Cardiac-coronary interactions in humans: Mechanistic Insights from wave intensity analysis
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Chapter 4

Transcatheter replacement of stenotic aortic valve normalizes cardiac-coronary interaction by restoration of systolic coronary flow dynamics

M. Cristina Rolandi, Esther M.A Wiegerinck, Ze-Yie Yong, Karel T. Koch, Marije Vis, Jan J. Piek, Jos A.E. Spaan, Jan Baan jr., Maria Siebes
ABSTRACT

Aortic 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 due to transcatheter aortic valve implantation (TAVI).

Intracoronary pressure and flow velocity were measured at rest and at maximal hyperemia in undiseased vessels in 15 patients with AS before and after TAVI and in 12 control patients. Coronary flow reserve (CFR), systolic and diastolic velocity time integrals (VTI) were derived. The energies of forward (aorta originating) and backward (microcirculatory originating) coronary waves were determined. CFR was 2.8 ± 0.2 in control and 1.8 ± 0.1 in AS (p<0.005) and was not restored by TAVI. Compared to control, the resting backward expansion wave (BEW) was 45% higher in AS. The peak of the systolic forward compression wave (FCW) was delayed in AS, in relation to the delay in peak aortic pressure, which was partially restored after TAVI. The energy of forward waves doubled after TAVI, while the BEW increased by more than 30%. The increase in FCW with TAVI was related to an increase in VTIsys. AS or TAVI did not alter VTIdia.

Coronary forward wave energy and VTIsys indicate a compromised systolic flow velocity with AS that is restored after TAVI, suggesting an acute relief of excess subendocardial compression in systole.
INTRODUCTION

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 LV mass and inotropic state [1-2]. Thirty to forty percent of patients with AS suffer from angina despite unobstructed coronary arteries and it is therefore important to understand the origin of ischemia that causes these anginal symptoms [3-5]. Ischemia is in general associated with reduced coronary flow reserve (CFR) which in AS occurs especially at the subendocardial layer [6-7]. A reduction in CFR may be the result augmented basal flow due to an increase in myocardial oxygen demand [8] and a compromised hyperemic flow in AS-related hypertrophy due to both the capillary rarefaction and the intensified compression of intramural vessels resulting from the enhanced inotropic state and left ventricular pressure [9-10]. After valve replacement, the long-term regression of hypertrophied left ventricular mass is associated with a decrease in resting myocardial flow and restoration of CFR [11-12].

Cardiac contraction is at the basis of the coronary blood flow waveform via the intramyocardial pump mechanism [13], which is modulated by aortic pressure ($P_a$), left ventricular pressure ($P_{LV}$), and inotropic state [9,14]. Cardiac contraction increases intramural tissue and microvascular blood pressures, causing systolic flow impediment, which normally is partly counteracted by the systolic $P_a$ [13]. However, in case of AS, systolic $P_{LV}$ increases far above systolic $P_a$ such that systolic flow impediment is less compensated. Transcatheter aortic valve implantation (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 alteration in coronary waveforms induced by changes in coincident waves coming from the microcirculation and from the aorta. The direct effect of TAVI has been investigated with this analysis, but significant changes were reported only for the diastolic microcirculatory-generated wave and only after an additional challenge of the cardiac-coronary interaction by increasing heart rate [15].

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. Since the forward wave at the beginning of systole drives the rise in systolic flow this would principally benefit subendocardial perfusion.

METHODS

Subject characteristics

Twenty-seven patients participated in the study. Twelve patients without AS (9 male) and an angiographically normal vessel who were scheduled for elective percutaneous coronary intervention formed the control group. Exclusion criteria for this control group were subtotal or serial lesions, significant left main coronary artery stenosis, recent myocardial infarction (<6 weeks), prior cardiac surgery or severe heart failure. Fifteen patients with AS (7 male) scheduled for TAVI 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. 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. Aortic pressure ($P_a$) was obtained via a 6F or 7F guiding catheter, which was advanced into the coronary ostium. Intracoronary pressure ($P_d$) and coronary blood flow velocity ($U$) were measured with a 0.014-in dual-sensor guidewire (ComboWire® XT, model 9515, Volcano Corp., San Diego, CA). In the control group, left ventricular pressure ($P_{LV}$) was measured simultaneously with the intracoronary hemodynamics via 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 after digitization at a sampling frequency of 200 Hz.

