ORIGINAL ARTICLE

Determining the Predominant Lesion in Patients With Severe Aortic Stenosis and Coronary Stenoses

A Multicenter Study Using Intracoronary Pressure and Flow

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BACKGROUND: Patients with severe aortic stenosis (AS) often have coronary artery disease. Both the aortic valve and the coronary disease influence the blood flow to the myocardium and its ability to respond to stress; leading to exertional symptoms. In this study, we aim to quantify the effect of severe AS on the coronary microcirculation and determine if this is influenced by any concomitant coronary disease. We then compare this to the effect of coronary stenoses on the coronary microcirculation.

METHODS: Group 1: 55 patients with severe AS and intermediate coronary stenoses treated with transcatheter aortic valve implantation (TAVI) were included. Group 2: 85 patients with intermediate coronary stenoses and no AS treated with percutaneous coronary intervention were included. Coronary pressure and flow were measured at rest and during hyperemia in both groups, before and after TAVI (group 1) and before and after percutaneous coronary intervention (group 2).

RESULTS: Microvascular resistance over the wave-free period of diastole increased significantly post-TAVI (pre-TAVI, 2.71±1.4 mm Hg·cm·s^{-1} versus post-TAVI 3.04±1.6 mm Hg·cm·s^{-1} [P=0.03]). Microvascular reserve over the wave-free period of diastole significantly improved post-TAVI (pre-TAVI 1.88±1.0 versus post-TAVI 2.09±0.8 [P=0.003]); this was independent of the severity of the underlying coronary stenosis. The change in microvascular resistance post-TAVI was equivalent to that produced by stenting a coronary lesion with an instantaneous wave-free ratio of ≤0.74.

CONCLUSIONS: TAVI improves microcirculatory function regardless of the severity of underlying coronary disease. TAVI for severe AS produces a coronary hemodynamic improvement equivalent to the hemodynamic benefit of stenting coronary stenoses with instantaneous wave-free ratio values <0.74. Future trials of physiology-guided revascularization in severe AS may consider using this value to guide treatment of concomitant coronary artery disease.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: aortic valve stenosis ■ diastole ■ hyperemia ■ microcirculation ■ myocardium

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WHAT IS KNOWN

- Patients with severe aortic stenosis undergoing transcatheter aortic valve implantation often have concomitant coronary artery disease. If they present with chest pain or dyspnea, it can be unclear if the coronary stenosis or the aortic valve stenosis is responsible for an individual patient's symptoms.
- It has been demonstrated that hyperemic indices are significantly affected by severe aortic stenosis, with hyperemic flow increasing significantly after transcatheter aortic valve implantation. Resting hemodynamics are less susceptible to this, specifically in the wave-free period of diastole, where it has previously been shown that flow during this period is unchanged post-transcatheter aortic valve implantation.

WHAT THE STUDY ADDS

- Transcatheter aortic valve implantation improves microcirculatory function regardless of the severity of underlying coronary disease.
- This improvement in microcirculatory function is only matched by stenting coronary lesions with an instantaneous wave-free ratio <0.74.
- The predominant lesion affecting microvascular resistance in patients with severe aortic stenosis and coronary stenoses seems to be the aortic stenosis unless the instantaneous wave-free ratio value is ≤0.74.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
CAD	coronary artery disease
FFR	fractional flow reserve
iFR	instantaneous wave–free ratio
PCI	percutaneous coronary intervention
TAVI	transcatheter aortic valve implantation

Patients with severe aortic stenosis (AS) often have coronary artery disease (CAD).[1] If they present with chest pain or dyspnea, it can be unclear if the coronary stenosis or the aortic valve stenosis is responsible for an individual patient's symptoms.

The cause of chest pain or shortness of breath in these patients is a result of an inability of the microcirculation to increase blood flow in response to increased demand. While the effects of both the coronary lesion[2] and the aortic valvular stenosis[3] on the microcirculation have been individually studied, it is not known how the 2 interact when they are present in the same patient, and which is the predominant lesion.

It has been demonstrated that hyperemic indices are significantly affected by severe AS,[4] with hyperemic flow increasing significantly after transcatheter aortic valve implantation (TAVI). Resting hemodynamics are less susceptible to this, specifically in the wave-free period of diastole, where it has previously been shown that flow during this period is unchanged post-TAVI.

This study uses the resting hemodynamics of the wave-free period to determine the relative effects of TAVI and percutaneous coronary intervention (PCI) on myocardial perfusion. Microvascular resistance over the wave-free period has been demonstrated to reflect coronary stenosis severity[5]; with low resistance suggesting a more severe stenosis and higher resistance suggesting a less severe stenosis. It has also been shown that microvascular resistance over the wave-free period is affected by severe AS. In patients with both severe AS and CAD, the relative contribution of each to microvascular resistance is unknown.

In this study, we aim to determine when a patient has severe AS and coronary disease which is the predominant lesion affecting myocardial blood flow. We aim to do this by (1) quantifying the effect of severe AS on the function of the coronary microcirculation and determine if this is influenced by concomitant coronary disease; (2) quantifying the effect of a coronary stenosis on the function of the coronary microcirculation; and (3) determining the severity of coronary stenosis that, when stented, provides equivalent improvement in microcirculatory function as TAVI.

METHODS

The methods and materials that support the findings of this study are available from the corresponding author on reasonable request.

Patient Population

Part 1: 55 patients with severe AS undergoing TAVI with moderate coronary lesions were recruited from 4 European centres (The Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; Amsterdam Medical Center, Amsterdam, the Netherlands; Skane University Hospital, Lund, Sweden; and Aarhus University Hospital, Aarhus, Denmark). The study was approved by an institutional review committee at each site. All patients had prospectively collected combined coronary pressure and flow measurements, with paired measurements pre- and post-TAVI. All patients were scheduled for TAVI on clinical grounds in accordance with clinical guidelines,[6] after a decision at a Heart Team meeting, and gave written informed consent for the study protocol. Exclusion criteria were known nonviable myocardium in the area of the corresponding coronary artery being studied, contra-indication to the administration of adenosine, inability to consent or weight over 200 kg. All patients had concomitant AS and CAD, and physiological assessments were performed in each patient. There was no PCI performed in this group, after Heart Team decision that it was not required before TAVI and enrollment in the study.

