With progressive outflow obstruction in aortic valve stenosis (AS), myocardial adaptations ensue to maintain adequate left ventricular (LV) output. These compensatory mechanisms lead to hypertrophy with increased compression of the intramural microcirculation, especially at the subendocardium. We assessed coronary wave intensity and phasic flow velocity patterns to unravel changes in cardiac–coronary interaction because of transcatheter aortic valve implantation (TAVI).

**Background**—Aortic valve stenosis (AS) can cause angina despite unobstructed coronary arteries, which may be related to increased compression of the intramural microcirculation, especially at the subendocardium. We assessed coronary wave intensity and phasic flow velocity patterns to unravel changes in cardiac–coronary interaction because of transcatheter aortic valve implantation (TAVI).

**Methods and Results**—Intracoronary pressure and flow velocity were measured at rest and maximal hyperemia in undiseased vessels in 15 patients with AS before and after TAVI and in 12 control patients. Coronary flow reserve, systolic and diastolic velocity time integrals, and the energies of forward (aorta-originating) and backward (microcirculatory-originating) coronary waves were determined. Coronary flow reserve was 2.8±0.2 (mean±SEM) in control and 1.8±0.1 in AS (P<0.005) and was not restored by TAVI. Compared with control, the resting backward expansion wave was 45% higher in AS. The peak of the systolic forward compression wave was delayed in AS, consistent with a delayed peak aortic pressure, which was partially restored after TAVI. The energy of forward waves doubled after TAVI, whereas the backward expansion wave increased by >30%. The increase in forward compression wave with TAVI was related to an increase in systolic velocity time integral. AS or TAVI did not alter diastolic velocity time integral.

**Conclusions**—Reduced coronary forward wave energy and systolic velocity time integral imply a compromised systolic flow velocity with AS that is restored after TAVI, suggesting an acute relief of excess compression in systole that likely benefits subendocardial perfusion. Vasodilation is observed to be a major determinant of backward waves. (Circ Cardiovasc Interv. 2016;9:e002356. DOI: 10.1161/CIRCINTERVENTIONS.114.002356.)

**Key Words:** aortic valve stenosis ■ cardiac–coronary interaction ■ coronary flow ■ transcatheter aortic valve implantation ■ wave intensity
WHAT IS KNOWN

- Patients with aortic valve stenosis frequently have exertional angina despite unobstructed coronary arteries.
- Myocardial compensatory remodeling associated with progressive outflow obstruction in aortic valve stenosis alters coronary–ventricular coupling, which may adversely affect coronary flow waveforms.
- Transcatheter aortic valve implantation immediately improves ventricular mechanics and contraction pattern.

WHAT THE STUDY ADDS

- Coronary flow accelerating forward and backward waves are intensified immediately after transcatheter aortic valve implantation.
- Aortic valve stenosis induces depressed systolic coronary flow and delays peak aortic pressure and the associated peak of the flow accelerating forward wave.
- Transcatheter aortic valve implantation largely reduces the delay and restores systolic coronary flow, thereby improving subendocardial perfusion, which mechanistically may contribute to relief of anginal complaints.

microvascular blood pressures, causing systolic flow impedance, which normally is partly counteracted by the systolic $P_s$$^{13}$ However, systolic LV pressure in AS far exceeds systolic $P_s$, and systolic flow impediment is less compensated. TAVI relieves the pressure gradient across the aortic valve, and one may expect an immediate change in especially the systolic coronary flow waveform.

Wave intensity analysis (WIA) allows studying coronary pressure and flow velocity waveforms in terms of coincident forward traveling waves arriving via the aorta and backward traveling microcirculatory-generated waves.$^{15}$ The direct effect of TAVI has been investigated previously with WIA,$^{16}$ but significant changes were reported only for the diastolic microcirculatory-generated wave.

Based on the contraction–coronary perfusion interaction, we hypothesized that by reducing LV outflow resistance, TAVI promptly induces a rise in the forward waves from the aorta into the coronary arteries. Because the forward wave at the beginning of systole drives the rise in systolic flow, this would principally benefit subendocardial perfusion.

