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Serial changes of coronary flow reserve over one year after transcatheter aortic valve implantation in patients with severe aortic stenosis☆

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ABSTRACT

Background: Impaired coronary flow reserve (CFR) portends a poor prognosis in patients with aortic stenosis. The present study aims to investigate how CFR changes over one year after transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis, and to explore factors related to the changes.

Methods: Consecutive patients undergoing TAVI were registered. CFR in the left anterior descending artery was measured by transthoracic echocardiography on three occasions pre-TAVI, one-day post-TAVI, and one-year post-TAVI.

Results: A total of 59 patients were enrolled, 46 of whom completed one-year follow-up. CFR was impaired in 35 (59.3%) patients pre-TAVI, but the impairment was only seen in 2 patients (4%) one-year post-TAVI. CFR value improved from 1.75 (1.50–2.10) cm/s pre-TAVI, to 2.00 (1.70–2.30) one-day post-TAVI, and further to 2.60 (2.30–3.10) one-year post-TAVI ($P < 0.001$). The median difference in CFR between pre-TAVI and one-year post-TAVI was 0.90 (0.53–1.20). Patients with significant improvement of CFR (more than the median value of 0.9) had larger aortic valve area (1.55 [1.38–1.92] vs. 1.36 cm^2 [1.26–1.69], $P = 0.042$) and greater improvement in left ventricular ejection fraction (3.10 [−1.67–4.24] vs. −1.46 [−3.42–1.48] percentage points, $P = 0.019$) than those without.

Conclusions: CFR is impaired in a considerable proportion of patients with severe aortic stenosis, but improvement is seen immediately after TAVI, and one year later. Patients with significant improvement of CFR had larger aortic valve area and greater increase in left ventricular ejection fraction after TAVI.

1. Introduction

Coronary flow reserve (CFR) is impaired in patients with severe aortic stenosis (AS), even those without significant coronary artery disease. Pathological changes in the left ventricular myocardium and coronary microcirculation are thought to diminish the response of coronary flow to the increased demand [1,2]. Impairment of CFR is correlated with the severity of AS and also portends future adverse cardiovascular events [3–6]. Impaired CFR can be restored within six months [7] and within one year after surgical repair in patients with severe AS who undergo surgical aortic valve replacement (SAVR) [8], and the increase of CFR reportedly occurs in parallel with the regression of left ventricular (LV) hypertrophy [7,8].

Transcatheter aortic valve implantation (TAVI) has become the standard treatment for patients with severe AS since it was shown that it can provide clinical outcomes equivalent to or even better than SAVR in high-, intermediate-, and low-risk populations. Although TAVI may positively affect CFR, as seen in patients that underwent SAVR [9],

Abbreviations: AS, aortic stenosis; AVA, aortic valve area; AV-PG, aortic valve pressure gradient; AVR, aortic valve replacement; CFR, coronary flow reserve; LAD, left anterior descending coronary artery; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

☆ All listed authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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studies are currently limited; they have been short-term evaluations (≤6 months follow-up) [10] and most were simply two-point (pairwise) assessments of pre- and post-TAVI [11–13]. Serial changes of CFR after TAVI over a long-term period have not yet been investigated. The mechanisms of the restoration of CFR after TAVI also require proper examination. This study therefore aims to investigate the serial changes of CFR over a one-year period in patients undergoing TAVI, and to explore factors related to the changes of CFR.

2. Methods

2.1. Study population

We retrospectively reviewed consecutive patients with severe AS undergoing TAVI at the Wakayama Medical University Hospital between September 2017 and March 2020. Patients were enrolled unless they met exclusion criteria described below. Severe AS was defined by the following conditions: an aortic valve area (AVA) of ≤ 1.0 cm^2 with a peak transaortic velocity of ≥ 4 m/s or a mean aortic valve pressure gradient (AV-PG) of ≥ 40 mmHg by transthoracic Doppler echocardiography [14]. Exclusion criteria were: i) history of myocardial infarction in the left anterior descending coronary artery (LAD), ii) history of cardiac surgery, iii) significant stenosis (≥70% stenosis on visual estimation) in the LAD, iv) severe mitral or tricuspid valve disease, vi) unstable hemodynamic conditions, and vii) hypertrophic cardiomyopathy. This study complies with the Declaration of Helsinki and has been approved by Wakayama Medical University Hospital Ethics Committee. Informed consent was obtained from all participating patients.

