Valvular Heart Disease

Evaluation of Aortic Blood Flow and Wall Shear Stress in Aortic Stenosis and Its Association With Left Ventricular Remodeling

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Background—Aortic stenosis (AS) leads to variable stress for the left ventricle (LV) and consequently a broad range of LV remodeling. The aim of this study was to describe blood flow patterns in the ascending aorta of patients with AS and determine their association with remodeling.

Methods and Results—Thirty-seven patients with AS (14 mild, 8 moderate, 15 severe; age, 63±13 years) and 37 healthy controls (age, 60±10 years) underwent 4-dimensional-flow magnetic resonance imaging. Helical and vortical flow formations and flow eccentricity were assessed in the ascending aorta. Normalized flow displacement from the vessel center and peak systolic wall shear stress in the ascending aorta were quantified. LV remodeling was assessed based on LV mass index and the ratio of LV mass:end-diastolic volume (relative wall mass). Marked helical and vortical flow formation and eccentricity were more prevalent in patients with AS than in healthy subjects, and patients with AS exhibited an asymmetrical and elevated distribution of peak systolic wall shear stress. In AS, aortic orifice area was strongly negatively associated with vortical flow formation (P=0.0274), eccentricity (P=0.0070), and flow displacement (P=0.0021). Bicuspid aortic valve was associated with more intense helical (P=0.0098) and vortical flow formation (P=0.0536), higher flow displacement (P=0.11), and higher peak systolic wall shear stress (P=0.0926). LV mass index and relative wall mass were significantly associated with aortic orifice area (P=0.0611, P=0.0058) and flow displacement (P=0.0058, P=0.0283).

Conclusions—In this pilot study, AS leads to abnormal blood flow pattern and peak systolic wall shear stress in the ascending aorta. In addition to aortic orifice area, normalized flow displacement was significantly associated with LV remodeling. (Circ Cardiovasc Imaging. 2016;9:e004038. DOI: 10.1161/CIRCIMAGING.115.004038.)

Key Words: aorta ■ aortic valve stenosis ■ heart valve diseases ■ heart ventricles ■ magnetic resonance imaging

There are many attempts to better characterize the severity of aortic stenosis (AS). The increased stress on the left ventricle (LV) caused by AS can be highly variable and leads to a broad range of LV impairment. As a result, it is challenging to quantitatively determine the burden on the ventricle caused by AS in the individual patient. Conversely, unfavorable LV remodeling is an important prognostic factor and contributes significantly to the development of heart failure in patients with AS.

Aortic orifice area (AOA) and blood flow velocity are often considered insufficient to characterize the severity of aortic stenosis (AS). The increased stress on the left ventricle (LV) caused by AS can be highly variable and leads to a broad range of LV impairment. As a result, it is challenging to quantitatively determine the burden on the ventricle caused by AS in the individual patient. Conversely, unfavorable LV remodeling is an important prognostic factor and contributes significantly to the development of heart failure in patients with AS.

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There are many attempts to better characterize the myocardial stress provoked by AS. Whereas a decline of LV ejection fraction is regarded as a late sign of LV impairment, systolic longitudinal strain assessed by transthoracic echocardiography has been proven to be a valuable marker for early LV dysfunction in AS. ECG signs of LV hypertrophy and LV strain as well as elevated blood markers such as troponin and brain natriuretic peptide have also been reported to predict outcome in patients with AS. Moreover, the presence of fibrosis assessed by late gadolinium enhancement cardiovascular magnetic resonance (CMR) is associated with poorer outcome with and without aortic valve replacement.

Altered poststenotic blood flow in the presence of AS is another potential cause of elevated LV afterload.

Altered helical and vortical blood flow formations have been described to cause power loss caused by friction and viscous dissipation and to alter wall shear stress (WSS).
Integrated over time, these losses can cause an increase in energy required for blood circulation. The recent use of 4-dimensional (4D) flow CMR to characterize blood flow patterns and the distribution of WSS is an opportunity to investigate this theory. In this hypothesis-generating study, 4D flow CMR of patients with AS was used to characterize the poststenotic blood flow and to analyze the association of aortic hemodynamics with LV remodeling.

