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Variation of computed tomographic angiography–based fractional flow reserve after transcatheter aortic valve implantation

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Abstract

Objectives We sought to identify the impact of transcatheter aortic valve implantation (TAVI) on changes of fractional flow reserve computed tomography (FFR_{CT}) values and the associated clinical impact.

Methods A retrospective analysis was done with CT obtained pre-TAVI, prior to hospital discharge and at 1-year follow-up, which provided imaging sources for the calculation of FFR_{CT} values based on an online platform.

Results A total of 190 patients were enrolled. Patients with pre-procedural FFR_{CT} value > 0.80 (i.e., negative) and ≤ 0.80 (i.e., positive) demonstrated a significantly opposite change in the value after TAVI (0.8798 vs. 0.8718, $p < 0.001$ and 0.7634 vs. 0.8222, $p < 0.001$, respectively). The history of coronary artery disease (CAD) was identified as an independent predictor for FFR_{CT} changing from negative to positive after TAVI (odds ratio [OR] 2.927, 95% confidence interval [CI] 1.130–7.587, $p = 0.027$), with lesions more severely stenosed (OR 1.039, 95% CI 1.003–1.076, $p = 0.034$) and in left anterior descending coronary artery (LAD) (OR 3.939, 95% CI 1.060–14.637, $p = 0.041$) being prone to change.

Conclusions TAVI directly brings improvement in FFR_{CT} values in patients with compromised coronary flow. Patients with a history of CAD, especially with lesions more severely stenosed and in LAD, were under risk of FFR_{CT} changing from negative to positive after TAVI.

Key Points

- *The effect of TAVI on coronary hemodynamics might be influenced by different ischemic severity and coronary territories reflected by FFR_{CT} values.*
- *As different FFR_{CT} variations did not impact outcomes of TAVI patients, AS, but not coronary issues, may be the primary problem to affect, which needs further validation.*

Keywords Transcatheter aortic valve replacement · Coronary artery disease · Computed tomography · Functional flow reserve

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Abbreviations

%DS	Percent diameter stenosis
AS	Aortic stenosis
CAD	Coronary artery disease
CTA	Computed tomography angiography
FFR	Fractional flow reserve
FFR_{CT}	Fractional flow reserve computed tomography
LAD	Left anterior descending coronary artery
LCx	Left circumflex coronary artery
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
TAVI	Transcatheter aortic valve implantation

Introduction

Concomitant coronary artery disease (CAD) is common in patients with aortic stenosis (AS) [1]. As transcatheter aortic valve implantation (TAVI) is now an established treatment choice for symptomatic severe aortic stenosis and continues to expand to patients of younger age and lower risk, the timing to intervene concomitant coronary lesions becomes an important aspect to consider [2]. The severity of coronary stenosis is conventionally assessed by coronary angiography, and more recently through fractional flow reserve (FFR) to reflect the functional status. However, the change of coronary flow after the correction of AS and the most reliable way to evaluate coronary lesions in the setting of TAVI are not yet well determined. Such information has important clinical implications on the management of concomitant CAD in TAVI patients.

Coronary angiography is not routinely indicated post-TAVI. Recently, fractional flow reserve computed tomography (FFR_{CT}) has been validated to be able to assess the functional stenoses of coronary arteries efficiently as compared to invasive FFR [3]. Computed tomography angiography (CTA) is now routinely obtained for pre-TAVI planning and incorporated in some centers for post-TAVI follow-ups; thus, FFR_{CT} is a potential tool to explore variations in coronary flow in TAVI patients. In this study, we sought to offer insights into serial changes of FFR_{CT} before and after TAVI to identify the impact of the procedure on functional status of myocardial perfusion and the associated clinical impact of such changes in a cohort of TAVI patients.

Materials and methods

Patient population

This was a retrospective, single-center, observational study involving consecutive patients who have successfully received TAVI due to symptomatic severe AS from September 25, 2012, to August 15, 2019, with CTA done pre-procedurally and at least once post-procedurally. The indication for TAVI was discussed by our multidisciplinary Heart Team. Baseline clinical, echocardiographic, and angiographic characteristics and procedural and post-procedural details were collected in a dedicated prospective TAVI database. Patients with the history of percutaneous coronary intervention (PCI) treatment prior to the index TAVI were not excluded from the study. This study was approved by the institutional review board. Written informed consents were obtained from all patients.