2.2. Transthoracic Doppler echocardiography

Transthoracic Doppler echocardiography was performed by a dedicated sonographer or an experienced physician on three occasions (pre-TAVI, post-TAVI [on the day following TAVI], and one year after TAVI) through the use of a GE Vivid E9 digital ultrasound system equipped with a 3.5–8.0 MHz frequency transducer probe (GE Healthcare, Horten, Norway) or Aplio i800 TUS-A1800 digital ultrasound system equipped with a 4.0 MHz frequency transducer probe (Canon Medical Systems Corporation, Tochigi, Japan). Two consecutive cycles in apical long-axis, apical four-chamber, and two-chamber views were obtained. LV diameters, left ventricular end-diastolic volume index, LV end-systolic volume index, LV ejection fraction (LVEF), and left atrial volume index (LAVI), LV mass index (LVMI), E/A, mean E/e' ratio and systolic trans-tricuspid pressure gradient were measured according to the methods established by the American Society of Echocardiography [15].

AVA was estimated with quantitative Doppler using the continuity equation. AVA was indexed by body surface area (BSA) and abbreviated as AVAI. Peak and mean AV-PG were obtained by placing the continuous wave Doppler cursor as parallel as possible with the flow across the aortic valve [14].

2.3. Coronary flow reserve measurement

Coronary flow velocity reserve was measured in LAD by transthoracic echocardiography and regarded as CFR. For color Doppler flow mapping for CFR measurements, the velocity range was set in the range of 12–25 cm/s. We acquired echocardiographic images from an acoustic window in the mid clavicular line in the fourth or fifth intercostal space in the left lateral decubitus position. After the lower portion of the interventricular sulcus had been located in a long-axis cross-section, the ultrasound beam was laterally tilted. Coronary flow velocity was measured by pulsed-wave Doppler echocardiography using a sample volume of 3–4 mm placed on the color signal in the mid to distal portion of LAD before and during intravenous continuous infusion of adenosine 5′-triphosphate administered at 0.14 mg/kg/min over 2 min for maximal hyperemia. Blood pressure and heart rate were measured at baseline and at hyperemia. The electrocardiogram was monitored continuously during the coronary flow measurements.

Coronary flow velocity measurements were performed offline by two experienced investigators who were blinded to the patient data by contouring the spectral Doppler signals using the integrated software package of the ultrasound system. Mean diastolic coronary flow velocity was measured at rest and at peak flow response during adenosine 5′-triphosphate administration. CFR was calculated as a ratio of resting and hyperemic coronary flow velocities. Final values of flow velocity represented an average of flow velocities from three cardiac cycles [16].

The inter- and intra-observer reproducibility of CFR measurements were assessed by repeating measurements of coronary flow in the same vessels. With regard to the inter-observer reproducibility, the scatter plot showed a very strong correlation ($r = 0.97$, $P < 0.001$) between the two observers, and the Bland-Altman plot demonstrated that the mean difference was −0.04, and the lower and upper limits of agreement were −0.38 and 0.30, respectively. In terms of the intra-observer reproducibility, the scatter plot also showed a strong correlation ($r = 0.97$, $P < 0.001$) between the first and the second measurements, and the Bland-Altman plot demonstrated that the mean difference was 0.01, and the lower and upper limits of agreement were −0.23 and 0.24, respectively (Fig. S1).

2.4. Transcatheter aortic valve implantation

All patients underwent TAVI using the transfemoral access. A 5-F sheath was inserted into the femoral vein for a temporary pacing wire, which was advanced into the right ventricle. A 6-F sheath was inserted into either side of the femoral arteries for angiography. An 8-F sheath was inserted into the contralateral femoral artery, and then the TAVI sheath (e-sheath [Edwards Lifesciences LCC, Irvine, CA] or Dryseal introducer sheath [W. L. Gore & Associates, Flagstaff, Ariz]) was inserted over a stiff wire for balloon valvuloplasty and valve implantation. The used valve types were either Edwards SAPIEN 3 valves (Edwards Lifesciences LCC) or Medtronic Evolut R valves (Medtronic Inc, Minneapolis, MN). Valve types and sizing were at the discretion of the heart team.

