Valvular Heart Disease

Aortic Valve Adaptation to Aortic Root Dilatation
Insights Into the Mechanism of Functional Aortic Regurgitation From 3-Dimensional Cardiac Computed Tomography

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Background—The 3-dimensional relationship between aortic root and cusp is essential to understand the mechanism of aortic regurgitation (AR) because of aortic root dilatation (ARD). We sought to test the hypothesis that the stretched cusps in ARD enlarge to compensate for ARD.

Methods and Results—Computed tomography imaged 92 patients (57 with ARD, 29 with moderate to severe AR, 28 without significant AR) and 35 normal controls. Specialized 3-dimensional software measured individual cusp surface areas relative to maximal mid-sinus cross-sectional area and minimal 3-dimensional annular area, coaptation area fraction, and asymmetry of sinus volumes and intercommissural distances. Total open cusp surface area increased (P<0.001) from 7.6±1.4 cm²/m² in normals to 12.9±2.2 cm²/m² in AR-negative and 15.2±3.3 cm²/m² in AR-positive patients. However, the ratio of closed cusp surface area to maximal mid-sinus area, reflecting cusp adaptation, decreased from normals to AR-negative to AR-positive patients (1.38±0.20, 1.15±0.15, 0.88±0.15; P<0.001), creating the lowest coaptation area fraction. Cusp distensibility (closed diastolic versus open area) decreased from 20% in controls and AR-negative patients to 5% in AR-positive patients (P<0.001). Multivariate determinants of AR and coaptation area fraction reflected both sinus size and cusp-to-annular adaptation. ARD was also progressively asymmetrical with root size, and individual cusp surface areas failed to match this asymmetry.

Conclusions—Aortic cusp enlargement occurs in ARD, but cusp adaptation and distensibility become limited in prominent, asymmetrical ARD, leading to AR. Optimal AR repair tailored to individual patient anatomy can benefit from appreciating valve adaptation and 3-dimensional relationships; understanding cusp adaptation mechanisms may ultimately provide therapeutic opportunities to improve such compensation. (Circ Cardiovasc Imaging. 2014;7:828-835.)

Key Words: aortic aneurysm ■ aortic regurgitation ■ aortic valve insufficiency ■ computed tomography ■ three dimensional imaging

Aortic root dilatation (ARD) has long been recognized to cause functional aortic regurgitation (AR) with anatomically normal aortic valve (AV) cusps that are stretched by the dilated root and, therefore, fail to close. Although AV sparing operations have been developed to manage this clinical condition, the mechanism of AR has been poorly understood to explain why patients with similar aortic root size show different AR severity (Figure 1). Quantifying valve and aortic root geometry in patients with ARD is necessary to address the fundamental question of whether the aortic cusps enlarge in response to aortic root stretch, and whether such adaptation effectively compensates for root dilatation. Although aortic cusp elongation has been reported in a limited number of patients with ARD by either 2-dimensional echocardiography or intraoperative measurement of cusp height, the linear dimensions failed to correlate with the degree of AR. Ideally, the relationship between aortic cusps and adjacent ascending aorta can be most comprehensively assessed by 3-dimensional (3D) methods, because cusp surface area (CSA) is an inherently 3D measurement. To date, there have been several reports on the accuracy and clinical importance of 3D analysis of the aortic root primarly for transcatheter AV replacement, but only limited data on the other aspect of the tethering equation: whether there is compensatory cusp enlargement and, if so, how does it relate to AR. These questions require comprehensive 3D analysis of the aortic root with separate analysis of each component, including CSAs and sinus geometry. We, therefore, used 3D imaging to test the hypothesis that aortic cusp enlargement occurs with ARD, but the degree of cusp enlargement relative to the annulus becomes limited with greater root dilatation, resulting in insufficient cusp tissue and AR.

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Methods

Study Population
We retrospectively analyzed cardiac computed tomographic (CT) images from 92 subjects, including 57 patients (57±13 years) with ARD (maximal aortic sinus diameter ≥45 mm by transthoracic echocardiography) and 35 healthy control subjects (57±7 years) with normal echocardiographic findings and no history of cardiovascular disease or hypertension. ARD patients included 29 with moderate to severe AR because of a central coaptation defect with morphologically normal aortic cusps (group 1) and 28 without significant AR (group 2). Exclusion criteria were bicuspid AV, echocardiographic evidence of organic AV disease such as stenosis, prolapse or rheumatic disease, and poor image quality not feasible for image analysis. This study was approved by the Asan Medical Center institutional review board.