FFR_{CT} analysis and subgroup analysis

CTA was routinely obtained in all patients pre-TAVI and prior to hospital discharge as well as at 1-year follow-up if no contraindications presented. The specific details of the CTA examination were mentioned in a previous study [4]. No nitrates or beta-blocker were used during CTA scanning, but patients with symptomatic arrhythmia had been given conservative therapy once after hospitalization. Post-procedural and further 1-year CT procedures were conducted so as to evaluate the condition of hypo-attenuated leaflet thickening, prosthesis in bicuspid aortic valve with complex anatomy, and occurrence of morphological structural valve deterioration. To lower the risk of radiation, effective lead protection was conducted for gonads and thyroid glands. In order to monitor the risk of contrast media administration during follow-up CT scan, renal function would be checked by laboratorial parameter like creatinine. The FFR_{CT} values were calculated (one for each of the 3 main branches, i.e., left anterior descending coronary artery, LAD; left circumflex coronary artery, LCx; and right coronary artery, RCA) from diastolic CTA images based on the online DEEPVESSEL-FFR platform using deep learning technique (Keya Medical Technology Inc.) [5]. CTA images which showed severe coronary calcification, artifacts, image noises, insufficient artery brightening, coronary artery occlusion, and the lack of slices were excluded for FFR_{CT} analysis. The calculating process and the construction and validation of the platform can be found in the Supplementary Material. After obtaining all FFR_{CT} values, patient-level subgroup analyses were performed taking the conventional cutoff value of 0.80 to stratify patients (Fig. 1). The details of grouping method were listed in Fig. 1.

Coronary angiography and quantitative coronary analysis (QCA)

The value of percent diameter stenosis (%DS) evaluated from invasive coronary angiography or CTA (i.e., anatomical stenosis) was routinely assessed in our center (details in Supplementary Materials). Then, we classified the stenoses into tertiles (10–30%, 30–50%, and 50–70%) to compare FFR_{CT} variations (Fig. 1). Anatomical features of lesions evaluated on invasive angiography and CTA were also extracted to test their correlation with FFR_{CT} changes (Fig. 1).

TAVI procedure and follow-up

The choice of the aortic valve prosthesis was based on device availability at the time of intervention and left to operator's discretion. A total of 4 self-expanding valve types, namely Venus A-valve (Venus MedTech) [6], VitaFlow valve (MicroPort Medical (Group) Co.) [7], TaurusOne valve (Peijia Medical Technology Co.) [8], and CoreValve