2.5. Statistical analysis

Statistical analyses were performed using JMP software version 14.1.0 (SAS Institute Inc., Cary, NC) and R version 4.0.3 (R Foundation, Vienna, Austria). Values are expressed as median and interquartile range for continuous variables and as counts and percentages for categorical variables. Continuous variables between the two groups were compared by Mann-Whitney *U* test. Comparisons of continuous variables between pre-TAVI, post-TAVI, and one year after TAVI were performed using Friedman test. In the event that there was a significant difference in values across all the three occasions, we then performed Nemenyi post-hoc tests to compare all the pairs. Categorical variables were compared by the chi-square test or Fisher's exact test as appropriate. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

During the study period, 94 patients with severe AS underwent TAVI. Of these, patients were excluded if they had a prior myocardial infarction in the LAD (n = 1), previous cardiac surgeries (n = 8), significant stenoses in the LAD (n = 14), severe mitral or tricuspid valve diseases (n = 2), unstable hemodynamic conditions (n = 9), or hypertrophic cardiomyopathy (n = 1). The remaining 59 patients were enrolled in this study (Fig. S2). The median age was 85 (83 – 88) years, 42 patients (71.2%) were female, and 48 patients (81.4%) had hypertension. Patient characteristics are summarized in Table e-1. All patients had successful

transthoracic echocardiography evaluations and underwent TAVI. One patient had surgical conversion, two died in the hospital, and two had unstable hemodynamic conditions, so 54 patients underwent echocardiographic assessments on the day following TAVI. One-year follow-up was available in 46 patients because six patients were lost to follow up and one cardiac and one non-cardiac death occurred during the follow-up period.

3.2. Transcatheter aortic valve implantation

Edwards SAPIEN 3 valve (Edwards Lifesciences LCC) was used in 57 patients (96.6%) and Medtronic Evolut R valve (Medtronic Inc.) was used in 2 patients (3.4%). The procedures were performed under general anesthesia in 55 patients and under moderate sedation with local anesthesia in 4 patients.

3.3. Transthoracic echocardiography

Echocardiographic characteristics are summarized in Table 1. The median AVA was 0.65 cm^2 (0.55 – 0.71) in the pre-TAVI assessments, and significantly improved (1.49 cm^2 [1.28 – 1.74], $P < 0.001$) on the following day, and the improvement was maintained (1.54 cm^2 [1.34 – 1.83], $P = 0.170$) at the one-year follow-up. There was no significant difference in LVEF (60.5% [57.5 – 63.6] vs. 61.7% [58.0 – 63.9] vs. 61.0% [59.4 – 64.4], $P = 0.630$) or left ventricular end-diastolic volume index (57.3 mL/m^2 [53.0 – 66.6] vs. 56.9 mL/m^2 [50.7 – 65.1] vs. 57.0 mL/m^2 [51.2 – 69.5], $P = 0.582$) between pre-TAVI, one-day post-TAVI, and one-year follow-up. Meanwhile, LVMI decreased significantly between the three assessment occasions (147.4 mL/m^2 [133.1 – 173.2] vs. 149.0 mL/m^2 [130.0 – 172.3] vs. 132.6 mL/m^2 [115.1 – 160.5], $P < 0.001$).

Table 1
Echocardiographic characteristics.

Variable	Pre-TAVI (n = 59)	Post-TAVI (n = 54)	One year after TAVI (n = 46)	*P*-Value
LVDd, mm	42.5 (40.0–46.0)	43.5 (40.0–47.0)	42.0 (39.0–45.3)	0.161
LVDs, mm	27.0 (24.0–31.0)	28.5 (25.0–32.0)	27.0 (25.0–29.0)	0.010
LVEDVI, ml/m^2	57.3 (53.0–66.6)	56.9 (50.7–65.1)	57.0 (51.2–69.5)	0.582
LVESVI, ml/m^2	22.3 (19.5–30.0)	21.4 (18.5–28.2)	22.5 (19.8–26.1)	0.530
LVEF, %	60.5 (57.5–63.6)	61.7 (58.0–63.9)	61.0 (59.4–64.4)	0.630
LVMI, ml/m^2	147.4 (133.1–173.2)	149.0 (130.0–172.3)	132.6 (115.1–160.5)	<0.001
LAVI, ml/m^2	46.2 (35.1–64.8)	47.5 (34.7–61.3)	42.7 (36.8–58.8)	0.492
E/A ratio	0.70 (0.50–0.90)	0.70 (0.50–0.80)	0.60 (0.55–0.80)	0.602
Mean E/e' ratio	16.3 (13.6–19.8)	17.3 (14.3–22.3)	15.9 (12.9–19.9)	0.087
TR–PG, mmHg	26.0 (22.0–30.0)	26.0 (22.0–31.0)	22.5 (19.0–27.0)	0.016
AVA, cm^2	0.65 (0.55–0.71)	1.49 (1.28–1.74)	1.54 (1.34–1.83)	<0.001
AVAI, cm^2/m^2	0.44 (0.39–0.49)	1.04 (0.90–1.18)	1.03 (0.92–1.21)	<0.001
Peak velocity, m/s	4.50 (4.20–5.10)	2.35 (2.00–2.60)	2.15 (2.00–2.43)	<0.001
Peak AV–PG, mmHg	82.0 (70.9–104.0)	22.1 (16.3–26.7)	19.0 (16.0–23.1)	<0.001
Mean AV–PG, mmHg	52.5 (44.8–65.2)	11.9 (9.1–15.1)	10.5 (8.0–12.2)	<0.001

