Replicating Patient-Specific Severe Aortic Valve Stenosis With Functional 3D Modeling

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Background—3D stereolithographic printing can be used to convert high-resolution computed tomography images into life-size physical models. We sought to apply 3D printing technologies to develop patient-specific models of the anatomic and functional characteristics of severe aortic valve stenosis.

Methods and Results—Eight patient-specific models of severe aortic stenosis (6 tricuspid and 2 bicuspid) were created using dual-material fused 3D printing. Tissue types were identified and segmented from clinical computed tomography image data. A rigid material was used for printing calcific regions, and a rubber-like material was used for soft tissue structures of the outflow tract, aortic root, and noncalcified valve cusps. Each model was evaluated for its geometric valve orifice area, echocardiographic image quality, and aortic stenosis severity by Doppler and Gorlin methods under 7 different in vitro stroke volume conditions. Fused multimaterial 3D printed models replicated the focal calcific structures of aortic stenosis. Doppler-derived measures of peak and mean transvalvular gradient correlated well with reference standard pressure catheters across a range of flow conditions ($r=0.988$ and $r=0.978$ respectively, $P<0.001$). Aortic valve orifice area by Gorlin and Doppler methods correlated well ($r=0.985$, $P<0.001$). Calculated aortic valve area increased a small amount for both methods with increasing flow ($P=0.002$).

Conclusions—By combing the technologies of high-spatial resolution computed tomography, computer-aided design software, and fused dual-material 3D printing, we demonstrate that patient-specific models can replicate both the anatomic and functional properties of severe degenerative aortic valve stenosis. (Circ Cardiovasc Imaging. 2015;8:e003626. DOI: 10.1161/CIRCIMAGING.115.003626.)

Key Words: aortic stenosis ■ 3D printing ■ echocardiography ■ functional modeling ■ TAVR

The accurate identification and characterization of severe aortic stenosis (AS) has long been important, and novel therapies, such as transcatheter aortic valve replacement, have further emphasized this clinical need. We have previously reported a proof-of-concept that patient-specific multimaterial 3D printed models of AS can be created based on clinical computed tomography (CT) imaging data.1 Diagnostic challenges, such as low-flow low-gradient AS, evaluation of afterload effect on AS severity quantification, and selection or optimization of catheter-based valve therapies are clinical problems that could be further investigated by using patient-specific functional models to replicate the geometry and flow conditions of aortic valve stenosis. The goal of this study was to investigate the effect of various flow conditions across numerous patient-specific AS models and to evaluate the correlation between Doppler and catheter-based techniques for the assessment of aortic valve area (AVA) under controlled and reproducible flow conditions.

See Clinical Perspective

Methods

All patients with severe degenerative AS being evaluated for transcatheter aortic valve replacement at our institution undergo an ECG-gated 64 slice multi-detector CT (Philips 64 Brilliance, Best, Netherlands). The high spatial resolution and isotropic voxel data acquisition of CT provide clear depiction of the aortic valve cusps and calcific regions. From a pool of patients who had undergone a clinical transthoracic echocardiogram and a transcatheter aortic valve replacement assessment CT within 30 days (N=300), 8 patients with a clinical diagnosis of severe AS (6 with tricuspid AV and 2 with bicuspid AV) were selected for anatomic modeling to represent a wide range of aortic valve geometry and function. The patient studies were selected based on aortic annulus diameter, calcium distribution, Doppler AVA, number of functional valve cusps, and baseline echocardiographic left ventricular stroke volume (SV; Table 1). Each patient provided informed written consent to participate in the study as approved by the institutional review board.

Gated CT DICOM images at mid-systole (30% phase of the R wave–R wave interval) were imported into anatomic modeling software (Mimics, Materialise, Belgium) for each patient. The left ventricular outflow tract (LVOT), valve cusps, ascending aorta, and all calcified tissues were segmented individually and then reconstructed into a model consisting of 2 paired stereolithographic...
files composed of the calcified and noncalcified structures within the data set. These stereolithographic files were exported to an Objet260 Connex Printer (Stratasys) where the 2 files were used to create a fused material 3D construct of the predefined anatomic region. The region printed consisted of the LVOT (2 cm proximal to the aortic annulus), the entire aortic valve complex (annulus, cusps, and sinuses of Valsalva), and the proximal ascending aorta (≤10 cm distal to the aortic annulus). Cusp calcification was replicated using rigid print material (VeroWhitePlus RGD835, Objet) and soft tissue structures, including the noncalcified cusp segments, LVOT, and ascending aorta; were replicated using a rubber-like material (TangoPlus FLX930, Objet; Figure 1). Each model was coated externally with a thin <0.5 mm layer of silicone. Print material properties were chosen to best represent the complex tissue properties of a diseased aortic root. The print material used for the noncalcified anatomic regions (TangoPlus) has a manufacturer-reported elastic modulus of 0.146 MPa at 20% strain. The print material used for the calcified anatomic region (VeroWhitePlus) has a manufacturer-reported elastic modulus of 2000 to 3000 MPa. Before functional studies, each fabricated model underwent a static multidetector 64 slice CT to assess the geometric accuracy of the printed model compared with the previously acquired clinical CT study. At this scan, we compared the regional calcium deposition and the geometric aortic valve orifice area by direct short-axis planimetry. In addition, we performed an imaging overlay of matched short-axis slices from the clinical and model CT to ensure that regional calcium landmarks were accurately replicated for each model (as in Figure 1).