CT Technique
Mean heart rate during the CT examination was 70.7 beats per minute. Retrospective ECG-gated spiral scan was done in 92 subjects and ECG-based tube current modulation was applied. Axial CT images were reconstructed in 10% intervals from 0% to 90% of the R-R interval (see the Data Supplement).

Echocardiography
All patients underwent comprehensive 2-dimensional and Doppler echocardiographic examinations. Using the stored digital images, left ventricular dimensions were measured and semiquantitative AR assessment was performed by the guidelines reported by the American Society of Echocardiography.14

3D CT Image Analysis
Custom software (Omni4D) was modified to interface with CT Digital Imaging and Communications in Medicine (DICOM) images and analyze aortic cusp–root geometry. The software allowed realtime interactive visualization of volume-rendered images and manipulation of multiple 2-dimensional cross-sectional planes through the AV to guide accurate tracing of the annulus, cusps, sinuses, and sinotubular junction (Figure I in the Data Supplement). The detailed tracing methods are described in the Data Supplement.

Aortic Root and Individual Cusp Sinus Volumes
(Figures 2 and 3)
A single continuous mesh surface was computed conforming to the sinus traces bounded by the left ventricular outflow tract and sinotubular junctions of the annulus. To assess the asymmetry of sinus dilatation, individual sinus volumes were computed by quantifying the cup-like region between the sinus surface and an enclosing or capping surface (see the Data Supplement).

Cusp Surface Area
(Figures 4 and 5)
Separate triangular mesh surfaces were automatically fitted to the cusp traces. The surface boundary was defined by the corresponding annular and cusp tip traces. The 3D surface area was computed by summing the areas of the mesh triangles. CSA was measured at the open (mid-systolic by frame count) and closed (mid-diastolic) times and normalized to body surface area. The ratio of open to closed CSA was measured and expresses the degree to which the cusps can change area in response to the superimposed pressure across the valve in diastole (ratio=1.0 implies no stretch; ratio <1.0 implies stretch).

Cusp Coapted Surface Area
Cusp coaptation was quantified objectively with a surface proximity algorithm, with coaptation defined when adjacent cusp surfaces separated by less than a cutoff distance from each other. Proximity values were color-mapped onto the cusps at intercusp distances of <1.0, 2.0, and 3.0 mm. For statistical analysis, a proximity of <1.0 mm was considered coapted (red area in Figure 5). Coaptation area fraction (CAF) was calculated as the percentage of the coaptation area over the closed CSA.

Anatomic Regurgitant Orifice Area
The uncoapted cusp tips in diastole in patients with AR define the AR orifice boundary. The area of this boundary was projected onto the plane of the commissural reference points to obtain a 2-dimensional orifice area that is roughly perpendicular to the direction of flow and has been previously validated.15

Intercommissural Distances
Asymmetry of ARD was also assessed by the relative distances between each pair of commissural reference points.

Two areas were used to compare with CSA to assess cusp adaptation to ARD:

Mid-Sinus Maximal Cross-Sectional Area
Using the set of short-axis views of the aortic root parallel to the reference plane in which 3 commissural points are located, the image with the largest cross-sectional area was selected and traced to obtain the 2-dimensional maximal mid-sinus maximal cross-sectional area (AoCSA; Figure 6A).

Minimal 3D Annular Area (Figure 6B)
Computing the minimal 3D surface area that entirely covers the annulus involved constructing an initial polyhedral mesh surface and then adjusting it to minimize its area (see the Data Supplement).
Cusp Thickness

Thickness of each cusp was measured in the mid portion of each cusp at end systole to minimize the impact of stretch.

Reproducibility

All geometric parameters including CSA were consistently measured by 1 physician (D.-H.K.), and variability was compared with blinded measurements of a radiologist with 10 years of research experience (D.H.Y.). Intra- and interobserver variability were assessed by intra-class correlation coefficient and coefficient of variation between the 2 independent observers for 15 randomly selected subjects (5 from each group).