Values are given as n (%) or median (interquartile range). TAVI = transcatheter aortic valve implantation; LV = left ventricular; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LAVI = left atrium volume index; TR-PG = trans tricuspid pressure gradient; AVA = aortic valve area; AVAI = aortic valve area index; AV–PG = aortic valve pressure gradient.

3.4. Coronary flow reserve

The median value of CFR was 1.75 (1.50 – 2.10) pre-TAVI, and improved to 2.00 (1.70 – 2.30) one-day post-TAVI, and then further increased up to 2.60 (2.30 – 3.10) one year after TAVI ($P < 0.001$) (Table 2 and Fig. 1). The prevalence of the impairment in CFR was 59.3% (35 of 59) pre-TAVI, 38.9% (21 of 54) one day post-TAVI, and 4.3% (2 of 46) at one-year follow-up, respectively. Resting coronary flow velocity stayed stable on the three measurement occasions (24.0 cm/s [20.0 – 32.0] pre-TAVI, 23.0 cm/s [17.0 – 27.1] one day post-TAVI, and 25.0 cm/s [17.4 – 31.3] one year after TAVI, $P = 0.218$). Meanwhile, hyperemic coronary flow velocity significantly increased between the three measurement occasions (46.0 cm/s [34.3 – 54.4] pre-TAVI, 49.5 cm/s [39.0 – 59.5] one day post-TAVI, and 65.5 cm/s [49.8 – 79.0] one year after TAVI, $P < 0.001$) (Fig. 1), which indicates the improvement of CFR was derived from the increase of the hyperemic coronary flow. In a sub-group of 37 patients whose LAD was free from a stenosis, identical coronary flow patterns were found: the median value of CFR was 1.80 (1.50 – 2.20) pre-TAVI, 2.00 (1.80 – 2.20) one day post-TAVI, and 2.70 (2.30 – 3.05) one year after TAVI ($P < 0.001$) (Table e-2). A representative case is shown in Fig. S3.

The improvement of CFR between pre-TAVI and one year after TAVI

Table 2
Coronary flow reserve and hemodynamic data.

	Pre-TAVI (n = 59)	Post-TAVI (n = 54)	One year after TAVI (n = 46)	*P* Value
Baseline				
Heart rate, bpm	65.5 (57.5–74.8)	72.0 (63.0–77.3)	60.0 (54.0–69.3)	<0.001
Systolic blood pressure, mmHg	121.5 (106.3–130.8)	139.5 (118–154.3)	132.5 (119–142.0)	<0.001
Diastolic blood pressure, mmHg	52.5 (47.0–58.0)	48.0 (41.0–52.3)	70.5 (61.8–77.3)	<0.001
Coronary flow velocity, cm/s	24.0 (20.0–32.0)	23.0 (17.0–27.1)	25.0 (17.4–31.3)	0.218
Hyperemia				
Heart rate, bpm	68.0 (60.5–75.8)	75.0 (67.8–81.0)	67.0 (58.0–74.0)	<0.001
Systolic blood pressure, mmHg	108.5 (99.0–121.0)	127.5 (109.5–147.3)	120.0 (109.8–131.3)	0.010
Diastolic blood pressure, mmHg	46.5 (41.3–52.8)	44.5 (37.0–51.0)	63.0 (56.0–71.3)	<0.001
Coronary flow velocity, cm/s	46.0 (34.3–54.4)	49.5 (39.0–59.5)	65.5 (49.8–79.0)	<0.001
Coronary flow reserve	1.75 (1.50–2.10)	2.00 (1.70–2.30)	2.60 (2.30–3.10)	<0.001
Coronary flow reserve < 2.0	35 (59.3)	21 (38.9)	2 (4.3)	<0.001

Values are given as n (%) or median (interquartile range). TAVI = transcatheter aortic valve implantation.