Part 2: 85 patients with intermediate coronary lesions undergoing PCI were included from 4 European centres as part of the

IDEAL collaboration[2] (Amsterdam Medical Center, Amsterdam, the Netherlands; The Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; Hospital Clinico San Carlos, Madrid, Spain; and VU University Medical Center, Amsterdam, the Netherlands). The study was approved by an institutional review committee at each site. All patients had combined coronary pressure and flow measurements, with paired measurements pre- and post-PCI. All patients recruited were scheduled for elective coronary angiography with physiological stenosis assessment by fractional flow reserve and gave written informed consent for acquisition of additional physiological data for study purposes. Exclusion criteria were acute myocardial infarction within 48 hours; contraindication to the administration of adenosine; severe valvular heart disease; weight >200 kg; previous coronary artery bypass surgery; vessels with angiographically identifiable myocardial bridging or collateral arteries; and vessels supplying an infarcted territory. All patients in this group underwent PCI as had been determined by the treating clinical team.

Cardiac Catheterization Protocol

In all patients, cardiac catheterization and coronary angiography was performed via either the transradial or transfemoral route at the operator's discretion. A guiding catheter was used to intubate the target artery. Therapeutic dose heparin was administered. A dual pressure and Doppler sensor-equipped 0.014" guidewire was used for all physiological assessments (ComboWire, Volcano Corp, San Diego, CA). The pressure signals were normalized in the aorta before advancing the wire a minimum of 3-vessel diameters distal to the coronary stenosis. Doppler signals were optimized and stabilized to ensure good tracking profiles. All flow measurements were made by experienced operators; the reproducibility of flow measurements in such hands has been previously demonstrated.[7] At this stage, resting pressure and flow measurements were recorded. Hyperemia was then induced using adenosine, either as an intracoronary bolus of 150 µg or an intravenous infusion of 140 µg/kg per minute. Physiological measurements under hyperemic conditions were then recorded. At the end of each recording, the pressure sensor was returned to the catheter tip to ensure that there was no pressure drift. When drift was identified (≥0.02), all measurements were repeated. For TAVI patients, left ventricular pressures were recorded using a pigtail catheter placed in the LV cavity. All patients then either underwent PCI (for patients without AS) or TAVI (for patients with AS). Subsequent to either intervention, the entire protocol was repeated with the wire sited in the same location as the preintervention measurements.

PCI Procedures

Drug-eluting stents were used as standard of care. Optimization using intracoronary imaging and postdilatation were performed at the operator's discretion.

TAVI Procedures

All patients were treated under local anesthesia and conscious sedation. The valves used were either the Edward's Sapien XT/S3 valves (Edwards Lifesciences LCC, Irvine, CA), the Medtronic CoreValve/Evolut-R valves (Medtronic, Inc, Minneapolis, MN), or Lotus valve (Boston Scientific, Natick, MA). Valve choice was at the Heart Team and operator's discretion.

Analysis of Hemodynamic Data

ECG, pressure, and flow velocity signals were processed with the dedicated device console (ComboMap; Volcano Corp, San Diego, CA). Analog output feeds were taken from the pressure-velocity console and ECG, fed into a National Instruments DAQ-Card AI-16E-4, and acquired at 1 kHz with Labview. Data were analyzed offline with a custom software package designed with Matlab (Mathworks, Natick, MA), which permitted phasic analysis including that of the wave-free period. The wave-free period was identified using wave-intensity analysis[7] and used to perform phasic analysis. Coronary pressure, flow, and resistance were measured during resting conditions and during hyperemia.

Microvascular reserve was derived as a metric of improvement in coronary hemodynamics after intervention. This was defined as a ratio of hyperemic microvascular resistance to resting microvascular resistance.

Definitions of other hemodynamic variables were as follows:

$$\text{Instantaneous wave}-\text{free ratio}\,(\text{iFR}) = \frac{Pd_{wfp}}{Pa_{wfp}}$$

$$\text{Hyperemic microvascular resistance}\,(\text{HMR}) = \frac{Pd_h}{v_h}$$

$$\text{Basal microvascular resistance}\,(\text{BMR}) = \frac{Pd_b}{v_b}$$

$$\text{Vasodilator reserve}\,(\text{VDR}) = \frac{BMR}{HMR}$$

$$\text{Wave}-\text{free period resistance}\,(\text{Wfp}-\text{res}) = \frac{Pd_{wfp}}{v_{wfp}}$$

Where Pa=mean aortic pressure; Pd=mean intracoronary pressure distal to a stenosis; Wfp=the wave-free period of diastole; v_h=mean flow velocity distal to a stenosis during hyperemia; v_b=mean flow velocity distal to a stenosis at baseline.

Statistical Methods

Continuous variables are presented as mean and SD unless otherwise stated. Comparisons before and after intervention were performed with a paired *t* test for continuous variables. Paired ordinal categorical data such as LV function were analyzed using the Wilcoxon signed-rank test. The threshold for statistical significance was set at 0.05. Pearson correlation coefficient was used to assess correlations. All analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Population

TAVI Group

Fifty-five patients (81.7 [±5.9] years; 49.1% male) were included. Baseline clinical characteristics are shown in Table 1. The baseline echocardiographic characteristics are summarized in Table 2.