Statistical Analysis

Results are presented as mean±SD. Statistical significance among the 3 groups was determined using 1-way ANOVA and post hoc analysis with Bonferroni correction. For categorical variables, \( \chi^2 \) or Fisher exact test was performed, and Bonferroni correction was used for pairwise comparison (Table 1). To overcome differences at baseline in Table 1, we used ANCOVA model adjusted for age, sex, and presence or absence of Marfan syndrome (Table 2). A binary logistic regression analysis was performed to find the determinants of significant AR (present [moderate to severe] or absent [trace or none]). Linear regression analysis evaluated determinants of CAF. Statistical analyses were performed using SAS 9.1 (Cary, NC). Two-tailed \( P \) values and Bonferroni-corrected \( P \) values <0.05 were considered significant.

Results

Baseline Characteristics

There was no significant difference in age or body surface area among the 3 groups. Male sex was more frequent in patients with ARD. Nine patients diagnosed with definite Marfan syndrome were included in ARD patients (4 [14%] in group 1 and 5 [18%] in group 2). Left ventricular dimension indices were largest in patients with AR, and there was no difference between group 2 and normal controls.

Aortic Root Geometry

Individual sinus volumes were larger in patients with ARD compared with normal controls, and the volumes were significantly larger in patients with AR (group 1) than without AR (group 2). The asymmetry of sinus volumes, modest in normals, was exaggerated in patients with ARD: the right coronary cusp remains relatively small. Asymmetry of ARD can also be easily appreciated by measurement of intercommissural distances. The cusp surfaces are color-coded to show differences in the distance of closest approach to neighboring cusp surfaces: red, green, blue, and yellow correspond to surface regions that are <1, 2, 3, and >3 mm of adjacent cusps. For statistical analysis, we considered the red areas <1 mm as coapted. L indicates left; N, noncoronary; and R, right cusp.

Cusp Surface Area

Total open CSA was significantly larger in patients with ARD (groups 1 and 2) compared with normal controls, and larger in patients with than without AR (15.2±3.3 versus 12.9±2.2...
cm²/m²; \( P<0.001 \)). On average, total open CSA in patients with AR was about twice that in controls and was 1.7 times larger in patients with ARD and no AR (group 2) than in controls. The asymmetry observed in aortic sinus volumes and intercommissural distances was paralleled by asymmetries in right coronary CSA and noncoronary CSA, which were consistently larger than left coronary CSA. The ratio of largest to smallest open CSA increased from 1:1.8 in normal controls to 1:4.0 in patients with ARD.

Diastolic closed CSA was larger than systolic open CSA in normal controls (9.5±1.3 versus 7.6±1.4 cm²/m²; \( P<0.001 \)) and in ARD patients without significant AR (16.2±2.7 versus 12.9±2.2 cm²/m²; \( P<0.001 \)), consistent with a cusp distensibility of roughly 23%; this measure of distensibility significantly decreased to 5% in ARD patients with significant AR (16.1±3.6 versus 15.2±3.3 cm²/m²; \( P=0.007 \)), whose cusps are considerably stretched by the dilated aortic root even in the open position. Accordingly, the open to closed CSA ratio was significantly increased in ARD patients compared with controls (0.95±0.09 versus 0.80±0.06; \( P<0.001 \)), without difference between ARD patients without significant AR and normals (0.80±0.06 versus 0.80±0.12; \( P=1.00 \)). Annular height was also greatest in AR-positive patients. Thickness of each cusp was significantly increased from normal in ARD groups (Table 2).

Minimal 3D annular area (AA) and AoCSA were largest in ARD patients with significant AR. The ratios of closed CSA to minimal 3D AA and to mid-sinus maximal AoCSA showed strong differences among the 3 groups, with the smallest values in the ARD patients with significant AR (Figures 7 and 8). The ratio of CSA to minimal 3D AA was greater in ARD patients without AR (group 2), suggesting adequate cusp adaptation to lesser degrees of root dilation. That ratio then decreased significantly in patients with AR, suggesting that adaptation becomes limited as ARD becomes more prominent. The ratio of CSA to mid-sinus AoCSA decreased from normal to AR-negative to AR-positive groups, reflecting progressive limitation in ability of the cusps to adapt to the sinus dilatation (Figure 8).