Methods

Fifteen patients with AS (7 male) and angiographically unobstructed coronary arteries were included. TAVI was indicated according to international recommendations. Exclusion criteria were any previous coronary intervention in the study vessel or severely impaired renal function. Twelve patients without AS (9 male), scheduled for elective percutaneous coronary intervention in a different vessel, formed the control group. Exclusion criteria were subtotal or serial lesions, significant left main coronary artery stenosis, recent myocardial infarction (<6 weeks), prior cardiac surgery, or severe heart failure. The local medical ethics committee approved the study protocol, and all patients gave written informed consent.

Instrumentation

All intracoronary data were acquired during cardiac catheterization using a femoral artery approach. $P_a$ was obtained via a 6-F or 7-F guiding catheter. Intracoronary pressure ($P_c$) and flow velocity ($U$) were measured with a 0.014-in dual-sensor guidewire (ComboWire XT; Volcano Corp, San Diego, CA). In the control group, LV pressure was measured simultaneously with a 5-F pigtail catheter. The hemodynamic signals were processed with the associated instrument console (ComboMap; Volcano Corp, San Diego, CA) and stored for offline analysis.

Hemodynamic Measurements

All patients were pretreated with antiplatelet therapy and were heparinized (5000 IU). In the control group, nitroglycerin (0.1 mg, intracoronary) was administered. In the AS patients, hemodynamic measurements were obtained just before and immediately after the TAVI procedure. Intracoronary signals were obtained in an angiographically unobstructed vessel. Once the sensor-equipped guidewire was positioned and an optimal and stable velocity signal was obtained, hyperemia was induced by a 40 μg intracoronary bolus of adenosine. In 4 AS patients, the guidewire tip was advanced into the LV before TAVI to measure LV pressure for clinical purposes.

Transcatheter Aortic Valve Implantation

A temporary pacing wire was advanced into the right ventricle via a 7-F sheath in the femoral vein. A 7-F arterial sheath was inserted for angiography and for the coronary measurements with a guiding catheter. An 8-F sheath was inserted in the other femoral artery for balloon valvuloplasty and valve implantation. Nine patients were treated with the CoreValve Revalving System (Medtronic, Minneapolis, MN) and 6 patients with the Edwards SAPIEN/SAPIENXT bioprosthesis (Edwards Lifesciences, Irvine, CA) at the discretion of the operator. The procedure was performed under general anesthesia (n=4) or with local anesthesia in combination with a mild systemic sedative (n=11). Thoracic aortic echocardiography was performed preprocedurally and 2 to 5 days after TAVI.

Data Analysis

Quantitative coronary angiography (QAngio XA 7.2; Medis Medical Imaging Systems, Leiden, The Netherlands) was performed to obtain the diameter reduction of the study vessel.

Hemodynamic signals were analyzed using a custom-made program (Delphi v. 2010, Embarcadero, CA). Two to 5 consecutive representative beats were selected at baseline and 2 at peak hyperemia. Arterial pulse pressure (PP) was assessed from intracoronary pressure. Microvascular resistance (MR) was defined as the ratio between $P_s$ and $U$. Fractional flow reserve was calculated as the ratio of $P_s$ and $P_a$ at maximum hyperemia and CFR as the ratio between flow velocity at hyperemia and baseline. DTF was expressed as the percent duration of diastole in a cardiac cycle. Systolic and diastolic velocity time integrals (VTI) were quantified by the respective areas under the velocity curve. The beginning of diastole was derived from the ECG.

Net wave intensity ($dW$) was calculated as the product of incremental changes in local pressure ($dP$) and flow velocity ($dU$)$^{15}$ and ensemble-averaged over the selected beats as previously described.$^{17}$ Forward traveling waves arriving via the aorta and backward traveling microcirculatory-generated waves were separated using coronary wave speed as determined by the sum-of-squares technique.$^{18}$ Because wave speed during hyperemia is underestimated by this technique,$^{19}$ baseline wave speed was used for WIA at maximum hyperemia.$^{20}$

Four dominant coronary waves can typically be recognized within the cardiac cycle: the backward and forward compression waves.

