Subject-specific finite-element modeling of normal aortic valve biomechanics from 3D+t TEE images

Michel R. Labrosse a,⇑, Carsten J. Beller b, Munir Boodhwani c, Christopher Hudson c, Benjamin Sohmer d

a Department of Mechanical Engineering, University of Ottawa, 161 Louis Pasteur, Ottawa, K1N 6N5 Ontario, Canada
b Department of Cardiac Surgery, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, K1Y 4W7 Ontario, Canada
c Division of Cardiac Surgery, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, K1Y 4W7 Ontario, Canada
d Division of Cardiac Anesthesiology, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, K1Y 4W7 Ontario, Canada

ARTICLE INFO

Article history:
Received 19 July 2013
Received in revised form 25 July 2014
Accepted 7 November 2014
Available online xxxx

Keywords:
3D+t ultrasound imaging
Normal aortic valve
Subject-specific anatomy
Finite element biomechanical models

ABSTRACT

In the past decades, developments in transesophageal echocardiography (TEE) have opened new horizons in reconstructive surgery of the aortic valve (AV), whereby corrections are made to normalize the geometry and function of the valve, and effectively treat leaks. To the best of our knowledge, we propose the first integrated framework to process subject-specific 3D+t TEE AV data, determine age-matched material properties for the aortic and leaflet tissues, build a finite element model of the unpressurized AV, and simulate the AV function throughout a cardiac cycle. For geometric reconstruction purposes, dedicated software was created to acquire the 3-D coordinates of 21 anatomical landmarks of the AV apparatus in a systematic fashion. Measurements from ten 3D+t TEE datasets of normal AVs were assessed for inter- and intra-observer variability. These tests demonstrated mean measurement errors well within the acceptable range. Simulation of a complete cardiac cycle was successful for all ten valves and validated the novel schemes introduced to evaluate age-matched material properties and iteratively scale the unpressurized dimensions of the valves such that, given the determined material properties, the dimensions measured in vivo closely matched those simulated in late diastole. The leaflet coaptation area, describing the quality of the sealing of the valve, was measured directly from the medical images and was also obtained from the simulations; both approaches correlated well. The mechanical stress values obtained from the simulations may be interpreted in a comparative sense whereby higher values are indicative of higher risk of tearing and/or development of calcification.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

1.1. Clinical context

An integral part of the circulatory system, the aortic valve (AV) is normally made of three leaflets that open when the left ventricle of the heart contracts (systole) to eject blood into the aorta. The AV function is to close and prevent backflow when the left ventricle relaxes (diastole). The AV leaflets are attached inside the aortic root which balloons out around each of the leaflets’ attachments, creating the three aortic sinuses. Severely diseased valves may be replaced by mechanical or biological prosthetic valves. When the underlying pathology is aortic regurgitation or insufficiency (AI) of moderate or greater severity, as happens in 0.5% of the population, the valve may also be repaired (Maurer, 2006). AI occurs when the leaflets do not properly seal the valve in diastole, allowing blood to flow in reverse direction and increasing the ventricular workload. Both AV replacement and repair are open-heart procedures which require the patient to be placed on cardiopulmonary bypass and for the heart to be temporarily arrested. However, AV repair, instead of replacement, presents important benefits for AI patients because it avoids or minimizes the risks associated with prosthetic valve replacement including long-term anticoagulation related hemorrhage, prosthetic valve structural deterioration, thromboembolism (clot formation on the prosthetic valve), and endocarditis (valve infection) late after surgery (Aicher and Shafer, 2012). Indications for AV repair keep rising (Matalanis et al., 2010) although most AI cases still undergo replacement because few surgeons are trained in AV repair, a challenging procedure. The primary obstacles in the widespread application of AV repair techniques is an incomplete understanding of the pathoanatomy and pathophysiology of AI, the inability to translate...
findings from preoperative imaging to intraoperative assessment, lack of predictability in the outcome of the surgical techniques employed, and the irreproducibility of results of AV repair by different surgeons. The valve is repaired while unpressurized and thus shows different dimensions from those under physiological loads. It may look competent intra-operatively and yet exhibit residual AI post-operatively. This residual AI is most often due to cusp prolapse (Boodhwani et al., 2009a,b) whereby contact (or coaptation) between neighboring leaflets occurs below the physiological level of coaptation in a normal AV. Normal coaptation is associated with optimal long-term function of the valve (le Polain de Waroux et al., 2009) and should be restored. The coaptation of individual leaflets can be adjusted using leaflet correction techniques, such as central or commissural plication, or resuspension of the leaflet free margin (Boodhwani et al., 2009b). Portions of individual leaflets may also be replaced using either the patient’s own pericardium or bovine pericardium (Duran et al., 1991). The often dilated aortic root is usually replaced by reimplanting the valve within a straight aortic conduit (David and Feindel, 1992) or one with built-in sinuses, or using the remodeling technique where the sinuses are replaced over the AV using a scalloped graft (Yacoub et al., 1998). Finally, annuloplasty, or stabilization of the base of the aortic root, may also be performed in a number of different ways (Lansac et al., 2006; de Kerchove et al., 2012). So many possibilities make it difficult for surgeons to predict the outcome of AV repair. In practical terms, what surgeons ultimately need is predictive simulation of the repaired AV to ascertain its overall function. In this manner, the valve is repaired while unpressurized and/or long-term calcification. The present work is a first step toward this ultimate objective.