**Measurement Protocol**

All patients were pre-treated with antiplatelet therapy and received a bolus of heparin (5000 IU) at the beginning of the procedure. In the control group, nitroglycerin (0.1 mg, intracoronary) was administered. In the AS patients, hemodynamic measurements were obtained just prior to and immediately after the TAVI procedure. Intracoronary signals were measured in an angiographically normal reference vessel. Once the sensor-equipped guidewire was positioned and an optimal and stable velocity signal was obtained, maximum hyperemia was induced by a 40 µg intracoronary bolus of adenosine. In four AS patients, the guide wire tip was advanced into the left ventricle prior to TAVI in order to measure $P_{LV}$ for clinical purposes. Transthoracic echocardiography was performed pre-procedurally as well as 2 to 5 days after TAVI.

**Transcatheter Aortic Valve Implantation**

A temporary pacing wire was advanced into the right ventricle via a 7F sheath in the femoral vein. A 7F arterial sheath was inserted for aortic angiography with a pigtail catheter and for the coronary measurements with a guiding catheter. An 8F sheath was inserted in the other femoral artery for balloon valvuloplasty and valve implantation. Nine patients were treated with the Medtronic CoreValve Revalving System (CRS™ CoreValve Inc, Irvine, CA) and six patients with the Edwards Sapien/Sapien XT (Edwards Lifesciences Inc, Irvine, CA), at the discretion of the operator. The procedure was performed with the patient under general anesthesia (n=11) or with local anesthesia in combination with a mild systemic sedative (n=4) at the discretion of the cardiac anesthesiologist.

**Data Analysis**

Quantitative coronary angiography (QAngio XA v. 7.2, Medis Medical Imaging Systems, Leiden, 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, USA). Two to five consecutive representative beats were selected at baseline and 2 at maximum hyperemia. Arterial pulse pressure (PP) was assessed from intracoronary pressure. Microvascular resistance (MR) was defined as the ratio between P and U. Fractional flow reserve (FFR) was calculated as the ratio of P at maximum hyperemia and coronary flow velocity reserve (CFR) as the ratio between flow velocity at hyperemia and baseline. The diastolic time fraction (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.

WIA of the coronary hemodynamic waveforms started with correcting for the time lag between P and U. Time derivatives were obtained after smoothing the raw signals with a 19-point 3rd order polynomial Savitzky-Golay filter [16] followed by ensemble-averaging the selected beats. Net wave intensity (dI) is defined as the product of incremental changes in local pressure (dP) and flow velocity (dU) [17] and reflects the effect of cardiac contraction and relaxation on coronary hemodynamics. Forward traveling waves entering from the aorta and backward traveling microcirculatory-generated waves are superimposed to form the net wave intensity at the measuring location. Coronary wave speed was determined from the sum-of-squares technique [18]. Since wave speed during hyperemia is underestimated by this technique [19], baseline wave speed was used for WIA at maximum hyperemia as proposed by Rolandi et al [20]. The wave energy (in J·m⁻²·s⁻²) was obtained by integrating the area under each of the separated dominant waves.

Four dominant coronary waves can typically be recognized [21]. The backward compression wave (BCW) starts with isovolumic contraction, while the forward compression wave (FCW) appears after opening of the aortic valve. The forward expansion wave (FEW) coincides with the onset of cardiac relaxation and the backward expansion (or suction) wave (BEW) starts after valve closure. The BCW and FEW decelerate coronary blood flow, whereas the FCW and BEW are flow-accelerating waves.