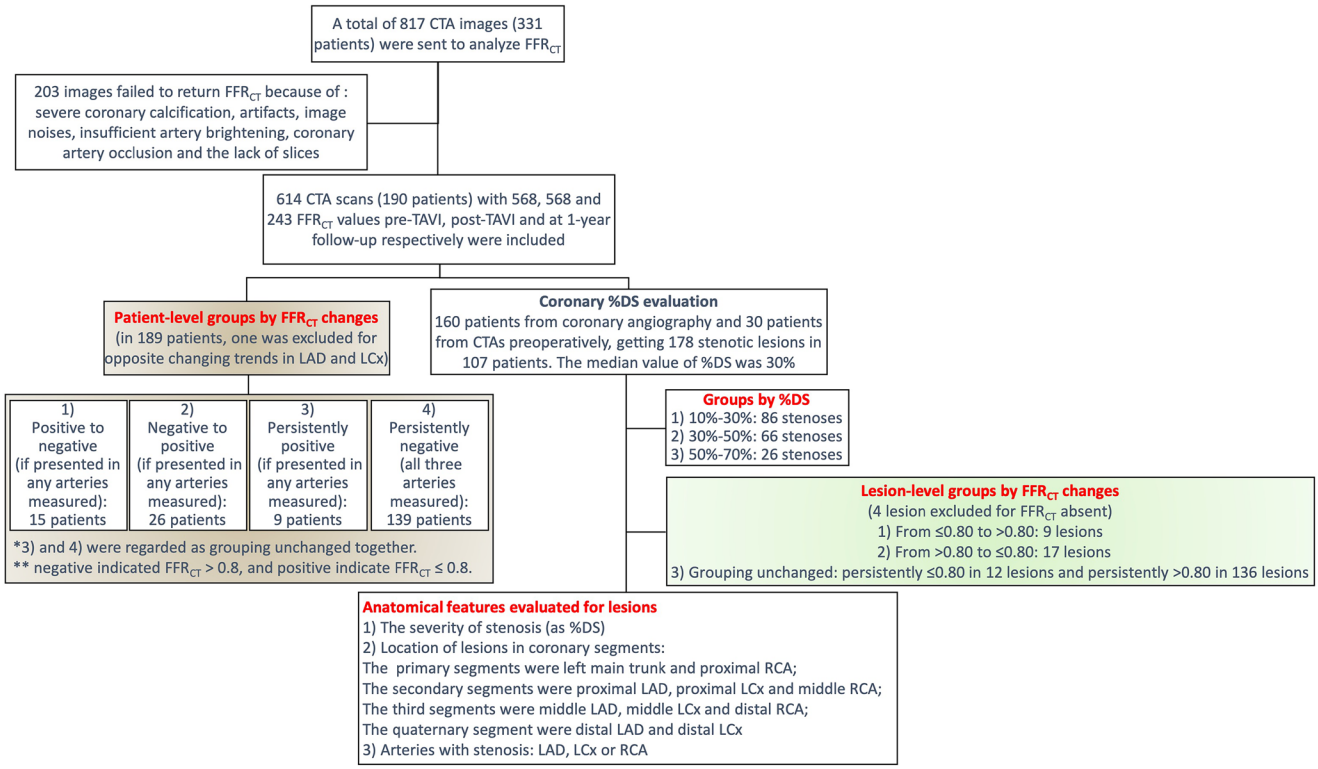

Fig. 1 Flowchart of image collection and data analysis

(Medtronic Inc.), as well as Sapien-XT valve (Edwards Lifesciences Co.) and Lotus valve (Boston Scientific Co.) were utilized in the study. Procedural details of TAVI in our center have been reported [9]. TAVI-specific endpoints were defined according to the VARC-2 criteria [10].

Transthoracic echocardiography (TTE) follow-ups were arranged at 1 and 6 months and 1 year after TAVI. The degree of post-TAVI paravalvular leak (PVL) was evaluated by echocardiography and classified as none (I), trace (II), mild (III), moderate (IV), and severe (V). Left ventricular (LV) mass was calculated in accordance with guideline recommendations [11]. Prosthesis performance was evaluated through transaortic maximal velocity (V_{max}) and mean gradient (PG_{mean}), together with PVL during follow-up.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (25th, 75th quartile). Categorical variables were presented as frequencies and percentages. Comparison of FFR_{CT} values at different time points was performed by a paired Student *t* test. Among groups, the differences of continuous variables were compared using the one-way ANOVA analysis or Kruskal-Wallis *H* test as appropriate, while comparisons between groups of categorical variables were conducted by using the chi-square test. Binary logistic regression analyses were carried out between the groups to determine the odds ratio (OR) and 95% confidence intervals (CI) for covariates, with those of *p* values < 0.10 in univariate analyses being entered into multivariate analyses. A 2-tailed *p* value < 0.05 was considered statistically significant. IBM SPSS Statistics 26.0 was used to perform all statistical analyses.

Results

Baseline characteristics and procedural details

A total of 190 patients were included. A history of CAD was documented in 38.9% of patients from their medical records. There were 2 patients who had received PCI treatment 3 years and 2 months before TAVI respectively. All patients had pre-TAVI and post-TAVI (prior to discharge) CTA scans and 82 patients (43%) had a further 1-year CTA scan. The median age of this cohort was 74.0 (69.0, 78.0) years and the median Society of Transthoracic Surgeons Predicted Risk of Mortality (STS-PROM) was 6.5 (4.1, 9.0) %. Baseline characteristics were summarized in Table 1 grouping on patient level. Procedural details were displayed in Supplementary Table 1.

Effect of TAVI on FFR_{CT} values

The variation of FFR_{CT} was shown in Fig. 2. The mean FFR_{CT} value in total decreased after TAVI compared with

