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# Progressive aortic valve calcification: Three-dimensional visualization and biomechanical analysis

Rotem Halevi [1,a], Ashraf Hamdan [1,b], Gil Marom [c], Mor Mega [a], Ehud Raanani [c,d], Rami Haj-Ali [a,*]

[a] Faculty of Engineering, Tel-Aviv University, Tel-Aviv 69978, Israel
[b] Heart Institute, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel
[c] Biomedical Engineering Department, Stony Brook University, 11794 NY, USA
[d] Cardiothoracic Surgery Department, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel

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ABSTRACT

Calcific aortic valve disease (CAVD) is a progressive pathology characterized by calcification mainly within the cusps of the aortic valve (AV). As CAVD advances, the blood flow and associated hemodynamics are severely altered, thus influencing the mechanical performance of the AV. This study proposes a new method, termed reverse calcification technique (RCT) capable of re-creating the different calcification growth stages. The RCT is based on three-dimensional (3D) spatial computed tomography (CT) distributions of the calcification density from patient-specific scans. By repeatedly subtracting the calcification voxels with the lowest Hounsfield unit (HU), only high calcification density volume is presented. RCT posits that this volume re-creation represents earlier calcification stages and may help identify CAVD initiation sites. The technique has been applied to scans from 12 patients (36 cusps) with severe aortic stenosis who underwent CT before transcatheter aortic valve implantation (TAVI). Four typical calcification geometries and growth patterns were identified. Finite elements (FE) analysis was applied to compare healthy AV structural response with two selected CAVD-RCT configurations. The orifice area decreased from 2.9 $cm^2$ for the healthy valve to 1.4 $cm^2$ for the moderate stenosis case. Local maximum strain magnitude of 0.24 was found on the edges of the calcification compared to 0.17 in the healthy AV, suggesting a direct relation between strain concentration and calcification geometries. The RCT may help predict CAVD progression in patients at early stages of the disease. The RCT allows a realistic FE mechanical simulation and performance of calcified AVs.



## 1. Introduction

Calcific aortic valve disease (CAVD) is one of the most common heart valve diseases in the western world, affecting about 25% of adults over 65 years old (Stewart et al., 1997). The disease is characterized by the formation of tissue similar to bone (Mohler et al., 2001) on the cusps of the aortic valve (AV). The calcification initiates with non-interacting nodules, which grow and coalesce until blood flow to the body is blocked (Weinberg et al., 2009). Patients usually do not have symptoms until the disease has progressed to an advanced stage (Rosenhek et al., 2000). It is therefore rare to have a CT scan of the early stages of the disease.

Calcification growth and associated spatial geometry are not random. Thubrikar et al. (1986) examined calcified cusps excised from 96 patients. They found that 87% of the cusps had one of two identified pattern types. The first pattern was arc shaped. This arc pattern was located along the coaptation line, and named the "coaptation pattern". The second pattern was calcification along the attachment line (AL), and named the "radial pattern". It was suggested that these patterns might be related to the areas of maximum cyclic flexion; however, no information was given about the calcification growth process.

Two biomechanical parameters are known to affect the calcification process – tissue strain and hemodynamic shear loads (Balachandran et al., 2009, 2010; Bouchareb et al., 2014; David Merryman, 2010; Freeman and Otto, 2005; Yap et al., 2012). It was suggested that local strain enhancement (similar to strain concentration) caused by a rigid core in the tissue can significantly impact the calcification growth (Fisher et al., 2013). CAVD has been studied using numerical tools and in-vitro tests to find the mechanical stress, hemodynamics and kinematics of the valve.

* Corresponding author at: School of Mechanical Engineering, The Fleischman Faculty of Engineering, Tel Aviv University, Ramat Aviv 69978, Israel.
Tel.: +972 3 640 8207.
*E-mail address:* rami98@tau.ac.il (R. Haj-Ali).
[1] The first two authors have made equal contributions to this paper.

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Kim (2009) built a finite element model of polymeric aortic valve with calcification. Calcification was modeled in accordance with Thubrikar et al.'s (1986) patterns by thickening the cusp while retaining the material properties of the polymer. The calcification modeled was severe, covering about 45% of the cusp's area. Weinberg et al. (2009) studied the aging of the aortic valve from age 20 to 80 years using a Fluid–Structure Interaction (FSI) model. Aging simulation included tissue flexibility degradation, thickening and calcification. Calcification was modeled by adding calcification nodules and by growing them for older ages. Calcification nodules were simulated by stiffening two-dimensional (2D) shell elements of the aortic valve. The need for three-dimensional (3D) representation of the calcification was recommended for future work. Van Loon (2010) used an FSI model to study aortic valve stenosis. The calcification was modeled by stiffening the cusp material in two patterns: increased stiffness toward the valve ring, and increased stiffness toward the cusp's free edge. Maleki (2010) investigated the stenotic aortic valve using a finite element (FE) model and FSI model. The model was validated by comparison to a pulsatile loop test. The different stenosis severities were modeled by stiffening the cusps of a silicone valve. Katayama et al. (2012) examined the flow and stresses/strain of bicuspid and tricuspid aortic valves for both non-pathologic and stenotic cases. Calcification was modeled by thickening the cusp based on the curvature which represents strain. Chandra et al. (2012) developed a two-dimensional FSI analysis of bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV) including CAVD simulation. The calcification was modeled by stiffening the elements at the base of the cusp. The elastic properties of the calcification were based on the properties of calcium phosphate (83 GPa). Four calcified models were generated – mild and moderate TAV and mild and severe BAV. Most prior studies lack true geometrical representations of the calcification and often ignore the strong asymmetry of the AV calcified cusps. Moreover, there is no methodology combining mechano-biology with biomechanical modeling for predicting the initiation and growth of AV calcification patterns.