### Coaptation Area Fraction

The CAF was smallest in ARD patients with significant AR (23.4% versus 28.1–37.4%) consistent with increased cusp tethering by the dilated root acting to decrease approach of the cusps toward each other (Figures 5 and 7). CAF showed positive correlation with CSA to 3D AA ratio (\( r=0.63; \ P<0.001 \)), CSA to mid-sinus maximal CSA (\( r=0.41; \ P<0.001 \)), and negative correlation with open to closed CSA ratio (\( r=0.42; \ P<0.001 \)). Anatomic regurgitant orifice area in patients with

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**Table 1. Baseline Characteristics and Echocardiographic Data of Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=29)</th>
<th>Group 2 (n=28)</th>
<th>Normal (n=35)</th>
<th>( P ) Value*</th>
</tr>
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<tr>
<td>Age, y</td>
<td>58±13</td>
<td>55±16</td>
<td>57±7</td>
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<td>Male sex, n (%)</td>
<td>20 (69)</td>
<td>26 (93)†‡</td>
<td>17 (49)</td>
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<td>Body surface area, m²</td>
<td>1.71±0.18</td>
<td>1.80±0.20</td>
<td>1.71±0.18</td>
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<tr>
<td>Marfan syndrome, n (%)</td>
<td>4 (14)†</td>
<td>5 (18)†</td>
<td>0 (0)</td>
<td>0.037</td>
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<tr>
<td>Ascending aorta diameter by 2-dimensional echo</td>
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<tr>
<td>Annulus, mm</td>
<td>28.4±5.2†‡</td>
<td>26.5±3.7†</td>
<td>21.3±2.1</td>
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<td>Sinus, mm</td>
<td>55.8±7.3†‡</td>
<td>51.3±3.4†</td>
<td>34.5±2.5</td>
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<tr>
<td>ST junction, mm</td>
<td>45.2±8.9†‡</td>
<td>38.4±4.8†</td>
<td>32.2±2.4</td>
<td>&lt;0.001</td>
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<tr>
<td>Tubular, mm</td>
<td>46.3±6.9†‡</td>
<td>39.0±6.4†</td>
<td>33.8±2.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD for continuous variables. AR indicates aortic regurgitation; EDD, end-diastolic dimension; EF, ejection fraction; ESD, end-systolic dimension; LV, left ventricular; and ST, sinotubular.

*\( P \) value of 1-way ANOVA across all 3 groups.
†Bonferroni-corrected \( P \) value <0.05 for difference from normal controls.
‡\( \chi^2 \) or Fisher exact test involving 3 groups.
§Bonferroni-corrected \( P \) value <0.05 for difference between groups 1 and 2.

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**Figure 6.** Representative images showing measurement of the mid-sinus maximal cross-sectional area (A) and minimal 3-dimensional (3D) annular area (B). A, A volume-rendered 3D aortic root image (left) guides selection of a long-axis plane (middle) to localize the maximal cross-sectional area parallel to the plane of the reference commissural points (not shown). LCA indicates left coronary artery; and RCA, right coronary artery. On the resulting plane (right), the sinus border is traced and area measured. In this example, cross-sections through the cusps are visible allowing identification of the area associated with the left (L), right (R), and noncoronary (N) cusps. B, The top row is an en face view into the reference plane and the bottom is an angled view. From left to right are the 3D annulus, the 3D minimal annular area of closure with polyhedral vertices used to calculate the surface (white), and the mesh surface is color-coded based on association with the nearest cusp. The 3 white spheres in each panel show the coaptation points of the annulus. The central white sphere in the middle panel is the centroid of the annular coaptation (reference commissural points) used to define the initial polyhedral mesh for surface minimization. CSA indicates cusp surface area; LCC, left coronary cusp; NCC, noncoronary cusp; and RCC, right coronary cusp.


Reproducibility

For all parameters derived from 3D tracing, including CSA, the 2 independent observers achieved an interobserver variability of 0.909 to 0.987 (intraclass correlation coefficients) and an intraobserver variability of 0.920 to 0.989. All measurements were <10% of coefficient of variation (range, 4.2–9.1%).

Discussion

The results of this study indicate that the aortic cusps do have larger total surface area in ARD, but that this enlargement becomes inadequate with larger and more asymmetrical root dilatation. The normal adaptive ability of CSA to increased diastolic aortic pressure, promoting coaptation, is also reduced in the stretched cusps.