Table 1 Baseline characteristics of the study population

	All patients (n = 190)	Positive to negative (n = 15)	Negative to positive (n = 26)	Grouping unchanged (n = 148)	
				Persistently positive (n = 9)	Persistently negative (n = 139)
Age, years	74.0 (69.8, 78.0)	69.0 (66.0, 76.0)	76.0 (72.3, 79.0)	76.0 (69.5, 80.5)	74.0 (69.0, 77.0)
Height, cm	160.0 (155.0, 165.0)	162.0 (157.5, 167.5)	158.0 (153.0, 167.5)	160.0 (158.0, 167.0)	160.0 (155.0, 165.0)
Weight, kg	58.0 (50.0, 64.0)	60.0 (53.0, 63.0)	60.0 (53.0, 63.0)	55.0 (50.3, 68.0)	57.5 (50.0, 63.0)
Female, n (%)	89 (46.8%)	4 (26.7%)	14 (53.9%)	4 (44.4%)	67 (49.6%)
STS-PROM, %	6.5 (4.1, 9.0)	4.9 (3.0, 8.3)	7.1 (5.4, 10.8)	7.9 (5.6, 8.8)	6.2 (4.0, 8.8)
NYHA functional class III–IV, n (%)	166 (87.4%)	14 (93.3%)	24 (92.3%)	9 (100%)	118 (84.9%)
LV mass, g	261.8 (213.3, 322.9)	279.8 (241.2, 329.8)	266.1 (196.4, 326.0)	245.7 (196.8, 300.2)	249.4 (208.9, 322.3)
Follow-up duration, days	726.0 (368.8, 1279.3)	380.0 (362.0, 1089.0)	721.0 (380.0, 1295.8)	370.0 (353.0, 723.0)	731.0 (371.0, 1359.0)
Comorbidities					
Hypertension, n (%)	80 (42.1%)	6 (40.0%)	12 (46.2%)	5 (55.6%)	56 (40.3%)
Diabetes mellitus, n (%)	29 (15.3%)	1 (6.7%)	3 (11.5%)	1 (11.1%)	24 (17.3%)
Coronary artery disease, n (%)	74 (39.0%)	10 (66.7%)	15 (57.7%)	7 (77.7%)	41 (29.5%)
Chronic lung disease, n (%)	118 (62.1%)	8 (53.33%)	20 (76.9%)	4 (44.4%)	85 (61.2%)
Peripheral vascular disease, n (%)	97 (51.1%)	6 (40.0%)	14 (53.9%)	7 (77.8%)	70 (50.4%)
Chronic kidney disease, n (%)	21 (11.1%)	0 (0%)	2 (7.7%)	2 (22.2%)	17 (12.2%)
Cancer, n (%)	7 (3.7%)	1 (6.7%)	0 (0%)	1 (11.1%)	22 (15.8%)
Atrial fibrillation, n (%)	33 (17.4%)	3 (20.0%)	6 (23.1%)	1 (11.1%)	5 (3.6%)
Pre-procedural echocardiography					
Transaortic maximal velocity, m/s	5.0 (4.5, 5.6)	4.9 (4.2, 5.3)	5.0 (4.6, 5.9)	5.0 (4.8, 5.9)	5.0 (4.4 , 5.5)
Transaortic mean gradient, mmHg	62.0 (49.0, 78.0)	56.0 (46.0, 71.0)	68.5 (51.5, 88.0)	63.0 (60.0, 85.0)	61.0 (49.0, 77.0)
Left ventricular ejection fraction, %	62.0 (45.0, 78.0)	49.0 (35.0, 59.0)	63.0 (46.5, 70.5)	64.0 (54.5, 70.0)	62.0 (46.0, 68.0)

STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; *NYHA*, New York Heart Association; *LV mass*, left ventricular mass

that before the procedure (0.8731 vs 0.8690, p = 0.024), whereas there were no significant differences between the mean value before discharge and at 1-year follow-up (Table 2). For FFR_{CT} > 0.80 pre-TAVI, there were 6.6% of the values changing to 0.7 ≤ FFR_{CT} ≤ 0.80 post-TAVI (including 27 patients, six of them with FFR_{CT} = 0.8 showing in 4 LAD and 2 RCA arteries; one of them with FFR_{CT} of LAD, LCx, and RCA arteries 0.75, 0.8, and 0.76, respectively). For 0.7 ≤ FFR_{CT} ≤ 0.80 pre-TAVI (including 25 patients, one of them with FFR_{CT} of LAD and LCx arteries 0.7 and 0.8, respectively), there were 58.1% of the values changing to > 0.8 post-TAVI.

When grouping patients with the conventional 0.80 cutoff value, patients with pre-procedural FFR_{CT} value > 0.80 demonstrated a mild but statistically significant drop after TAVI from 0.8798 to 0.8718 (p < 0.001). However, patients with pre-procedural FFR_{CT} value ≤ 0.80 experienced a statistically and clinically significant increase after TAVI from 0.7634 to 0.8222 (p < 0.001). At 1-year follow-up, no significant differences were observed in both groups from discharge (Table 2).

Effect of TAVI on FFR_{CT} stratified by QCA values

From the reports of 160 coronary angiograms and the assessment of CTA images in 30 patients, a total of 178 stenosed lesions of various degrees were identified in 107 patients (Fig. 1). Among 56% (107/190) of patients diagnosed by angiography and CTA with CAD, only 24% (26/107) had range of quantitative diameter stenosis from 50% to 70% without angina, elevated myocardial enzyme, or acute ischemic electrocardiography. When stratifying patients into tertiles of angiographically assessed stenosis, differences of mean value of FFR_{CT} at different time points could not be observed (Supplementary Table 2).

