Collagen Bundle Orientation Explains Aortic Valve Leaflet Coaptation

Peter E. Hammer[1], Christina A. Pacak[2], Robert D. Howe[3], Pedro J. del Nido[1]

[1] Department of Cardiac Surgery, Children's Hospital Boston, MA 02115, USA
[2] Department of Anesthesia, Children's Hospital Boston, MA 02115, USA
[3] Harvard School of Engineering and Applied Sciences, Cambridge, MA 02138, USA
peter.hammer@childrens.harvard.edu

Abstract. The aortic valve owes its strength and durability to a network of collagen fibers within the leaflets. However, the pattern of these fibers and their role in valve function is not well understood. We imaged and quantified the macroscopically visible pattern of collagen fibers in seven porcine aortic valves with particular attention to measuring this pattern in the unstrained leaflet. We then used a structural finite element model of the aortic valve to study the effect of the observed collagen pattern on the configuration of the loaded valve. Results showed that collagen is oriented oblique to the free edge over much of the leaflet in its unstrained state, and simulations suggest that this architecture plays an important role by enabling adequate valve leaflet coaptation. Simulation results were validated by comparison with images of a porcine aortic valve under load.

Keywords: Aortic valve, collagen, simulation, coaptation

1 Introduction

The normal aortic valve is able to open with negligible outflow resistance during systole and close tightly to maintain systemic pressure during diastole. In the closed state, the valve exhibits considerable overlap between adjacent leaflets, and this overlap, or coaptation, allows the valve to close effectively over a wide range of normal diastolic pressures. The normal adult aortic valve is characterized by 3-5 mm of coaptation at the point where the three leaflets meet in the valve center, and surgeons have noted that central coaptation height is a strong predictor of the durability of a surgically reconstructed valve [1].

The structure and mechanical behavior of the valve is believed to play an important role in its complex function. The leaflets are comprised of a layered arrangement of extracellular matrix proteins that together exhibits highly nonlinear, anisotropic in-plane behavior and minimal bending stiffness. Many groups have studied leaflet structure in order to better understand valve function [2,3,4].

We have been developing computational modeling tools to study aortic valve function and surgical repair, focusing on structural finite element models aimed at simulating the closed, loaded state of the valve [5]. Our work and that of others has

shown that an accurate structural model of the valve requires realistic leaflet geometry and an accurate material law that can describe the nonlinear, anisotropic mechanical behavior of the collagen and elastin reinforced leaflets. Applying the material law to a computational model requires knowledge of how the direction of reinforcement fibers varies throughout the leaflets. Early studies of aortic valve leaflet histology reported that macroscopically visible collagen bundles predominately run circumferentially in the leaflets (i.e., parallel to the free edge) [4]. Our initial simulations, based on anatomically accurate leaflet shape, an experimentally-derived constitutive law, and this uniform principal fiber direction, predicted a loaded valve shape with abnormally low central coaptation height and considerably greater leaflet billow compared to the normal aortic valve. We hypothesized, based on preliminary observations of isolated aortic valve leaflets, that the principal fiber direction in the normal aortic valve leaflet in its unstrained configuration differs from this uniform, circumferential pattern and that this more realistic, oblique fiber arrangement has an important effect on the configuration of the loaded valve.

In this study, we explore the effect of collagen bundle pattern on aortic valve function during loading. We measure the orientation of macroscopically visible collagen bundles in the unstrained leaflets of seven porcine hearts. We test the effect of collagen bundle orientation on the loaded valve using a structural finite element model based on the average leaflet shape and collagen bundle orientation from the porcine valves along with an experimentally derived leaflet constitutive equation. Finally, we assess the validity of our simulations by comparing coaptation height and other features of the simulated valve under load with images of a normal porcine valve under the same load.

2 Methods

Aortic valve leaflets were excised from seven fresh porcine hearts, placed in a petri dish on a thin layer of phosphate-buffered saline (PBS), and photographed on a light box to record their unstrained configuration. In order to better visualize the network of collagen bundles, especially in the thick central portion of the leaflets, the leaflets were submerged in Sircol dye reagent (Sircol Collagen Assay, Biocolor, UK, Cat. # S1000) for 30 minutes, rinsed in PBS then placed in 0.05% trypsin for 48 hours at 37^{o}C to remove the surface layer of endothelial cells. Leaflets were then rinsed in PBS and placed in 0.5 M sodium acetate for 5 days to remove soluble proteins including proteoglycans. The leaflets were rinsed, and any remaining unstained tissue was excised. The remaining collagen structure (dyed red) of each leaflet was imaged on a white light box using a 9 mega pixel digital SLR camera.

