The effect of the fibrocalcific pathological process on aortic valve stenosis in female patients: a finite element study

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Abstract
Calcific aortic valve disease (CAVD) is the most common heart valvular disease in the developed world. Most of the relevant research has been sex-blind, ignoring sex-related biological variables and thus under-appreciate sex differences. However, females present pronounced fibrosis for the same aortic stenosis (AS) severity compared with males, who exhibit more calcification. Herein, we present a computational model of fibrocalcific AV, aiming to investigate its effect on AS development. A parametric study was conducted to explore the influence of the total collagen fiber volume and its architecture on the aortic valve area (AVA). Towards that goal, computational models were generated for three females with stenotic AVs and different volumes of calcium. We have tested the influence of fibrosis on various parameters as fiber architecture, fibrosis location, and transvalvular pressure. We found that increased fiber volume with a low calcium volume could actively contribute to AS and reduce the AVAs similarly to high calcium volume. Thus, the computed AVAs for our fibrocalcific models were 0.94 and 0.84 cm² and the clinical (Echo) AVAs were 0.82 and 0.8 cm². For the heavily calcified model, the computed AVA was 0.8 cm² and the clinical AVA was 0.73 cm². The proposed models demonstrated how collagen thickening influence the fibrocalcific-AS process in female patients. These models can assist in the clinical decision-making process and treatment development in valve therapy for female patients.

1. Introduction
Calcific aortic valve disease (CAVD) is the most common heart valvular disease in the developed world. Untreated symptomatic patients with severe stenosis have a mortality rate of 37% one year after symptom onset [1]. Aortic Stenosis (AS) is characterized by fibrosis and calcification of the aortic valve (AV) leaflets, which eventually impairs leaflet motion [1–3]. Patients are asymptomatic until the disease has progressed to an advanced stage when the tissue becomes thicker and stiffer, which leads to a reduction in the effective orifice area and, thus, stenosis from an incomplete valve opening [4].

Males have higher AV calcium scores than females in computed tomography (CT) scans for the same severity of AS [5, 6] since calcium deposits, unlike fibrosis, are detectable non-invasively with CT imaging. Moreover, females exhibit impaired valve function dominated by fibrosis and denser connective tissue, rather than calcification, hard to detect in CT scans [6–14]. Most cardiovascular research has focused on males and often ignores sex as an important biological variable. This phenomenon has led to the under-appreciation of sex differences in cardiovascular disease (CVD) from an etiological, prognostic, diagnostic, and therapeutic perspective. Research in the field has historically favored the study of calcification over fibrosis [15].

The mechanics of the AV have been investigated extensively using computational models. Although fiber architecture and fibrosis cannot be derived from CT data, computational simulations can provide an improved understanding of the AV fibrosis effect. For example, Hammer et al, 2013 [16] used a structural AV Finite Element (FE) model to find the relationship...
between the collagen pattern and the structural coaptation changes. Marom et al (2013) [17] used 3D Fluidstructure interaction (FSI) simulations of AV with porcine valve-specific collagen fiber alignment, determined after mapping of the collagen fiber network [18]. They demonstrated that the asymmetric internal structure has a considerable impact on the hemodynamics of a healthy valve. Additional computational models studied different AV pathologies, such as calcification [19–22], bicuspid AV [23, 24], and aging [22, 25]. However, as of today, no model combines the effect of calcification and fibrosis on AV stenosis [26, 27].

Herein, we present for the first time a computational model that accounts for the fibrocalcific effect on the AS using a parametric study investigating the influence of total collagen fiber volume and architecture on the aortic valve area (AVA). Towards that goal, computational models were generated for three females with stenotic AVs with patient-specific of calcium deposits and two different collagen architectures. The influence of increased fiber volume and thickening were tested numerically in different spatial locations, pressures, and architectures to evaluate the fibrocalcific effect in AS.