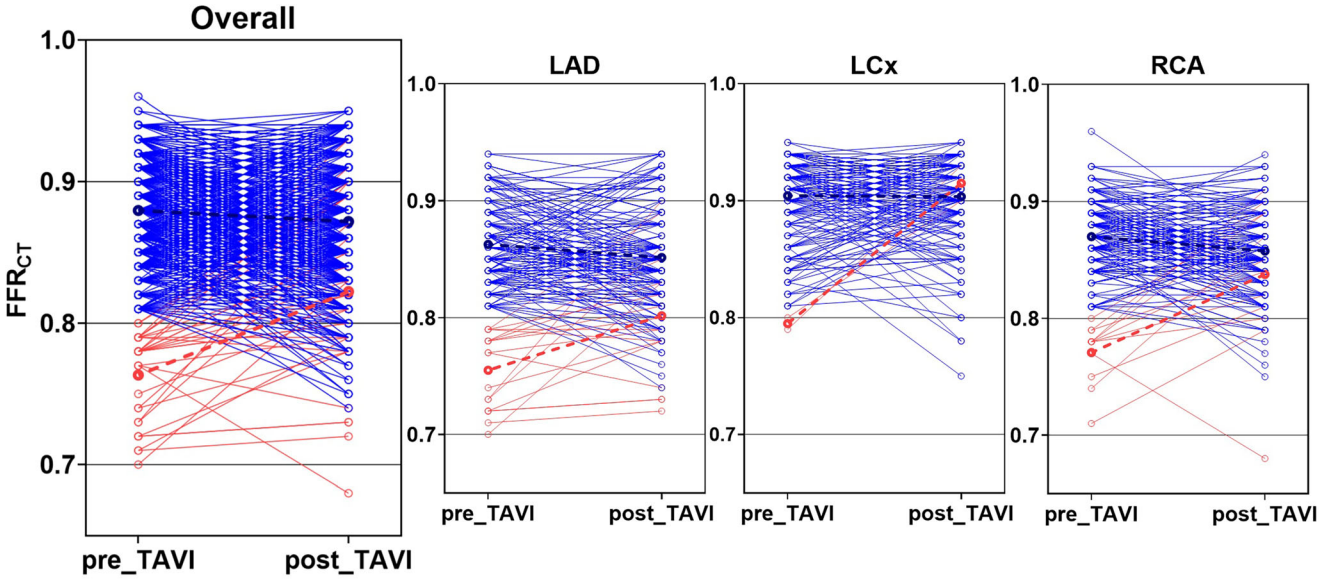

Fig. 2 FFR_{CT} changing trends after TAVI procedure

Analysis for baseline and anatomical predictors of FFR_{CT} changes post-TAVI

In the multivariate regression analysis, only the history of CAD remained an independent predictor for FFR_{CT} changing from negative to positive (OR 2.927, 95% CI 1.130–7.587, p = 0.027) (Table 3). There were no independent predictors identified for FFR_{CT} changing from positive to negative (Table 3).

The analysis of anatomical features on invasive angiography and CTA that might result in cross 0.80 FFR_{CT} changes included 174 angiographical lesions in total (4 of 178 stenosed lesions were excluded because of data loss of FFR_{CT} values) at lesions-level analysis. FFR_{CT} values in arteries with more severely stenosed lesions tended to change from negative to positive after TAVI rather than being persistently negative (OR 1.039, 95% CI 1.003–1.076, p = 0.034) (Supplementary Table 3). Taking the RCA as a reference, lesions in the LAD were with an increased risk of FFR_{CT} value changing from negative to positive after TAVI rather than remaining negative persistently (OR 3.939, 95% CI 1.060–14.637, p = 0.041) (Supplementary Table 3). No anatomical features were found to predict FFR_{CT} values changing from positive to negative.

Association of clinical parameters and outcomes

Clinical outcomes are summarized in Supplementary Table 4. There were no differences among groups in terms of bioprosthesis hemodynamics and LV mass (Table 4). A total

Table 2 FFR_{CT} variation classified by values before TAVI

	Pre-TAVI vs. post-TAVI	p value	Post-TAVI vs. 1-year	p value
FFR_{CT} in total	0.8731 vs. 0.8690	**0.024**	0.8725 vs. 0.8689	0.228
LAD	0.8523 vs. 0.8468	0.106	0.8480 vs. 0.8490	0.865
LCx	0.9031 vs. 0.9036	0.859	0.9086 vs. 0.8998	0.059
RCA	0.8636 vs. 0.8562	**0.018**	0.8608 vs. 0.8579	0.562
Pre-FFR > 0.8	0.8797 vs. 0.8718	**< 0.001**	0.8735 vs. 0.8706	0.323
Pre-FFR_LAD > 0.8	0.8626 vs. 0.8515	**0.001**	0.8491 vs. 0.8496	0.932
Pre-FFR_LCx > 0.8	0.9043 vs. 0.9035	0.794	0.9086 vs. 0.8998	0.059
Pre-FFR_RCA > 0.8	0.8699 vs. 0.8575	**< 0.001**	0.8612 vs. 0.8610	0.977
Pre-FFR ≤ 0.8	0.7634 vs. 0.8222	**< 0.001**	0.8350 vs. 0.8050	0.379
Pre-FFR_LAD ≤ 0.8	0.7550 vs. 0.8017	**0.002**	0.8200 vs. 0.8333	0.578
Pre-FFR_LCx ≤ 0.8	0.7950 vs. 0.9150	0.105	/	/
Pre-FFR_RCA ≤ 0.8	0.7708 vs. 0.8375	**0.003**	0.8500 vs. 0.7767	0.283

p values < 0.05 were statistically significant and presented as bold entries

LAD, left anterior descending artery; *LCx*, left circumflex artery; *RCA*, right coronary artery