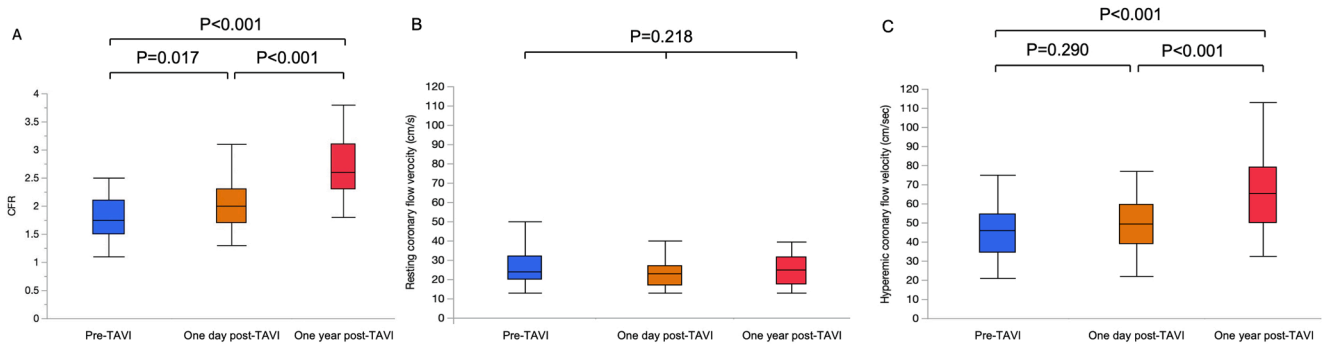

Fig. 1. (A) Coronary flow reserve, (B) resting coronary flow velocity, and (C) hyperemic coronary flow velocity TAVI = transcatheter aortic valve implantation.

was seen in 44 of the 46 patients that were followed up (96%). The median increase of CFR was 0.90 (0.53 – 1.20) (Fig. S4). The patients with large increase of CFR (the median value of 0.90 or more increase between pre-TAVI and one-year follow up) had significantly larger AVA (1.55 cm^2 [1.38 – 1.92] vs. 1.36 cm^2 [1.26 – 1.69], $P = 0.042$), lower peak velocity (2.10 m/s [1.80 – 2.35] vs. 2.30 m/s [2.10 – 2.50], $P = 0.021$), and smaller mean AV-PG (9.0 mmHg [7.0 – 11.5] vs. 11.0 mmHg [10.0 – 13.5], $P = 0.033$) at one-year follow-up, although there was no significant difference in those variables at pre-TAVI assessments. In addition, the patients with the large CFR increase had lower LVEF (59.6% [57.1 – 62.2] vs. 62.9% [60.2 – 64.1], $P = 0.018$) at pre-TAVI, but they had greater improvement in LVEF (3.10 [−1.67 – 4.24] vs. −1.46 [−3.42 – 1.48] percentage points, $P = 0.019$) at one-year follow-up than those without the large CFR increase. Details of comparisons between patients with and without the large increase of CFR are summarized in Table 3.

4. Discussion

The main findings of the current study are summarized as follows. First, CFR was impaired (CFR < 2.0) in 59.3% of the patients with severe aortic stenosis before TAVI, but the impairment of CFR was only seen in 4% of the patients one-year after TAVI. Second, CFR increased immediately after TAVI, and further improved one year later. Thirdly, there was no significant difference in the resting coronary flow velocity between pre-TAVI, one day post-TAVI, and one year after TAVI, although the hyperemic coronary flow velocity increased by degrees during the one-year follow-up period, indicating the improvement of CFR was attributed to the increase in hyperemic coronary flow velocity. Finally, the patients with large improvement in CFR were those who had lower LVEF at baseline but significant improvement at one-year follow-up, and larger AVA and lower AV-PG one year after TAVI compared with those without the significant improvement of CFR.