A single patient-specific model construct was sectioned and subjected to tests of its material properties. The rubber-like material underwent tensile testing, and the rigid, calcific region underwent compression testing to determine stiffness properties of each component material. For compression testing, each sample was cut into a short cylinder with a 2 mm diameter. For tensile testing, the rubber-like material samples were cut into strips with a height of 2 mm and a width of 4 mm.

**Patient-Specific Functional Evaluation**

Each fabricated patient-specific model was coupled to our pulsatile flow loop to assess the functional characteristics of the valve under a range of controlled forward flow conditions. The details of the flow loop system have been previously described. The flow loop includes a pulsatile pump driven by a heartbeat simulator, arterial compliance/loop system have been previously described. The flow loop to assess the functional characteristics of the valve under a flow condition was used for all pressure measurements. Continuous wave Doppler ultrasound was interrogated from an imaging window representing the suprasternal view, with the Doppler ultrasound beam aligned parallel to the stenotic flow. Transvalvular peak and mean gradient, peak velocity, time velocity integral, and Doppler ejection time were recorded for each model under the 7 different flow conditions. An average of 3 consecutive beats were recorded for each flow condition using an offline echo workstation. Aortic valve area was calculated by the Gorlin catheter-based method and by the Doppler continuity method. Specifically, the AVA was calculated as follows:

\[
AVA_{Dop} = \frac{\text{Stroke volume}}{\text{TVI}} \quadAVA_{Cath} = \frac{Q}{44.3 \sqrt{\text{mean gradient}}}
\]

SV is measured in mL/beat; TVI is measured by continuous wave Doppler; \(Q\) is mean transaortic flow in mL/s measured by ultrasonic flow probe; and mean gradient is measured by high-fidelity transducer placed 20 mm on either side of the geometric orifice area. An average of 12 consecutive beats was used for all pressure measurements.

### Table 1. Patient Characteristics

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AVA by CT, cm²

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*Body surface area.

### Statistical Analysis

Data are expressed as mean value and standard deviation. Correlation between echocardiography and catheter-derived parameters was...
assessed using Pearson’s coefficient. The Bland–Altman method was used to assess agreement between the Doppler and Gorlin methods. To evaluate differences between the AVA, SV, and measurement technique, a linear mixed model was used. The linear mixed model included the fabricated valve model as a random effect (modeled with random slope and intercept) and the SV and the measurement technique (Doppler or Gorlin) as fixed effects. A P value <0.05 was considered statistically significant. Statistical analysis was performed using R 3.0.2 software.

Results

Geometric and Material Properties
The qualitative comparison of each patient-specific model to the corresponding clinical CT demonstrated accurate reproduction of the calcific deposits within the LVOT, aortic cusps, and aortic root. Additionally, the shape of the maximal orifice area at the level of the cusp tips was similar to that of the clinical CT study, and the calcium deposition was substantially replicated for each of the 8 models created (Figure 3). There was no significant discrepancy between the geometric orifice area by direct planimetry of each model compared with the corresponding geometric orifice area of the clinical CT. Compression testing of calcific materials yielded a Young’s modulus of 62 MPa. Tensile testing of the rubber-like material yielded a Young’s modulus of 0.4 MPa.

Functional AS Performance
When coupled to the in vitro flow loop, we were able to successfully replicate the basal transvalvular SV and prespecified adjusted volume conditions for each of the 8 patient-specific models tested. All fabricated constructs retained structural integrity under the range of pressure (mean Doppler peak gradient 70.8 mmHg; limits 26.7–116.5 mmHg) and SVs (mean 66.9 mL; limits 34.3–124.2 mL) tested.