WHAT THE STUDY ADDS

- Coronary flow accelerating forward and backward waves are intensified immediately after transcatheter aortic valve implantation.
- Aortic valve stenosis induces depressed systolic coronary flow and delays peak aortic pressure and the associated peak of the flow accelerating forward wave.
- Transcatheter aortic valve implantation largely reduces the delay and restores systolic coronary flow, thereby improving subendocardial perfusion, which mechanistically may contribute to relief of anginal complaints.
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=12)</th>
<th>AS (n=15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56±9</td>
<td>82±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>9 (75)</td>
<td>7 (47)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diameter reduction, %</td>
<td>19±9</td>
<td>12±5</td>
<td>0.06</td>
</tr>
<tr>
<td>Diameter at site of measurements, mm</td>
<td>2.2±0.6</td>
<td>3.0±0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Study vessel (LAD/LCX/RCA)</td>
<td>6/5/1</td>
<td>13/2/0</td>
<td></td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (8)</td>
<td>1 (7)</td>
<td>0.68</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (58)</td>
<td>8 (53)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7 (58)</td>
<td>1 (7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>1 (8)</td>
<td>2 (13)</td>
<td>1.00</td>
</tr>
<tr>
<td>Smoking history</td>
<td>4 (30)</td>
<td>4 (27)</td>
<td>1.00</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>1 (8)</td>
<td>6 (40)</td>
<td>0.09</td>
</tr>
<tr>
<td>Statins</td>
<td>10 (83)</td>
<td>6 (40)</td>
<td>0.047</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>10 (83)</td>
<td>6 (40)</td>
<td>0.047</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>3 (25)</td>
<td>3 (20)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or n (%). ACE indicates angiotensin-converting enzyme; AS, aortic valve stenosis; LAD, left anterior descending artery; LCX, left circumflex; and RCA, right coronary artery.

Table 2. Echocardiographic Variables of AS Group (n=14)

<table>
<thead>
<tr>
<th></th>
<th>Before TAVI</th>
<th>After TAVI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak gradient, mm Hg</td>
<td>72.17±18.5</td>
<td>18.9±7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean gradient, mm Hg</td>
<td>47.7±1.5</td>
<td>10.8±4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic valve area, cm²</td>
<td>0.79±0.17</td>
<td>2.00±0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effective orifice area index</td>
<td>0.42±0.08</td>
<td>1.1±0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td></td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>10</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Systolic LV function</td>
<td></td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diastolic LV function</td>
<td></td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>No information</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM or frequency. AS indicates aortic valve stenosis; LV, left ventricle; and TAVI, transcatheter aortic valve implantation.

Results

Patient Characteristics

Patient characteristics are depicted in Table 1. Subjects in the control group were younger and differed somewhat in distribution of comorbidities and medication. All AS patients had concentric LV hypertrophy. As summarized in Table 2, TAVI normalized aortic valve variables assessed by echocardiography. One patient did not survive the TAVI procedure for >24 hours. Postprocedure echocardiography data therefore include 14 patients.

Hemodynamics

Figure 1 shows representative examples of coronary hemodynamic signals and associated wave intensity obtained at rest (A) and peak hyperemia (B). In the control subject (left), a characteristic biphasic flow velocity waveform is present, with symmetrical dips at the beginning and end of systole. In the AS patient before TAVI (middle), a lower early systolic dip and less pronounced late systolic dip are apparent, especially during hyperemia. After TAVI (right), the mid-systolic velocity peak is much more evident with a clear late systolic dip. Mean P was similar in all conditions, whereas PP increased after TAVI. In general, peak P appears delayed both before and after TAVI. The corresponding net wave intensity profile (thick line) and its forward and backward components illustrate the increased energy of the dominant coronary waves during hyperemia that was further augmented after TAVI.