2. Methods

2.1. Study population and CT acquisition protocol

The CT scans and Echo data were acquired from Rabin Medical Center (Petah Tikva, Israel) and taken from a CT database of patients with severe AS undergoing CT before Transcatheter aortic valve replacement (TAVR). The clinical AVA was calculated by continuity equation using VTI (velocity time integral) in Echocardiography (Echo). All the data were anonymized in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements.

2.2. Finite element model

2.2.1. Aortic valve 3D parametric geometry

A finite element model was introduced to create a biomechanical structural analysis using a general parametric geometry of the AV, developed by Haj-Ali et al (2012) [28]. This parametric geometry represents the AV, including the root with its three sinuses and three leaflets (figures 1(a)–(b)). The mathematical equations for the parametric AV geometry were programmed in the TrueGrid (XYZ Scientific Applications Inc., Livermore, CA, USA) mesh generator to create an FE mesh. The mesh was imported to ABAQUS commercial FE software (ABAQUS CAE 2019, Dassault Systèmes, SIMULIA Corp., Johnston, RI).

2.2.2. Valve leaflets

The leaflet was assumed to be a heterogeneous solid structure composed of collagen fibers tied to the elastin matrix layer. The collagen fibers were represented by beam elements integrated into the model using tie constraint to the leaflet solid tetrahedral elements [17, 29]. The valve model consists of three symmetrical and identical sinuses, leaflets, and fiber architecture with patient-specific calcium deposits reconstructed from the CT data scans [19]. Hyperelastic mechanical behavior (Ogden third order) was assumed for the elastin and collagen materials and described in figure 1(e) [17, 19, 23]. The material properties for the calcium and the soft tissue are detailed in table 1 and figure 1.

![Figure 1](image-url)
2.2.3. Collagen fiber bundle architecture

Two sets of collagen fiber architectures were modeled (figures 1(c)–(d)). The first fiber bundle architecture is based on a porcine AV (type I) and was previously described in [17, 27, 33]. It represents symmetric collagen bundle orientations along circular arcs. The second architecture (type II) (figure 1(d)) is also symmetric and oriented in the circumferential direction. It was designed to better represent an aged patient with appropriate fiber remodeling. It was generated based on a confocal microscopy image of an aortic leaflet of a 49-year-old human patient [25] (figure 2). The left side bundles were traced using Inkscape-vector graphics editor. They were then duplicated to create a symmetric bundle architecture to generate the leaflet-curved surface nodes using python code. The nodes were imported to Abaqus to create beam elements as a separate part, tied to the elastin matrix. The initial fibers’ radius was chosen to match the volume of the type I bundle architecture [17, 27, 33]. The bundles’ volume was changed throughout the simulations by increasing the radius of the beam elements’ profile. The effect of fiber volume on the AVA was examined in different locations on the cusps belly.

2.2.4. Patient selection and patient-specific calcification modeling

Three female patients with severe stenosis were chosen based on their calcium volume: two fibrocalcific patients with a relatively low calcium volume (0.142 and 0.08 cm$^3$) and severe stenosis (AVA of 0.82 and 0.8 cm$^2$), and one patient with a high calcium volume (0.763 cm$^3$) with severe stenosis (AVA of 0.73 cm$^2$). High calcium volume is accompanied by a high peak pressure gradient (PPG) required to increase the orifice area and stroke volume. For all three patients, the computed AVA was smaller than 1 cm$^2$, one of the criteria for severe AS [34]. Patients 1 and 2 have a lower amount of calcium, but their mean pressure gradient is higher than 40 mmHg (47 mmHg and 50 mmHg, respectively), which is also defined as criteria for severe AS. Additionally, leaflet thickening is observed in those patients’ CT scans. The fibrocalcific leaflets were relatively thick, as shown by the dark areas in the side view and the open valve of the en face view in the CT scan in figure 3.

High Hounsfield unit (HU) voxels were isolated from the CT scans of the patients using ScanIP software (Synopsys, Mountain View, CA) [19]. The calcium deposits were assumed as homogenous elastic linear [21] and were embedded inside the leaflet matrix (figure 3), using SpaceClaim software (ANSYS, Canonsburg, PA). The calcified cusps were then remeshed with tetrahedral 3D elements (ANSYS Fluent Meshing) to assure mesh continuity at the interface between calcifications and surrounding soft tissue. The resulting mesh was exported to ABAQUS for FE analyses.