**Statistical Analysis**

All values are expressed as mean ± standard error of the mean unless specified otherwise. Continuous variables of the control and AS group were compared with an unpaired Student’s t-test for different variances. Comparisons within the AS group before and after TAVI were performed with a paired Student’s t-test. A χ² test was used to assess differences in categorical variables. SPSS 20 (IBM, Armonk, NY) was used for the statistical analysis. Relationships between variables were investigated with linear regression analysis and Pearson’s correlation coefficient (Grapher v. 8.7, Golden Software Inc., Golden, CO). A value of p<0.05 was considered statistically significant.
RESULTS

Patient Characteristics
Age ranged from 38 to 67 years (56 ± 9 y) in the control group and from 66 to 93 years (82 ± 9 y, p< 0.001) in the AS group (Table 1). The study vessels were minimally diseased with a diameter reduction of 19 ± 9% for the control group and 12 ± 5% for the AS group. All AS patients had concentric left ventricular hypertrophy. Coronary diameter at the site of measurement was 3.0 ± 0.9 mm in the AS group vs. 2.2 ± 0.6 mm (p<0.05) in the control group. As summarized in Table 2, TAVI normalized aortic valve parameters assessed by echocardiography. One patient did not survive the TAVI procedure for longer than 24h and data are shown for 14 patients.

Hemodynamics
Figure 1 shows a representative example of hemodynamic signals and associated coronary wave intensity obtained at rest (top panels) and peak hyperemia (bottom panels). In the control patient (left), a characteristic biphasic flow velocity waveform is present, with symmetric dips at the beginning and end of systole. In the AS patient before TAVI (middle), the flow velocity waveform displays a lower early systolic dip especially during hyperemia, and the late systolic dip is less apparent. After TAVI (right), the mid-systolic velocity peak is much more pronounced with a clearly established late systolic dip. Although mean aortic pressure was similar in all conditions, the pressure waveform lacks a discernible dicrotic notch in AS, while pulse pressure is noticeably increased after TAVI. In general, peak aortic pressure appears delayed both before and after TAVI. The corresponding net wave intensity profile (thick line) and its forward (positive) and backward (negative) components are depicted below the respective hemodynamic signals. The energy of the dominant coronary waves increased during hyperemia and was clearly augmented after TAVI.

Mean systemic and coronary hemodynamic variables are summarized in Fig 2. Heart rate remained relatively constant between 66 ± 2 and 70 ± 2 bpm across all groups and conditions. The absence of a significant stenosis was confirmed by a diagnostically non-significant FFR between 0.93 and 0.97. Left ventricular end-diastolic pressure (LVEDP) was 8.4 ± 2.4 mmHg in the control group and 20.9 ± 1.7 mmHg (p<0.001) in those four AS patients where PLV was measured before TAVI. Also peak \( P_{LV} \) tended to be higher in the presence of AS (157 ± 8 vs.141 ± 4 mmHg).

At rest, \( P_a \) was 11% lower in the AS group compared to control (88 ± 3 vs. 98 ± 4 mmHg, p<0.05), with no difference in the other variables. Distal vasodilation induced a 68% decrease in MR in the control group and a 50% decrease in the AS group before and after TAVI (p<0.0001). Flow velocity was enhanced in both groups (p<0.0001) with a small reduction in \( P_a \) and \( P_d \) (p<0.05), however, hyperemic flow velocity was 23% lower in the AS group (40.7 ± 2.4 vs. 53.2 ± 4.4 cm/s, p<0.02) and was not altered by TAVI. CFR was 34% lower in the AS group compared to control (1.8 ± 0.1 vs. 2.8 ± 0.2) and did not improve after TAVI. Only \( P_{Pd} \) increased after TAVI from 64 ± 5 to 76 ± 4 mmHg (p<0.01).
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>10 (83)</td>
<td>7 (47)</td>
<td>0.15</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</td>
<td>1 (8)</td>
<td>1 (7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (58)</td>
<td>8 (53)</td>
<td>0.80</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7 (58)</td>
<td>1 (7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>1 (8)</td>
<td>2 (13)</td>
<td>0.68</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>0.06</td>
</tr>
<tr>
<td>Statins</td>
<td>10 (83)</td>
<td>6 (40)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>10 (83)</td>
<td>6 (40)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>3 (25)</td>
<td>3 (20)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