4.1. Coronary flow reserve in patients with severe AS

Patients with severe AS often have impaired CFR, even when they are free from significant stenosis in their coronary arteries. The impairment of CFR has been reported to be an independent predictor for future cardiovascular events in this population [3–6]. Left ventricular myocardium and coronary microcirculation have been reported to be affected in patients with AS [1,2]. CFR decreases in parallel with the severity of AS, reflecting the damages of LV myocardium and microcirculation [3]. In patients who underwent SAVR, impaired CFR was restored after the surgical repair [7]. The restoration of CFR was derived from the increase of hyperemic coronary flow rather than from changes in resting coronary flow. The majority of our study population similarly had impaired CFR, and it increased after TAVI, driven by the increase in the hyperemic coronary flow rather than because of the changes in the resting flow. Limited hyperemic coronary flow velocity appears to be a large contributor to the impaired CFR in patients with severe AS, implying the presence of microvascular dysfunction in this population.

4.2. Serial changes of CFR after TAVI

Several studies assessing the effects of AVR on CFR, whether TAVI or SAVR, have shown improvement of CFR after AVR [7–13]. Most of the studies were simply two-point comparisons, however: before and after AVR. There has been only one study to our knowledge in which serial changes of CFR were investigated at three points of measurement: before, immediately after, and six months after TAVI. Impaired CFR at baseline increased immediately after TAVI and further improved at six-month follow-up [10]. Our study showed similar findings: impaired CFR increased one day after TAVI and further improved one year later. This study therefore confirmed that TAVI has a positive effect on CFR immediately and lately, and extended these findings by showing that the improvement of CFR after TAVI lasted not only for the mid-term of six months, but also for the long-term of one year. The previous study also showed that the hyperemic flow continued to increase within the six-month period, while resting coronary flow velocity remained stable [10]. Our study echoed these findings; resting flow did not change, but hyperemic coronary flow velocity showed stepwise increase after TAVI.

4.3. Effects of TAVI on long-term follow-up CFR and related factors

Several studies have shown improvement of CFR after AVR, but its mechanisms have not been fully investigated [7–13]. Previous studies have reported an increase of postoperative CFR in correlation with regression of left ventricular hypertrophy [7,8]. In our study, LVMI decreased after TAVI as had been seen in the previous studies, but the regression of LVMI was not associated with the improvement of CFR. Instead, patients with a large increase of CFR were characterized by having a larger AVA and a smaller AV-PG after TAVI and a significant improvement was shown in cardiac function despite a low LVEF at baseline. Large AVA and low AV-PG after SAVR were reported to be associated with the improvement of CFR in patients undergoing SAVR [8]. In keeping with the findings in patients with SAVR, we have found for the first time that the same applies to patients with TAVI. The large AVA would lead to an increase in cardiac output and enhance the blood flow into the coronary artery. In addition, the low AV-PG would lower the end-diastolic LV pressure and reduce the resistance to the coronary blood flow in the diastole. These two mechanisms would contribute to the increase of hyperemic flow. Large AVA should take effect from the moment a prosthetic valve has been placed, so this probably contributed to the immediate increase of CFR after TAVI. Regarding the positive relationship between LVEF and CFR after TAVI, it can be explained in two ways; the improvement of LVEF might restore CFR, or to the contrary it might be the cause. Proving the causal relationship between LVEF and CFR after TAVI in an observational study is difficult. The improved cardiac function can be reasonably considered to be related to

Table 3
Comparisons of patient and echocardiographic characteristics with and without large increase of CFR (ΔCFR ≥ 0.9) between pre-TAVI and one-year follow up.