Table 1. Baseline Clinical Characteristics of TAVI Group

	n (%)
Age, y	81.7 (±5.9)
Male	27 (49.1)
Body mass index, kg/m²	27.36 (±5.0)
Diabetes mellitus	16 (29.1)
Hypertension	37 (67.3)
Hyperlipidemia	22 (40.0)
Former smoker	20 (36.4)
Previous myocardial infarction	4 (7.3)
Previous percutaneous coronary intervention	8 (14.5)
Previous coronary artery bypass grafting	3 (5.5)

TAVI indicates transcatheter aortic valve implantation.

PCI Group

Eighty-five patients were included (61.3 [±9.4] years; 74.1% male). Baseline clinical characteristics are shown in Table 3.

Quantitative Coronary Angiography

TAVI Group

Quantitative coronary angiography for the patients undergoing TAVI is summarized in Table 4.

PCI Group

Quantitative coronary angiography for the patients undergoing PCI is summarized in Table 5.

Coronary Physiological Parameters Before and After TAVI

Commonly reported coronary physiological parameters before and after TAVI are summarized in Table 6. There was a significant reduction in fractional flow reserve immediately (P<0.001) post-TAVI, and a significant increase in coronary flow reserve immediately post-TAVI (P=0.03). Instantaneous wave–free ratio (iFR) was unchanged immediately post-TAVI (P=0.80).

Microvascular Resistance Over the Wave-Free Period of Diastole Before and After TAVI

Changes in resistance after TAVI are summarized in Figure 1. Resting resistance over the wave-free period of diastole increased significantly post-TAVI (pre-TAVI 2.71±1.4 mm Hg·cm·s⁻¹ versus post-TAVI 3.04±1.6 mm Hg·cm·s⁻¹ [P=0.03]). Hyperemic resistance over the wave-free period of diastole did not change post-TAVI (pre-TAVI 1.58±0.8 mm Hg·cm·s⁻¹ versus post-TAVI 1.49±0.7 mm Hg·cm·s⁻¹ [P=0.36]). Microvascular reserve over the wave-free period of diastole significantly improved post-TAVI (pre-TAVI 1.88±1.0 versus post-TAVI 2.09±0.8 [P=0.003]).

Table 2. Baseline Echocardiographic Characteristics of TAVI Group

	Pre-TAVI	Post-TAVI	P Value
Peak velocity, cm/s	416.73 (±88.44)	218.38 (±47.60)	<0.001
Peak gradient, mm Hg	70.99 (±28.21)	14.41 (±7.6)	<0.001
Mean gradient, mm Hg	41.78 (±17.84)	10.17 (±5.0)	<0.001
Aortic valve area, cm²	0.69 (±0.23)	1.48 (±0.3)	<0.001
LV systolic function			0.484
Normal	44 (80.0)	44 (80.0)	
Mildly impaired	6 (10.9)	6 (10.9)	
Moderately impaired	2 (3.6)	4 (7.3)	
Severely impaired	3 (5.5)	1 (1.8)	
Left ventricular end-diastolic pressure, mm Hg	17.43 (±7.4)	15.43 (±6.4)	0.03
Paravalvular leak			
None		28 (50.9)	
Mild		23 (41.8)	
Moderate		4 (7.3)	
Severe		0 (0)	

Continuous variables are analyzed using paired t-tests. The categorical variable of LV systolic function was analyzed using the Wilcoxon signed-rank test. LV indicates left ventricular; and TAVI, transcatheter aortic valve implantation.

Improvement in Wave-Free Period Resistance Achieved by TAVI and PCI According to Baseline iFR

Overall, microvascular resistance over the wave-free period improved significantly post-PCI. This improvement was dependent on the baseline iFR value (Figure 2). The more severe the coronary stenosis, the greater the improvement in microvascular resistance. Therefore, microvascular resistance over the wave-free period is a marker of coronary stenosis severity.

Overall, microvascular resistance over the wave-free period improved significantly post-TAVI (Figure 3). This improvement was independent of the baseline iFR value: the improvement in microvascular resistance over the wave-free period post-TAVI is consistent across the spectrum of coronary stenosis severity.

Table 3. Baseline Clinical Characteristics of PCI Group

	n (%)
Age, y	61.3 (±9.4)
Male	63 (74.1)
Diabetes mellitus	22 (25.9)
Hypertension	43 (50.6)
Hyperlipidemia	64 (75.3)
Former smoker	38 (44.7)
Previous myocardial infarction	11 (12.9)

PCI indicates percutaneous coronary intervention.

Table 4. Quantitative Coronary Angiographic Data for TAVI Patients

Target vessel	
LAD	31 (55.5%)
Cx	10 (18.5%)
RCA	14 (26.0%)
Stenosis location	
Proximal	26 (46.3%)
Mid	26 (48.1%)
Distal	3 (5.6%)
Diameter stenosis by QCA, %	56.11 (±11.1)
Area stenosis by QCA, %	79.42 (±9.7)
Stenosis length, mm	17.64 (±9.0)
Minimum luminal diameter, mm	1.22 (±0.4)
Minimum luminal area, mm²	1.32 (±0.9)

Cx indicates circumflex; LAD, left anterior descending; QCA, quantitative coronary angiography; RCA, right coronary artery; and TAVI, transcatheter aortic valve implantation.

Table 5. Quantitative Coronary Angiographic Data for PCI Patients

Target vessel	
LAD	50 (58.8%)
Cx	17 (20.0%)
RCA	18 (21.2%)
Stenosis location	
Proximal	43 (50.6%)
Mid	39 (45.9%)
Distal	3 (3.5%)
Diameter stenosis by QCA, %	62.69 (±13.4)
Area stenosis by QCA, %	85.00 (±9.9)
Stenosis length, mm	20.86 (±11.3)
Minimum luminal diameter, mm	0.92 (±0.4)
Minimum luminal area, mm²	0.76 (±0.6)

Cx indicates circumflex; LAD, left anterior descending; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; and RCA, right coronary artery.