1.2. Practical AV imaging modalities

Magnetic resonance (MRI) or computed tomography (CT) with contrast agents can provide high resolution 4-D scans of AV over the cardiac cycle. “Such volumetric time-resolved data encodes comprehensive structural and dynamic information, which however is barely exploited in clinical practice, due to its size and complexity, as well as the lack of appropriate medical systems” (Ionescu et al., 2010). Instead, for reasons including lower cost, better accessibility and absence of allergic reactions to contrast agents or exposure to ionizing radiation and good spatial resolution and accuracy, transesophageal echocardiography (TEE) has established its superiority for pre-, intra- and post-operative imaging of cardiac valves (Lang et al., 2006). Even though TEE has recently become available in 4-D, it is still mostly used in 2-D, which limits the assessment of the complex spatial relationships in the AV structure, and may hinder more widespread use of AV repair. Recent image processing developments reported on in (Ionescu et al., 2010; Calleja et al., 2013) describe that patient-specific modeling and quantification of the AV from 4-D cardiac CT and TEE is feasible. However, subject-specific simulation of the AV biomechanics presents with challenges that have yet to be met.

1.3. Biomechanical models of AV physiology

Computational engineering tools have been used to study the AV for decades (Mackerle, 2005; Hashim and Richens, 2006; Weinberg et al., 2010). Lately, sophisticated finite element (FE) models have been used to explore AV mechanics (Koch et al., 2010), and compare the reimplantation and remodeling techniques (Ranga et al., 2006; Soncini et al., 2009). However, the latter studies ignore the fact that AV repair is done when the valve is unpressurized. In (Conti et al., 2010), MRI data from patients were averaged to create an idealized asymmetric AV model and study its dynamics over a cardiac cycle. Very importantly, references (Koch et al., 2010; Soncini et al., 2009; Conti et al., 2010) confirm the previously established fact (Howard et al., 2003; Carmody et al., 2006) that spatial (as opposed to temporal) variations in distribution of blood pressure on the valve components have a minimal influence on the AV dynamics. Therefore, assuming a time-dependent pressure pulse is sufficient and does not require computationally expensive fluid–structure interaction modeling.

1.4. Aim of the study

In this context, the aim of the present work was to establish the feasibility of assessing the AV biomechanics in a subject-specific manner. This is a challenging goal for at least three technical reasons: (1) the complexity of the AV geometry (e.g. absence of symmetry, large inter-patient variability), (2) the impracticality of determining the exact material properties of the AV tissues in subjects, and (3) the necessity to determine the unpressurized geometry to satisfy requirements of continuum mechanics for finite deformations.

Given these complications, initial demonstration is made on normal intact valves instead of diseased or repaired ones. First, the integrated framework developed to extract geometrical information about the AV from 3D+t TEE images is described. Next, details are given on how to build a scalable FE model of the AV, how to determine material properties for the aorta and the aortic leaflets based on the age of the subject, and how to iteratively find suitable unpressurized dimensions for the AV. Then, the intra- and inter-operator variability in manual measurements is assessed and the proposed methodology tested and discussed.

2. Methods

2.1. Estimation of AV apparatus from 3D+t TEE images

The AV anatomy was estimated from images in late diastole extracted from the 3D+t TEE datasets. The AV model consisted of an idealization of the left-ventricular outflow tract (LVOT), the aortic leaflets, the aortic sinuses and the proximal portion of the ascending aorta. To capture a broad spectrum of morphological variations, the model was parameterized by the positions of 21 anatomical landmarks, 6 of which were used to determine the individual free edge lengths and heights of the aortic leaflets. The number of landmarks was chosen to be as low as possible to be practical while still allowing for an accurate representation of individual AV anatomies. The landmarks were manually extracted from the images using an automated graphical-user interface dubbed AVQ, which was specially designed for this purpose in MatLab (The MathWorks, Natick, MA, USA). The process is described in the following.

Stage 1: Valve alignment and centering: Equally-spaced approximate short-axis views taken from a 3D+t TEE dataset in late diastole are presented in one screen. The user is first prompted to select three views showing the LVOT, the valve center (e.g. where the three leaflets meet), and the ascending aorta, respectively. In three consecutive screens, the user is then asked to approximate a circle around the LVOT contour, select a point at the center of the valve, and approximate a circle around the ascending aorta. Based on this information, AVQ aligns the 3-D dataset such that the short axis views are centered and perpendicular to the AV centerline. To check whether or not the alignment is adequate, a screen shows the updated short-axis views with cross-hairs that should lie at the center of the AV (Fig. 1). Although one pass is usually enough for Stage 1, suboptimal user input can be improved upon by iterations.
From this stage onward, four sub-screens appear (Fig. 2). The bottom right sub-screen provides the user with step-by-step written directions on the use of the GUI. The bottom left sub-screen shows the short-axis view of the valve, while the top left and right sub-screens show orthogonal long-axis views of the valve. One cursor allows the user to select the short-axis view along the longitudinal axis of the AV, setting the $z$ coordinate; another cursor rotates all the AV views around its longitudinal axis, setting the $\theta$ coordinate; yet another cursor translates one plane of long-axis view, setting the $r$ coordinate. A fourth cursor sets the time in the cardiac cycle at which all 3 views are shown. While the images are to be processed in late diastole, the user can scroll through time to consider the dynamic evolution of the AV geometry and better interpret the images. Altogether, the four cursors allow the user to examine the valve from any point of view, and at any time in the cardiac cycle. After the user is asked to place a label identifying the right-coronary sinus in the short axis view in order for AVQ to be fully oriented, specialized cross-hairs and labels (namely

Fig. 1. Montage of 3D+t TEE short-axis views of a normal aortic valve in late diastole, from the left-ventricular outflow tract (top left) to the ascending aorta (bottom right). The yellow circle and cross are used to visually check for centering and alignment of the images before further processing in AVQ. Refer to Section 2.1 for details.