Mean systemic and coronary hemodynamic variables are summarized in Figure 2. Heart rate remained relatively constant across all groups and conditions. The absence of a significant stenosis was confirmed by a diagnostically non-significant fractional flow reserve >0.9. Left ventricular end-diastolic pressure (LVEDP) was 8.4±2.4 mm Hg in the control group and 20.9±1.7 mm Hg (P<0.001) in those 4 pre-TAVI AS cases where LV pressure was measured. Also, peak LV pressure tended to be higher in the presence of AS (157±8 versus141±4 mm Hg).

After Bonferroni adjustment, primary coronary hemodynamic variables were similar between all groups. (Symbols in parentheses indicate significance before Bonferroni adjustment.) Distal vasodilatation induced a 68% decrease in MR in
the control group and a 50% decrease in the AS group before and after TAVI ($P<0.001$). Hyperemic flow velocity was enhanced in all groups compared with baseline ($P<0.001$), with a small reduction in $P_a$ in the control group and $P_d$ in all groups ($P<0.02$). However, CFR was 34% lower in the AS group compared with control (1.8±0.1 versus 2.8±0.2; $P<0.0024$) and did not improve after TAVI. PPd increased significantly after TAVI from 64±5 to 76±4 mm Hg ($P<0.04$).

**Coronary Flow Velocity Pattern**

Characteristics of the coronary flow velocity profile are depicted in Figure 3. DTF remained unchanged for all groups, at rest and hyperemia. VTI$_{sys}$ in AS was higher than in control at rest (6.0±0.5 versus 2.9±0.7 cm; $P<0.02$) and increased after TAVI both at rest (from 5.9±0.5 to 7.7±0.8 cm) and hyperemia (to 15.6±1.5 cm; $P<0.02$). Similarly, VTI$_{dia}$ in AS pre- and post-TAVI was higher than in control ($P<0.001$) and increased further during hyperemia ($P<0.001$). The difference in VTI$_{sys}$ was associated with a reduction in early and peak systolic velocity (Figure 4). The flow velocity dip in early systole was lower in AS compared with control both at rest (4.4±0.4 versus 7.1±0.9 cm/s; $P<0.01$) and hyperemia (6.3±1.2 versus 20.1±3.8 cm/s; $P<0.005$). TAVI increased those values to 6.6±0.7 cm/s at rest and to 13.5 cm/s at hyperemia ($P<0.05$). Peak systolic flow velocity tended to be lower in AS compared with control at peak hyperemia (34.7±3.0 versus 46.0±5.4 cm/s) and increased by almost 40% to 49.8 cm/s after TAVI ($P<0.01$).

**Coronary Wave Intensity in Relation to Pulsatile Hemodynamics**

Coronary wave speed averaged 23±3 m/s in the control group, 18±2 m/s in the AS group before TAVI and 21±2 m/s after TAVI, with no significant differences between the groups. The energies of the compression waves in AS were equivalent
to those in the control group (Figure 5), whereas the BEW at rest tended to be higher in the AS group (9.3±1.2 versus 6.1±0.6×10³ J·m⁻²·s⁻²). In general, coronary wave energies increased with hyperemia, except for the forward expansion wave. Differences between rest and hyperemic values of the BEW in AS pre- and post-TA VI no longer reached significance after Bonferroni correction (P<0.009). As expected, removal of the outflow obstruction especially augmented the forward waves (Figure 5). Baseline FCW energy was moderately related to the AS valve area (r=0.40, P<0.05) and almost doubled after TAVI (from 6.2±0.6 to 12.3±1.4×10³ J·m⁻²·s⁻² at rest and from 10.1±1.3 to 18.4±1.9×10³ J·m⁻²·s⁻² at hyperemia; P<0.001). Similarly, the forward expansion wave increased more than 2-fold (from 1.7±0.5 to 6.3±1.5×10³ J·m⁻²·s⁻² at rest and from 1.7±0.5 to 9.2±1.4×10³ J·m⁻²·s⁻² at peak hyperemia; P<0.01). No changes in the BCW were observed.