The structural mesh part of the model included ~130 k 3D tetrahedral elements of soft-tissue and ~50–300 k tetrahedral elements of calcific tissue (depends on the model) and ~300 beam elements representing the fibers, per leaflet.

The computed AVA was measured by exporting the 3D structure of the deformed leaflets during peak systole to SpaceClaim (ANSYS, Canonsburg, PA) and measuring the contour of the opened valve. Different parameters were tested to examine the influence of collagen remodeling in the fibrocalcific models. Each model had a specific calcium volume and a PPG based on the CT and Echo data of the patients.

2.2.5. Boundary conditions

The simulations were performed under physiologic transvalvular pressure applied on the ventricular side of the leaflets, which constitutes the pressure gradient between the aorta and the left ventricle as a function
The structure solver employed a nonlinear dynamic analysis with an implicit direct displacement-based FE method. The root upper and lower edges, annulus, and the Sinotubular Junction were pinned, while the leaflets were tied to the root at the base of the leaflet, enabling rotational degrees of freedom. A master-slave contact algorithm was employed between the cusps assuming a non-friction contact to model the coaptation area. The patient-specific pressure gradient was based on the peak pressure gradient (PPG) taken from Echo data. Since all patients had a severe AS, the applied PPG was high (figure 1(f)). Patient-specific pressure profiles were created for each model based on the patient physiological data of peak pressure gradient (PPG) taken from Echo, according to a severe patient profile [19]. PPG for patients 1, 2, and 3 were 69 mmHg, 74 mmHg, and 99 mmHg, respectively.

3. Results

3.1. Comparison between the models and clinical data
The different fibrocalcific models are detailed in figure 4. The AVA of the patients was extracted from Echo during the systole and was compared to the AVA of each model (type II fiber architecture, figure 5). The AVA of the calcific model (model 3) was very close to the clinical AVA when using the initial fiber volume per leaflet (0.0383 cm$^3$) without collagen fiber volume increase. In the fibrocalcific models (1 and 2), the fiber bundle volume was increased by approximately 3-fold to simulate the collagen remodeling. The FE AVA was very close to the Echo results: the clinical AVAs were 0.82, 0.8, and 0.73 cm$^2$ and the computed AVA were 0.94, 0.84, and 0.8 cm$^2$ for models 1, 2, and 3, respectively. All computed AVAs were below 1 cm$^2$, which is the clinical limit for severe stenosis.

3.2. The effect of the spatial location of collagen remodeling on AVA
The increased volume was examined in two different spatial locations (upper and lower belly) to compare the effect of fibers’ remodeling location on AVA using type 1 collagen architecture (figure 6). For both fibrocalcific models (1 and 2), the AVA decreased when the fiber volume increased. However, the effect on the AVA of increasing the lower belly fibers volume was more moderate than the upper belly fiber volume. Increasing the lower belly fibers’ volume yielded a larger opening of the valve. Moreover, the lower belly fibers demonstrated a linear regime with the increased volume, whereas the upper belly demonstrated non-linear reduction. Thus, in the upper belly, for low fiber volumes (∼0.05 cm$^3$), the increase in fiber volume resulted in a more prominent AVA reduction (figures 6(a), (b)), and for the larger fiber volumes, the AVA was almost constant, and the change in AVA was minimal. Furthermore, the trend for each region of fibers was very similar between the models. The AVA reduction for the model of patient 2 with PPG of 69 mmHg was higher in both tested regions.

3.3. The effect of collagen bundles architecture on AVA
Two fibers architectures with changed bundle volume were compared, and their effect on AVA was examined on the fibrocalcific models (1 and 2). In both architectures, the enlarged fibers were located in the upper belly region of the leaflet, based on the results shown in figure 7. Here, we found that the change in the AVA trend was similar between the different architectures (figure 7) and the models. An increase in
the fiber volume resulted in a decrease in the AVA. The AVA decreased sharply at the beginning of the increase in fiber volume and then demonstrated a nearly constant value after doubling the initial amount of fiber volume.