Fig. 2. AVQ environment providing step-by-step guidance to the operator to navigate through the aortic valve and select anatomical landmarks.
RC, LC, NC for right-, left- and non-coronary sinus, respectively) are overlaid on the short-axis view (Fig. 2), and manual selection of anatomical landmarks can begin.

Stage 2: Selection of 15 anatomical landmarks in late diastole: The positions of the \((r, \theta, z)\) cursors are represented in the corresponding sub-screens as blue, red and green lines, respectively, such that each of the three views shows only two orthogonal colored lines at a time. The point in space where the three mutually orthogonal lines meet is uniquely defined by cylindrical coordinates \((r, \theta, z)\). Clicking on the selection button (Proceed/Grab button in Fig. 2) saves these coordinates for future use. The anatomical landmarks successively consist of the hinge point of the right leaflet at the nadir of the leaflet attachment line \((R0)\), the apex of the right-coronary sinus \((R1)\), and the top of the right-coronary sinus \((R2)\). Similarly, landmarks \(L0, L1, L2\) and \(N0, N1, N2\), are acquired for the left- and non-coronary portions of the AV root (Fig. 3). Thereafter, the commissures between the right-left, non-right and left-non leaflets are approximated as straight segments described by their two ends: \(RL1, RL2, LN1, LN2\), and \(NR1, NR2\), respectively (Fig. 3).

Stage 3: Visual assessment of the positions of the landmarks chosen so far: Three-dimensional (3-D) surfaces are automatically constructed from the selected landmarks using a combination of linear and bicubic Coons surface patches (Salomon, 2006). In turn, the assemblage of 3-D surfaces produces a surface model of the AV root without leaflets. It is displayed with labeled landmarks and embedded in the original 3-D gray scale dataset in late diastole. The three orthogonal projection planes can be moved, making it possible to compare 2-D contours of the reconstructed AV root with the original data. In case visual assessment of the reconstruction is unsatisfactory, landmark positions can be corrected as needed by going back to the steps of Stage 2.

Stage 4: Selection of 6 additional anatomical landmarks: Additional landmarks are defined toward the centerline of the valve and describe the bottom and top ends of the central coaptation heights between right- and left-; left- and non-, and non- and right-coronary leaflets. The landmarks are labeled \(RL3, RL4, LN3, LN4, NR3, NR4\), respectively. As illustrated in Fig. 4, the free edge length and height for the right-coronary leaflet can be approximated as the sum of \(dist(NR2, NR4)\), \(dist(NR4, RL4)\) and \(dist(RL4, RL2)\), and the sum of \(dist(mid(NR4, RL4), mid(NR3, RL3))\) and \(dist(mid(NR3, RL3), R0)\), respectively, where “dist” means distance between two points and “mid” means middle point between two points. Similar calculations apply to the left- and non-coronary leaflets. These calculations are done by AVQ based on the 3-D coordinates of the respective landmarks. Additionally, the leaflet coaptation areas approximated as the surface areas of polygons \((RL1, RL2, RL4, RL3), (LN1, LN2, LN4, LN3)\) and \((NR1, NR2, NR3, NR4)\) are calculated for later comparisons with numerical simulations.

After the landmark selection is complete, the user is asked to find the first time step in the 3D+t dataset when the valve is fully open (early systole), and the last time step when the valve is still fully open (late systole). AVQ then displays the valve in mid-systole and prompts the user to trace the contour of the open leaflets in the short-axis view (Fig. 5). The surface area enclosed by the curve represents an estimate of the geometric orifice area (GOA) in mid-systole, which is also one AV characteristic that can readily be compared to results from numerical simulations of the AV under consideration.

When the processing of an 3D+t dataset is complete, AVQ generates a summary file that contains (Fig. 6): the annulus (or LVOT) diameter, determined as the diameter of the circle circumscribing landmarks \(R0, L0, N0\); the sinotubular junction (STJ) diameter, determined as the diameter of the circle circumscribing the top commissures \(RL2, LN2,\) and \(NR2\); the valve height, determined as the longitudinal distance between the centers of the LVOT and STJ circles; the distances of the sinuses apices \(R1, L1, N1\) with respect to the valve centerline; the sinus heights, determined as the longitudinal distance between the center of the LVOT and the center of the circle circumscribing landmarks \(R2, L2,\) and \(N2\); the longitudinal distances between the sinuses apices \(R1, L1, N1\) and the plane of the LVOT circle; the angles between the top commissures \(RL2, LN2,\) and \(NR2\), as viewed from the valve centerline; the leaflet height and free edge lengths as described above; the commissure heights, determined as \(dist(RL1, RL2), dist(LN1, LN2)\) and \(dist(NR1, NR2)\), respectively; the central leaflet coaptation heights, determined as \(dist(RL3, RL4)\), \(dist(LN3, LN4)\) and \(dist(NR3, NR4)\), respectively; the leaflet coaptation areas and the GOA measured in mid-systole, as described above.

2.2. Biomechanical model of a subject-specific aortic valve

Leaving aside for now the issues related to the unknown unpressurized AV geometry and material properties, let us first describe how a FE model was built from the data collected in the procedure described above. The associated Matlab commands were organized into a custom program dubbed AVSim. From the 21 landmarks, points, lines and curves were drawn to sketch the aortic root. In addition, the leaflet contours were created in open position using a straight line for the leaflet height, and a sine curve for the leaflet free margin (Fig. 7).