Methods

Study Population

Participants were prospectively recruited. The diagnosis of AS was based on the AOA obtained from CMR cine imaging. Severe AS was defined as AOA <1 cm² or AOA indexed by body surface area <0.6 cm²/m², moderate AS 1 to 1.5 cm², and mild AS >1.5 cm². The status healthy was based on uneventful medical history, absence of any symptoms indicating cardiovascular dysfunction, normal ECG and normal cardiac dimensions, and function proven by CMR cine imaging. Subjects with impaired LV ejection fraction <50% or with evidence of coronary artery disease by coronary angiography, noninvasive imaging, or clinical assessment were excluded. Patients with arrhythmia, greater than mild valvular disease (other than AS), or general contraindications for CMR were also excluded. For each participant, written informed consent was obtained before the study, after due approval by the local ethical committee.

Four-Dimensional Flow CMR: Acquisition

All CMR examinations were performed with a 3T system (MAGNETOM Verio; Siemens Healthcare GmbH, Erlangen, Germany). Four-dimensional flow CMR data were acquired using a sagittal oblique volume covering the thoracic aorta. Prospective ECG gating was used in combination with a respiratory navigator placed on the lung–liver interface to permit data acquisition during free breathing. The following scan parameters were chosen: echo time=2.6 ms, repetition time=5.1 ms, bandwidth=450 Hz/pixel, imaging acceleration using PEAK GRAPPA (GraphPad Software Inc, San Diego, CA) and plug-in software for MATLAB. Categorical data are expressed as percentages; continuous data as mean±SD. Interobserver variability of helical and vortical flow parameters was determined for 8 regional segments along the aortic circumference for each plane S₁–S₃. Regional WSS was averaged with the preceding and 3 subsequent time steps to mitigate measurement noise.

Cine CMR

 steadystate free-precession cine images were obtained to assess wall motion, for chamber quantification and for planimetry of the AOA. Imaging parameters were as follows: repetition time=3.1 ms, echo time=1.3 ms, flip angle=45°, field of view (276x340) mm², matrix (156x192), slice thickness 6 mm (chambers) and 5 mm (aortic valve), bandwidth 704 Hz/pixel, parallel imaging using GRAPPA reconstruction (R=2), 30 cardiac phases. Axial steady-state free-precession still images of the thorax were used to estimate the size of the ascending aorta at the level of the pulmonary bifurcation. Image analysis was done using CVI42 (Circle Cardiovascular Imaging, Calgary, Canada).

LV remodeling was defined based on LV mass index (LVM) and relative wall mass (RWM=LVM divided by end-diastolic volume in g/mL). The categories were: (1) normal (LVM and RWM normal), remodeling (LVM normal and RWT ≥ 1.6 g/mL), hypertrophy (LVM abnormal and RWT ≥ 1.6 g/mL). Asymmetrical remodeling and hypertrophy were differentiated by wall thickening ≥13 mm that was also >1.5-fold the thickness of the opposing myocardial segment. RWM is reported to be more sensitive to detect LV remodeling than global LV mass or 2D diameters of the LV wall, in particular, for small concentric remodeled hearts.

Statistical Analysis

Statistical analysis of the data as outlined in this section was performed using SPSS 20 (IBM, Armonk, NY) and SAS 9.4 (SAS Institute Inc., Cary, NC). Graphics were created using PRISM 5 (GraphPad Software Inc, San Diego, CA) and plug-in software for MATLAB. Categorical data are expressed as percentages; continuous data as mean±SD. Interobserver variability of helical and vortical flow evaluation was assessed using the intraclass correlation coefficient. Comparisons between the 3 severity grades of AS were made using the Jonckheere–Terpstra test when a trend across groups was of major interest, or the Kruskal–Wallis test when looking for any difference between the groups. In case of significance, a Mann–Whitney U test was added to investigate into the actual effects. Correlation was assessed using the Spearman method.