Comparison of the Change in Microvascular Resistance Observed After TAVI and PCI

The average improvement in microvascular resistance over the wave-free period post-TAVI was 19.2±0.5%. Interpolating this data to the improvement of microvascular resistance over the wave-free period post-PCI suggests that at the iFR value 0.74, there is equipoise in the improvement achieved with PCI and TAVI (see Figure 4). That is, stenting lesions with iFR values of 0.74 also provides a 19% improvement in resistance (the same as TAVI). Therefore, the improvement in resistance achieved by PCI seems only able to surpass TAVI when the baseline iFR is <0.74.

DISCUSSION

In this study, we have shown that (1) in patients with severe AS and intermediate coronary lesions, treatment of the valve results in a significant increase in microvascular resistance; (2) this increase is independent of the severity of the underlying coronary lesion; and (3) TAVI for severe AS produces a hemodynamic improvement

equivalent to the hemodynamic benefit of stenting coronary stenoses with iFR values <0.74.

Microvascular Reserve and Coronary Stenoses

Microvascular reserve reflects the ability of the microcirculation to increase the blood supply to the heart in response to increased demand or workload. In patients with coronary disease, this ability to respond to increased work load is related to (1) the severity of the stenosis within the epicardial artery[2] and (2) autoregulation of coronary blood flow[8] and its effect on microvascular resistance. In patients with severe coronary disease, microvascular resistance is relatively lower than in patients with no coronary stenosis (Figure 5).

AS and Coronary Stenosis

In this study, we demonstrate that AS also influences coronary microvascular tone and its ability to respond to stress. In patients with AS, microvascular resistance at rest is significantly lower than that of post-TAVI patients. This suggests that the coronary microcirculation treats AS similarly to a coronary stenosis. As the aortic valve becomes more and more

Table 6. Values of Common Coronary Physiological Indices Pre- and Post-TAVI

	Pre-TAVI	Post-TAVI	*P* Value
Fractional flow reserve	0.86 (±0.08)	0.83 (±0.09)	<0.001
Instantaneous wave–free ratio	0.87 (±0.10)	0.87 (±0.09)	0.80
Coronary flow reserve	1.56 (±0.50)	1.74 (±0.50)	0.03
Whole cycle resting flow (PdPa-flow)	22.54 (±8.86)	23.02 (±10.45)	0.71
Whole cycle hyperemic flow (FFR-flow)	33.44 (±12.69)	38.51 (±16.31)	0.005
Wave-free period resting flow (iFR-flow)	28.29 (±12.77)	27.64 (±16.10)	0.63

Comparisons analyzed using paired *t* tests. FFR indicates fractional flow reserve; iFR, instantaneous wave–free ratio; and TAVI, transcatheter aortic valve implantation.
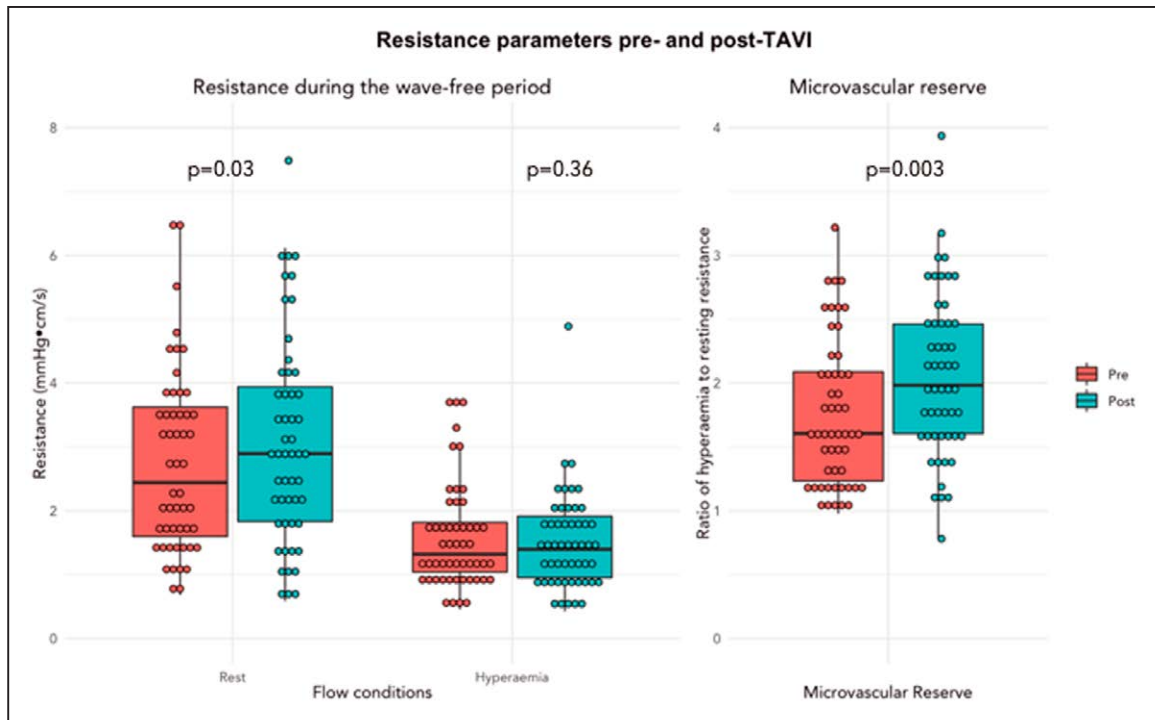
Figure 1. Figure outlining the changes in resting resistance, hyperemic resistance, and microvascular reserve pre- and post-transcatheter aortic valve implantation (TAVI).

constricted, the microcirculation dilates to maintain coronary flow and microvascular reserve is depleted (Figure 5).