However, TAVI augmented the BEW by 32% at rest (from 9.3±1.2 to 12.4±1.6×10³ J·m⁻²·s⁻²) and by 42% at hyperemia (from 13.5±1.3 to 19.2±2.5×10³ J·m⁻²·s⁻²), although this trend was no longer significant after Bonferroni adjustment. The hyperemic-to-rest BEW reserve was 3.3±0.3 in the control group, but only 1.7±0.2 in AS (P<0.005) and unchanged by TAVI. Notably, the BEW reserve was strongly related to CFR, with no effect of group membership (Figure 6). Similarly, the mixed-effects model confirmed that the BEW was significantly associated with the corresponding ratio for VTIdia with group as a significant factor (not shown). The increase in the FCW after TAVI was strongly associated with an increase in VTIdia both at rest (r=0.80; P<0.002) and hyperemia (r=0.63; P<0.05), whereas no significant relation was found between respective changes in BEW energy and VTIdia (Figure 7).

As illustrated in Figure 8, the FCW not only increased with coronary PP after TAVI (r=0.43, P<0.02 at rest, r=0.65, P<0.0005 at hyperemia), but the delayed time of peak FCW in the AS group (110 ms at rest and 70 ms at hyperemia, P<0.0005 compared with control) was shortened after TAVI to 50 and 23 ms, respectively (P<0.008). Moreover, the time of peak FCW was associated with the time of peak Pa both at rest (r=0.65, P<0.02) and hyperemia (r=0.42, P<0.02). Mixed-effect analysis demonstrated a significant influence of group membership in all relationships (P<0.0005, not shown).

**Discussion**

This study demonstrates that coronary flow velocity is depressed in early and mid-systole in AS and restored by TAVI, suggesting a relief of subendocardial compression in systole. WIA revealed a delayed systolic FCW in AS which correlated with a delayed peak Pa. These delays were substantially shortened after TAVI, and the energy of both forward traveling waves essentially doubled, in correspondence with an increased PP. Similarly, the diastolic flow accelerating BEW improved substantially after TAVI, although the response to hyperemia remained compromised as evidenced by a consistently lower CFR and hyperemic-to-rest BEW reserve. These changes point to a normalization of cardiac–coronary interaction induced by TAVI, despite the impediment as a result of the still present LV hypertrophy.

**Effect of AS and TAVI on Coronary Flow Velocity and CFR**

Patients treated by TAVI rapidly experience relief from angina after valve replacement. Angina in AS is related
to subendocardial ischemia resulting from excess systolic compression of the microcirculation close to the pressure-overloaded LV cavity. The observed changes in coronary flow velocity pattern and respective wave energies reflect these mechanisms of cardiac–coronary interaction causing ischemia.

By removing the outflow obstruction, TAVI lowers cardiac work, extravascular coronary resistance, or both. Consequently, one may expect a decreased baseline and increased hyperemic flow velocity after TAVI. However, mean flow velocities were unchanged by TAVI, and CFR remained below 2 in our AS patients. Camuglia et al recently also observed similar CFR levels as in the present study, with no acute changes after TAVI. Hence, an improved clinical condition is most likely the result of perfusion redistribution from nonischemic toward subendocardial ischemic regions by TAVI. This reasoning is supported by the rise in early and peak systolic flow velocity resulting in an increased VTIs (Figure 4), which is consistent with earlier observations.

In agreement with earlier studies, we did not observe a difference in VTIdia, which follows from the altered diastolic velocity profile, characterized by slow acceleration and a higher peak diastolic velocity in AS. This is consistent with delayed relaxation in diastolic dysfunction because of concentric hypertrophic LV remodeling in patients with AS and delayed diastolic untwisting as a mechanical link to the phasic coronary hemodynamic observations in this scenario.