Modeling of Flow Parameters

The flow parameters were modeled based on all available data using ordinal logistic regression or linear regression as appropriate for the parameter. The presence of a bicuspid aortic valve, aortic diameter, ejection fraction, age, AOA, AS grade, and AS (y/n) as well as the 2-way interaction between AS (y/n) and the aforementioned independent variables other than AS grade were independent variables in the models. Stepwise selection (P(entry)=0.15, P(stay)=0.15) was used to arrive at sparse models and to avoid spurious effects caused by correlations in the independent variables. As for some models,
significant interaction terms pointed toward different effect in patients and controls; models were also computed for patients only. The focus of interpretation was put into the main factors, whereas interaction terms will be subject to further investigation.

Modeling of Remodeling Parameters
The analysis of associations with the remodeling parameters LVMI, RWM, and presence of LV remodeling was based on patients only. Univariate linear or logistic regression models were used to assess univariate relationships between the remodeling parameters and the flow parameters helical and vortical flow formation, eccentricity, normalized flow displacement, and WSSpeak. In a first step of multiple modeling, multiple regression models using the influential factors systolic blood pressure, AOA, and age as independent variables were built to investigate the influence of these more familiar parameters on remodeling parameters. In a second step, the models were extended by the flow parameters helical and vortical flow formations, eccentricity, and normalized flow displacement (S−S), as well as WSSpeak (S−S). Stepwise selection (P<0.15, P<0.15) was used to identify flow parameters with added value for the explanation of variability in the remodeling parameters.

As this was an exploratory study, P values were considered as descriptive rather than confirmatory throughout. Except for the modeling approaches, P<0.05 were considered to be statistically significant.

Results

Study Sample
The study sample comprised n=37 patients with AS and n=37 healthy control subjects. All were in sinus rhythm. Tables 1 and 2 show the characteristics of the study participants.

Patients with AS had a higher body mass index, higher systolic blood pressure and larger aortic diameter, higher LVMI and higher RWM, lower stroke volume index and lower LV end-diastolic volume index than controls. Furthermore, patients with AS were slightly older than controls (63 versus 60 years; P<0.042), but can be regarded as being within a similar age class. There was no difference on the sex-distribution between both groups. With increasing severity of AS, AOA, and AOA index decreased (P<0.001). RWM and LVMI was significantly higher in severe AS than in mild AS (P<0.001 and P=0.037). The prevalence of LV remodeling increased with increasing AS severity (Figure 2).

Helical and Vortical Blood Flow Formations in the Ascending Aorta
Interobserver variability to assess helical and vortical flow formations was low with an intraclass correlation coefficient of 0.82 and 0.77, respectively. Examples for helical and vortical blood flow formations are shown in Figure 1. Marked helical and vortical flow formation were more prevalent in patients with AS than in healthy subjects, and with increasing AS severity grade the prevalence generally increased (Figure 3). Table 3 summarizes all models with model estimates and their respective P values after model selection.

Helical Flow Formations
Age, ejection fraction, aortic diameter, AS grade, and AOA were not relevant with respect to the intensity of helical flow formation within the AS sample. Only when considering both

![Figure 1. Schematic of the analysis planes at the sinotubular level, midascending, and distal ascending aorta (left). Examples for marked vortical and helical flow formation and eccentricity when compared with the flow of a healthy volunteer.](image-url)
patients and controls, a higher age and a smaller AOA were associated with more intense helical flow formation \((P=0.14)\). Helical flow formation was significantly more intense for AS patients with a bicuspid aortic valve than for AS patients with a tricuspid valve \((P=0.0098)\).

**Vortical Flow Formations**

Within the AS sample, the smaller the AOA and the larger the ascending aortic diameter, the more intense the vortical flow formation was \((P=0.0274, P=0.14)\). Vortical flow formations were more pronounced for subjects with a bicuspid aortic valve than for AS patients with a tricuspid valve \((P=0.0536)\).

**Eccentricity of the Blood Flow in the Ascending Aorta**

An example for marked eccentricity is shown in Figure 1. The strong eccentricity of the blood flow, which is present in all AS severity grades, is illustrated by the mapping of the peak flow velocity in Figure 4. Marked eccentricity was more prevalent in patients with AS than in healthy subjects, and with increasing AS severity grade the prevalence generally increased (Figure 3). In the regression model, a lower AOA was strongly associated with a higher eccentricity \((P<0.0001 in all subjects, P=0.0070 in patients)\). The results of the normalized flow displacement, which quantitatively describes blood flow eccentricity, are summarized in Table 4. Normalized flow displacement was strongly associated with AOA \((P_{s2}=0.0021)\) and age \((P_{s3}=0.0662)\) among the patients with AS, with the smaller the AOA and the higher the age, the larger the flow displacement. The presence of a bicuspid aortic valve was weakly related to normalized flow displacement \((P_{s1}=0.11)\).