### 3.4. The effect of pressure on AVA

The model of patient #1 (with type II fiber architecture) was loaded with three different imposed PPGs: 69 mmHg, 74 mmHg, and 99 mmHg (figure 8(a)). These pressures represent the physiologic pressures of all three models. The AVA difference between the two lower PPGs was minor; however, the AVA obtained under a PPG of 99 mmHg was much larger. Additionally, the AVA was larger per fiber volume for a larger PPG while the PPG of 69 mmHg obtains almost prominently the lowest AVAs, and the PPG of 99 mmHg obtains the highest AVAs. Moreover, we tested the AVA of the three models with low and high fiber volumes for a similar pressure (figure 8(b)) for low fiber volume and increased fiber volume. With the low volume of collagen fibers, the AVA of the highly calcified model is much smaller and affected mostly by the calcification.

### 3.5. Stress distribution on the collagen fibers at systole

The models were loaded with patient-specific PPG with type I architecture and fiber volume of 0.0387 cm$^3$ per leaflet. The maximum principal stress contours plotted on the deformed fibers during peak systole are shown in figure 9. The fibers were subjected to larger stress values than the leaflet matrix since they carried most of the load. These results are also

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**Figure 4.** CT scans and models of the fibrocalcific and calcific patients' AVs. The CT scans panel includes the side view of the leaflet thickness and the AV in systole (opened valve) and diastole (closed valve). The calcium deposits appear in white, the soft tissues are in gray, and the opening area during the systole in green. The Calcium isolation panel demonstrates the patients' geometric model including calcification deposits (white) and AV root (red), using ScanIP. The Fibrocalcific models panel includes collagen fibers architecture and calcium deposits for each FE model.
consistent with Marom et al (2015) [29]. The stress distribution is asymmetric in all three models.

4. Discussion

This study is based on the hypothesis that AS in females is also derived from collagen remodeling and fibrosis rather than only from calcification [7, 8]. Although collagen cannot be identified and quantified accurately with current gold standard clinical practice, the thickening of the leaflet can be observed with CT and Echo. Using collagen bundles parameterization, we investigated the collagen content increase on the AVA. The architecture of collagen bundles is not fully known yet. The circumferential direction is stiffer than the radial direction of the AV leaflet. The collagen fibers are highly aligned along the circumferential direction [36] and oriented obliquely to the free edge in its unstrained state [16], while a more hammock-like structure is seen in the belly [37]. However, since dealing with biological tissue, the orientation and concentration of fibers vary between the leaflets and inside each leaflet with distinctive fiber alignment and varying sizes of the fiber bundles [17]. A denser network of fibers was observed in the belly region, even in healthy valves [18, 27]. Moreover, fibrosis was observed in this region as well [38].

4.1. The effect of the spatial location of collagen remodeling on AVA

Two different trends of AVA decrease were observed with fiber content accumulation and bundles increase, depending on the spatial location of the fibers on the leaflet. The moderate effect of the lower belly fibers might be related to the position of calcium depositions in the two models in the lower belly area. However, the lowest AVA obtained by the accumulation of lower belly fibers was much larger than the AVA affected by the upper belly fibers. This difference implies that the fiber orientation and distribution over the cusp geometry might contribute to the resulted AVA combined with the pressure regions and related

![Figure 5. Comparison of the clinical data to patient-specific FE models. The CT scans of the three investigated patients, on systole. The valve opening area is marked in green and the measured AVA, by Echo, for each patient is detailed (left column). The models at peak systole, including the 3D geometry of the calcification and the collagen fibers architecture. The AVA, as was measured from the model, is presented as well (middle column). The three models at a closed configuration, including the calcification and the collagen fibers (right column). The fibrocalcific models (1 and 2) have the same volume of fiber bundles per leaflet, while the calcific model (3) has a lower volume of collagen bundles per leaflet.](image-url)
modifications in the model. An additional increase of the fiber volume for the lower belly could reduce the AVA. However, it requires a massive increase of fiber volume to obtain an AVA smaller than 1 cm². In our model, fiber bundle radii larger than 0.6 mm were not simulated, mainly due to geometrical restrictions. Still, according to [3, 39, 40], the fibrils number or the area of the fibers in the fibrotic cusps is approximately two times greater than healthy cusps. Thus, a maximum radius of 0.6 mm is satisfying since it is more than double the initial radius (0.1–0.2 mm) of the bundles that were increased in the model.