Sinus and Cusp Asymmetry

Surgeons have had a great interest in aortic root geometry to develop repair operations, and a mathematical model has been suggested to describe AV geometry using human cadaver hearts. The normal human AV was represented as 3 hemispheres intersecting a cylinder, all with equivalent radii, and this hemispherical model was tested in isolated porcine aortic roots with further ellipsoidal refinements using CT images. Quantifying pathological geometry and engineering devices for AV reconstruction are theoretical benefits of the model with cusp symmetry. However, the plane intersecting the sinotubular junction and the plane intersecting basal attachment of aortic annulus is reported to be nonparallel in normal controls, suggesting that geometric assumption of a symmetrical cylindrical aortic model fails to assess complex aortic root anatomy adequately. The anatomic complexity of the aortic root is further illustrated by emerging evidence for sinus and cusp asymmetry, previously unexpected, with the left coronary cusp and sinus being smallest. Our data also confirmed cusp asymmetry, and more importantly, the asymmetry becomes greater with increasing ARD. The physiological implications of sinus asymmetry and its marked species differences require further investigation.

Aortic Cusp Remodeling in ARD

Knowing the precise mechanism of AR in patients with ARD is required to design the most effective repairs with the greatest opportunity for valve preservation. Clinical studies have long indicated a central role for sinus dilatation at the level of the sinotubular junction; the sinotubular junction represents the most superior cusp attachments that, when splayed outward, increase cusp stress and tether the cusps. Prior studies have focused on the aorta and assumed anatomically normal aortic cusps without the potential for adaptive enlargement in response to mechanical stress in ARD. Beside restoration of dilated aortic root dimensions, aortic cusp geometry has become a focus of valve repair surgery, and 1-dimensional measurements of intercommisural distance, length of cusp insertion, amount of cusp tissue (cusp effective or geometric height), and length of free margin have been main efforts to define cusp geometry. Cusp effective height was useful to assess prolapse severity and decreased with increased amount of residual valve incompetence after repair surgery. The geometric height was useful to diagnose decreased amount of cusp tissue leading to cusp retraction.

Univariate and Multivariate Analysis

Table I in the Data Supplement and Table 3 summarize the results of univariate and multivariate analysis for variables associated with significant AR in patients with ARD and determinants of CAF in all subjects. Binary logistic regression analysis showed that the ratios of open to close CSA and the ratio of closed CSA to minimal 3D AA were independently associated with AR (area under the curve, 0.976; Hosmer–Lemeshow test P=0.94). Mid-sinus maximal CSA and ratio of closed CSA to minimal 3D AA were independent determinants of coaptation fraction ($R^2=0.548$).

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<td>Distance between CP$<em>{L-R}$ and CP$</em>{N-L}$, mm</td>
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<td>Distance between CP$<em>{L-L}$ and CP$</em>{N-L}$, mm</td>
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<td>Mid-sinus maximal cross-sectional area, cm²/m²</td>
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<td>Closed CSA/mid-sinus maximal cross-sectional area</td>
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<td>Coaptation area fraction, %</td>
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Values are mean±SD for continuous variables. CP indicates commissural point; CSA, cusp surface area; LCC, left coronary cusp; NCC, noncoronary cusp; and RCC, right coronary cusp. For example, CP$_{L-R}$ indicates commissural point between LCC and RCC.

*Bonferroni-corrected $P$ value <0.05 for difference from normal controls.
†Bonferroni-corrected $P$ value <0.05 for difference between groups 1 and 2.
‡$P$ value <0.05 for difference from normal controls.
another cause of repair failure. However, these 1-dimensional measures failed to correlate with the degree of AR, suggesting complex geometric interrelation between the cusps and aortic root.

Three-dimensional cardiac CT analysis in this study shows that the aortic cusps have substantially larger CSA in patients with ARD compared with normal, increasing with aortic root size. However, the ability of the valve to compensate fully for greater degrees of AR seems to be limited—evident from the presence of AR itself and the decreased ratios of cusp area to aortic root size in the AR group relative to those without AR. A further limitation in the AR group is the ability of the cusps to expand under closure pressures. That expansion is ≈20% in normals and patients with ARD and no AR, but is no longer evident in the already overstretched cusps of patients with larger aortic roots and important AR. This further compromises the ability of the cusps to coapt effectively. Finally, aortic sinus asymmetry increases with ARD, with the right and noncoronary sinuses dilating relative to the left; the aortic cusps, however, do not keep pace with the increase in the corresponding sinuses. Combined, these factors lead to substantial AR, measured by the previously validated CT anatomic orifice area.