Variables	ΔCFR < 0.9 (n = 21)	ΔCFR≧0.9 (n = 25)	P Value
Baseline			
Age, years	85.0 (83.0–88.0)	85.0 (83.0–88.0)	0.877
Male	8 (38.1)	6 (24.0)	0.301
Body surface area, m^2	1.50 (1.40–1.55)	1.40 (1.30–1.60)	0.582
Hypertension	19 (90.5)	20 (80.0)	0.325
Diabetes mellitus	2 (9.5)	2 (8.0)	0.855
Dyslipidemia	7 (33.3)	12 (48.0)	0.314
Current smoker	2 (9.5)	0 (0)	0.115
Chronic kidney disease	15 (71.4)	17 (68.0)	0.801
Serum hemoglobin, g/dL	11.1 (10.8–12.9)	11.8 (10.7–12.3)	0.886
Serum creatinine, mg/dL	0.85 (0.68–1.14)	0.82 (0.68–1.14)	0.965
Serum BNP, pg/mL	90.7 (51.0–199.5)	196.5 (69.0–412.3)	0.213
Pre-TAVI			
LVDd, mm	42.0 (41.0–48.5)	42.0 (39.0–45.5)	0.325
LVDs, mm	27.0 (24.5–29.5)	27.0 (24.0–31.0)	0.991
LVEDVI, ml/m^2	55.0 (52.0–61.5)	57.7 (50.7–69.4)	0.716
LVESVI, ml/m^2	20.8 (19.4–23.8)	23.8 (19.3–31.8)	0.225
LVEF, %	62.9 (60.2–64.1)	59.6 (57.1–62.2)	0.018
LVMI, ml/m^2	145.8 (132.2–159.2)	143.2 (129.4–177.7)	0.675
LAVI, ml/m^2	44.0 (33.1–57.2)	48.9 (37.5–68.7)	0.217
E/A ratio	0.70 (0.53–0.88)	0.60 (0.50–0.90)	0.751
Mean E/e' ratio	14.8 (11.0–20.8)	16.7 (14.0–20.0)	0.348
TR-PG, mmHg	25.0 (22.8–30.0)	26.0 (21.0–27.0)	0.916
AVA, cm^2	0.66 (0.58–0.70)	0.64 (0.56–0.71)	0.800
AVAI, cm^2/m^2	0.44 (0.39–0.48)	0.44 (0.40–0.48)	0.590
Peak velocity, m/s	4.50 (4.20–4.90)	4.7 (4.30–5.30)	0.237
Peak AV-PG, mmHg	81.8 (71.0–94.0)	87.9 (72.8–111.7)	0.285
Mean AV-PG, mmHg	52.0 (43.9–56.9)	54.0 (46.6–67.5)	0.310
Post-TAVI			
LVDd, mm	44.0 (39.5–47.5)	43.0 (41.0–46.0)	0.707
LVDs, mm	28.0 (24.5–30.5)	29.0 (25.5–32.0)	0.407
LVEDVI, ml/m^2	57.1 (49.6–63.7)	55.4 (50.6–66.9)	0.749
LVESVI, ml/m^2	20.7 (19.3–23.7)	21.7 (19.3–29.4)	0.165
LVEF, %	63.5 (60.1–65.7)	60.5 (56.3–62.8)	0.010
LVMI, ml/m^2	138.7 (127.1–163.5)	152.7 (131.2–181.8)	0.384
LAVI, ml/m^2	47.5 (32.4–59.7)	51.6 (36.2–69.2)	0.301
E/A ratio	0.70 (0.53–0.80)	0.70 (0.50–0.88)	0.709
Mean E/e' ratio	16.7 (13.1–24.7)	18.6 (15.2–22.3)	0.386
TR-PG, mmHg	27.0 (21.5–29.0)	27.0 (24.0–31.5)	0.177
AVA, cm^2	1.42 (1.26–1.66)	1.59 (1.28–1.80)	0.217
AVAI, cm^2/m^2	0.99 (0.86–1.07)	1.13 (0.90–1.26)	0.074
Peak velocity, m/s	2.50 (2.10–2.70)	2.20 (2.00–2.50)	0.087
Peak AV-PG, mmHg	24.5 (17.5–28.3)	19.2 (16.1–24.6)	0.155
Mean AV-PG, mmHg	13.5 (11.0–17.0)	10.3 (9.0–12.6)	0.052
One year after TAVI			
LVDd, mm	44.0 (41.5–47.0)	41.0 (38.0–43.5)	0.018
LVDs, mm	28.0 (26.5–30.0)	26.0 (24.0–28.5)	0.067
LVEDVI, ml/m^2	57.7 (52.0–66.7)	56.0 (50.0–65.1)	0.349
LVESVI, ml/m^2	23.3 (20.3–26.4)	21.3 (19.3–25.7)	0.321
LVEF, %	60.7 (59.4–61.7)	61.3 (59.3–62.5)	0.530
ΔLVEF*, percentage points	−1.46 (−3.42–1.48)	3.10 (−1.67–4.24)	0.019
LVMI, ml/m^2	139.1 (117.4–166.2)	130.4 (112.9–154.1)	0.256
LAVI, ml/m^2	42.9 (38.1–54.3)	42.5 (34.6–61.7)	0.749
E/A ratio	0.60 (0.53–0.88)	0.60 (0.55–0.80)	0.989
Mean E/e' ratio	14.2 (12.3–19.9)	16.9 (14.6–20.5)	0.549
TR-PG, mmHg	24.0 (20.0–27.0)	22.0 (19.0–27.0)	0.569
AVA, cm^2	1.36 (1.26–1.69)	1.55 (1.38–1.92)	0.042
AVAI, cm^2/m^2	0.99 (0.90–1.14)	1.05 (0.98–1.33)	0.062
Peak velocity, m/s	2.30 (2.10–2.50)	2.10 (1.80–2.35)	0.021
Peak AV-PG, mmHg	20.9 (17.0–25.5)	17.0 (13.0–21.5)	0.032
Mean AV-PG, mmHg	11.0 (10.0–13.5)	9.0 (7.0–11.5)	0.033