**WSS in the Ascending Aorta**

The distribution of WSSpeak along the aortic circumference is illustrated in Figure 5. Patients with AS exhibited an asymmetrical elevation of WSSpeak at the right/right anterior/anterior side of the aorta at level \(S_1\). The magnitude and the asymmetry of WSSpeak became more marked in \(S_2\). In \(S_3\), mild and moderate AS approached the WSSpeak of healthy controls. Severe AS still showed increased and asymmetrical WSSpeak results with peaks at the anterior/left anterior wall (even though there was no statistical difference).

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**Table 2. Patient Characteristics Separated by Aortic Stenosis Severity Grade**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>14</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/6</td>
<td>3/5</td>
<td>12/3</td>
<td>0.12</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±17</td>
<td>63±13</td>
<td>68±8</td>
<td>0.13</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168±9</td>
<td>169±11</td>
<td>172±8</td>
<td>0.18</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81±14</td>
<td>82±14</td>
<td>85±13</td>
<td>0.36</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.6±4.0</td>
<td>28.8±3.6</td>
<td>29.0±4.9</td>
<td>0.89</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.93±0.20</td>
<td>1.95±0.22</td>
<td>2.01±0.15</td>
<td>0.12</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>140±14</td>
<td>143±18</td>
<td>140±16</td>
<td>0.93</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>82±15</td>
<td>85±20</td>
<td>82±11</td>
<td>0.90</td>
</tr>
<tr>
<td>Heart rate, min(^{-1})</td>
<td>67±15</td>
<td>68±10</td>
<td>69±11</td>
<td>0.48</td>
</tr>
<tr>
<td>Aortic diameter, mm</td>
<td>33±7</td>
<td>38±7</td>
<td>35±6</td>
<td>0.52</td>
</tr>
</tbody>
</table>
| Aortic orifice area, cm\(^2\)    | 2.09±0.39| 1.28±0.18| 0.94±0.21| \(<0.001^*\)
| Aortic orifice area index, cm\(^2\)/m\(^2\) | 1.10±0.24| 0.66±0.06| 0.47±0.11| \(<0.001^*\)
| Morphology of aortic valve       |      |          |        |             |
| (tricuspid/bicuspid)             | 11/3 | 5/3      | 5/10   | 0.10        |
| LVEF, %                          | 64±6 | 66±6     | 67±6   | 0.19        |
| LSVV-index, mL/m\(^2\)           | 45±12| 42±10    | 44±10  | 0.89        |
| LVEDV-index, mL/cm               | 0.80±0.20| 0.75±0.15| 0.76±0.18| 0.63       |
| LV mass index, g/cm              | 0.79±0.19| 0.93±0.21| 1.08±0.36| 0.036*     |
| Relative wall mass, g/mL         | 1.00±0.15| 1.28±0.39| 1.43±0.42| 0.001*     |

The \(P\) value stems from the Jonckheere–Terpstra test and for sex and valve morphology from the \(\chi^2\) test.

BMI indicates body mass index; BSA, body surface area; LVEF, left ventricular end-diastolic volume; LVSV, left ventricular systolic volume.

\(^*P<0.05\).

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**Figure 2.** Prevalence of LV remodeling in patients with aortic stenosis (AS) separated for AS severity grades. AS severity grades were found statistically significant for severity of left ventricular (LV) remodeling in ordinal logistic regression \((P<0.0001)\).
In the regression model, a bicuspid aortic valve was associated with higher WSS\textsubscript{peak} in S\textsubscript{2} \((P=0.0926)\). In patients with AS, ejection fraction correlated positively with WSS\textsubscript{peak} in level S\textsubscript{1} \((P=0.0474)\) and S\textsubscript{3} \((P=0.0592)\), and a higher age was associated with higher WSS\textsubscript{peak} in level S\textsubscript{3} \((P=0.0469)\).