Therefore, in patients with severe AS and coronary disease, the microcirculation is adapting to 2 variables that affect blood flow: the stenosed aortic valve and the stenosis in the coronary artery. Resting microvascular resistance and therefore microvascular reserve in these patients is therefore limited by both.

Because the microcirculation treats the 2 stenoses similarly, determining the predominant lesion is akin to attempting to determine which stenosis is predominant in a vessel with tandem lesions. It has been demonstrated that this is not possible with hyperemia due to both stenoses influencing the blood flow across the other.[9] However, it has been demonstrated to be possible to isolate the significance of a specific lesion with iFR.[10]

This finding for tandem lesions can be extrapolated to the TAVI population. In these patients, the tandem lesions are the coronary stenosis and the aortic valvular stenosis. Placing a pressure wire in the vessel distal to the coronary stenosis in a patient with severe AS is therefore analogous to placing a pressure wire between 2 serial lesions
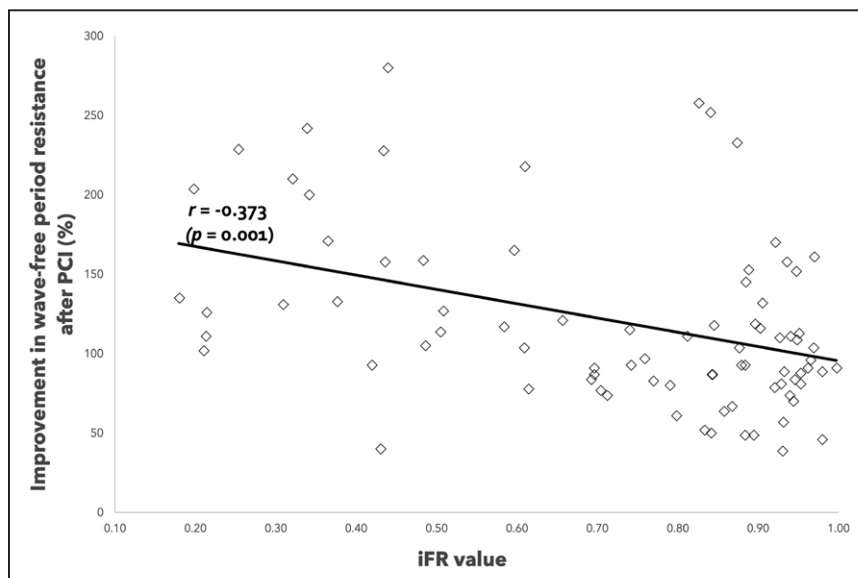
Figure 2. Correlation between underlying coronary stenosis severity (baseline instantaneous wave–free ratio [iFR] value) and improvement in resistance after percutaneous coronary intervention (PCI) with a strongly statistically significant association.
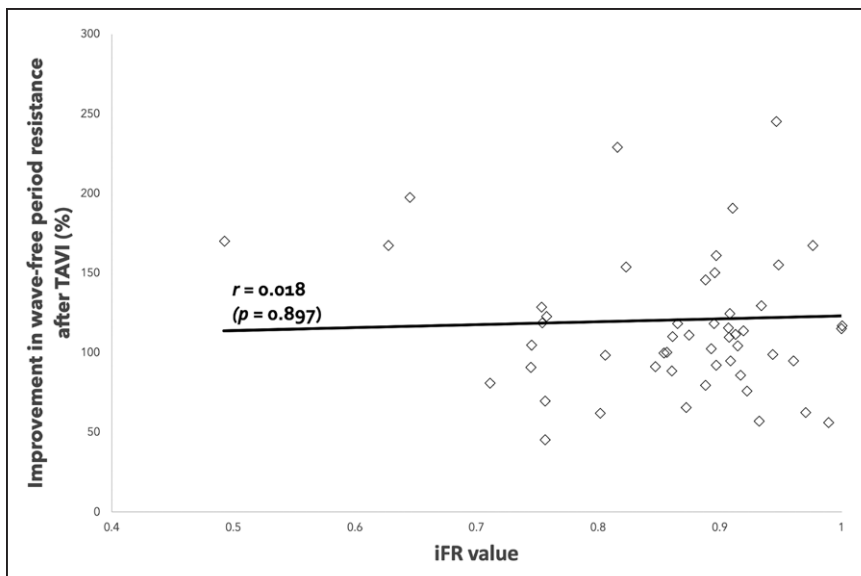
Figure 3. Correlation between underlying coronary stenosis severity (baseline instantaneous wave–free ratio [iFR] value) and improvement in resistance after transcatheter aortic valve implantation (TAVI) with no significant association seen.

in a coronary artery. We have previously demonstrated that hyperemic flow changes significantly post-TAVI suggesting that hyperemic indices cannot be used to isolate coronary stenosis severity in the context of severe AS. However, we have demonstrated that iFR can accurately isolate the coronary stenosis severity independent to the aortic valve in this setting[4]; the iFR pre-TAVI is equivalent to the iFR post-TAVI. Previous studies in the field have also demonstrated identical values of iFR before and after TAVI.[11] The same study also suggested a 15% classification change of coronary stenosis significance by iFR after TAVI, but this is confounded by the use of a conventional 0.89 cut point and also the distribution of iFR values close to this cut point.[12] As in our present study, the iFR and fractional flow reserve values were similar pre-TAVI reflecting the inability of adenosine to augment flow in patients with severe AS.

Post-TAVI, resting microvascular resistance increases because one lesion affecting coronary flow has been treated. It does not normalize, however, as there is a residual coronary stenosis that needs to be accommodated.

The change in microvascular resistance post-TAVI is independent of the underlying coronary stenosis.