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

Table 2: Echocardiographic Parameters 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, mmHg</td>
<td>72.17 ± 18.5</td>
<td>18.9 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean gradient, mmHg</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></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>2</td>
<td>0.54</td>
</tr>
<tr>
<td>Mild</td>
<td>11</td>
<td>7</td>
<td>0.11</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>5</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± sem.
Figure 1: Hemodynamic waveforms and associated coronary WI patterns.
Waveforms are depicted for the control group (left) and in the AS group before (middle) and after (right) TAVI during rest (top panels) and maximum hyperemia (bottom panels). Although mean Pa is similar, the pulsatility is reduced in AS, with a less pronounced dicrotic notch, and increases after TAVI. The asymmetry of the systolic U waveform in AS is restored to a biphasic pattern after TAVI. Wave intensity patterns show that the four dominant coronary waves are enhanced during hyperemia. In this example TAVI strongly increases all dominant waves. AS, aortic valve stenosis; Pa, aortic pressure; Pd, coronary pressure; U, coronary flow velocity; dI, wave intensity; BCW, backward compression wave; FCW, forward compression wave; FEW, forward expansion wave; BEW, backward expansion wave.
Figure 2. Systemic and coronary hemodynamics.
Pa, U, and CFR were reduced in aortic stenosis (AS) compared to control. TAVI did not immediately affect hemodynamic parameters except for an increase in coronary pulse pressure both at rest and hyperemia.
Pa, aortic pressure; HR, heart rate; PPd, pulse pressure; Pd, coronary pressure; MR, microvascular resistance; U, flow velocity; CFR, coronary flow reserve. *p<0.05 compared to control, †p<0.05 compared to AS, ‡p<0.01 compared to resting condition.

Figure 3. Phasic components of coronary flow velocity
Hyperemic VTIsys in aortic stenosis (AS) was lower than in control. TAVI increased this index both at baseline and hyperemia. DTF, diastolic time fraction; VTIsys and VTIdia, systolic and diastolic velocity time integrals, resp. *p<0.05 compared to control, †p<0.05 compared to AS, ‡p<0.01 compared to resting condition.
Coronary Flow Velocity Pattern

Characteristics of the coronary flow velocity profile are depicted in Fig 3. While the relative duration of diastole was on average the same for all groups, diastolic perfusion time was about 5% shorter in AS and did not improve after TAVI. VTIidia did not differ between the groups at rest or hyperemia. In contrast, VTIsys in the AS group was lower than control at hyperemia (10.7 ± 0.9 cm vs. 16.0 ± 2.1 cm, p<0.05) and increased after TAVI both at rest (from 5.9 ± 0.5 to 7.7 ± 0.8 cm, p<0.05) and hyperemia (to 15.6 ± 1.5 cm, p<0.005). This difference in VTIsys was associated with a reduction in early and peak systolic velocity (Fig. 4). Early systolic flow velocity dip was lower in AS compared to control both at rest (4.4 ± 0.4 vs. 7.1 ± 0.9 cm/s, p<0.01) and hyperemia (6.3 ± 1.2 vs. 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 was lower in AS compared to control at peak hyperemia (34.7 ± 3.0 vs. 45.6 ± 5.4 cm/s, p<0.05) and increased by almost 40% (p<0.05) after TAVI both at rest and hyperemia.

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 difference between the groups.