Leaflet shape was digitized by manually tracing the leaflet profile in the digital image. The average leaflet profile for each of the three anatomical leaflets (left coronary cusp, or LCC, right coronary cusp, or RCC, and non-coronary cusp, or NCC) was computed by normalizing and aligning each profile to the two termini of the free edge, resampling each profile to an equal number of points, then averaging the locations of those points across all seven valves.

The orientation of collagen bundles in an image was quantified by computing the predominant direction of the gradient in a neighborhood around each pixel [6]. This was computed as the spatially weighted gradient tensor. For an image I of two variables, the gradient vector can be written

$$\nabla I = \frac{\partial I}{\partial x} \quad \frac{\partial I}{\partial y},$$

and the gradient tensor can be expressed as

$$S_0 = (\nabla I)' (\nabla I).$$

Spatially weighting this tensor function gives

$$S_w(p) = \int_r w(r) S_0(p - r) dr,$$

where $p=(x,y)$, w is a weighting function, and r is a weighting neighborhood. This quantity was computed and averaged across all seven leaflets for each of the three leaflet types. A pixel in the averaged image was determined to lie near or on a strong oriented structure (i.e., a bundle of collagen fibers) if the ratio of maximum to minimum eigenvalue of the weighted gradient tensor exceeded 3:1. The direction at that pixel was determined by the eigenvector associated with the smaller eigenvalue.

A structural FE model of the average porcine aortic valve was constructed by computing an unstructured mesh of approximately 600 triangles within the three averaged leaflet profiles then connecting the leaflet meshes at the free edge termini and wrapping them into a cylinder. Closure and diastolic loading of the valve are simulated by applying transvalvular pressure of 80 mmHg across the leaflets and across the aortic root to which the leaflets attach, which is modeled implicitly as an elastic cylinder. Leaflets are treated as membrane elements with an experimentally-derived anisotropic hyperelastic constitutive equation. We simulate the equations of motion, including contact handling, and solve for the final deformed state of the valve using semi-implicit numerical integration with adaptive time-step control. All simulation and analysis software was written in the Matlab programming language (Mathworks, Natick, MA, USA). See our previous work for details of the modeling method [5].

The computational model is validated by comparing features of the simulated loaded valve to data from a computed tomography (CT) scan of an excised porcine aortic valve loaded by 80 mmHg of static pressure. The image is segmented and meshed to facilitate visualization.

3 Results

Images of the collagen-stained leaflets show a pattern of macroscopically visible collagen bundles originating from the commissures and angled downward toward the leaflet midline. It is also possible to observe that as the large collagen bundles separate, many of the branches form continuous, concave-up arcs across the leaflet (Fig. 1).

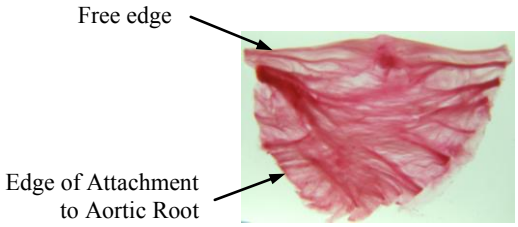

Fig. 1 Porcine aortic valve leaflet (non-coronary cusp) that has been stained for collagen, laid in its unstrained state on a thin layer of PBS, and photographed on a light box.

Quantitative analysis showed that for each of the three leaflet types, collagen bundles tend to be oriented at angles downward from the commissures of up to 40 degrees from the leaflet free edge, while near the leaflet midline and along the lower attachment line, there are few locations where the orientation consistently differs from zero degrees (Fig. 2).

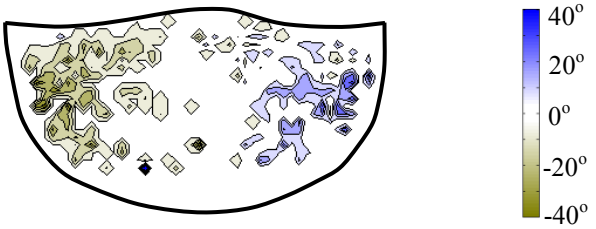

Fig. 2 Average collagen bundle orientation across 7 aortic valve leaflets (right coronary cusp). Color represents angle (degrees) relative to horizontal. Thick black line shows the profile of the right coronary cusp, averaged across 7 valves.

The loaded state of the valve was simulated for 9 different meshes corresponding to collagen fiber orientations of 0, 5, 10, 15, 20, 25, 30, 35, and 40 degrees downward from the commissures toward the leaflet midline. As the fiber angle increased, the simulated closed leaflets underwent a flattening (decrease in curvature) near the leaflet attachment and exhibited increased central coaptation height as seen in cross-sections at the leaflet midline (Fig. 3).