Furthermore, in this study, we compare the increase in resting microvascular resistance post-TAVI to the effect of treating a coronary stenosis in a cohort of patients with a coronary stenosis but no AS. When we do this, it can be seen that stenting coronary stenoses with iFR values <0.74 are able to produce increases in microvascular resistance equivalent to that observed by treating the AS. This is likely to be a conservative estimate because treating a coronary lesion in a patient post-TAVI may not lead to equivalent microvascular change; due to factors such as advanced age, left ventricular hypertrophy, and elevated left-ventricular end-diastolic pressure.[13,14] As a result, in patients with severe AS, the coronary stenosis may have to be even more severe to achieve similar increases in microvascular resistance as those seen by treating the AS. This would suggest that in patients with AS and coronary disease the predominant lesion is the aortic valve unless the coronary stenosis has an iFR value <0.74.
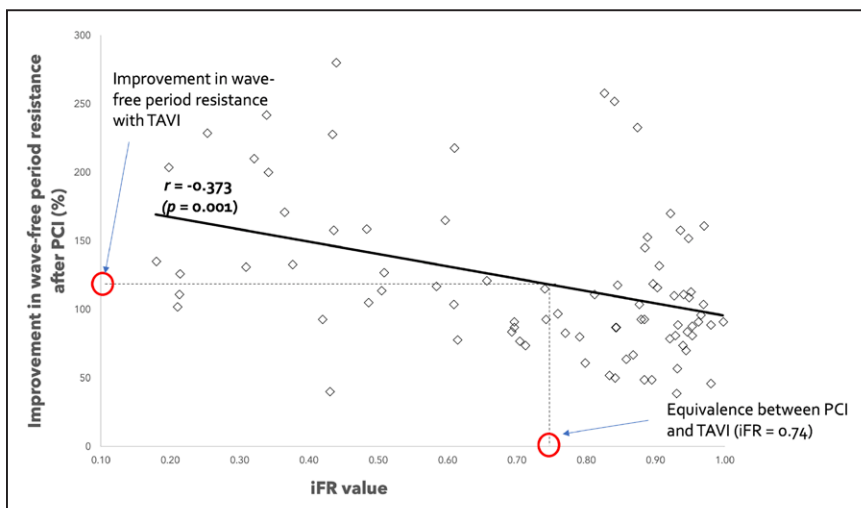

Figure 4. Correlation between underlying coronary stenosis severity (baseline instantaneous wave–free ratio [iFR] value) and improvement in resistance after percutaneous coronary intervention (PCI). When the improvement in resistance achieved with transcatheter aortic valve implantation (TAVI) is interpolated, equipoise between PCI and TAVI is seen at iFR values of 0.74.
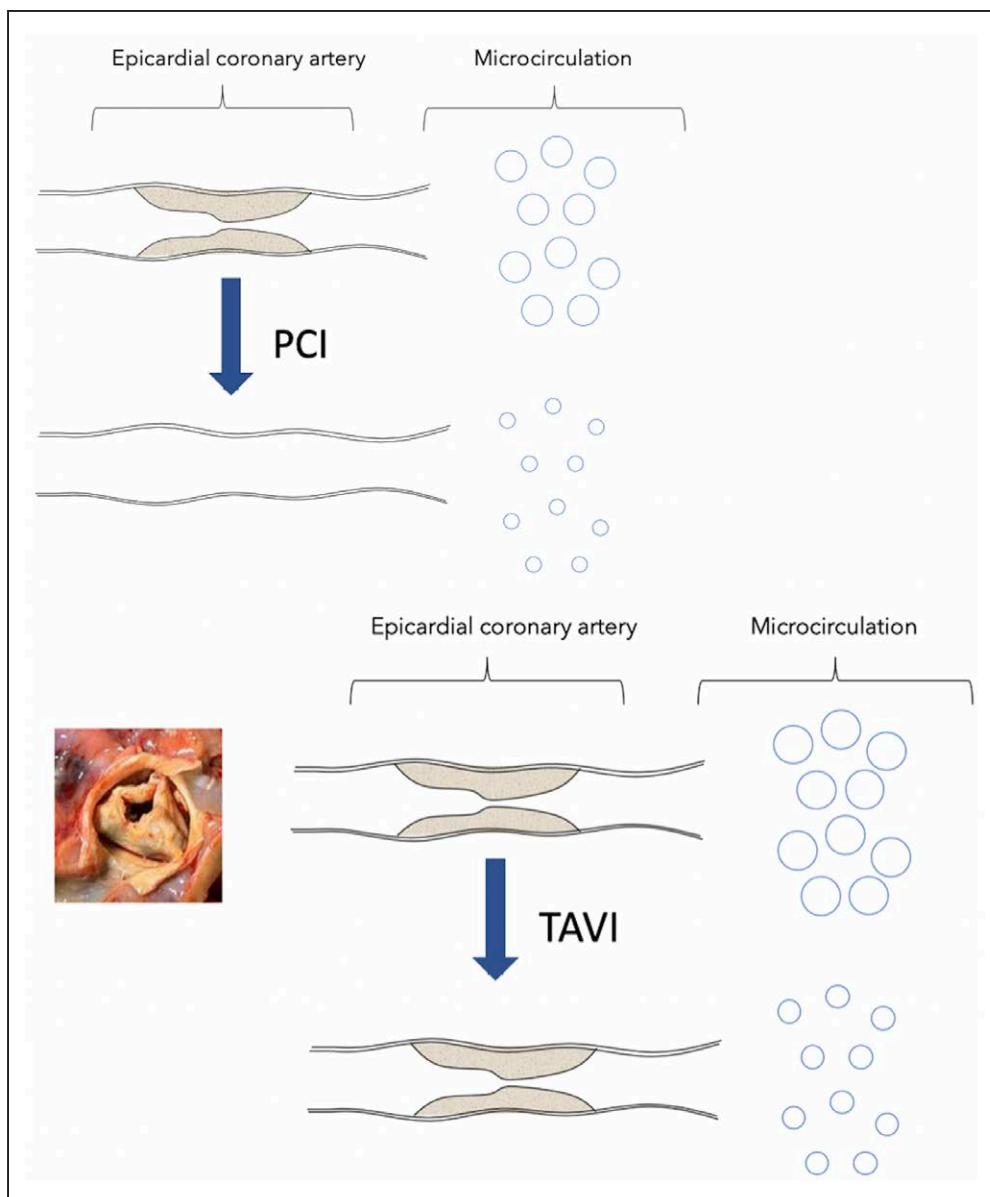
Figure 5. Figure outlining coronary autoregulation in patients with coronary stenoses and aortic stenosis.
In the top, a patient with a severe coronary stenosis; here, the microcirculation is relatively dilated at rest to maintain coronary flow. In these patients, when the need arises to increase coronary flow further, the capacity of the microcirculation to dilate further to increase flow is limited; therefore, the difference between resting and hyperemic flow (microvascular reserve) is small. In patients with no coronary stenosis, or after percutaneous coronary intervention (PCI), the opposite is true. In these patients, the microcirculation is relatively constricted. Therefore, when the need arises to increase coronary flow further, the capacity of the microcirculation to dilate further to increase flow is large; and the difference between resting and hyperemic flow (microvascular reserve) is also large, resulting in greater microvascular reserve. In the bottom, a patient with coronary stenosis and aortic stenosis. As the aortic valve stenoses, so the microcirculation dilates to maintain coronary flow and microvascular reserve is depleted. Therefore, in patients with severe aortic stenosis and coronary disease, the microcirculation is adapting to 2 variables that affect blood flow: the stenosed aortic valve and the stenosis in the coronary artery. Post-transcatheter aortic valve implantation (TAVI), resting microvascular resistance increases because one lesion affecting coronary flow has been treated. It does not normalize, however, as there is a residual coronary stenosis that needs to be accommodated.