The curves created formed the edges of linear and bicubic Coons surfaces (Salomon, 2006), each of which was discretized using structured meshing. The process was repeated to produce 4 surfaces at a small distance from each other to allow for the creation of 3 finite elements through the aortic thickness, as a structured hexahedral FE mesh of the whole valve was generated by connecting the nodes from adjacent surfaces. The leaflets were meshed similarly, but with two elements across their thicknesses. The final mesh consisted of approximately 13,500 nodes and 10,000 8-node solid elements (Fig. 7). Previous sensitivity analyses established
that with such discretization, the results of the computations were not dependent on mesh size (Labrosse et al., 2010).

Given the shortage of usable experimental information on human aortic sinus tissues, the material properties of the ascending aorta were assumed identical to those of the aortic sinuses and established as follows. We used the circumferential and longitudinal stretch ratios in 14 excised pressurized human ascending aortas under closed ends and free extension conditions, as obtained in Labrosse et al. (2013), to determine the average circumferential and longitudinal stretch ratios for pressures between 0 and 160 mmHg in two average groups, one at age 54, and one at age 72. Based on evidence of linear variation of these stretches with age (see for example Figs. 5 and 6 in Labrosse et al., 2013), we linearly interpolated the circumferential and longitudinal stretch ratios at any given age based on those at 54 and 72. Combining these data with an average measured unpressurized human ascending aortic wall thickness of 1.86 mm (Labrosse et al., 2013), and the patient-specific ascending aortic diameter interpreted as the STJ diameter determined from AVQ, we calculated the parameters of a hyperelastic, transversely isotropic material representing the age-matched human ascending aorta. Specifically, we used Guccione’s material model with strain energy function

\[ W = \frac{1}{2} \left[ c_1 E_\theta^2 + c_2 (E_z^2 + E_r^2) \right] - 1 \]

where \( c_1, \ldots, c_3 \) are material constants, \( E_\theta \) are Green strains, and subscripts \( \theta, z, r \) refer to the circumferential, longitudinal and radial directions, respectively. Although this material model was initially developed to represent myocardial tissue (Guccione et al., 1991), it has been shown to give accurate representations of human aortic and leaflet tissues (Labrosse et al., 2009, 2010). The numerical techniques to estimate the material constants rely on nonlinear optimization procedures such as the Levenberg–Marquardt method and are not repeated here. To illustrate the changes in aortic material properties according to age, simulated stress–strain curves for planar equibiaxial testing under a maximum membrane tension of 2000 N/m are shown in Fig. 8a.

For the aortic leaflets, we relied on the planar equibiaxial data published in Martin and Sun (2012), from porcine aortic valves (age 6–9 months) and human aortic valves (average age of...
The strains were measured under controlled membrane tensions. The data were digitized from the published document and averaged for the three leaflets. We considered that the porcine data obtained from pigs were valid to describe aortic leaflets in 18-year old humans, as suggested in Martin and Sun (2012). For lack of more detailed data, and as in Weinberg et al. (2009) where observations reported in Christie and Barratt-Boyce (1995) were simplified, we assumed a linear variation of circumferential and radial stretch ratios with age. Therefore, we linearly interpolated the circumferential and radial strains under set membrane stresses at any given age based on those at 18 and 80.6 years. In addition, the thickness of the leaflets was linearly interpolated from the human aortic leaflet thicknesses at age 15 and 85 (McDonald et al., 2002). For simplicity, thickness was assumed

Fig. 7. (a) Unpressurized aortic root model built with hexahedral elements according to the procedure detailed in Section 2.2; (b) view of the leaflets inside the model shown in figure (a).

Fig. 8. (a) Simulated stress–strain curves for planar equibiaxial testing of human ascending aortas at ages 54 and 72, under maximum tension of 2000 N/m, as derived from the experimental data in (Labrosse et al., 2013); (b) simulated stress–strain curves for planar equibiaxial testing of human aortic leaflets at ages 18 and 80.6, under maximum tension of 1000 N/m, as derived from the experimental data in (Martin and Sun, 2012).
identical for the three leaflets and constant across each leaflet. With stress–strain and thickness information, age-matched Guccioni's material constants were determined for the aortic leaflets of the subject. To illustrate the changes in aortic leaflet material properties according to age, simulated stress–strain curves for planar equiaxial testing under a maximum membrane tension of 1000 N/m are shown in Fig. 8b.

The unpressurized geometry was assumed stress-free, because no residual stress or strain data is available for the aortic valve, and because the left-ventricular pressure is almost zero at end-diastole in a physiological cardiac cycle. To estimate the unpressurized geometry of the subject-specific AV model, an iterative approach was followed to minimize the error between the measured dimensions of the LVOT, STJ, leaflet free edge lengths and heights, and their simulated counterparts. Both the measured and simulated parameters were evaluated in late diastole. The unpressurized dimensions of the AV components were individually scaled up or down between iterations to improve the simulation results in late diastole. The implementation of the method in AVSim benefited from the automated measurement of the AV components in the FE model as obtained from the positions of the associated nodes in late diastole.

All FE analyses were carried out with commercial software LS-Dyna 971 (LSTC, Livermore, CA, USA) interfacing with AVSim on a workstation with two Intel Xeon E5640 2.67 GHz 4-core processors and 6 GB of RAM. The mass density of the aortic and leaflet tissues was set at 1000 kg/m³. To simulate one cardiac cycle, known aortic and left-ventricular pressure pulses were applied to the aortic and the left-ventricular sides of the AV components, respectively (Labrosse et al., 2010). However, since the analysis started from the unpressurized geometry, the pressure was ramped from 0 up to 80 mmHg before the cardiac cycle started in early systole.