4.2. The effect of collagen bundles architecture on AVA

Two types of architectures were tested in this study. Type I architecture was previously published and based on fiber alignment observed in a porcine leaflet (Kim 2009; Marom, Halevi, et al 2013; Marom, Peleg, et al 2013) architecture of type II is presented here for the first time. The second fiber bundle architecture was designed to represent aged human fiber bundles. Although porcine leaflet is similar to human leaflet [36], aged human aortic tissues were significantly stiffer than the corresponding porcine tissues in both
the circumferential and longitudinal directions [41]. Furthermore, porcine samples are usually taken from young animals, affecting collagen architecture compared with elder human samples [36, 41]. Moreover, Histological analysis revealed that porcine samples were composed of more elastin and fewer collagen fibers than the respective human samples. However, in humans, stiffness has been shown to increase with age due to an increase in collagen content. Therefore, there is a need to simulate aged human collagen architecture as our type II collagen architecture. It is based on a confocal microscopy image of the collagen fibers [25]. This architecture is also supported by the data taken from [4, 18, 26, 27, 37, 42–50]. The fibers network in type II was denser in the belly region, and the fibers were oriented more straight in the lower belly and in a cross configuration in the upper belly compared to the type I architecture. The AVA shape was changed between the different architectures. Type II architecture reduced the coaptation between the cusps, close to the commissures, and also reduced the whole AVA per a specific fiber volume.

Additionally, we can correlate the arc shape calcification, which stiffens the leaflet area [21], to the increased radius of fibers at the upper belly area, which also stiffens the leaflet. They both have a similar influence on the same region of the leaflet, although having different material properties. Fibers type II had a larger similarity to the calcification arc shape than type I. This similarity could explain the larger decrease in AVA for similar fiber volume for the type II architecture over type I.

Figure 7. The collagen fiber architecture influence on AVA for the fibrocalcific models for (a) patient 1 and (b) patient 2. (c) The initial and final collagen fractions and the resulted reduction in AVA. Type I is based on porcine collagen architecture, and Type II represents a human collagen architecture. The influence of fiber volume increase on the AVA for type I upper belly (yellow) and type II (green) architectures. The initial fiber volume of type I is 0.0387 cm³ for type II is 0.0383 cm³ per leaflet. The final fiber volume of type I is 0.104 cm³ of type II is 0.123 cm³ per leaflet. The data was based on the models of patients 1 and 2 with maximum PPG of 74 mmHg and 69 mm Hg.
4.3. The effect of pressure on AVA

The pressure gradient is derived physiologically from the stenosis severity and is one of the compensation mechanisms to the reduced mobility of the AV leaflets. It has a significant influence on AV functionality and hemodynamics. Comparing the fibrocalcific models under different pressure gradients implies that the PPG has a relatively large impact on AVA: model 1, with the higher pressure gradient, was opened broader, although it has higher calcium volume. This observation is strengthened when comparing the models under an equal pressure gradient, and the AVA obtained for the model with the higher calcium volume (1) was smaller than the AVA of model 2. In this comparison (figure 9), no significant difference in AVA was found between the models. Still, at the very low volume of fibers, the patient with less calcium (2) had a larger AVA. This difference almost disappears with fiber accumulation, which might indicate an equilibrium between the pressure, the material properties, and the structure of the collagen fibers. Nevertheless, calcium has a considerable influence on the leaflet’s mobility and hence affects the AVA. The exact calcium volume, shape, and location have a large role in this equilibrium. It is noticeable when comparing the small AVA of the calcific model (model 3) with a calcium volume of over two-fold more than models 1 and 2.