**WIA in LV Hypertrophy and AS**

Davies et al reported a reduced energy of the BEW in patients with a normal aortic valve and hypertrophic cardiomyopathy compared with controls. In contrast, we observed a higher BEW after TAVI in patients with AS-induced hypertrophy than in the control group. Apart from the influence of aortic outflow obstruction, this difference may also be related to the specific patterns of LV remodeling in response to different causes of hypertrophy, which in turn may affect the interaction between contraction and coronary microcirculation. Importantly, the baseline BEW in our study increased after TAVI, whereas a decrease was reported by Davies et al. Also, the strongly increased energies in both forward waves observed in the present study after TAVI were only marginally present in their study.

The internal consistency of our observations on the BEW at control and with LV hypertrophy pre- and post-TAVI can be understood by the respective roles of arteriolar resistance and LV relaxation on pulsatile coronary flow. According to the intramyocardial pump concept, the higher baseline energy of the pre-TAVI BEW compared with control can be explained by ameliorated propagation of this wave, attributable to metabolic vasodilation as corroborated by the additional augmenting effect of adenosine hyperemia. TAVI further increases this wave at baseline by improved LV relaxation. This is supported by the lower hyperemic BEW in AS, which reaches control levels when relaxation is restored post TAVI.
It is important to note that the intramyocardial pump concept dissociates systolic–diastolic coronary arterial flow variations from the mean flow and with it the energy of microvascular originating waves. Time-averaged flow is governed by the arterial–venous pressure difference and total MR, whereas microvascular-originating waves depend on LV compression and relaxation of the microcirculation and only the arteriolar resistance. LVEDP is increased in AS compared with control and remains high after TAVI. Coronary venous pressure is similar to LVEDP, and hence, the pressure head for mean coronary flow is reduced, but the phasic difference between arterial and microcirculatory pressure is not affected by LVEDP.

Vasodilation by adenosine also affected the BCW, but no significant effect of AS and TAVI on hyperemic energy in this wave could be detected. This may be because of the timing of the waves with respect to LV pressure development. The BCW appears rather early in systole when the elastance of the myocardium is still poorly developed and the effect of LV pressure development on tissue pressure is stronger than later in systole when elastance of the myocardium had time to develop.

Hence, the postulated role of contractility on generation of the backward waves seems to hold better for the BEW than for the BCW.

Adenosine caused also a moderate increase in the energies of both forward waves that theoretically should not be affected by microvascular vasodilation. This is likely related to the similar length of the waves compared with the length of the coronary epicardial arteries.

The dominant role of phasic aortic pressure in the creation of the FCW follows from the strong correlation between the energy of this wave and coronary PP and by the relationship between the time of peak FCW and the time of peak $P_a$ as shown in Figure 8. Moreover, the time of peak FCW is clearly delayed in AS and only partly restored by TAVI, which is consistent with a delayed contraction associated with hypertrophy.

**Relation Between WIA and Coronary Perfusion**

Diastolic perfusion time has been implicated as an important player in impairing myocardial perfusion in AS. We did not observe a significant difference in DTF between the patient groups or conditions; however, Davies et al. used pacing stress, thereby reducing DTF to possibly different values pre- and post-TAVI, despite the same heart rate.

As discussed earlier, direct associations between wave intensity or energy and myocardial perfusion should be done with caution because by definition, waves are related to rapid changes in velocity rather than its mean values and only influenced by the proximal microvessels. This is also demonstrated by the poor correlation between the TAVI-induced changes in BEW and diastolic VTI (Figure 7, right). Surprisingly, good correlations were found between TAVI-induced changes in the FCW with systolic VTI (Figure 7, left). This finding underscores the role of contraction–perfusion interaction and the positive effect of TAVI on systolic perfusion.

Although the correlation between absolute values of the BEW and velocity-based perfusion indices were poor, the
hyperemia-induced relative changes in these variables were strongly correlated (Figure 6). This holds true not only for the reserve of BEW and perfusion index VTI_dia but also for the BEW and CFR. These observations emphasize that the physiological variables involved in the BEW, although not identical, are highly relevant for myocardial perfusion. Relations between BEW and velocity-based reserves hold despite similar energies in the hyperemic BEW in the 3 groups. Hence, the lower hyperemic reserve of the BEW is the consequence of a higher baseline BEW in the AS and TAVI group, and the reduction in CFR in AS is not only because of increased oxygen demand but also because of a reduction of vasodilatory capacity.