While the normal duration of diastole is approximately 0.60 s, it was shortened to 0.10 s in the simulation to save computational time. In addition, the simulation time was 1/10 of the real time, as previous analyses with real time or scaled time yielded results within 2% of each other, due to comparatively small inertial loads (Labrosse et al., 2010). The time step was automatically set and updated by LS-Dyna to achieve numerical stability of the solution. The longitudinal stretch ratio applied to the whole AV model was set at the age-matched value estimated from closed-end, free-extension pressurization testing under diastolic pressure (Labrosse et al., 2013). This value ranges between 1.10 and 1.20 in normal physiological conditions (Han and Fung, 1995).

### 2.3. Processing of the results from the simulations

When a converged solution was reached (i.e. when unpressurized AV dimensions had been found such that, given the determined age-matched material properties, the AVQ measured and AVSim simulated dimensions in late diastole were within a few percent of each other), the maximum values of mechanical stress in the leaflet were determined, along with their location and timing. For simplicity, Von Mises stresses were chosen, as they summarize in one number the stress values present in different directions of the material at one location.

In addition, to evaluate the valve's opening and closing characteristics, the geometric orifice area (GOA) of the valve was measured as a function of time throughout one cardiac cycle. Again, a MatLab program was written to have the post-processor of LS-Dyna take top view snapshots of the valve at regular time intervals during the cardiac cycle and to measure the projected area left open by the leaflets.

Lastly, dynamic leaflet contact pressure data generated during the simulation were processed to determine the surface area of leaflet coaptation at the time of maximum downward movement of the valve during diastole. Those leaflet elements with contact pressure over 5 mmHg were considered to be part of the coaptation area.

### 3. Experiments and results

#### 3.1. Datasets

We acquired 3D+t TEE AV images in ten consecutive patients with structurally and functionally normal AV (Sohmer et al., 2012) as part of routine intra-operative monitoring. A Philips iE33 3-D Transesophageal X7-2t probe and Q Lab platform (Philips Ultrasound, Andover, MD, USA) were used to obtain electrocardiography-gated full-volume 3-D datasets at the mid-esophageal short-axis AV level. To optimize image resolution, imaging depth was limited to include only the AV while keeping the width of the sector screen such that we could visualize the mitral valve; seven cardiac cycles were utilized, and ventilation and electrocautery were interrupted during acquisition. A complete cardiac cycle was captured in a series of approximately 42 volumes. Image resolution and size were typically on the order of 0.35 mm and 224 × 208 × 224 voxels, respectively. The datasets were stored digitally for off-line analysis.

<table>
<thead>
<tr>
<th>#</th>
<th>Age</th>
<th>LVOT</th>
<th>STJ</th>
<th>H</th>
<th>HR</th>
<th>HL</th>
<th>HN</th>
<th>FR</th>
<th>FL</th>
<th>PN</th>
<th>CA</th>
<th>GOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>24.4</td>
<td>25.4</td>
<td>14.1</td>
<td>16.2</td>
<td>14.4</td>
<td>17.0</td>
<td>29.4</td>
<td>27.9</td>
<td>28.8</td>
<td>152</td>
<td>401</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>23.4</td>
<td>25.4</td>
<td>15.5</td>
<td>16.4</td>
<td>17.7</td>
<td>18.2</td>
<td>28.2</td>
<td>26.2</td>
<td>28.8</td>
<td>204</td>
<td>345</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>25.3</td>
<td>28.2</td>
<td>14.4</td>
<td>15.3</td>
<td>16.1</td>
<td>20.7</td>
<td>31.4</td>
<td>29.3</td>
<td>30.4</td>
<td>201</td>
<td>410</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>25.4</td>
<td>28.8</td>
<td>14.5</td>
<td>16.2</td>
<td>16.3</td>
<td>16.3</td>
<td>31.2</td>
<td>30.6</td>
<td>34.0</td>
<td>211</td>
<td>439</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>20.4</td>
<td>22.4</td>
<td>10.5</td>
<td>12.3</td>
<td>16.0</td>
<td>13.0</td>
<td>24.6</td>
<td>25.3</td>
<td>24.6</td>
<td>152</td>
<td>248</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>24.0</td>
<td>24.4</td>
<td>14.9</td>
<td>17.8</td>
<td>16.6</td>
<td>17.2</td>
<td>27.0</td>
<td>26.7</td>
<td>25.8</td>
<td>186</td>
<td>413</td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>19.1</td>
<td>21.2</td>
<td>13.4</td>
<td>14.0</td>
<td>12.1</td>
<td>14.2</td>
<td>24.5</td>
<td>22.3</td>
<td>24.0</td>
<td>142</td>
<td>252</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>26.3</td>
<td>31.1</td>
<td>16.9</td>
<td>17.6</td>
<td>17.2</td>
<td>16.5</td>
<td>35.5</td>
<td>32.6</td>
<td>34.7</td>
<td>202</td>
<td>406</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>24.4</td>
<td>24.6</td>
<td>13.5</td>
<td>12.8</td>
<td>15.7</td>
<td>17.1</td>
<td>28.1</td>
<td>25.4</td>
<td>28.3</td>
<td>144</td>
<td>346</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>25.3</td>
<td>28.5</td>
<td>14.5</td>
<td>17.8</td>
<td>17.1</td>
<td>16.2</td>
<td>30.7</td>
<td>30.8</td>
<td>30.7</td>
<td>199</td>
<td>498</td>
</tr>
<tr>
<td>Ave</td>
<td>59.3</td>
<td>23.8</td>
<td>26.0</td>
<td>14.2</td>
<td>15.6</td>
<td>15.9</td>
<td>16.6</td>
<td>29.1</td>
<td>27.7</td>
<td>29.0</td>
<td>185</td>
<td>381</td>
</tr>
<tr>
<td>SD</td>
<td>7.1</td>
<td>2.3</td>
<td>3.1</td>
<td>1.7</td>
<td>2.0</td>
<td>1.6</td>
<td>2.1</td>
<td>3.3</td>
<td>3.1</td>
<td>3.6</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