Figure 1. Fabrication of patient-specific models. Clinical computed tomography (CT) DICOM data (top left) are analyzed to identify calcified and noncalcified aortic tissues then converted into computer-aided design (CAD) stereolithographic (STL) files (top right). The CAD–STL files of the 2 tissue types are exported to a 3D printer to create a physical dual-material fused construct (bottom right) of the predefined anatomic region (outflow tract, aortic root, leaflets, and ascending aorta). CT of the model demonstrates a planar replication valve orifice geometry (bottom left).

Figure 2. Flow loop schematic and hemodynamics. Flow direction is indicated. Inset, Example of flow and pressure gradient waveforms.
Under pulsatile flow conditions, each model was assessed for its 2D echocardiographic image quality and compared with the corresponding clinical echocardiogram. In general, the ultrasound imaging properties of the functional patient-specific constructs were qualitatively similar to the clinical echocardiogram images. In each case, the replication of aortic root geometry and cusp calcification was notably similar between clinical and in vitro echo studies. In addition, when matched to the SV and pressure gradient reported during the clinical echocardiogram, the continuous wave Doppler study of the patient-specific model demonstrated Doppler signal quality, (Figure 4) as well as Doppler-derived measures of mean gradient and peak velocity, which were qualitatively and quantitatively similar to the clinical Doppler study (Table 2).

### Aortic Valve Area

By Doppler method, the mean $AVA_{Dop}$ was 0.71±0.20 cm$^2$ for all flow conditions and all patient-specific models (limits 0.40–1.15 cm$^2$). The Doppler peak transvalvular pressure gradient was 70.8±23.4 mm Hg (limits 26.7–116.5 mm Hg), and the Doppler mean gradient was 35.7±13.0 mm Hg (limits 12.6–62.2 mm Hg). By catheter method, mean $AVA_{Cath}$ was 0.74±0.22 cm$^2$ (limits 0.41–1.23 cm$^2$); the transvalvular peak gradient was 70.8±23.1 mm Hg (limits 26.7–116.6 mm Hg), and the mean transvalvular gradient was 33.9±12.1 mm Hg (limits 13.6–61.3 mm Hg). $AVA_{Dop}$ correlated well with catheter-derived $AVA_{Cath}$ ($r=0.985$, $P<0.001$). There was good agreement between the 2 methods (bias=−0.03 cm$^2$ and limits of agreement −0.11 to 0.05 cm$^2$; Figure I in the Data Supplement). The Doppler transvalvular peak and mean gradients correlated well with the catheter-derived peak and mean gradients ($r=0.988$ and $r=0.978$, $P<0.001$, respectively). Agreement between methods was excellent with minimal bias for both peak and mean gradient (bias=0.1 mm Hg and bias=1.8 mm Hg, respectively; Figure I in the Data Supplement). Individual regression lines and within patient-specific model correlation estimates for Doppler and catheter-derived parameters are shown in Figure II and Table in the Data Supplement. Figure 5 depicts the relationship between the Gorlin and...
the Doppler methods of AVA determination for each patient model under multiple flow conditions. The 8 fabricated models together (modeled with a linear mixed model) demonstrated that the quantification of AVA was dependent on both the SV ($P=0.002$) and the measurement technique ($P<0.001$). The range of SVs assessed for each patient-specific model, as well as the regression line for each AVA measurement method, are depicted in Figure 6. Each patient-specific model demonstrated a different slope of flow dependency for the AVA measurement, with only model No. 4 failing to show flow dependence ($P=0.435$).

The contraction coefficient of flow across the aortic valve was calculated for each model as the ratio of the effective AVADop divided by the geometric AVA (as measured by direct CT planimetry). For the baseline flow condition, the contraction coefficients were as follows: patient 1=0.65, patient 2=0.59, patient 3=0.78, patient 4=0.67, patient 5=1.0, patient 6=0.69, patient 7=0.85, and patient 8=0.85.

**Discussion**

We describe the creation of 8 patient-specific multimaterial 3D models of severe AS and performed a functional assessment of each model under 7 different flow conditions. Each model replicated well the specific anatomic geometry of degenerative severe AS with a faithful reproduction of the calcium deposition, cusp thickening, and valve orifice shape for each patient. We demonstrate that whether measured by Gorlin or Doppler method, the AVA of a 3D printed model is dependent on the transvalvular flow rate and that the magnitude of this flow dependence is variable between models. As such, these patient-specific models provide a novel environment to explore the functional characteristics of degenerative AS.