**Mechanistic and Clinical Implications**

Recent investigations using in vivo imaging for validated surface area measurements and molecular biology techniques have proven that anatomically normal human mitral valve cusps can undergo active elongation when stretched by displaced papillary muscles in the infarcted heart, yet such adaptation is often insufficient, resulting in ischemic or functional mitral regurgitation. As in the case of the mitral valve, the clinical evidence in this study suggests the activation of cells and thickening of the interstitial matrix with an altered cellular and molecular biology processes that allow the AV to increase in size and thickness in response to mechanical stresses imposed by tethering structures—in this case the aortic root. The data also suggest that there are limitations to such adaptation, resulting in the presence of AR. As indicated by Thubrikar et al, the presence of larger cusps needs to be considered in tailoring AV-sparing repairs to avoid prolapse and further AR. Judging the adequacy of cusp adaptation can in principle be important to achieving the optimal valve-sparing repairs. Considering that a symmetrical circle that includes all 3 commissures has been generally assumed to predict the

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**Figure 7.** Representative images showing inadequate cusp enlargement in patients with aortic root dilatation (ARD) and aortic regurgitation (AR). Compared with normal controls, patients with ARD had markedly increased cusp surface area (CSA). However, the ratio of closed CSA to maximal mid-sinus area, reflecting cusp adaptation, decreased from normal to AR-negative to AR-positive patient (1.22 to 0.97–0.76). CAF indicates coaptation area fraction; L, left; N, noncoronary; and R, right cusp.

**Figure 8.** Geometric changes in the aortic root and cusps by 3-dimensional data analysis. Error bars indicate standard deviation. *P<0.05 between normal controls and aortic root dilatation with aortic regurgitation (AR); §P<0.05 between aortic root dilatation with and without AR. CSA indicates cusp surface area.
ideal diameter of a tubular graft during AV-sparing operations, the increasing recognition of aortic sinus asymmetry probably associated with different compliance of aortic sinus and uneven distribution of stress has relevance to the design of surgical repairs as well as to insuring optimal seating of transcatheter valve prostheses without paravalvular leak

Limitations
This study shows that cusps are larger in ARD patients with AR, but prospective studies are needed to prove that CSA increases over time within the same patients. This study raises important mechanistic questions, but by its nature does not provide pathological tissue to assess mechanisms of adaptive growth such as stretch-induced endothelial-to-mesenchymal transformation or factors limiting valve growth in more dilated aortas. Although the perfusion pattern of the AV cusp has not been demonstrated as that of the mitral valve, the finding that cuspal tissue contains nerves whose endings have active transmitters suggests the possibility that active molecular signaling can contribute to aortic cusp remodeling. Although patients with Marfan syndrome were included in this study, impact of genetic aneurysm and age needs to be clarified further.

Conclusions
Three-dimensional CT analysis shows that the aortic cusps have the ability to enlarge in compensation for ARD, including its asymmetrical nature, but that adaptation becomes limited in patients with larger and more asymmetrical aortic roots. These findings shift our focus from the aorta alone to include a dynamically adapting valve. The ability to analyze the 3D relationships of the valve to its surroundings may be helpful in planning the most effective repair tailored to individual patient anatomy. The findings suggest that understanding the underlying mechanisms may ultimately provide therapeutic opportunities to improve such compensation.

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Disclosures
None.

References
Clinical Perspective

Recent investigations using in vivo 3-dimensional imaging for leaflet area measurements and molecular biology techniques have proven that human mitral valve cusps can undergo active elongation when stretched by displaced papillary muscles, yet such adaptation is often insufficient, resulting in ischemic or functional mitral regurgitation. We explored whether there is compensatory cusp enlargement to the stress imposed by a dilated aortic root and, if so, how does it relate to aortic regurgitation. Three-dimensional images from computed tomography were used to measure aortic cusp area and sinus volumes.