LVOT: left-ventricular outflow tract diameter (mm).
STJ: Sinotubular junction diameter (mm).
HR, HL, HN: Height of the right, left and non-coronary leaflets, respectively (mm).
FR, FL, PN: Free edge length of the right, left and non-coronary leaflets, respectively (mm).
CA: Total leaflet coaptation surface area (sq.mm).
GOA: Geometric orifice area of the valve in mid-systole (sq.mm).

Please cite this article in press as: Labrosse, M.R., et al. Subject-specific finite-element modeling of normal aortic valve biomechanics from 3D+t TEE images. Med. Image Anal. (2014), http://dx.doi.org/10.1016/j.media.2014.11.003
3.2. Measurements in 10 normal AV using AVQ

Following a protocol approved by the Ottawa Hospital Research Ethics Board, the datasets were de-identified and exported through 3-D Cartesian Export from QLab for processing as detailed in Section 2.1 by three observers. Using AVQ, it took 10–15 min to select all the landmarks in the diastolic volume, and a few more seconds to measure the GOA in the systolic volume. One series of measurements by Observer 1 is summarized in Table 1.

![Figure 9](image-url)

**Fig. 9.** Bland–Altman plots for inter-operator variability between: (a) operators A and B, (b) operators A and C, (c) operators B and C, (d) Intra-operator variability for operator A. All plots based on 9 individual measured dimensions in millimeters (namely LVOT, STJ, H, HR, HL, HN, FR, FL, FN) in each of the 10 datasets (one symbol per dataset).

<table>
<thead>
<tr>
<th>Comparison between observers</th>
<th>Mean difference (SD)</th>
<th>95% Limits of agreement</th>
<th>Correlation coefficient</th>
<th>95% Confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A–B</td>
<td>0.1 (1.2)</td>
<td>−2.2 to 2.5</td>
<td>0.9831</td>
<td>0.9753–0.9893</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>B–C</td>
<td>0.0 (1.8)</td>
<td>−3.5 to 3.5</td>
<td>0.9654</td>
<td>0.9478–0.9772</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A–C</td>
<td>0.1 (1.9)</td>
<td>−3.7 to 4.0</td>
<td>0.9588</td>
<td>0.9379–0.9727</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A–Abis</td>
<td>−0.2 (0.9)</td>
<td>−2.0 to 1.6</td>
<td>0.9900</td>
<td>0.9848–0.9934</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Table 2** Summary of Bland–Altman and correlation analyses between measurements obtained by observers A, B and C.

![Figure 10](image-url)

**Fig. 10.** Finite element analysis by AVSim for AV in subject #6. Von Mises stress results (MPa) in peak systole (a) and late diastole (b).
The results from Bland–Altman and correlation analyses between valve dimensions obtained by observers A, B and C are presented in Fig. 9 and summarized in Table 2.

### 3.3. Results from AVSim

Patient-specific FE simulations of one cardiac cycle were run with AVSim for all the datasets as outlined in Section 2.2. Patient-specific simulations were successful in all 10 valves. All the valves opened and closed fully, as expected of normal competent valves (Fig. 10). Characteristics of the simulated valves are listed in Table 3.

The results from Bland–Altman and correlation analyses between different parameters determined with AVQ and AVSim are summarized in Table 4.

The maximum mechanical stress in the AV models was systematically reached at the commissures of the leaflets in mid- to late diastole (Fig. 10). There and then, the Von Mises stress averaged 1007 ± 719 kPa. Not unexpectedly, the smallest valve (# 7) exhibited the lowest stress value (417 kPa).

### 4. Discussion and conclusions

#### 4.1. Discussion

The present study provides a novel systematic approach to address the technical challenges outlined in the Introduction about subject-specific modeling of normal AV biomechanics.

Firstly, the AVQ program makes it possible to acquire the subject-specific geometry of an AV in a matter of minutes with good inter- and intra-observer repeatability. The maximum mean error in measurements of valve dimensions was 0.2 (0.9) mm (Table 2). This compares well to the mean error of 1.3 (0.3) mm between measurements from an automated processing system and human experts in 36 CT aortic valve datasets reported by Ionasec et al. (Table III in Ionasec et al., 2010). The accuracy of AVQ also compares well with another method recently proposed by Haj-Ali et al. for the 3-D parametric reconstruction of the native aortic valve (Haj-Ali et al., 2012). They report a mean error between their calculated geometry and 3-D TEE measurements in one specific valve of 0.8 (0.6) mm. The relatively low temporal resolution of 3D+t TEE images is admittedly a problem for their method which requires imaging of the valve in late systole. In addition, their method relies on accurate measurement of specific parameters (e.g. radius of the root, radius at the commissures) for which no procedural guidelines are provided. By contrast, the integrated workflow in AVQ allows anyone to use it with little training.