Clinical Implications

It is not uncommon for patients with severe AS referred for TAVI to have concomitant CAD.[15] Both conditions can present with angina or dyspnea on exertion. It can therefore be challenging for clinicians to determine which lesion is predominantly responsible for an individual patient's presentation. There is currently no clear evidence that PCI before TAVI improves clinical outcomes[16] but the importance of accurately assessing the functional significance of coronary disease in these patients is becoming increasingly important as TAVI is being offered to younger, lower-risk patients.

Our study suggests that in such patients, coronary physiology can help to clarify the situation. In patients

with severe AS and coronary lesions, if the iFR value is >0.74, then it is likely that TAVI will lead to a greater improvement in coronary hemodynamics than PCI—and may therefore be the preferred initial strategy. Conversely, if the iFR value is <0.74, then the coronary stenosis may provide a greater contribution to the patient's hemodynamic status. In such a situation, the treating clinician may give greater consideration to treating the coronary lesion in addition to the valve.

This iFR value of 0.74 is not designed to be interpreted as a hard cut point to guide PCI or defer TAVI. Rather, it is more intended to provide a framework for clinicians when treating this challenging patient cohort; when it is unclear whether the aortic valve stenosis or coronary stenosis is the major factor in the patient's presentation. Ultimately, in the absence of robust randomized data in this field, the decision of whether to perform PCI in patients with severe AS scheduled for TAVI must be undertaken on a case by case basis and after the deliberation of the Heart Team. This study suggests iFR may add to these deliberations, along with other factors such as the location of the coronary stenosis, the amount of subtended myocardium, suitability for dual antiplatelet therapy,[17] the ability to access the coronary ostia post-TAVI and the patient's symptoms.

Our findings should be considered hypothesis-generating, and the true clinical value of intracoronary physiology in patients with severe AS will only be appreciated when tested in prospective fashion in a clinical trial.

Limitations

The analysis performed in this study compared the hemodynamic benefit of TAVI with the hemodynamic benefit of PCI. The patients undergoing PCI did not have severe AS, and there were other baseline differences in the groups. These differences are likely to underestimate the true effect of TAVI on coronary flow.[18–20]

Our post-TAVI measurements were all made within the same cath-lab procedure, immediately after the aortic valve had been replaced. This helped to minimize the effect of any potential confounding factors and to truly isolate the effect of the TAVI on coronary hemodynamics. It is possible that there would be further longer-term hemodynamic benefits of TAVI, which would be seen with regression of left ventricular mass and remodeling of the ventricle. We cannot comment on this from our study, but it is the subject of ongoing research. Regardless, the decision to intervene on a coronary stenosis in the context of AS is clinically most relevant before valve treatment, suggesting that the acute effect of TAVI on the microcirculation is most relevant for this analysis and in clinical practice.

We have demonstrated that, in the presence of both AS and CAD, TAVI improves microcirculatory perfusion. However, we cannot tell if (1) concomitant treatment of coronary artery stenosis with percutaneous intervention would have afforded additional benefits; (2) or, if in fact treating CAD would have reduced the benefits of TAVI on microcirculation, as it is conceivable that the negative effects of severe AS could be more prominent in the presence of concomitant CAD.

A larger proportion of patients in the PCI group had more severe coronary lesions with lower iFR values than in the TAVI group. Nevertheless, our patients were representative of a clinical population with severe AS and CAD who were referred for TAVI.

Conclusions

TAVI improves microcirculatory function regardless of the severity of underlying coronary disease. TAVI for severe AS produces a coronary hemodynamic improvement equivalent to the hemodynamic benefit of stenting coronary stenoses with iFR values <0.74. Future trials of physiology-guided revascularization in severe AS may consider using this value to guide treatment of concomitant CAD.