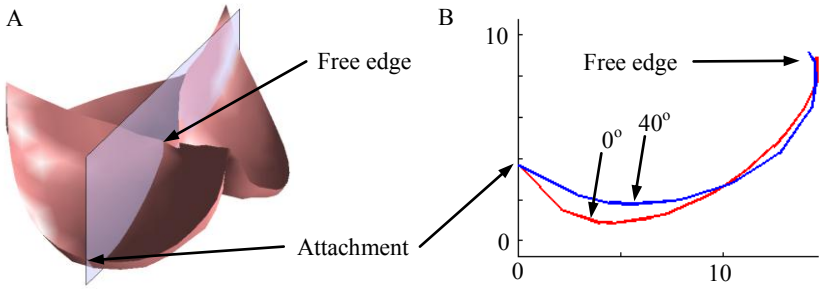

Fig. 3 (A) Simulation result showing mesh of loaded valve with cut plane through leaflet midline. (B) Leaflet midline for right coronary cusp for collagen bundle angle of 0° (red) and 40° (blue). Axis labels are in mm.

The portion of a leaflet that is involved in coaptation can be visualized by demarcating it on an outline of the undeformed leaflet. For example, coaptation area can be seen to increase from the case of purely circumferential fibers (angle of 0^o) to the case of fibers at 20^o (Fig. 4). Plotting coaptation area as a function of fiber angle shows that mean coaptation area increases by almost 20 mm^2 (15%) as fiber angle increases from 0 to 35^o (Fig. 5A). Plotting the central coaptation height as a function of fiber angle shows that mean central coaptation height increases by approximately 1 mm (40%) as fiber angle increases from 0 to 35^o (Fig. 5B).

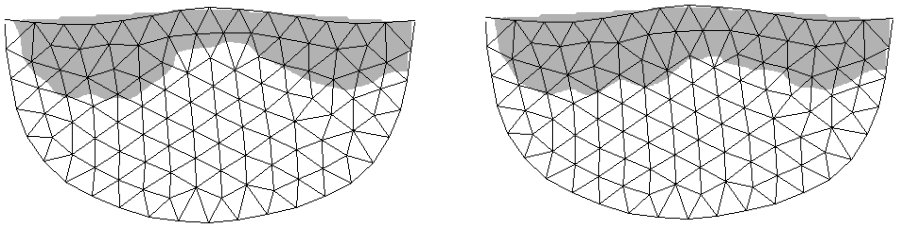

Fig. 4 Region of leaflet (right coronary cusp) involved in coaptation for fiber bundle angle of 0^o (left) and 20^o (right).

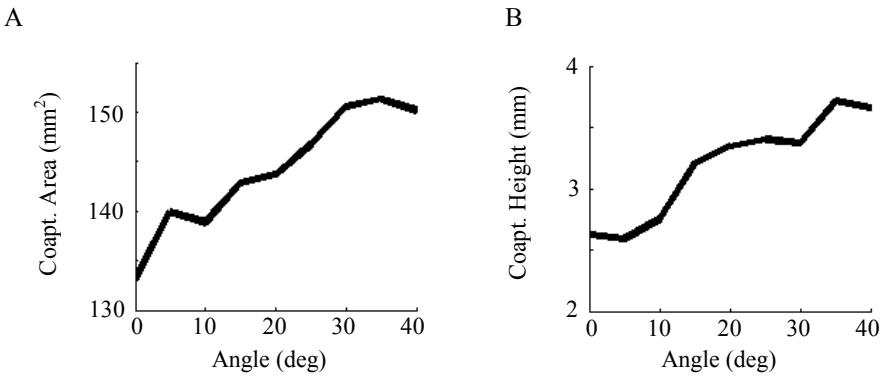

Fig. 5 (A) Total valve coaptation area (mm^2) as a function of collagen bundle angle (degrees). (B) Average central coaptation height (mm) of all three leaflets as a function of collagen bundle angle (degrees).

To compare the simulation results to imaging data from a loaded valve, we computed the intersection of a mesh of the segmented image of the valve with a plane that passes through the central coaptation axis and the midpoint of the leaflet attachment (Fig. 6A). A central coaptation height of approximately 3 mm was measured from the cut plane intersection (Fig. 6B). A region of low curvature can be seen for $x < 6$ mm, changing to a region of higher curvature for $6 < x < 10$ mm.