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SUPPLEMENTAL MATERIAL
Supplemental Methods

CT Technique

Patients with no contraindication to beta blocker and with initial heart rates above 65 beats per minute received 2.5 mg oral bisoprolol (Concor, Merck) 1 hour before scanning. Mean heart rate during the CT examination was 70.7 beats/min. A bolus of 70–90 mL contrast agent was administered using a power injector (Stellant D; Medrad) at 4.0 mL/s, followed by 40 mL saline. The scan delay was determined by the bolus-tracking method (region of interest, ascending aorta; attenuation threshold level, 100 HU; scan delay, 8 sec). Retrospective ECG-gated spiral scan was done in 92 subjects and ECG-based tube current modulation (dose pulsing window, 30–80% of R-R interval) was applied. Tube voltage and tube current-time product were adjusted by body size, and scan parameters were as follows: tube voltage, 80–120 kV; and tube current-time product, 185–380 mAs; collimation, 128 x 0.6 mm; gantry rotation time, 280 sec. Axial CT images were reconstructed in 10% intervals from 0 to 90% of the R-R interval for these retrospective ECG-gated scans.

Tracing

The borders of the open and closed cusps could be manually traced on image planes intersecting the AV from different orientations as well as on volume-rendered surfaces using a cursor. For each cusp, unique color tags allowed identification of the annulus, cusps, sinuses, and sinotubular junction (STJ, Figure S1).

Three commissural reference positions were first identified at the points where adjacent annuli came together (Figure 2), identified by translation and tilt of a short-axis image plane to find the most superior points at which the cusp edges meet.
These reference points define a standardized coordinate system for the analysis among different patients, with its origin at the centroid of the 3 commissural points. Cusp and sinus structures were then traced using a series of short- and long-axis planes translated and rotated to optimize definition of those structures, which were checked for consistency and retraced if needed in 3D-rendered views. Annular hinge points were traced where the cusp insertions make the most perpendicular insertion to the sinus walls in longitudinal views. Aortic root volume computations required tracing the junction of the LV outflow tract (LVOT) with the aortic root (lowest annular points) and the boundary of the STJ with the ascending aorta (Figure 3). The STJ for each cusp was defined as the inflection point where the root meets the ascending aorta and changes curvature. Once features were identified, an automated analysis routine computed the boundaries and surfaces to quantify the following geometric measures, with results automatically exported to a spreadsheet

1) **Aortic root and individual cusp sinus volumes (Figure 3):** A single continuous mesh surface was computed conforming to the sinus traces bounded by the LVOT and STJ junctions of the annulus. To assess the asymmetry of sinus dilatation, individual sinus volumes were computed by quantifying the cup-like region between the sinus surface and an enclosing or “capping” surface (Figure 3, lower right). The capping surface is bounded by the annular trace between commissures for each sinus and by the curve connecting the commissures to the STJ along the sinus surface. These annular and sinus curves are seen from the side for one cusp (blue) in the lower right panel of Figure 3. The capping surface was constructed by connecting the centroid of these sinus boundaries to the boundaries themselves.
The sinus volume was then computed by summing the internal tetrahedral volumes between the cup-like sinus surface and its umbrella-like capping surface.

7) **Minimal 3D annular area (Figure 6B):** Computing the minimal 3D surface area that entirely covers the annulus involved constructing an initial polyhedral mesh surface and then adjusting it to minimize its area. The initial mesh was made by connecting the three-dimensional annular curve to its centroid and then iteratively adjusting the surface until its area has been minimized. The resulting surface is similar to the membrane formed if the 3D annular ring were dipped into a soap solution and removed. The surface tension of the film exerts a force that results in surface area minimization.

**Statistical Analysis**

Results are presented as mean±standard deviation for continuous variables. Categorical variables are expressed as number and proportion. Normality was tested using the Shapiro–Wilk W test (p<0.05). In Table 1, statistical difference among the three groups was determined using one-way ANOVA and post hoc analysis with Bonferroni correction. Chi-square or Fisher’s exact test was performed for categorical or dichotomous variable, and Bonferroni corrected p-value was used for pairwise comparison. For comparison of CT data among three groups, we performed analysis of covariance model adjusted for BSA, gender and the presence or absence of Marfan syndrome, because three groups are so different at baseline. Bonferroni corrected p-value was also used for pairwise comparison.