Secondly, the AVSim program seamlessly uses the measurements from AVQ to create a FE model of the AV in seconds. Using a novel method to estimate the age-matched properties of the aorta and aortic leaflets and based on an original solution scheme, AVSim iteratively scales the AV’s unpressurized dimensions and drives the analysis of its dynamic mechanical behavior during a cardiac cycle until the AV dimensions in late diastole match those measured by AVQ within a few percent error. Although several assumptions and simplifications were necessary to implement the age-matched material properties in particular, success of the method is illustrated by the competence achieved in all the simulated normal valves, as well as by the expected close agreement between dimensions in AVQ and AVSim, with a mean difference of 0.4 (1.1) mm (Table 4). The geometric scaling method proposed herein generalizes the approach introduced by Conti et al. (2010) whereby the unpressurized dimensions of the aortic root (namely, aortic sinus and STJ diameters) is iteratively refined until the end-diastolic dimensions differed from MRI data by less than 2%. In AVSim, the dimensions of the leaflet are also part of the optimization procedure, in addition to those of the aortic root, ensuring enhanced modeling of the valve function.

Importantly also, especially in the larger context of AI and aortic valve repair, the leaflet coaptation surface areas obtained with AVQ matched those computed by AVSim, with a mean difference of 8 (25) sq.mm (Table 4), out of a nominal value in the range of 140–260 sq.mm (Tables 1 and 2). The coaptation areas measured with AVQ also correlated well with those determined manually by Sohmer et al. using QLab (Sohmer et al., 2012). Indeed, the correlation coefficient r between the coaptation areas found with AVQ and QLab was 0.7606 (95% CI: 0.2513–0.9400), P = 0.0106. However, the values from AVQ or AVSim were systematically higher. A Bland–Altman analysis yielded a mean difference between AVQ and QLab coaptation areas of 24 (25) sq.mm (95% limits of agreement: −25, +73). Similarly, the mean difference between AVSim and QLab coaptation areas was found to be 32 (33) sq.mm (95% confidence interval: −21, +56).

### Table 3

Measurements from simulations with AVSim of the 10 normal valves in Table 1.

<table>
<thead>
<tr>
<th>#</th>
<th>LVOT (mm)</th>
<th>STJ (mm)</th>
<th>H (mm)</th>
<th>HR (mm)</th>
<th>HL (mm)</th>
<th>HN (mm)</th>
<th>FR (mm)</th>
<th>FL (mm)</th>
<th>FN (mm)</th>
<th>CA (sq.mm)</th>
<th>GOA (sq.mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24.6</td>
<td>25.0</td>
<td>14.0</td>
<td>16.3</td>
<td>15.0</td>
<td>17.2</td>
<td>30.0</td>
<td>28.2</td>
<td>29.5</td>
<td>136</td>
<td>387</td>
</tr>
<tr>
<td>2</td>
<td>23.2</td>
<td>25.4</td>
<td>15.2</td>
<td>17.0</td>
<td>16.8</td>
<td>17.1</td>
<td>29.9</td>
<td>27.8</td>
<td>31.1</td>
<td>240</td>
<td>386</td>
</tr>
<tr>
<td>3</td>
<td>25.0</td>
<td>28.2</td>
<td>14.7</td>
<td>17.0</td>
<td>15.6</td>
<td>20.0</td>
<td>31.1</td>
<td>29.6</td>
<td>28.4</td>
<td>235</td>
<td>477</td>
</tr>
<tr>
<td>4</td>
<td>26.4</td>
<td>28.4</td>
<td>14.8</td>
<td>16.8</td>
<td>17.2</td>
<td>17.3</td>
<td>33.3</td>
<td>30.8</td>
<td>34.8</td>
<td>182</td>
<td>480</td>
</tr>
<tr>
<td>5</td>
<td>20.8</td>
<td>22.4</td>
<td>10.7</td>
<td>13.1</td>
<td>14.6</td>
<td>13.6</td>
<td>25.3</td>
<td>26.7</td>
<td>26.1</td>
<td>133</td>
<td>284</td>
</tr>
<tr>
<td>6</td>
<td>23.8</td>
<td>24.6</td>
<td>14.7</td>
<td>17.9</td>
<td>17.1</td>
<td>17.5</td>
<td>27.7</td>
<td>26.8</td>
<td>26.2</td>
<td>202</td>
<td>362</td>
</tr>
<tr>
<td>7</td>
<td>19.0</td>
<td>20.8</td>
<td>13.6</td>
<td>14.5</td>
<td>12.4</td>
<td>14.6</td>
<td>25.1</td>
<td>23.2</td>
<td>24.6</td>
<td>187</td>
<td>269</td>
</tr>
<tr>
<td>8</td>
<td>27.0</td>
<td>32.2</td>
<td>16.3</td>
<td>15.9</td>
<td>16.1</td>
<td>16.2</td>
<td>39.2</td>
<td>36.9</td>
<td>39.9</td>
<td>273</td>
<td>590</td>
</tr>
<tr>
<td>9</td>
<td>24.6</td>
<td>25.0</td>
<td>12.8</td>
<td>13.6</td>
<td>16.0</td>
<td>18.0</td>
<td>26.3</td>
<td>25.0</td>
<td>28.2</td>
<td>139</td>
<td>370</td>
</tr>
<tr>
<td>10</td>
<td>25.4</td>
<td>28.0</td>
<td>14.3</td>
<td>18.2</td>
<td>17.2</td>
<td>16.2</td>
<td>31.3</td>
<td>31.6</td>
<td>30.9</td>
<td>205</td>
<td>450</td>
</tr>
</tbody>
</table>