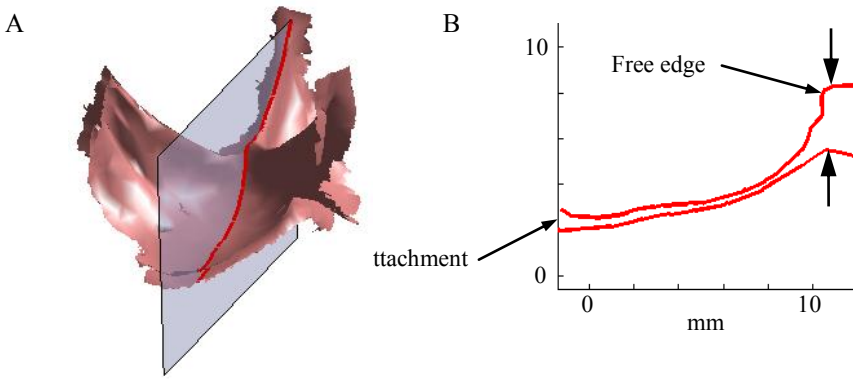

Fig. 6 (A) Segmented and meshed CT scan of a normal porcine aortic valve loaded with 80 mmHg, with cut plane and its intersection shown. (B) Intersection of cut plane with single leaflet (non coronary cusp). Central coaptation height is indicated by arrows. (Note that intersection is shown with two red lines because mesh covers both top & bottom surfaces of leaflet.

4 Discussion

The aim of this study was to quantify the macroscopic collagen bundle architecture in the unstrained aortic valve leaflets and to explore the role that collagen bundle orientation plays in valve function. Results show that over much of the leaflet surface, the typical collagen bundle pattern is not simply parallel to the leaflet free edge but rather forms a series of curved or bent paths oriented downward from the leaflet attachment. Results of simulations show that an important functional difference depends on the fiber orientation. Fig. 5B shows that central coaptation height increases by 40% as fiber angle increases from 0 to 35°. Surgeons report that central coaptation height is critical for good repairs and a key feature of normal valve function. The healthy valve also forms a nearly flat surface in the closed state, and the observed fiber pattern also leads to reduced downward billow of the leaflets under load. The effect of varying the angle of reinforcement fibers in a polymer valve has been reported by others [7], but they considered only the stress field, not functional shape changes, in the loaded valve.

The leaflet changes during loading can be understood in terms of two different phenomena. First, as transvalvular pressure increases, the straightening of the initially curved collagen bundles is opposed by tension in the leaflet in the radial direction (i.e., from the leaflet attachment toward the middle of the free edge). This is the direction in which the leaflets are most distensible due to the predominance of oriented elastin fibers. Thus when the valve is open, transvalvular pressure and collagen bundle tension are negligible, so the collagen bundles remain curved and the leaflet maintains a relatively short radial dimension, potentially reducing outflow resistance through the open valve. When the valve closes, transvalvular pressure and collagen bundle tension rise causing the bundles to straighten and causing tangential (in-plane) displacement of leaflet material toward the coaptation region. Our results

show that this effect reaches a maximum at a fiber angle of 35°, and at steeper angles the in-plane displacement shifts too much from the free edge toward the leaflet midline. We have also noted that due to the angled fiber pattern, the rise in collagen bundle tension is opposed by the relatively compliant leaflet behavior in the radial direction, and this may serve to dampen transient stresses in the leaflets caused by the rapid reversal of blood flow in the aorta in early diastole [8].

A second way to interpret the leaflet changes during loading is in terms of membrane stresses. The straightening of the collagen bundles during leaflet loading causes an increase in the radial membrane tension between the leaflet attachment and the straightening bundles and a decrease in membrane tension between the straightening bundles and the leaflet free edge. Consequently, the membrane curvature decreases in the former region and increases in the latter according to the law of Laplace. This results in a flattening of the leaflets between the attachment and the base of the coaptation region while allowing the leaflets to curve rather abruptly up into the coaptation region.

Limitations to this modeling study include the assumption of constant leaflet thickness and constitutive properties across each leaflet. While not strictly true, these assumptions allow us to isolate the effect of the collagen bundle pattern independent of these other properties. We also neglected to model the effect of blood flow and of fluid-structure interaction. However, during loading of the valve leaflets at end-diastole, there is no flow through the valve, and the leaflets are under an essentially static load.

5 Conclusion

We have shown that macroscopically visible collagen fiber bundles form an oblique pattern in aortic valve leaflets in the unstrained state, and simulations show that these fibers straighten as the leaflets are loaded, enhancing leaflet coaptation and reducing downward billow of the leaflets. These results illuminate a previously undescribed mechanism that appears to play an important role in normal aortic valve function. This mechanism may also have important implications for the design of prosthetic and tissue engineered replacement heart valves as well as for techniques for surgical repair of valves.

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