**Replication of Regional Calcium Heterogeneity and Valve Orifice Geometry**

One of the strengths of clinical CT imaging is the robust ability to identify calcified tissues. The CT digital data were processed within computer-aided design software and exported to a multimaterial 3D printer to create dual material–fused 3D models of severe AS. This printing process created constructs that accurately reflected the anatomy with excellent visual correlation to the corresponding clinical CT. In each case, the unique pattern and distribution of calcium deposition was faithfully replicated, and the geometric orifice area

<table>
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<th>Table 2. Comparison of the Average Variables of Aortic Stenosis Severity Between Patients and the Corresponding 3D Printed Models</th>
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<td>Stroke volume, mL/beat</td>
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<tr>
<td>Mean Doppler gradient, mmHg</td>
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<tr>
<td>Peak Doppler velocity, cm/s</td>
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<td>AVA Doppler, cm²</td>
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</table>

AVA indicates aortic valve area.

Figure 5. Clinical and in vitro aortic valve area for each patient model. The AVA from a clinical echocardiogram is plotted along with the range of AVA by Gorlin and Doppler method for each patient model. AVA indicates aortic valve area.
of the aortic valve was remarkably consistent with the clinical geometric orifice area measurements.

Material Properties

Young’s Modulus is a measure of material stiffness pertaining to elastic materials and is calculated as the slope of the linear portion of a stress/strain curve. Compression testing of calcific printed material yielded a Young’s modulus of 62 MPa. Although this sample of the material stiffness of a single printed model is slightly lower than the reported values of 100 to 1000 MPa for calcified human tissue tested using nano-indentation, it demonstrates a reasonable replication of tissue, which can vary widely in the extent and thickness of calcification. The modulus value of 62 MPa is significantly less than the isolated material properties of the calcific print material (2000–3000 MPa), which likely reflects an appropriate fusion of calcified and noncalcified regions within the printed model. Tensile testing yielded a Young’s Modulus of 0.4 MPa. Comparably, nondiseased human aortic root tissue analyzed using biaxial mechanical testing methods have been reported with a slightly higher elastic modulus of 1.24±0.563 MPa.9

There are several important considerations when comparing the material properties of 3D printed models with human tissues. The described models represent a rudimentary replication of the multifaceted and highly variable material properties of a diseased human aortic root complex. Within each anatomic region, the printed materials are homogenous and isotropic as opposed to actual human tissues, which are anisotropic because of collagen and elastic fiber alignment. In addition, the amount and location of calcium deposition is highly variable for any given patient with severe AS. Despite these inherent limitations, the models we describe performed well as functional models of AS under varied flow conditions. An initial examination of the mechanical properties of our fused-material models demonstrated an acceptable fusion of material properties (mixing elastic and calcific properties), which approximate the published values for the human aortic root.8,9

Image Quality and Hemodynamics Achieved

Doppler evaluation revealed that the patient-specific models showed similar signal quality and replicated the clinically meaningful hemodynamic values, such as AVA and mean pressure gradient. The functional testing of each patient model began by replicating the transvalvular SV as defined by the patient’s clinical Doppler echocardiogram. Under these conditions, the Doppler evaluation of the model stenosis was similar to the clinically derived Doppler AVA (Figure 4). For the flow conditions tested, the differences between the model AVA and clinical AVA measures were small (1.9%–5.7% average difference; Table 2). In addition, the geometric valve area of the models were an accurate replication of the patients’ valve area, and the ultrasound properties of the models were sufficient to permit Doppler imaging quality that was similar to the clinical Doppler imaging quality. Although other investigators have created models of the aortic root, heart valves, and other congenital heart defects from echocardiographic and CT imaging data, none of these anatomic models were designed to be functional constructs or were studied as a tool to replicate a clinical pathological flow condition. We present a combination of anatomic and functional flow modeling of patient-specific conditions which is novel.

Relation Between AVA and Flow

In keeping with clinical expectations, our Doppler echocardiography results correlated well with the catheter hemodynamic data for the derivation of AVA across a range of flow rates. Under the controlled flow conditions tested, the AVA derived by either the Gorlin Method or Doppler method was well correlated. This correlation of methods is higher than expected clinically and may in part be because of our methodology where the Doppler AVA calculation relied on a reference
standard SV (flowmeter measurement) and not a Doppler-derived estimate of LVOT SV. At the baseline flow (defined by the clinical Doppler SV), the ratio between the $AVA_{Dop}$ and the geometric orifice area (the contraction coefficient) ranged between 0.6 and 1.0. This value is consistent with prior clinical reports and supports the notion that the difference between the effective and anatomic valve area can be influenced by both the shape of the valve inflow and the size of the valve orifice.16

