CHAPTER 29 ANTERIOR LEAFLET STIFFNESS

In Chapters 09 and 13 we showed that the anterior leaflet in the closed valve maintains a nearly invariant shape and position in the ventricle as the leaflet is subjected to the large and variable trans-leaflet pressures in the beating heart. This implies that the leaflets must be quite stiff—and this stiffness depends on leaflet shape, boundary conditions, and elastic moduli.

The elastic modulus of a region of a leaflet in a given direction at a given stress-strain level is defined as the slope of the stress-strain curve of that region in that direction at that stress-strain point. Figure 29.1 shows the radial and circumferential stress-strain curves and moduli obtained at two specific points on each curve in the classic study of May-Newman and Yin\(^1\) of the belly region of whole, excised, flattened, preconditioned porcine leaflets subjected to equibiaxial stretches. Note that the anterior leaflet belly is very compliant for strains up to about 0.15, but becomes 40X-100X stiffer above this “transitional” point; that posterior leaflets are very compliant for larger strains (up to about 0.30); and that circumferential stiffness is greater than radial stiffness for both anterior and posterior leaflets.

In our studies, we employed inverse finite element analysis to derive the circumferential and radial elastic moduli of the ovine leaflet in vivo, in each region and each instant, given the instantaneous leaflet geometry and boundary conditions from our marker studies. Figure 29.2, from Krishnamurthy, et al.\(^3\), shows the miniature radiopaque markers sewn to the anterior leaflet and annulus. Figure 29.3 specifies the marker numbers and the orientation of the circumferential and radial axes used in this analysis.
In our experiments, left ventricular pressure (LVP), left atrial pressure (LAP), and the 3D coordinates of the anterior and posterior papillary tip markers and each of the anterior leaflet markers shown in Figures 29.2 and 29.3 were recorded every 16.67ms throughout several sequential heartbeats. We were thus able to quantify the change in LVP and LAP on each side of the leaflet in the closed valve during a given time interval and associate that change in trans-leaflet pressure with leaflet deformation measured during this interval.

Inverse finite element analysis, described by Krishnamurthy, et al., was used to associate such changes in pressure with leaflet deformation. A computer model of the leaflet was first developed using the 3D coordinates of the markers shown in Figures 29.2 and 29.3. This model incorporated regional leaflet thickness values and assigned strut chords from the papillary tip markers to their insertion points in the leaflet belly. The model was then subjected to LVP and LAP measured at time T1 and again at time T2 and leaflet displacements over this same time interval from T1 to T2 was predicted for initial estimates of radial ($E_{rad}$) and circumferential ($E_{circ}$) moduli. The computer-predicted displacements were then compared with the actual measured displacements and this information used to improve the $E_{rad}$ and $E_{circ}$ estimates for the next computer iteration. This process was repeated until the $E_{rad}$ and $E_{circ}$ values stabilized at values producing a specified minimum difference between the measured and predicted leaflet displacements. These final $E_{rad}$ and $E_{circ}$ values are those reported in this chapter.

Applying this technique to data from 17 hearts (control run datasets provided in Appendix F), Krishnamurthy, et al., found that the elastic moduli of the ovine anterior leaflet during IVR (T1 at end-IVR, assumed as the minimum-stress reference state; T2 at IVR onset) were $E_{circ} = 43\pm18$ N/mm² and $E_{rad} = 11\pm3$ N/mm², respectively; thus the ovine anterior leaflet in vivo was found to be anisotropic, roughly 4x stiffer in the circumferential than radial direction. With these values, the computer model predicted the anterior leaflet shape at T2 with group mean residuals of $0.4\pm0.2$ mm (mean±SD, range 0.2-0.7 mm). These small residuals suggest that the anterior leaflet material is remarkably homogeneous during IVR, because a single type of finite element with constant moduli, applied throughout the leaflet and modified only by regional leaflet geometry, allowed a very close fit to very complex leaflet displacements. Further, this stiff leaflet, exhibiting small leaflet displacements, appeared to be operating over a very limited range of strains for a wide range of trans-leaflet pressures, as pointed out in Chapter 11.

These $E_{circ}$ and $E_{rad}$ values from beating hearts were considerably greater than post-transitional values from excised leaflets ($E_{circ}$ 5-12X greater, $E_{rad}$ 2-55X greater) and several orders of magnitude greater than pre-transitional moduli from such leaflets. Although Krishnamurthy, et al., found that leaflet stiffness was quite sensitive to leaflet thickness (as expected), large variations in the elastic moduli assumed for the strut chords inserted at correct anatomical positions into the anterior leaflet belly had only negligibly small effects on the computed circumferential and radial moduli. Thus it appears, as discussed previously in this book, that the strut chords have only a minor role in supporting the leaflet belly against systolic pressures.

Our next series of experiments tested whether leaflet stiffness was greater during isovolumic contraction (IVC), at the beginning of each beat, than during isovolumic relaxation (IVR), at the end of that same beat. These experiments were motivated by the work of Cooper, et al., who demonstrated the presence of atrial muscle in the anterior leaflet, Sonnenblick, et al., who showed that isolated anterior leaflets exhibited active contraction in response to electrical stimulation, and Curtis and Priola who demonstrated that the leaflets were electrically excited at the beginning of each beat. Itoh, et al., found that this was indeed the case, with both circumferential and radial moduli being from 50-70% greater during IVC than during IVR (C>R, Figure 29.4). Thus the anterior leaflet experiences a stiffness “twitch” at the beginning of each beat; a twitch that is abolished by β-blockade with esmolol (C=0, ESML, Figure 29.4). Such a twitch may stiffen the leaflet to absorb the shock of the rapidly rising LVP at the beginning of each beat.
Because Marron, et al.⁸ had shown that the anterior leaflet is richly innervated and Curtis and Priola⁶ showed that anterior leaflet motion could be influenced by neural stimulation, our next experiment was performed to determine whether leaflet stiffness in vivo could be altered by neural stimulation. Itoh, et al.⁷ found that sub-threshold pulse stimulation of the saddlehorn region (near Marker #22) at 320 min⁻¹ left all other measured cardiac variables unchanged (by design), but nearly doubled both circumferential and radial moduli (STIM, Figure 29.4). Note that neural stimulation had no effect on the leaflet stiffness twitch (C>R, Figure 29.4), unlike β-blockade. Subsequent work by Swanson et al.⁹ showed that both circumferential and radial moduli could also be reduced by central vagal stimulation. These findings suggest the possibility of both local and central control of leaflet stiffness, a speculation strengthened by the known presence of sensory nerves in the leaflet that might be reporting leaflet stretch.