The energies of the compression waves in AS were equivalent to those in the control group both at rest and at hyperemia (Fig. 5), whereas the energy of the BEW at rest was significantly higher in the AS group (9.3 ± 1.2 vs. 6.1 ± 0.6 J·m⁻²·s⁻², p<0.01). In general, coronary wave energies increased with hyperemia (p<0.05), except for the FEW. The ratio of hyperemic-to-rest BEW 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 ratio was strongly related to CFR in all conditions (Fig. 6) and was associated with the corresponding ratio for VTIdia both in the control (r= 0.70, p<0.05) and the AS group (r= 0.83, p<0.0001).

As expected, removal of the outflow obstruction especially augmented the forward waves (Fig. 5). Baseline FCW energy was moderately related to the valve area (r=0.40, p<0.05) and almost doubled after TAVI (from 6.2 ± 0.6 to 12.3 ± 1.4 J·m⁻²·s⁻² at rest and from 10.1 ± 1.3 to 18.4 ± 1.9 J·m⁻²·s⁻² at peak hyperemia, p<0.005). Similarly, the FEW increased more than two-fold (from 1.7 ± 0.5 to 6.3 ± 1.5 J·m⁻²·s⁻² at rest and from 1.7 ± 0.5 to 9.2 ± 1.4 J·m⁻²·s⁻² at peak hyperemia, p<0.005). TAVI augmented the BEW by 32% at rest (from 9.3 ± 1.2 to 12.4 ± 1.6 J·m⁻²·s⁻², p<0.05) and by 42% at hyperemia (from 13.5 ± 1.3 to 19.2 ± 2.5 J·m⁻²·s⁻², p<0.05). No changes in the BCW were observed. As shown in Fig. 7, the increase in the FCW after TAVI was strongly associated with an increase in VTIsys during both rest (r= 0.80, p<0.002) and hyperemia (r=0.63, p<0.05), whereas no relation was found between respective changes in BEW energy and VTIdia.

As illustrated in Fig. 8, not only the energy of the FCW increased with the pulsatility of Pa (r=0.42, p< 0.005 at rest ; r=0.66, p<0.0001 at hyperemia) but also the peak of the FCW was delayed in the AS group compared to control and occurred 110 ms later at rest and 70 ms later at hyperemia (p<0.0005). This delay was shortened after TAVI to 50 and 23 ms, respectively. Moreover, the time of peak FCW was strongly associated with the time of peak Pa during both rest (r=0.99, p<0.00001).
**Figure 4: Systolic components of flow velocity**

Left: the broken line is the line of identity and indicates symmetry between early and late systolic dip in flow velocity. In control early (U early dip) and late (U late dip) systolic flow velocities are equal in control but the late systolic dip is somewhat higher at hyperemia. In aortic stenosis (AS) early systolic flow velocities at baseline and hyperemia were lower than in control but were increased by TAVI. TAVI improves symmetry between early and late systolic dips. Right panel: maximum systolic flow at hyperemia is impaired by AS but restored by TAVI. *p<0.05 compared to control; †p<0.05 compared to AS before TAVI; ‡p<0.01 compared to resting condition.

**Figure 5: Energy of the four dominant separated waves at rest and hyperemia.**

Energies of the forward compression wave (FCW), forward expansion wave (FEW), backward compression wave (BCW), and backward expansion wave (BEW) are depicted for the three groups at rest and hyperemia. AS affected the BEW at rest and hyperemia except BCW. Except for the FEW all waves are increased by hyperemia. AS, aortic stenosis. *p<0.05 compared to control; †p<0.05 compared to AS before TAVI; ‡p<0.01 compared to resting condition.
and hyperemia ($r=0.98$, $p<0.05$), which was also delayed in AS patients by 70 ms at rest and 90 ms at hyperemia.

**Figure 6: Relation between BEW reserve, CFR VTIdia reserve.**
Left: There is a strong relationship between the BEW reserve (hyp/rest BEW) and coronary flow velocity reserve (CFR) in all three groups: control ($r=0.60$, $p<0.05$), AS ($r=0.66$, $p<0.001$) and TAVI ($r=0.59$, $p<0.05$). Grouping all the patients together the relationship was excellent ($r=0.76$, $p<0.0001$); Right: The relation with hyperemic to rest VTIdia was significant in the control group ($r=0.70$, $p<0.05$) and in the AS group ($r=0.83$, $p<0.0001$) but not after TAVI. Considering all the patients together the relationship was strong ($r=0.76$, $p<0.0001$).