Table 3 Analysis for baseline predictors of FFR_{CT} changes after TAVI

	Univariate analysis				Multivariate analysis			
	Positive to negative*		Negative to positive**		Positive to negative*		Negative to positive**	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	0.876 (0.754, 1.018)	0.083	1.015 (1.020, 1.198)	**0.015**	0.869 (0.721, 1.047)	0.140	1.050 (0.953, 1.157)	0.32
Weight	1.018 (0.916, 1.131)	0.744	1.019 (0.976, 1.063)	0.394	/	/	/	/
Female	0.455 (0.080, 2.598)	0.375	1.387 (0.589, 3.266)	0.454	2.939 (0.244, 35.393)	0.396	1.799 (0.687, 4.712)	0.232
STS-PROM	0.866 (0.659, 1.138)	0.302	1.112 (1.006, 1.228)	**0.037**	/	/	1.065 (0.938, 1.210)	0.332
NYHA-III/IV***	/	/	2.029 (0.445, 9.256)	0.361	/	/	/	/
LV mass	1.007 (0.995, 1.019)	0.274	1.001 (0.996, 1.006)	0.672	/	/	/	/
Hypertension	0.533 (0.100, 2.839)	0.461	1385 (0.589, 3.254)	0.455	/	/	/	/
Diabetes mellitus	0.571 (0.031, 10.435)	0.706	0.659 (0.183, 2.380)	0.524	/	/	/	/
Coronary artery disease	0.571 (0.85, 3.833)	0.564	3.622 (1.504, 8.724)	**0.004**	/	/	2.927 (1.130, 7.587)	**0.027**
Chronic lung disease	1.429 (0.271, 7.518)	0.674	2.588 (0.918, 7.301)	0.072	/	/	1.876 (0.608,5.786)	0.274
Peripheral vascular disease	0.190 (0.029, 1.249)	0.084	1.273 (0.541, 2.997)	0.581	/	/	/	/
Chronic kidney disease	/	/	0.629 (0.136, 2.909)	0.553	/	/	/	/
Cancer	0.571 (0.031, 10.435)	0.706	/	/	/	/	/	/
Atrial fibrillation	2.000 (0.175, 22.799)	0.577	1.694 (0.608, 4.718)	0.313	/	/	/	/
Transaortic mean gradient	0.962 (0.912, 1.015)	0.155	1.009 (0.988, 1.030)	0.404	/	/	/	/
Left ventricular ejection fraction	0.932 (0.869, 0.999)	**0.048**	1.000 (0.971, 1.029)	0.995	0.922 (0.843, 1.008)	0.075	/	/

p values < 0.05 were statistically significant and presented as bold entries

*For reference: persistently positive

**For reference: persistently negative

***For reference: NYHA I/II

Table 4 Differences in echocardiographic parameters classified by FFR_{CT} changing trend

	Positive to negative (n = 15)	Negative to positive (n = 26)	Grouping unchanged (n = 148)		
			Persistent positive (n = 9)	Persistently negative (n = 139)	p value
Baseline					
V_{max}, m/s	4.4 (4.3, 5.2)	4.85 (4.2, 5.7)	6 (5.3, 6.2)	5.2 (4.4, 5.8)	0.438
PG_{mean}, mmHg	55.0 (48.0, 66.0)	63.0 (44.0, 79.0)	85.0 (69.0, 94.5)	65.5 (48.0, 82.0)	0.426
LV mass, g	279.8 (279.6, 322.9)	232.3 (196.3, 306.8)	245.7 (245.7, 289.1)	275.0 (219.1, 347.9)	0.337
6-month follow-up					
V_{max}, m/s	2.1 (1.6, 2.3)	2.2 (1.9, 2.7)	2.6 (2.3, 2.7)	2.3 (1.9, 2.5)	0.853
PG_{mean}, mmHg	9.0 (6.0, 12.0)	10.5 (8.5, 16.0)	15.0 (11.5, 15.0)	11.5 (9.0, 14.0)	0.842
LV mass, g	200.6 (146.8, 217.4)	176.8 (144.7, 184.7)	141.6 (134.3, 174.7)	197.0 (162.9, 234.6)	0.575
1-year follow-up					
V_{max}, m/s	1.6 (1.6, 1.9)	2.2 (2.1, 2.7)	2.3 (2.1, 2.4)	2.3 (1.9, 2.6)	0.090
PG_{mean}, mmHg	6.0 (5.0, 8.0)	11.5 (9.5, 17.5)	12.0 (10.0, 12.0)	12.0 (9.0, 15.0)	0.078
LV mass, g	212.9 (131.0, 220.6)	209.3 (177.8, 224.8)	212.0 (169.5, 250.3)	196.7 (162.9, 232.3)	0.926