A binary logistic regression analysis was performed to find the determinants
of significant AR (present [moderate to severe] or absent [trace or none]). Variables with univariate \( P \leq 0.10 \) were candidates for the multivariable logistic models. To overcome multicollinearity, clinically more relevant variables potentially associated with AR development were entered into the multivariable models including the right coronary (RC)/left coronary (LC) sinus volume ratio, the non-coronary (NC)/LC sinus volume ratio, total open CSA, annular height, the open to closed CSA ratio, mid-sinus maximal cross-sectional area, and the ratios of closed CSA to minimal 3D annular area and to mid-sinus maximal cross-sectional area. Backward elimination method (remove if \( p > 0.10 \)) was used to develop the final multivariable model, and adjusted odds ratios with 95% confidence intervals were calculated. Hosmer-Lemeshow test was used to assess model fit.

Stepwise multiple linear regression (enter if \( p < 0.05 \), remove if \( P > 0.10 \)) evaluated determinants of coaptation area fraction, entering the RC/LC sinus volume ratio, the NC/LC sinus volume ratio, mid-sinus maximal cross-sectional area, the open to closed CSA ratio, and the ratios of closed CSA to minimal 3D annular area and to mid-sinus maximal AoCSA. Regression diagnostics by residual plots revealed no relevant violations. Statistical analyses were performed using SAS 9.1 (Cary, NC).

Two-tailed \( p \)-values and Bonferroni-corrected \( p \)-values <0.05 were considered significant.
**Supplemental Table S1. Univariate logistic and linear regression analysis**

<table>
<thead>
<tr>
<th></th>
<th>Binary logistic regression for AR (Presence or absence of AR)</th>
<th>Linear regression for coaptation area fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
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<tr>
<td>Age</td>
<td>1.018</td>
<td>0.980-1.058</td>
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<tr>
<td>Sex</td>
<td>1.140</td>
<td>0.376-3.459</td>
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<td>Marfan syndrome</td>
<td>0.704</td>
<td>0.168-2.954</td>
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<tr>
<td>Aortic sinus diameter</td>
<td>1.174</td>
<td>1.035-1.331</td>
</tr>
<tr>
<td>LC sinus volume</td>
<td>1.282</td>
<td>0.960-1.713</td>
</tr>
<tr>
<td>RC sinus volume</td>
<td>1.274</td>
<td>1.069-1.518</td>
</tr>
<tr>
<td>NC sinus volume</td>
<td>1.206</td>
<td>1.060-1.370</td>
</tr>
<tr>
<td>RC/LC SV ratio</td>
<td>4.693</td>
<td>1.547-14.242</td>
</tr>
<tr>
<td>NC/LC SV ratio</td>
<td>1.945</td>
<td>1.140-3.317</td>
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<tr>
<td>Distance between left CP</td>
<td>1.700</td>
<td>1.286-2.248</td>
</tr>
<tr>
<td>Distance between right CP</td>
<td>1.369</td>
<td>1.156-1.621</td>
</tr>
<tr>
<td>Distance between non-coronary CP</td>
<td>1.330</td>
<td>1.132-1.562</td>
</tr>
<tr>
<td>Total open CSA</td>
<td>1.319</td>
<td>1.075-1.618</td>
</tr>
<tr>
<td>Total closed CSA</td>
<td>0.988</td>
<td>0.834-1.171</td>
</tr>
<tr>
<td>Open/closed CSA**</td>
<td>1.307</td>
<td>1.141-1.496</td>
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<tr>
<td>Annular height</td>
<td>1.226</td>
<td>0.981-1.532</td>
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<tr>
<td>Minimal 3D annular area</td>
<td>2.459</td>
<td>1.421-4.258</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------</td>
<td>----------------</td>
</tr>
<tr>
<td>Closed CSA/ minimal 3D annular area*</td>
<td>0.599</td>
<td>0.454-0.791</td>
</tr>
<tr>
<td>Mid-sinus maximal cross-sectional area</td>
<td>1.571</td>
<td>1.210-2.041</td>
</tr>
<tr>
<td>Closed CSA/mid-sinus maximal cross sectional area*</td>
<td>0.367</td>
<td>0.227-0.593</td>
</tr>
</tbody>
</table>

Odd ratio (OR) and beta coefficients (β) are for 1 unit increase of the independent variable.
*; OR and beta coefficients are for 10 unit increases in the independent variable
**; OR and beta coefficients are for 100-unit increases in the independent variable
Supplemental Figure S1. Representative CT images showing the tracing process using volume-rendered images.