![Flow parameters](image)

**Figure 3.** Qualitative grades for helical flow formation, vortical flow formation, and eccentricity. Aortic stenosis (AS) severity grades were found statistically significant for helical and vortical flow formation and eccentricity in ordinal logistic regression (all \(P<0.0001\)).

**Table 3.** Multiple Regression Models on the Association of Flow Parameters (Helical and Vortical Flow Formation, Eccentricity, Normalized Flow Displacement, WSS\textsubscript{peak}) With Potential Influencing Factors, Parameter Estimates, and \(P\) Values of Final Models After Stepwise Selection

<table>
<thead>
<tr>
<th>Flow Parameter (Model)</th>
<th>Independent Variable</th>
<th>All Subjects (n=74) Estimate (\beta\pm SE (P\text{Value}))</th>
<th>Patients (n=37) Estimate (\beta\pm SE (P\text{Value}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helical flow*</td>
<td>Age</td>
<td>(-0.04\pm0.02 (P=0.14))</td>
<td>(-0.04\pm0.02 (P=0.14))</td>
</tr>
<tr>
<td></td>
<td>Bicuspid morphology</td>
<td>(0.98\pm0.48 (P=0.0406))</td>
<td>(1.13\pm0.44 (P=0.0098))</td>
</tr>
<tr>
<td></td>
<td>Aortic orifice area</td>
<td>(-1.81\pm0.38 (P=0.0001))</td>
<td>(-1.81\pm0.38 (P=0.0001))</td>
</tr>
<tr>
<td>Vortical flow*</td>
<td>Bicuspid morphology</td>
<td>(0.80\pm0.38 (P=0.0375))</td>
<td>(0.74\pm0.38 (P=0.0536))</td>
</tr>
<tr>
<td></td>
<td>Aortic diameter</td>
<td>(0.12\pm0.06 (P=0.0522))</td>
<td>(0.10\pm0.07 (P=0.14))</td>
</tr>
<tr>
<td></td>
<td>Aortic orifice area</td>
<td>(-1.84\pm0.55 (P=0.0009))</td>
<td>(-1.42\pm0.64 (P=0.0274))</td>
</tr>
<tr>
<td></td>
<td>AS (y/n)</td>
<td>(-2.71\pm1.22 (P=0.0258))</td>
<td>(-2.71\pm1.22 (P=0.0258))</td>
</tr>
<tr>
<td></td>
<td>Eccentricity*,†</td>
<td>(-2.74\pm0.47 (P=0.0001))</td>
<td>(-2.17\pm0.81 (P=0.0070))</td>
</tr>
<tr>
<td>Normalized flow displacement, (S_1)†</td>
<td>Bicuspid morphology</td>
<td>(0.032\pm0.02 (P=0.11))</td>
<td>(0.032\pm0.02 (P=0.11))</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction</td>
<td>(0.002\pm0.001 (P=0.0668))</td>
<td>(0.002\pm0.001 (P=0.0668))</td>
</tr>
<tr>
<td></td>
<td>AS×aortic diameter</td>
<td>(0.002\pm0.0003 (P=0.0001))</td>
<td>(0.002\pm0.0003 (P=0.0001))</td>
</tr>
<tr>
<td>Normalized flow displacement, (S_2)†</td>
<td>Aortic orifice area</td>
<td>(-0.039\pm0.004 (P=0.0788))</td>
<td>(-0.041\pm0.004 (P=0.0021))</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>(-0.001\pm0.0004 (P=0.788))</td>
<td>(-0.001\pm0.0004 (P=0.788))</td>
</tr>
<tr>
<td>Normalized flow displacement, (S_3)†</td>
<td>Age</td>
<td>(0.001\pm0.0001 (P=0.0662))</td>
<td>(-0.001\pm0.0001 (P=0.0662))</td>
</tr>
<tr>
<td></td>
<td>AS×age</td>
<td>(0.002\pm0.0002 (P=0.0001))</td>
<td>(0.002\pm0.0002 (P=0.0001))</td>
</tr>
<tr>
<td>(WSS_{peak}^* S_1)†</td>
<td>Ejection fraction</td>
<td>(0.01\pm0.01 (P=0.0269))</td>
<td>(0.02\pm0.01 (P=0.0474))</td>
</tr>
<tr>
<td></td>
<td>AS×ejection fraction</td>
<td>(0.01\pm0.001 (P=0.0001))</td>
<td>(0.02\pm0.01 (P=0.0001))</td>
</tr>
<tr>
<td>(WSS_{peak}^* S_2)†</td>
<td>Age</td>
<td>(-0.01\pm0.003 (P=0.0002))</td>
<td>(-0.01\pm0.003 (P=0.0002))</td>
</tr>
<tr>
<td></td>
<td>Bicuspid morphology</td>
<td>(0.22\pm0.13 (P=0.0926))</td>
<td>(0.22\pm0.13 (P=0.0926))</td>
</tr>
<tr>
<td></td>
<td>AS×ejection fraction</td>
<td>(0.01\pm0.002 (P=0.0001))</td>
<td>(0.01\pm0.002 (P=0.0001))</td>
</tr>
<tr>
<td></td>
<td>AS×aortic orifice area</td>
<td>(-0.22\pm0.07 (P=0.0043))</td>
<td>(-0.22\pm0.07 (P=0.0043))</td>
</tr>
<tr>
<td>(WSS_{peak}^* S_3)†</td>
<td>Age</td>
<td>(-0.01\pm0.003 (P=0.0001))</td>
<td>(-0.01\pm0.004 (P=0.0469))</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction</td>
<td>(-0.01\pm0.003 (P=0.0001))</td>
<td>(-0.01\pm0.004 (P=0.0469))</td>
</tr>
<tr>
<td></td>
<td>AS×ejection fraction</td>
<td>(0.01\pm0.004 (P=0.0004))</td>
<td>(0.01\pm0.004 (P=0.0004))</td>
</tr>
<tr>
<td></td>
<td>AS×aortic diameter</td>
<td>(-0.01\pm0.01 (P=0.0859))</td>
<td>(-0.01\pm0.01 (P=0.0859))</td>
</tr>
<tr>
<td></td>
<td>AS×aortic orifice area</td>
<td>(-0.13\pm0.07 (P=0.0540))</td>
<td>(-0.13\pm0.07 (P=0.0540))</td>
</tr>
</tbody>
</table>