of 19 patients died during a median follow-up of 726.0 (368.8, 1279.3) days. All-cause mortality was similar between the groups of positive to negative and persistently positive (6.7% vs. 0%, p = 0.429) and between the groups of negative to positive and persistently negative (0% vs. 12.9%, p = 0.052). During follow-up, one patient was hospitalized because of angina at 855 days and 1037 days post-procedurally, and got discharge after symptom remission by conservative therapy. In addition, no other myocardial infarction or need for revascularization was found during follow-up.

Discussion

This is one of the few studies to analyze FFR values derived from CT in the setting of TAVI patients. The major findings in our study are as follows: (i) After TAVI procedure, the FFR_{CT} value tended to weakly descend in general, but different variation patterns could be observed in different subgroups; (ii) Patients with compromised coronary flows (i.e., $FFR_{CT} \leq 0.8$) could benefit directly from the correction of AS with the value normalized post-TAVI; (iii) Patients with documented history of CAD might be more prone to a deterioration of FFR_{CT} value from > 0.8 to ≤ 0.8, as well as more severely stenosed and LAD-located lesions; (iiii) Aortic stenosis, but not coronary issues, was likely to be the primary problem to affect hemodynamics and clinical outcomes, as the change of FFR_{CT} failed to be associated with any clinical parameters.

As TAVI is an efficient alternative to surgery across all risk profiles, this progress requires further improvements in aspects that are otherwise not prominent in patients with shorter life expectancy, such as prosthesis durability and the management of concomitant CAD [2]. Concomitant CAD presents in approximately 50% of TAVI patients and was reported to be associated with worse survival post-TAVI [12], but there is no consensus on the timing and criteria for coronary interventions in the setting of TAVI. Evaluation of the severity of coronary stenosis is routinely conducted by invasive coronary angiography, but in patients with AS and the subsequent myocardial hypertrophy, an anatomic-hemodynamic mismatch is more likely to be presented [13]. On the contrary, FFR can assess the functional stenoses of coronary territories, with better major adverse event–free survival than angiography when guiding coronary revascularization in TAVI patients [14]. Invasive FFR variations post-TAVI have been explored in small sample cohorts, and found to acutely improve FFR via lowering of mean aortic pressure, but decrease FFR in another study [15, 16]. Although it is safe and feasible to perform functional assessment with invasive FFR in TAVI patients, the evaluation process needs the injection of adenosine, which bears certain risk of adverse events.

In this study, FFR was evaluated from readily available CTA scans with a validated deep learning platform. Although overall FFR_{CT} values weakly decreased post-TAVI, TAVI seems to play a neutral role considering its different effects in different subgroups: TAVI could weakly but significantly reduce the pre-procedurally negative FFR_{CT} values before discharge, but increased pre-procedurally positive FFR_{CT} values into negative, particularly in LAD and RCA, but not LCx. The slight drop in FFR_{CT} of preoperatively negative ones from 0.8797 to 0.8718 seemed difficult to explain, but the similar changing trend has been shown in invasive FFR values before [17]. Although the cutoff value of FFR_{CT} for PCI treatment in severe AS patients was not settled and generally accepted, a significant drop like this might be too slight to be considered clinically relevant. Importantly, this

