State Examination	24.6±5.1	22.1±4.5	0.24
Geriatric Depression Scale	4.3±4.1	3.4±2.1	0.94
Logical Memory II	8.7±6.0	4.7±5.3	0.15

Categorical variables as n (%) and continuous variables are expressed as mean ± standard deviation (SD).

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker; MMSE, Mini Mental State Examination; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

Supplementary Table 2. Baseline Clinical Characteristics of Patients with Severe AS

	Patients (n=15)
Age, years	83.2±4.5
Female, n (%)	12 (80)
Body mass index, kg/m^2	22.8±2.2
Handedness - right-handed, n(%)	15 (100)
Hypertension, n (%)	14 (93)
Diabetes mellitus, n (%)	4 (27)
Dyslipidemia, n (%)	12 (80)
Atrial fibrillation, n (%)	5 (33)
New York Heart Association functional	
Class II, n (%)	12 (80)
Class III, n (%)	3 (20)
Coronary artery disease, n (%)	3 (20)
Previous myocardial infarction, n (%)	0 (0)
Previous stroke/transient ischemic attack, n (%)	4 (26.7)
Peripheral vascular disease, n (%)	2 (13)
Chronic obstructive pulmonary disease, n (%)	0 (0)
Chronic kidney disease, n (%)	10 (67)
STS-PROM, %	6.7±3.1
MMSE < 24	5 (33)
Echocardiographic characteristics	
Left ventricular ejection fraction, %	66.8±13.7
Peak velocity, m/s	4.62±0.74
Aortic mean gradient, mmHg	50.5±17.4
Aortic valve area, cm^2	0.71±0.15
Cardiac output, l/min	4.03±0.88
Medical treatments, n (%)	
ACE-I or ARB, n (%)	9 (60)
Beta-blocker, n (%)	3 (20)
CCB, n (%)	8 (53)
Diuretic, n (%)	7 (47)
Statin, n (%)	10 (67)
Acetylcholine esterase inhibitors, n (%)	0 (0)

Categorical variables as n (%) and continuous variables are expressed as mean ± standard deviation (SD).

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

Supplementary Figure Legends

Supplementary Figure 1. Study flow chart.

From January 2017 to September 2018, we examined consecutive 57 patients with severe AS at our Tohoku University Hospital as candidates for TAVI. Inclusion criteria were 1) heart failure with New York Heart Association functional class (NYHA) II to III symptoms, and 2) patient consent to receive cognitive function tests for at least 1 hour. Exclusion criteria were 1) acute decompensated heart failure and heart failure with NYHA IV symptoms, 2) refusal cognitive tests, and 3) insufficient quality of ^{99m}Tc SPECT. Based on these criteria, we excluded 35 patients in advance, including acute decompensated heart failure and heart failure with NYHA IV symptoms in 15, and refusal of receiving cognitive function tests for at least 1 hour in 20. Thus, we initially included 22 patients, in whom 7 were then excluded because of drop out owing to refusal of follow-up cognitive tests (n=2), and insufficient quality of 99mTc SPECT (n=5). Finally, we examined 15 patients in the present study with a special reference to the association of cerebral blood flow (CBF) and cognitive functions.

AS, aortic stenosis; NYHA, New York Heart Association; SPECT, single-photon emission computed tomography; TAVI, transcatheter aortic valve implantation.

Supplementary Figure 1