Values are given as n (%) or median (interquartile range). TAVI = transcatheter aortic valve implantation; LV = left ventricular; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LAVI = left atrium volume index;; TR-PG = transtricuspid pressure gradient; AVA = aortic valve area; AVAI = aortic valve area index; AV-PG = aortic valve pressure gradient. * ΔLVEF was calculated as LVEF at one-year after TAVI minus LVEF at pre-TAVI.

the long-term increase of CFR, however, because it usually occurs over a certain period of time.

5. Limitations

There are some limitations in this study. Firstly, it was a single center observational study with a relatively small number of cases. The limited number of patients did not allow multivariable analysis to clarify clinical, anatomic, and procedural factors contributing to the CFR recovery. However, this study included consecutive patients who underwent TAVI during the study period and it represents the population in a real-world setting. Additionally, all previous studies that investigated CFR pre- and post-SAVR or TAVI also had small sample sizes, the largest being 55 (7–13), so this study had at least an equivalent number of cases to them. Large-scale prospective multicenter registry is necessary to elucidate contributing factors to CFR recovery in patients undergoing TAVI. Secondly, CFR was measured by transthoracic echocardiography. Imaging coronary flow by echocardiography requires skills and the measurement locations might have not been exactly the same on each assessment. So, the coronary flow data might have been influenced by measurement error. However, transthoracic Doppler echocardiography of the LAD is recommended as one of the non-invasive methods for the assessment of CFR by the latest guidelines [17], and as a matter of fact, CFR was successfully measured in all the patients of this study. In addition, as a non-invasive method it had an advantage in assessing serial CFR changes, particularly in the long-term follow-up. In this respect, this method would make a future study in this kind feasible and this study would become a future reference. A third limitation of this study is that about 20% of the enrolled cases were lost to follow-up and it cannot be denied that cases with poor CFR recovery were less likely to be followed up. Finally, the results of this study are inapplicable to patients with poor left ventricular function because most cases in this study have relatively preserved left ventricular function.

6. Conclusions

Among patients with severe AS, CFR was impaired in a considerable proportion, but improved immediately after TAVI and further increased one year later. This improvement of CFR was driven by an increase in hyperemic coronary flow rather than changes in resting flow. Patients with greater restoration of CFR characteristically had a larger AVA, a lower AV-PG, and larger improvement in cardiac function after TAVI.

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CRediT authorship contribution statement

Teruaki Wada: Methodology, Investigation, Data curation, Writing – original draft. **Yasutsugu Shiono:** Conceptualization, Methodology, Formal analysis, Visualization, Investigation, Writing – review & editing, Project administration. **Kentaro Honda:** Writing – review & editing, Supervision. **Daisuke Higashioka:** Data curation, Investigation, Visualization. **Akira Taruya:** Data curation, Investigation, Visualization. **Masahiro Takahata:** Data curation, Validation. **Suwako Fujita:** Data curation, Validation. **Shingo Ota:** Data curation, Validation. **Keisuke Satogami:** Investigation, Visualization. **Yuichi Ozaki:** Investigation, Visualization. **Manabu Kashiwagi:** Investigation, Validation. **Akio Kuroi:** Investigation, Validation. **Takashi Yamano:** Investigation, Supervision. **Kazushi Takemoto:** Investigation, Supervision. **Takashi**

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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