special descending trend of FFR_{CT} might need concentration and further validation. However, positive FFR_{CT} experiencing significant increase into negative after TAVI was surprising at first sight. The one possible hypothesis of the augmented FFR_{CT} after TAVI might be the normalization of sympathetic nervous system hyperactivity among AS patients which was reported before [15, 18]. Similar evidences were available in patients with chronic heart failure who had similar left ventricular condition with severe AS patients, showing increased sympathetic outflow to coronary circulation [19]. Therefore, sympathetic hyperactivity might lead to overestimated FFR_{CT} values in physiologically abnormal coronary lesions. After TAVI, the normalization of sympathetic nervous system hyperactivity could cause increase of FFR_{CT} values. Because of limited researches, more data were needed to verify this hypothesis. The different variation patterns of FFR_{CT} in LCx indicated that the change of FFR_{CT} values after TAVI might be related to different anatomical features. The TAVI mainly influenced the coronary perfusion but not the anatomical stenosed severity. Therefore, less impact of TAVI on blood supply of LCx might be related to the relatively lower volume of perfusion in LCx compared with that in LAD and RCA. The FFR_{CT} value is calculated by artificial intelligence via analyzing and contrasting the characteristics of aorta root and coronary lesions on the CTA image, such as the sufficiency of blood flow, the change of arteries' angle, and the characteristics of myocardium. Thus, the characteristic of any change post-TAVI on CTA, primarily blood flow characteristics near the aorta root, will lead to the variation of FFR_{CT} presumably through different coronary perfusions. In our results, different variation patterns could be observed in different subgroups after TAVI, and FFR_{CT} remained stable in 1-year follow-up postoperatively, which indicated the proper time for FFR_{CT} evaluation for TAVI patients might be the time postoperatively rather than preoperatively. Cohort studies had indicated no statistically significant benefit from TAVI plus PCI compared with TAVI alone on short-term and long-term survival or myocardial infarction [20]. Therefore, AS patients with asymptomatic or non-acute CAD might not need progressive treatment. Moreover, using the conventional cutoff of 0.80, the aggressive coronary interventions may be postponed as a seemingly stenosed coronary flow can be improved by the correction of AS. However, this requires the design of newer iterations of devices to consider easy access of coronary ostia for future interventions, which is challengeable so that most PCI were done pre-procedurally.

Although in patients with intermediately stenosed coronary arteries ($50\% \leq \%DS < 70\%$) the value of FFR_{CT} in general stayed clinically unchanged post-TAVI, the severity of %DS as a continuous variable seemed to affect the possibility of FFR_{CT} changing from negative to positive. Thus, we advocate a multifactorial evaluation of the necessity of coronary revascularization in TAVI recipients, including the anatomical and functional characteristics. The failure to correlate the FFR_{CT} changing trend with clinical outcomes in our results might indicate the functional stenoses of coronary arteries in patients with AS might not be the main factor for the clinical prognosis, but the AS [21, 22]. However, it would be interesting to know whether patients with coronary lesions of a FFR_{CT} value ≤ 0.8 post-TAVI would benefit clinically from further coronary interventions, but this is beyond the purpose of our study.

As for predictive factors of FFR_{CT} variation after TAVI, the result indicated that patients with a history of CAD tended to have FFR_{CT} value changed from > 0.80 to ≤ 0.80 after TAVI instead of being > 0.80 constantly. Then, we attempted to identify a cutoff value of %DS on angiography for the need of revascularization in case of FFR_{CT} value turning positive, but failed to determine a value of practical specificity and sensitivity. However, more severely stenosed and LAD-located lesions were at higher risk of FFR_{CT} changing from > 0.80 to ≤ 0.80 after TAVI. Such characteristics deserve attentions since clinical decisions on coronary interventions might be changed due to the increased risk of FFR_{CT} value turning to positive.

This is a single-center retrospective study, which has intrinsic biases and limitations in its design. The failure to establish an association between FFR_{CT} values and clinical events might be due to the limited sample size. Moreover, invasive FFR measurements were not performed as a reference to the FFR_{CT} values used in this study. The stratification of FFR_{CT} values was based on the conventional cutoff of 0.80 obtained in CAD patients. The DEEPVESSEL-FFR platform is currently not as recognized as the HeartFlow (HeartFlow Inc.) platform and was used on relatively limited population with AS in this study [3], but it has undergone a rigorous validation (see Supplement Materials); thus, we believe the FFR_{CT} values in this study are reproducible. Patients in this study might have very high coronary artery calcification scores compared with pure CAD patients, which lead to poor performance of FFR_{CT} analysis, but strict process of CTA selection which had been introduced in method session might improve the final data quality. In addition, studies have shown that no statistical differences of diagnostic accuracy of FFR_{CT} values were found across Agatston score categories [23, 24].

Conclusion

Coronary flows are affected in AS, which can be readily evaluated through FFR_{CT}. The correction of AS by TAVI directly brings improvement in FFR_{CT} values in patients with compromised coronary flow ($FFR_{CT} \leq 0.80$), but may also result in a deterioration of FFR_{CT} values. History of CAD might be an independent risk factor for FFR_{CT} changing from negative to positive after TAVI, especially when the lesion is more severely stenosed and located in LAD. A reliable way to assess

coronary functions and the corresponding cutoff value for a clinically significant lesion in TAVI patients is desirable to guide patient management.

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Declarations

Guarantor The scientific guarantor of this publication is Mao Chen.

Conflict of interest M. Chen and Y. Feng are consultants/proctors of Venus MedTech, MicroPort, and Peijia Medical. D. Mylotte is a consultant/proctor for Medtronic. K. Cao, Y. Yin, and Q. Song are employees of Keya Medical Technology. The other authors do not have disclosures.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
•retrospective
•observational
•performed at one institution

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