Study Limitations
The patient group with AS differed from control in terms of age and comorbidity, which could affect both cardiac mechanics and wave transmission.20 However, coronary wave speed was similar in both groups. The mechanical consequences of AS likely surpass the potential effect of differences in age or comorbidities in the context of this investigation.

Wave intensity is derived from the derivatives of pulsatile signals, of which especially the flow velocity can be noisy. A combination of signal filtering and ensemble averaging over selected beats were used to extract physiological dynamic information.17 Filter settings were the same for all signals, and it is, therefore, unlikely that our conclusions are biased by the applied signal processing.

Nitroglycerine was administered only in control patients, but measurements were taken after its effect on WIA had passed.20 An increased LVEDP complicates interpretation of the ratio \( \frac{P_d}{U} \) as MR because resistance would be better reflected by \( \frac{(P_d-\text{LVEDP})}{U} \).17 A reduction of the pressure by 12 mmHg while \( P_d \) was ≈75 mmHg means that MR was overestimated by ≈25% in the AS and TAVI group. As a consequence, the unchanged flow velocity between control and AS at baseline implies some degree of dilatory adaptation of the coronary resistance vessels because of the reduced driving pressure.

In this small mechanistic study, post hoc multiple comparision correction was performed using a rather conservative Bonferroni adjustment. In some instances, this led to loss of statistical significance (as indicated by symbols in parenthesis in the figures), despite an obvious trend that suggests relevant physiological mechanisms. The results should, therefore, be considered hypothesis-generating and warrant further studies into the dynamic nature of cardiac–coronary interaction in radical interventions, such as TAVI.

Clinical Implications
Both rapid and long-term adaptations will take place after TAVI. Our results demonstrate that coronary waves as assessed by WIA are strongly influenced by the twist–untwist mechanics of cardiac contraction and relaxation, which are altered in the presence of the AS. Despite the direct effect of TAVI on cardiac mechanics, no acute change in CFR was observed. However, in terms of supply–demand ratio, removal of the AS by TAVI should benefit myocardial perfusion because the drop in oxygen consumption after the decrease in systolic LV pressure is not counterbalanced by a decrease in flow velocity. Moreover, TAVI rapidly improved 3 systolic flow velocity indices that reflect a better systolic inflow, which is associated with improved subendocardial perfusion.12

Changes in flow accelerating waves best reflect the acute effects of the TAVI procedure on cardiac–coronary interaction. Hence, the FCW and BEW are good candidates for prognostic value in future studies. Coronary wave intensity changes may also help elucidate the cause for onset of symptoms.

Conclusions
Our findings related to systolic perfusion are consistent with a disturbed systolic flow profile in AS, which is especially detrimental to subendocardial perfusion. Relief of systolic compression after TAVI normalizes respective systolic indices and augments the flow-accelerating FCW. TAVI restores the impaired energy of the BEW but changes in BEW were not correlated with changes in diastolic perfusion, and CFR remained essentially unaltered. The baseline BEW in AS was somewhat larger than in control, disputing a sole dominant role of compromised relaxation in the generation of this wave in AS patients. We postulate that elevated LVEDP associated with hypertrophy in the AS and TAVI groups reduces the coronary arterial–venous pressure difference explaining the lower CFR in AS and lack of acute improvement of this index by TAVI, whereas it does not affect the energy in the coronary waves. Vasodilation and LV relaxation should be better recognized as determining factors in wave intensity.

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Disclosures
Dr Piek has served as speaker at educational events organized by Volcano Corporation, St Jude Medical, and Boston Scientific, manufacturers of sensor-equipped guide wires. The other authors have no conflict of interest to disclose.

References
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