REFERENCES

1. Goel SS, Ige M, Tuzcu EM, Ellis SG, Stewart WJ, Svensson LG, Lytle BW, Kapadia SR. Severe aortic stenosis and coronary artery disease—implications for management in the transcatheter aortic valve replacement era: a comprehensive review. *J Am Coll Cardiol*. 2013;62:1–10. doi: 10.1016/j.jacc.2013.01.096

2. Nijjer SS, de Waard GA, Sen S, van de Hoef TP, Petraco R, Echavarría-Pinto M, van Lavieren MA, Meuwissen M, Danad I, Knaapen P, et al. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. *Eur Heart J*. 2016;37:2069–2080. doi: 10.1093/eurheartj/ehv626

3. Wiegerinck EM, van de Hoef TP, Rolandi MC, Yong Z, van Kesteren F, Koch KT, Vis MM, de Mol BA, Piek JJ, Baan J Jr. Impact of aortic valve stenosis on coronary hemodynamics and the instantaneous effect of transcatheter aortic valve implantation. *Circ Cardiovasc Interv*. 2015;8:e002443. doi: 10.1161/CIRCINTERVENTIONS.114.002443

4. Ahmad Y, Götberg M, Cook C, Howard JP, Malik I, Mikhail G, Frame A, Petraco R, Rajkumar C, Demir O, et al. Coronary hemodynamics in patients with severe aortic stenosis and coronary artery disease undergoing transcatheter aortic valve replacement: implications for clinical indices of coronary stenosis severity. *JACC Cardiovasc Interv*. 2018;11:2019–2031. doi: 10.1016/j.jcin.2018.07.019

5. Sen S, Asrress KN, Nijjer S, Petraco R, Malik IS, Foale RA, Mikhail GW, Foin N, Broyd C, Hadjiloizou N, et al. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). *J Am Coll Cardiol*. 2013;61:1409–1420. doi: 10.1016/j.jacc.2013.01.034

6. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, et al; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791. doi: 10.1093/eurheartj/ehx391

7. Davies JE, Whinnett ZI, Francis DP, Manisty CH, Aguado-Sierra J, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH, et al. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation*. 2006;113:1768–1778. doi: 10.1161/CIRCULATIONAHA.105.603050

8. de Waard GA, Cook CM, van Royen N, Davies JE. Coronary autoregulation and assessment of stenosis severity without pharmacological vasodilation. *Eur Heart J*. 2018;39:4062–4071. doi: 10.1093/eurheartj/ehx669

9. Gould KL, Kirkeeide R, Johnson NP. Coronary branch steal: experimental validation and clinical implications of interacting stenosis in branching coronary arteries. *Circ Cardiovasc Imaging*. 2010;3:701–709. doi: 10.1161/CIRCIMAGING.110.937656

10. Nijjer SS, Sen S, Petraco R, Escaned J, Echavarria-Pinto M, Broyd C, Al-Lamee R, Foin N, Foale RA, Malik IS, et al. Pre-angioplasty instantaneous wave-free ratio pullback provides virtual intervention and predicts hemodynamic outcome for serial lesions and diffuse coronary artery disease. *JACC Cardiovasc Interv*. 2014;7:1386–1396. doi: 10.1016/j.jcin.2014.06.015

11. Scarsini R, Pesarini G, Zivelonghi C, Piccoli A, Ferrero V, Lunardi M, Gottin L, Zanetti C, Faggian G, Ribichini F. Physiologic evaluation of coronary lesions using instantaneous wave-free ratio (iFR) in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *EuroIntervention*. 2018;13:1512–1519. doi: 10.4244/EIJ-D-17-00542

12. Sen S, Ahmad Y, Davies J. Assessing coronary disease in patients with severe aortic stenosis: the need for a 'valid' gold standard for validation studies? *EuroIntervention*. 2018;13:1499–1502. doi: 10.4244/EIJV13I13A240

13. van de Hoef TP, Nolte F, Rolandi MC, Piek JJ, van den Wijngaard JPHM, Spaan JAE, Siebes M. Coronary pressure-flow relations as basis for the understanding of coronary physiology. *J Mol Cell Cardiol*. 2012;52:786–793. doi: 10.1016/j.yjmcc.2011.07.025

14. Broyd CJ, Sen S, Mikhail GW, Francis DP, Mayet J, Davies JE. Myocardial ischemia in aortic stenosis: insights from arterial pulse-wave dynamics after percutaneous aortic valve replacement. *Trends Cardiovasc Med*. 2013;23:185–191. doi: 10.1016/j.tcm.2012.12.001

15. Iung B. Interface between valve disease and ischaemic heart disease. *Heart*. 2000;84:347–352. doi: 10.1136/heart.84.3.347

16. Kotronias RA, Kwok CS, George S, Capodanno D, Ludman PF, Townend JN, Doshi SN, Khogali SS, Généreux P, Herrmann HC, et al. Transcatheter aortic valve implantation with or without percutaneous coronary artery revascularization strategy: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6:e005960. doi: 10.1161/JAHA.117.005960

17. Ahmad Y, Demir O, Rajkumar C, Howard JP, Shun-Shin M, Cook C, Petraco R, Jabbour R, Arnold A, Frame A, et al. Optimal antiplatelet strategy after transcatheter aortic valve implantation: a meta-analysis. *Open Heart*. 2018;5:e000748. doi: 10.1136/openhrt-2017-000748

18. Layland J, Wilson AM, Whitbourn RJ, Burns AT, Somaratne J, Leitl G, Macisaac AI. Impact of right atrial pressure on decision-making using fractional flow reserve (FFR) in elective percutaneous intervention. *Int J Cardiol*. 2013;167:951–953. doi: 10.1016/j.ijcard.2012.03.087

19. Dixon JA, Spinale FG. Myocardial remodeling: cellular and extracellular events and targets. *Annu Rev Physiol*. 2011;73:47–68. doi: 10.1146/annurev-physiol-012110-142230

20. Heusch G. Alpha-adrenergic coronary vasoconstriction in humans. *J Am Coll Cardiol*. 2010;55:1278; author reply 1278–1278; author reply 1279. doi: 10.1016/j.jacc.2009.09.067