Only parameters remaining in the final model are shown. AS indicates aortic stenosis; and WSS\textsubscript{peak}, peak systolic wall shear stress.

*Ordinal logistic regression.
†Model without AS (y/n) and interaction terms as introduction of these led to quasi-complete separation.
‡Linear regression.
…Parameter not presented to selection process.
Association of Flow Parameters With Parameters of LV Remodeling

The results of the regression models are shown in Table 5. In the univariate investigation, stronger vortical flow formations were associated with higher LVMI, higher RWM, and higher probability of LV remodeling \((P=0.0213, P=0.0115, \text{and } P=0.0285, \text{respectively})\). Higher eccentricity was associated with higher RWM \((P=0.0270)\). A higher normalized flow displacement in level S2 was significantly associated with a higher LVMI \((P=0.0410)\), a higher RWM \((P=0.0023)\), and with the presence of LV remodeling \((P=0.0459)\). A higher normalized flow displacement in level S1 was significantly associated with higher LVMI \((P=0.0056)\) and higher RWM \((P=0.0076)\). A higher WSS peak at level S1 was significantly associated with higher LVMI \((P=0.0268)\).

In multiple regression, LVMI, RWM, and presence of LV remodeling were found to be significantly negatively associated with AOA. The covariates age and systolic blood pressure were not found to be significant for the remodeling parameters. The only parameter in addition to AOA that was linked to parameters of LV remodeling was the normalized flow displacement in level S3. Its addition improved the model for LVMI to \(R^2=0.3108\) when compared with \(R^2=0.1083\) \((P=0.0058)\) and for RWM to \(R^2=0.3351\) (from 0.2575; \(P=0.0713)\), indicating that a larger normalized flow displacement was associated with a higher LVMI and RWM.