As SV increased, so did the AVA calculated by either Gorlin or Doppler methods in 7 out of the 8 models. This finding supports the validity of the 3D printed models as appropriate functional constructs of AS. Although created from a single CT phase (30% phase of the R-R interval), the flow dependence of the AVA measurement indicates that the printed valve orifice area is not entirely fixed and that presumably the geometric orifice actually enlarges to a small degree under increased flow conditions. This finding is consistent with multiple prior clinical studies that demonstrated the measurement of the AVA is flow-dependent.17,18 However, in a clinical study of 27 patients with AS, Shively et al demonstrated that the degree of AVA flow dependence can vary widely between patients and may be highly influenced by the geometry of the aortic valve orifice.19 In that study, the patients with a star-shaped valve orifice demonstrated the greatest degree of AVA flow dependency, whereas patients with an off-center or ovoid valve orifice demonstrated little or no AVA flow dependence. Our modeling study suggests a similar phenomenon, with only one patient (model No. 4) not demonstrating flow dependence. On inspection of the orifice geometry of that model (Figure 3), we see that it has an ovoid valve orifice with no available cusp tissue, which could expand to create a greater AVA under higher flow conditions. This variable valve geometry highlights the importance of patient-specific anatomic considerations and demonstrates the potential utility of functional models—to identify and explain hemodynamic variations which may be encountered during clinical imaging evaluation.

Limitations
Each model was fabricated from CT imaging data representing only a single moment of the cardiac cycle (mid systole). Because severe AS is a pathological state with relatively fixed cusps, this snapshot approach to functional modeling is only a minor limitation. However, this concept would be more important for modeling other aortic valve conditions, such as mild AS or aortic regurgitation, where a more dynamic valve orifice area would be expected. We report results using 8 patient models in this initial investigation; however, each was chosen to represent a different variation in aortic root/valve complex geometry, calcification distribution, and aortic valve area. Each model was tested under multiple different flow conditions representing a large variation in potential flow scenarios for each patient-specific model.

Future Perspectives
Development of patient-specific physical 3D models that accurately replicate the unique anatomic and functional characteristics of severe AS has many potential applications. It is possible that patient-specific models could be used to refine Doppler-derived AS quantification under low flow/low gradient conditions. Additionally, patient-specific models could be used in the development and validation of 4D phase-contrast magnetic resonance imaging for the accurate quantification of aortic root flow properties and AS severity. Finally, a potential application of patient-specific modeling is the development of functional models to predict and improve the acute hemodynamic performance of transcatheter valve treatment strategies (Figure 7). As 3D printing technology becomes increasingly available, the expense and fabrication time for patient-specific functional modeling is expected to decrease.

Conclusions
Functional 3D models of patient-specific aortic valve and root anatomy can be produced by coupling together high-spatial resolution CT, computer-aided design software, and fused dual-material 3D printing. We demonstrate that patient-specific models can accurately replicate both the anatomic and functional properties of severe AS.

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References
Four-dimensional printing of patient-specific anatomic models can provide a novel environment to explore the functional characteristics of degenerative aortic stenosis. In this report, we describe the creation of 8 patient-specific multimaterial 3D models of severe aortic stenosis and performed a functional assessment of each model under different in vitro flow conditions. Each model replicated well the specific anatomic geometry of degenerative severe aortic stenosis with a faithful reproduction of the calcium deposition, cusp thickening, and valve orifice shape. The functional evaluation of each model by Doppler and catheter-based methods also replicated the patient-specific aortic stenosis severity. We demonstrate that 3D models of aortic stenosis can be readily created by combing the technologies of high-spatial resolution computed tomography, computer-aided design software, and fused dual-material 3D printing. Such patient-specific functional models may have multiple applications, including the exploration of clinical low flow conditions, novel imaging methods, and catheter-based interventions.
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Supplemental Figure 1. Agreement between Doppler and catheter-derived variables. Bland-Altman plots showing small bias and narrow limits of agreement between the two methods for AVA, peak gradient (PeakGr) and mean gradient (MeanGr) for all 8 models.
**Supplemental Figure 2.** Linear correlation between Doppler and catheter-derived variables within each Patient-Specific model. AVA, peak gradient and mean gradient correlation plots for all 8 Patient-Specific models.
**Supplemental Table.** Correlation between Doppler and catheter-derived variables within each Patient-Specific model.

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<td>&lt;0.001</td>
<td>0.997</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8</td>
<td>0.495</td>
<td>0.258</td>
<td>0.997</td>
<td>&lt;0.001</td>
<td>0.995</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Supplemental Video.** A patient-specific functional 3D model is shown during an in vitro flow study. Note the 3D printed “calcific” white regions within the aortic root as well as the preserved pulsatility of the non-calcified anatomic regions.