**Figure 7: Relation between TAVI induced absolute variations in FCW and BEW and systolic and diastolic perfusion indices.**
Left: The absolute increase in the FCW ($\Delta$FCW) energy by TAVI was strongly related to that of systolic VTI ($\Delta$VTIsy) at rest ($r=0.80$, $p<0.002$) and hyperemia ($r=0.63$, $p<0.05$). Right: Absence of relation between absolute changes in BEW ($\Delta$BEW) and the diastolic VTI ($\Delta$VTIdia)
DISCUSSION

This study demonstrate 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 pulse pressure. Similarly, the diastolic resting and hyperemic flow accelerating BEW improved significantly after TAVI, whereas the response to hyperemia remained compromised as evidenced by a consistently lower CFR and hyperemic-to-rest BEW ratio. These changes point to a normalization of cardiac-coronary interaction induced by TAVI despite the impediment due to the still present LV hypertrophy.

Effect of AS and TAVI on Coronary Flow Velocity and CFR

Patients treated by TAVI often immediately experience relief from angina after...
valve replacement [5]. Angina in AS is related to subendocardial ischemia resulting from excess systolic compression of the microcirculation close to the pressure-overloaded LV cavity [7]. Subendocardial compression is mainly responsible for the systolic coronary flow impedance and hence the changes in coronary flow velocity pattern and respective wave energies reflect the mechanisms of cardiac-coronary interaction causing ischemia.

By removing the outflow obstruction TAVI reduces cardiac work and extravascular resistance or a combination of both [22]. Consequently, one may expect a decreased baseline and/or increased hyperemic flow velocity after TAVI given that the mean Pa was not altered by the intervention. However, in our AS patients, mean flow velocities were unchanged by TAVI and CFR remained below 2, which indicates inducible ischemia with moderate exercise. Camuglia et al. recently observed similar levels of CFR as in our AS patients and also no immediate changes after TAVI [23]. Most likely an improved clinical condition is the result of redistribution of perfusion from non-ischemic regions towards subendocardial ischemic regions by TAVI [12]. Support for improved subendocardial perfusion in our patients comes from the rise in early and peak systolic flow velocity resulting in an increased VTIsys both at baseline and hyperemia as is illustrated in Fig 4. These findings on systolic flow velocity are consistent with earlier observations [24].

In agreement with earlier studies, we did not observe a difference in VTIdia, which is explained by the altered diastolic velocity profile, showing a slow acceleration in conjunction with a higher peak diastolic velocity in AS [25]. This is consistent with delayed relaxation reported in diastolic dysfunction due to concentric hypertrophic LV remodeling in patients with AS. Recent studies showing delayed diastolic untwisting provide a mechanical link to the phasic coronary hemodynamic observations in this scenario [26-27].

**WIA in LV Hypertrophy and AS**

In their seminal paper on coronary WIA, Davies et al. reported a reduced energy of the BEW in patients with normal aortic valve and hypertrophic cardiomyopathy compared to controls [28]. In contrast, we observed a higher BEW in patients with hypertrophy and AS than in the control group. This difference may be due to the specific patterns of LV remodeling in response to different causes of hypertrophy [29] which may in turn alter the interaction between contraction and coronary microcirculation. Such hypertrophy-specific remodeling may explain the reversal of the negative association of BEW with the degree of hypertrophy observed in that first study to a weakly positive association in a later study on AS-induced hypertrophy by the same group [15]. Importantly, the baseline BEW in our study increased after TAVI whereas a decrease was reported by Davies et al [15]. Also the increased energies in FCW and FEW found in the present study after TAVI were only marginally observed in their study. This difference in findings is difficult to explain and a direct improvement in the BEW after TAVI, as found in the present study, would have been more plausible [30].