Discussion

Patients with AS exhibited a high prevalence of abnormal flow patterns with regard to helical and vortical flow formations and eccentricity. Vortical flow formation, eccentricity, and normalized flow displacement were strongly associated with AOA, indicating that the obstruction influences boundary layer separation and leads to significant destabilization of the antegrade blood flow. As there was no difference in the ascending aortic size between the AS severity grades as well as only a weak general association between aortic size and vortical flow formation, these flow abnormalities can be mainly attributed to the abnormal AOA. In addition to the mere flow obstruction, the bicuspid morphology of the valve was a relevant contributor to abnormal blood flow. This finding is in agreement with previous studies that demonstrated altered blood flow in bicuspid valve disease even in the absence of a stenosis.17,31

Abnormal blood flow may reflect an elevated afterload for the LV, as energy is dissipated by frictional losses associated with the various flow phenomena and with the aortic wall.14 The latter hypothesis is strengthened by the observation of the univariate analysis, where vortical flow formation, eccentricity, and normalized flow displacement were associated with signs of LV remodeling. In the multiple model, however, normalized flow displacement was the only parameter that had impact on LV remodeling in addition to AOA. The relatively small impact of flow parameters on remodeling parameters in multiple models when compared

Table 4. Normalized Flow Displacement (Mean±SD)

<table>
<thead>
<tr>
<th>Aortic Level</th>
<th>Healthy Controls</th>
<th>Mild AS</th>
<th>Moderate AS</th>
<th>Severe AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>0.11±0.04</td>
<td>0.18±0.05</td>
<td>0.20±0.05</td>
<td>0.19±0.07</td>
</tr>
<tr>
<td>S2</td>
<td>0.08±0.05</td>
<td>0.14±0.04</td>
<td>0.17±0.04</td>
<td>0.19±0.05</td>
</tr>
<tr>
<td>S3</td>
<td>0.04±0.01</td>
<td>0.12±0.06</td>
<td>0.16±0.04</td>
<td>0.14±0.07</td>
</tr>
</tbody>
</table>

AS indicates aortic stenosis.
with univariate models might be explained by their high correlation to AOA (helix: $r = -0.31$, vortex: $r = -0.52$, eccentricity: $r = -0.48$, normalized flow displacement $r = -0.56$). Thus, the added value of flow parameters to models containing AOA is limited, but it was present at least for normalized flow displacement. The association of LV remodeling with AOA underlines that remodeling is a feature of AS severity. Whether it is also a feature of disease progression needs confirmation in a longitudinal study.

Hypertension is another contributor to LV remodeling. The mean systolic blood pressure was slightly elevated in the AS group when compared with the healthy controls, whereas the various severity grades of AS did not differ on the blood pressure. Nevertheless, a comparable blood pressure in a patient with severe versus mild AS may have varying degree of LV impact, as it is the combination of vascular and valvular LV hemodynamic load that is decisive. In this study, the multiple regression model on LV remodeling accounted for blood pressure and did not find a significant influence among the patients with AS.

Blood flow abnormalities are also thought to contribute to poststenotic aortic dilatation by the chronic vascular wall strain. Patients with AS revealed significantly elevated WSS$_\text{peak}$ at the level of the sinotubular junction and midascending aorta. This was observed similarly in all severity grades of AS, underlining that the aortic blood flow changes as soon as the morphology of the aortic valve changes, even in the absence of a clinically relevant obstruction. Higher WSS$_\text{peak}$ was not linked to markers of LV remodeling, but adds knowledge to the development of poststenotic dilatation in AS.

In conclusion, this hypothesis-generating study using 4D flow CMR provided new insights into the aortic blood flow in the presence of AS. Blood flow was abnormal in AS, with increasing intensity as the AOA decreased, and enhanced by the presence of a bicuspid aortic valve. In addition to AOA, the flow parameter normalized flow displacement was significantly linked to signs of LV remodeling and might therefore serve as surrogate of unfavorable blood transport and myocardial stress. WSS was elevated and asymmetrically distributed in the aorta in all severity grades of AS. Whereas this parameter was not associated with LV remodeling, the findings suggested that mechanotransduction risks for poststenotic dilatation are present already in the early stages of AS. At that time, the results are mainly descriptive and add to the knowledge base surrounding flow patterns in the proximity of AS. The added clinical value of this new information still has to be proven. Yet, we speculate that the fluid dynamics information might enable a better characterization of the disease stage in the future.