Additionally, from looking at the AVA of model 3 under the imposed lower pressure (69 mmHg), calcification patterns and size have a considerable influence on the flexibility of the leaflets and the orifice area obtained: when imposing lower pressure than the physiological one, the AVA reduced to 0.69 cm² from 0.8 cm² (figure 9(b)). Models 1 and 2 are fibrocalcific models, and their stenosis was also derived from the accumulation of collagen fiber content. Therefore, the AVA of those two models decreased due to increased collagen content, and the AVA is under 1 cm².

4.4. Stress distribution on the collagen fibers at systole

The fiber bundles carried most of the load and presented elevated stresses compared to the leaflet
matrix, which is also consistent with the work of Marom (2015) [29]. The fibers’ stresses were higher on the non-calciﬁed regions to bear the pressure load and restrict the leaflet deformation. The resistance to elastic deformation of collagen and calcium is larger than that of elastin. The calcification deposits were locally larger and stiffer than a ﬁber bundle. Therefore, a calcification resists the leaflet deformation even more than a large collagen bundle. Consequently, it is reasonable to assume that the ﬁbers that bear the load were subjected to smaller stress values, where the leaflet’s deformation was smaller, as seen in [17, 29], where the leaflet with the least dense ﬁber network had the largest deformations. Moreover, the ﬁbers’ stresses were also higher, close to the calcification edges. This stress concentration could be due to the signiﬁcant change in the material properties between the calcium and the leaflet tissues [29].

The importance of this work is manifested in understanding, for the ﬁrst time, how collagen ﬁbers can contribute to AS in ﬁbrocalcific models that are different from traditional calciﬁed models. These differences could be of signiﬁcant importance in clinical practice for the understanding of AS pathophysiology and the possible development of future individualized medical therapeutics targeting sex-speciﬁc pathways [7, 10].

5. Limitations

The main interest in this study was the systolic phase of the valve cycle; however, a more thorough representation is usually done through a Fluid-structure-interaction (FSI) model. The full cycle can then be analyzed under physiological conditions, and in particular, having an accurate load distribution applied on the cusps. In our ‘dry’ model, directly applying the high pressures on the whole leaflet surface did not generate an accurate physiological state. Thus, calibration of the pressure has to take into consideration the pressure distribution along the leaflet. During the early stage of the systolic phase, the pressure distribution is mainly determined by the paravalvular pressure drop.
across the valve. The collagen remodeling in the spongiosa and ventricularis layers of the leaflet was not taken into account, together with the elastin degradation [3, 51]. Additionally, the model did not consider the inner fiber bundle relationship and interface of fibrils and their diameter and density and their microstructure [37] or the misalignment of fibrils due to pathology [3]. The material behavior of the leaflets matrix was assumed to be that of the healthy valve leaflets. The bundles were modeled as circular structures, not as the pinnate structure that may facilitate strain distribution while permitting large flexion compliance or fan-like branching. The fibrils start to spread out but maintain some parallel organization [49]. Moreover, we assumed symmetry, except for the calcification, which was asymmetric.

6. Conclusions

We present new FE models based on female patients investigating the influence of various fibroses parameters in the fibrocalcific process. Patient clinical data was compared with the AVA obtained from the FE models and demonstrated the crucial role of collagen fibers in the fibrocalcific process, where any clinically used imaging modality cannot visualize them accurately. We found that collagen fibers remodeling combined with calcium deposits actively reduces the AVA, causing severe AS.

Fibrocalcific sex-based computational models can serve as a viable tool to aid the clinical decision-making process in AV replacement therapy. Understanding the mechanism of AS progression will enable developing new treatments for AS, as well as the proper follow-up, repair, and replacement solutions.

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Data availability statement

The data generated and/or analysed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request.

Ethical statement

All the data were anonymized in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements. The study was approved by the local institutional review board of Rabin Medical Center (Approval # RMC-0636–16).

Conflict of interest statement

All authors declare that they have no conflicts of interest.

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