We next examined the regional stiffening of the leaflet, motivated by the knowledge that muscle fibers are present almost exclusively in the annular half of the leaflet. Krishnamurthy et al.¹⁰ partitioned the leaflet as shown in Figure 29.5.
As shown in Figure 29.6, Krishnamurthy et al.\textsuperscript{10} found that both CTRL \(E_{\text{circ}}\) and CTRL \(E_{\text{rad}}\) were quite similar in the three leaflet regions (ANNULUS, BELLY, EDGE), but \(\beta\)-blockade (ESML) completely abolished the IVC twitch stiffening in the ANNULUS region, partially in the BELLY region, but not in the EDGE region. Because leaflet muscle is similarly distributed, most dense in the ANNULUS, sparse in the BELLY, and none in the EDGE, this strongly suggested that the leaflet twitch arises from stimulation of these fibers by atrial excitation at the beginning of every beat, with \(\beta\)-blockade eliminating the twitch stiffening of these fibers. Once again, and consistent with earlier results, \(\beta\)-blockade had no effect on IVR stiffness.

The extra IVC stiffness (relative to IVR stiffness) in the EDGE region remains an unresolved issue. It is not due to leaflet muscle fibers in this region, because they are not present. Further, this extra stiffness is not affected by \(\beta\)-blockade, once again reducing the probability of muscle fiber involvement. It is also unaffected by neural stimulation. As discussed in Krishnamurthy \textit{et al.}\textsuperscript{10}, this could relate to geometric stiffening due to edge curvature change during coaptation, but this will require further study. The stiffness support provided to the anterior leaflet edge by contact with the posterior leaflet edges during coaptation also has not been fully explored, although anterior leaflet edge markers do reflect the effect of this interaction.
If the leaflet stiffening twitch is due to slips of atrial muscle fibers in the anterior leaflet, then leaflet stiffening should drop to near-IVR values in the latter half of ventricular systole. To test this possibility, Krishnamurthy et al.\textsuperscript{2} measured anterior leaflet $E_{\text{circ}}$ and $E_{\text{rad}}$ for the four time intervals shown in Figure 29.7.

As postulated, Krishnamurthy et al.\textsuperscript{2} found that leaflet stiffness moduli, both $E_{\text{circ}}$ and $E_{\text{rad}}$, fell rapidly from IVC values to near-IVR values after mid-systole, adding further evidence that the early systolic stiffness twitch arises from transient contraction of excited muscle fibers in the leaflet that relax in late systole.

If the leaflet stiffness twitch arises from leaflet muscle fibers excited from atrial depolarization, then this twitch stiffening should be abolished in ventricular beats not preceded by atrial excitation. In order to test this postulate, Swanson et al.\textsuperscript{11} utilized high-septal left ventricular pacing to create ventricular beats that were not preceded by atrial depolarization. Figure 29.8 from this study (control run datasets provided in Appendix A) demonstrates that the leaflet stiffening twitch requires atrial excitation. Without such excitation, early systolic twitch stiffening is abolished in the annular region and attenuated in the leaflet belly. Note the similarity of these results to those after $\beta$-blockade (Figure 29.6), suggesting that leaflet muscle contraction, the basis of the early systolic stiffening twitch, requires excitation from atrial depolarization as well as intact $\beta$-receptors.

Further analysis by Swanson et al.\textsuperscript{11} of these CTRL and NAC data during the four time intervals defined in Figure 29.7 showed that total leaflet stiffness (Figure 29.9, red bars) is the sum of the leaflet early systolic stiffening twitch and a constant, steady-state baseline leaflet “tone” (Figure 29.9, blue bars) throughout systole.

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**Figure 29.8** Group mean anterior leaflet circumferential (top) and radial (bottom) moduli, control (CTRL) vs. no atrial contraction (NAC) intervention, for the three leaflet regions (ANNULUS, BELLY, EDGE) defined in Figure 29.5. IVR moduli (blue); IVC moduli for same beat (red).
If total leaflet stiffness is the sum of leaflet twitch plus leaflet tone, the question arises “do leaflet twitch and tone arise from a single mechanism with multiple responses, or multiple mechanisms with independent responses?” Swanson et al. studied this by first blocking leaflet β-receptors with systemic esmolol, then stimulating leaflet nerves with sub-threshold (320 min⁻¹) current pulses to the saddlehorn region (Marker #22, Figure 29.3). The results, shown in Figure 29.10, show that even when anterior leaflet myocyte contraction was blocked by β-blockade, neural stimulation stiffened all regions of the leaflet during both IVC and IVR. This demonstrated that there are at least two contractile systems in the leaflet; one being the leaflet cardiac muscle, involving a β-dependent pathway, others via a β-independent pathway, likely involving valvular interstitial cells and/or smooth muscle cells.
REFERENCES


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