The increased energy of the BEW by TAVI is consistent with an improvement of LV relaxation. However, the baseline energy of BEW with AS was also higher than in control. That is unexpected since in general, hypertrophy and AS are associated
with impaired relaxation [1]. The changes in BEW are not mimicked by chances BCW since the energies of these waves at control and hyperemia were not different between control, AS and TAVI.

The strength of the effects of contraction and relaxation on coronary flow and WIA are related to compressive forces but modulated by several factors and timing with the cardiac cycle. For example, at constant contractility the diastolic-systolic swing in coronary blood flow at hyperemia are dependent on perfusion pressure since intramural blood volume (Vim) increases with perfusion pressure [31-32]. This is consistent with the elastance model which predicts an amplification effect of contraction-coronary by Vim. The possible role of Vim on wave attenuation is consistent with the observed increase of both backward waves with vasodilation. This modulating effect of Vim may also play a role in the BEW which energies at baseline in the AS and TAVI group are higher than in the control group. We have no direct information on Vim in this study, but it is reasonable to assume that it is higher at higher values of coronary sinus pressure, which has been shown to equal LVEDP [33]. It should be noted that LVEDP remains elevated after TAVI. Although Vim seems to form a physiological explanation for the higher energies in the BEW one would expect similar effects on the BCW which are, however, absent. This may be due to the timing of the waves with respect to left ventricular pressure development. The BCW are 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 [14]. Hence, the postulated role of contractility on generation of the backward waves seems to hold better for the BEW than for the BCW.

The forward waves are caused by the aortic pressure waveform and theoretically should not be affected by microvascular vasodilatation. However, we found a moderate increase in the energies of both forward waves with adenosine induced vasodilation. This is probably related to the wave length of the waves compared to the path length of the coronary epicardial arteries which are of similar magnitude [19]. Hence, flow velocity at the site of measurement is affected by microvascular resistance during development of the wave.

The dominant role of Pa in the creation of the FCW follows from the strong correlation between the energy of this wave and PPa as demonstrated in Fig 8. A causal relationship between the FCW and Pa is further substantiated by the relationship between the time of the FCW with the time to peak Pa as shown in Fig. 8b and c. 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 the hypertrophy not affected by this intervention [25].

**Relation between WIA and coronary perfusion**

Diastolic perfusion time has been implicated as an important player in impairing myocardial perfusion in AS. However, we did not observe a significant difference in DTF between our patient groups, either at baseline or during hyperemia. Davies et al. used pacing as stress, thereby reducing DTF [15]. This may have contributed to the reduction in BEW in their study at elevated but not maximal HR.

As discussed earlier, one has to be very careful in directly relating wave intensity or energy to myocardial perfusion since per definition waves are related
to rapid changes in flow velocity rather than its absolute values [34]. This is also demonstrated by an absence of correlation between the TAVI induced changes in BEW with those in VTIdia (Fig. 7b). Good correlations are however found between TAVI induced absolute changes in the FCW with the systolic perfusion index VTIsys (Fig 7a). This finding underlines the role of contraction-perfusion interaction in TAVI and the positive effect of TAVI on systolic perfusion. Since these systolic effects are predominantly at the subendocardium our results indicate improved subendocardial perfusion after TAVI. Although the correlation between absolute values of the BEW and flow velocity based perfusion indices is poor, good correlations between the relative changes in these variables induced by hyperemia were found when grouped together (Fig 6). This holds not only true for the BEW and diastolic perfusion index VTI but also for the BEW and CFR. These observations underline that the physiological parameters involved in the BEW are highly relevant for myocardial perfusion as well.