Figure 5. Peak systolic wall shear stress (WSS$_\text{peak}$) distribution along the aortic circumference. Comparison of the aortic stenosis (AS) severity grades with healthy controls. Significant differences between the groups with *$P<0.05$ and **$P<0.001$. Tests were performed per location. A indicates anterior; L, left; LA, left anterior; LP, left posterior; P, posterior; R, right; RA, right anterior; RP, right posterior; S1, sinotubular junction; S2, midascending aorta; and S3, distal ascending aorta.
Limitations

There are several limitations in this work that make it a hypothesis-generating study. (1) Further studies with larger samples, more quantitative flow information and integration of multimodality information are needed to test the generated hypothesis that flow pattern and remodeling are linked and to allow adequate subgroup-analysis. (2) Helical and vortical flow patterns were only assessed qualitatively. Absolute quantification of flow and energy loss might be superior and more objective; furthermore, volumetric assessments might overcome limitations of 2D analyses. However, validation using magnetic resonance imaging, CFD, and particle image velocity data has only recently emerged, with mixed results relating to segmentation and resolution-related errors.35–39 The computation of these parameters requires specialized algorithms and volumetric segmentations, neither of which were available for this study. Additional development and validation needs to be performed before the quantitative approaches can be integrated in future clinically oriented studies. After having overcome these challenges, extending the definitions of the tested flow parameters from 2D to 3D and achieving a volumetric description will certainly be an important future direction. (3) Age is a known influencing factor for ascending aortic hemodynamics.29 The groups were statistically not perfectly age matched, but they were in the same age category (middle-aged adults). To account for this age difference, age was included in the regression models.

Acknowledgments

We acknowledge the technicians Kerstin Kretschel, Evelyn Polzin, Denise Kleindienst, and Franziska Neumann for acquiring the CMR data and the study nurses Elke Nickel-Szczech and Antje Els for assisting in the organization of the CMR scans. We thank Mrs Susanne Schwenke (scossis, Berlin) for her valuable support of the statistical analyses.

Sources of Funding

Deutsche Stiftung für Herzforschung (Frankfurt, Germany; F/37/12; Dr von Knobelsdorff-Brenkenhoff), National Institutes of Health (NIH) K25HL119608 (Dr Barker), and NIH R01HL115828 (Dr Markl).

Disclosures

None.

References

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Aortic Blood Flow in Aortic Stenosis


Aortic orifice area and blood flow velocity are sometimes considered incomplete to characterize the stress for the left ventricle caused by aortic stenosis, which is highly variable and leads to a broad range of ventricular impairment. Unfavorable left ventricular remodeling is an important prognostic factor and contributes significantly to the development of heart failure in patients with aortic stenosis. There are many attempts to better characterize the myocardial stress provoked by aortic stenosis. In this study, 4-dimensional flow magnetic resonance imaging was used to characterize the poststenotic blood flow in the ascending aorta, which is suspected to influence ventricular afterload and therefore ventricular remodeling. The aortic blood flow pattern in aortic stenosis was completely different when compared with healthy controls. Vortical and helical flow formations were more prevalent, the lower the orifice area was. Also, the peak blood flow velocity was more eccentric and the flow displacement higher in patients with aortic stenosis, and the wall shear stress elevated and asymmetrically distributed. In addition to aortic orifice area, flow displacement, which quantitatively describes the blood flow eccentricity, was associated with markers of left ventricular remodeling. These results are preliminary, but are hypothesis-generating and should stimulate future trials about the interplay of valvular disease, myocardial impairment, and blood flow to comprehensively characterize aortic valve disease.
Evaluation of Aortic Blood Flow and Wall Shear Stress in Aortic Stenosis and Its Association With Left Ventricular Remodeling
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_Circ Cardiovasc Imaging_. 2016;9:e004038
doi: 10.1161/CIRCIMAGING.115.004038

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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