The current study presents a new technique for computing 3D-geometry of calcification initiation and growth in AV cusps. This reverse calcification technique (RCT) is patient-specific and based on the Hounsfield unit (HU) distribution of the calcification provided by computed tomography (CT) scans. The technique is based on the hypothesis that older calcification points have higher density and thus higher HU levels, since it takes years to accumulate the calcium. By subtracting the low-HU volume, a smaller volume of an earlier calcification is identified. This hypothesis is tested by studying patient calcification distribution and calcification history. The technique provides a new way to view CAVD geometrical growth. RCT results are used later in this paper to simulate calcified valves using finite-element models.

## 2. Methods

### 2.1. Study population

The study group consisted of 12 patients (Table 1) with symptomatic severe TAV stenosis evaluated with CT before transcatheter aortic valve implantation (TAVI). The CT scans were evaluated for calcification initiation and growth using the proposed reverse calcification technique (RCT) method.

### 2.2. CT acquisition protocol

All patients underwent CT using a 256-slice system (Brilliance iCT, Philips Healthcare, Cleveland, Ohio) to evaluate the aortic annulus before TAVI. Patients were given intravenous injection of 60–90 ml of nonionic contrast agent (Iomeron 350, Bracco, Milan, Italy) at a flow rate of 3.5 ml/s, followed by a 30-ml saline chasing bolus (5 ml/s). Automated peak enhancement detection in the descending aorta was used for timing of the scan. Acquisition was performed during an inspiratory breath-hold while the electrocardiogram (ECG) was recorded simultaneously to allow retrospective gating of the data. All images were reconstructed with a slice thickness of 0.67 mm and a slice increment of 0.34 mm. The CT-data was reconstructed at 10% increments of the RR-interval and the diastolic phase (70% of RR interval) was used for data analysis.

**Table 1**
Patients' sex, age and orifice area.

| Patient number | Sex | Age | Orifice area [cm$^2$] (based on CT) |
|---|---|---|---|
| 1 | Male | 84 | 1.1 |
| 2 | Female | 88 | 0.68 |
| 3 | Female | 73 | 0.87 |
| 4 | Male | 82 | 1 |
| 5 | Female | 81 | 0.88 |
| 6 | Male | 83 | 0.95 |
| 7 | Female | 92 | 0.95 |
| 8 | Male | 80 | 1.1 |
| 9 | Male | 81 | 1.1 |
| 10 | Male | 81 | 0.8 |
| 11 | Male | 82 | 0.84 |
| 12 | Male | 77 | 1 |

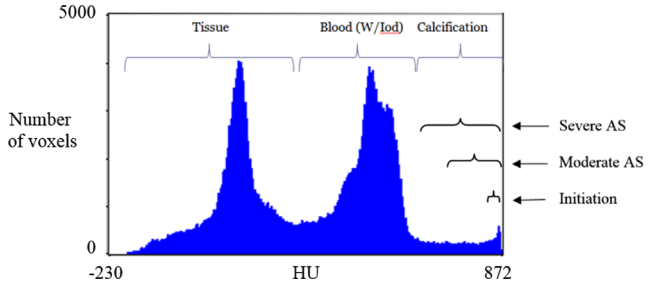


**Fig. 1.** Typical HU map of AV (patient #2), showing the HU range associated with tissue, iodized blood and calcification. The HU ranges at the right side are shown to indicate sub-regions of intensity of calcifications reflecting different stages leading to severe AS. The left axis indicates the number of volume units in each HU.

### 2.3. Reverse calcification technique

The ScanIP software version 6 (by SimpleWare Ltd., Devon, UK) was used to analyze the AV calcification and overall geometry from the acquired raw data of the CT scans. The software can show a 3D reconstruction of the AV based on scans HU histograms and differentiation of HU levels. It also allows volume calculation of a selected HU range.

A typical HU histogram of the volume around the AV is presented in Fig. 1. Three ranges of HU can easily be identified, representing different parts of the valve volume. The voxels with low HU are the valve tissue. By presenting this range alone, the valve geometry is reconstructed (colored in red in Fig. 2). Usually, it is not possible to identify the entire cusp tissue due to its thinness. However, the sinuses, commissures, coronaries and the coaptation line ("Mercedes" shape) can be identified. The calcification volume and geometry can be reconstructed by isolating the voxels with high HU. Fig. 2 (right column) illustrates the AV reconstructed geometry (tissue and calcification) for the existing AS state of three selected patients in the group. Tissue is colored red and calcification is colored green for clarification purposes.

The RCT method hypothesizes that voxels with the highest HU level can be used to identify the initiation of calcification nodules in the cusps. By adding lower levels of HU, the calcification volume grows, simulating a more advanced stage of the disease (see three cases/rows in Fig. 2). This process is repeated until the iodized blood HU level is reached.

In order to validate the method, pre-TAVI CT scans were compared to old CT scans of the same patients. The results were compared to RCT analysis results.

### 2.4. Finite element model

A finite element model was introduced to generate a bio-mechanical patient-specific structural analysis. Towards that goal, the general parametric geometry of the TAV, developed by Haj-Ali et al. (2012), was applied based on the CT valve measurements. Fig. 3a shows the parametric geometries and dimensions used to generate the full 3D geometry of the AV without calcification. The mathematical equations for the parametric AV geometry were programmed in the TrueGrid (XYZ

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