It is interesting to note that these relations between BEW and flow velocity reserves hold despite the similar energies of the hyperemic BEW in the three groups although TAVI did increase the BEW. Hence the reduction in range of relative change in the BEW induced by hyperemia is the consequence of higher BEW at baseline in the AS and especially the TAVI groups. This is consistent with the hypothesized role of Vim on the BEW which will play a bigger role at baseline then at hyperemia where Vim will be higher in all groups. Note that due to increased LVEDP microvascular pressure will be higher in AS and TAVI especially at baseline which implies a higher degree of vasodilatation of the resistance vessels in these groups due to an autoregulatory response. Hence, the reduction in CFR in AS is likely not due to increased oxygen demand alone but also to a reduction of vasodilatory capacity.

**Study Limitations**

The patient group with AS differed from control especially in terms of age and comorbidity which could affect both cardiac mechanics and wave transmission. Indeed an effect of age on coronary wave speed has been reported [18]. However, in this study coronary wave speed was similar for all the groups.

Wave intensity is derived from the derivatives of pulsatile signals, of which especially the flow velocity can be noisy. In order to extract physiological dynamic changes we applied a combination of signal filtering and ensemble averaging of beats. Filtering not only reduces noise but may also affect high-frequency physiological information. Filter settings were the same for all signals and for the same conditions, the same number of beats was used for ensemble averaging. Hence, it is unlikely that our conclusions are biased by the applied signal processing.

This study is limited to the immediate effect of TAVI on coronary hemodynamic and no long-term effect of this procedure has been investigated.

Coronary flow velocity at baseline was not significantly higher in AS compared to control, but volume flow was likely higher because of the larger vessel diameter at the site of velocity measurement in AS patients. Such outward remodeling of epicardial arteries is common in hypertrophy to compensate for elevated oxygen demand associated with increased cardiac work resulting from hypertrophy and increased $P_{LV}$.
This remodeling does obviously not play a role in the calculation of CFR. An increased LVEDP complicates interpretation of the ratio $P_d/U$ as microvascular resistance, since resistance would be better reflected by $(P_a - \text{LVEDP})/U$ [34]. The reduction of the pressure gradient by 12 mmHg while $P_a\,\text{was about 75 mmHg}$ means that MR was overestimated by about 20% 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 due to the reduced driving pressure.

Clinical Implications

Our results demonstrate that coronary waves as assessed by WIA are strongly related to the aortic pressure waveform and the twist-untwist mechanics of cardiac contraction and relaxation. Both components are hampered in the presence of the AS and some new adaptations will take place after TAVI. Despite the direct effect of TAVI on cardiac mechanics, no change in CFR is observed. However, in terms of supply-demand ratio, the removal of the AS by TAVI should be beneficial for myocardial perfusion since the drop in oxygen consumption expected by the decrease in systolic LV pressure is not counterbalanced by a decrease in flow velocity. Moreover, there is a direct improved effect of TAVI on three systolic flow velocity indices that indicates a better systolic inflow, which likely improves subendocardial perfusion. Such an improved subendocardial perfusion has been demonstrated after one year by PET studies [12].

The BEW is the wave that best reflects the effects of cardiac contraction on coronary flow velocity and also is the most sensitive to the TAVI procedure. Hence, BEW is a good candidate for prognostic value in future studies.

CONCLUSION

The indices related to systolic perfusion are consistent with an impeded systolic flow velocity in AS which will be especially detrimental to subendocardial perfusion. These indices are restored by TAVI as a result of increasing the forward compression wave. TAVI restores the impeded energy of the BEW but absolute changes in BEW are not correlated with absolute changes in diastolic perfusion and coronary flow velocity reserve remains unaltered. The baseline BEW in AS is significantly higher than in control contradicting a dominant role for reduced relaxation in the generation of this wave. It is postulated that an increased microvascular volume resulting from an increased LVEDP in the AS and TAVI groups potentiates the effect of relaxation on the BEW. This would also be a factor in explaining the reduced CFR in AS and absence of improvement of this index by TAVI since an LVEDP increased microvascular pressure will induce a compensatory vasodilatation of the resistance vessels.
REFERENCES