### Table 4

Summary of Bland–Altman and correlation analyses between parameters from AVQ and AVSim. The dimensions are LVOT, STJ, H, HR, HL, HN, FR, FL, and FN as in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean difference (SD)</th>
<th>95% Limits of agreement</th>
<th>Correlation coefficient</th>
<th>95% Confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimensions (mm)</td>
<td>0.4 (1.1)</td>
<td>−1.8 +2.5</td>
<td>0.9891</td>
<td>0.9834–0.9928</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coapt. area (sq.mm)</td>
<td>8 (25)</td>
<td>−42 +57</td>
<td>0.8499</td>
<td>0.4738–0.9638</td>
<td>0.0018</td>
</tr>
<tr>
<td>Max. GOA (sq.mm)</td>
<td>24 (54)</td>
<td>−81 +130</td>
<td>0.8307</td>
<td>0.4215–0.9588</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

Same notations and convention as in Table 1. Max. Stress is the maximum Von Mises stress (kPa) found in the AV model during diastole.
limits of agreement: –33, +98). This bias may be explained as follows: considering that the coaptation area between two adjacent leaflets can be approximated by a trapeze (Fig. 4b), analysis of (Sohmer et al., 2012) suggests that they conservatively truncated both the medial and lateral aspects of the trapeze in their proof-of-concept study. We believe that the measurements from AVSim in particular may produce a more accurate representation of the leaflet coaptation in the AV because, assuming correct measurements were made in AVQ, and adequate material properties are used, AVSim simply determines the sum of the areas of finite elements that came in contact during diastole without making use of any assumption regarding the expected shape of the coaptation area. As mentioned in the Introduction, in the context of AV repair in AI cases, it is important to be able to reliably simulate the amount of leaflet coaptation in a valve, as a predictor of long-term success of the procedure.

The maximum GOA values from AVQ and AVSim were practically similar, with a bias of 24 (54) sq.mm (Table 4), out of a nominal GOA in the range of 250–590 sq.mm (Tables 1 and 2).

Lastly, the mechanical stress analyses of the AV models with AVSim benefit from the latest experimental information available regarding human tissues for the aorta (Labrosse et al., 2013) and aortic leaflets (Martin and Sun, 2012). While many authors report the stresses in the belly of the aortic leaflets in late diastole, for the sake of brevity, we only reported those at the top of the commissures because they were consistently the highest in the models. We believe that the leaflet commissural stresses are especially relevant in the context of AV repair, where different surgical techniques influence these stresses differently (Labrosse et al., 2011). The average Von Mises stress of 1007 ± 713 kPa found herein should ideally be compared to the strength of the leaflets to evaluate their risk of rupture; however, to the authors’ best knowledge, the leaflets strength has not been reported on in the literature. Until such data become available, the stress level can be interpreted in a comparative sense, whereby higher values are indicative of higher risk of rupture and/or development of calcification (Yip and Simmons, 2011).

4.2. Limitations

Although the present study is comprehensive in that it describes the acquisition of in vivo measurements and their processing all the way to AV computational simulation during a cardiac cycle, a larger sample size would further strengthen the demonstration of robustness of the approach. The analysis was deliberately limited to normal valves to explain and validate the methodology before expanding it. On the other hand, the dynamic structural modeling of the aortic valve was not accompanied by or coupled with computational fluid dynamics (CFD) studies. This is because the hemodynamic properties of normal or well-repaired valves are normal and can easily be monitored post-operatively by Doppler imaging. Lastly, and although this was outside the scope of this presentation, a sensitivity analysis following (Becker et al., 2011) would be valuable to assess the relative effects on stress and overall valve function of a number of parameters, including dimensional measurement uncertainties, material properties variability (including distinctions for each individual leaflet), localized leaflet thickness variations, and subject-specific blood pressures.

4.3. Perspectives

More work is needed to address valves with ascending aortic aneurysms and bicuspid aortic valves. When these cases are feasible will the whole enterprise started herein take its full clinical significance, as it will be possible to do virtual surgeries on valves and provide surgeons with detailed information on the parameters of the most suitable repair procedures. Among the challenges ahead are the yet more complex geometries and the lesser known material properties of diseased leaflets and aortic tissues. Ultimately, the approach used in AVQ may also benefit from future refinements in ultrasound imaging regarding spatial and temporal resolutions. It may also be used successfully with other medical imaging modalities as well.

4.4. Conclusions

To the best of our knowledge, we propose the first integrated framework to process subject-specific 3D+t TEE AV data, determine age-matched material properties for the aortic and leaflet tissues, build a finite element model of the unpressurized AV, and simulate the AV function throughout a cardiac cycle. For geometric reconstruction purposes, dedicated software was created to acquire the 3-D coordinates of 21 anatomical landmarks of the AV apparatus in a systematic fashion. Measurements from ten 3D+t TEE datasets of normal AVs were assessed for inter- and intra-observer variability. These tests demonstrated mean measurement errors well within the acceptable range. Simulation of a complete cardiac cycle was successful for all ten valves and validated the novel schemes introduced to evaluate age-matched material properties and iteratively scale the unpressurized dimensions of the valves such that, given the determined material properties, the dimensions measured in vivo closely matched those simulated in late diastole. The leaflet coaptation area, describing the quality of the sealing of the valve, was measured directly from the medical images and was obtained from the simulations as well. Both approaches correlated well. The mechanical stress values obtained from the simulations can be interpreted in a comparative sense whereby higher values are indicative of higher risk of rupture and/or development of calcification.

Conflict of interest

None.

Acknowledgements

The authors gratefully acknowledge the Natural Sciences and Engineering Research Council of Canada for Discovery Grant 312065–2012 (M.R.L.), as well as Philips for access to Cartesian export from QLab and DICOM file reading. M.R.L would like to thank John Moore of the Robarts Research Institute in London, ON, Canada for an illuminating discussion about Cartesian export from Philips QLab.

References


