Mechanical properties of myxomatous mitral valves

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Objective: We sought to characterize the mechanical properties of normal and myxomatous mitral valve tissues.

Methods: We tested 113 mitral valve sections from patients undergoing mitral valve repair or replacement for myxomatous mitral valve prolapse and sections from 33 normal valves obtained at autopsy.

Results: Myxomatous mitral valve leaflets were more extensible than normal leaflets when tested parallel to the free edge ($41.2\% \pm 18.5\%$ vs $17.3\% \pm 6.7\%$ circumferential strain [mean $\pm$ SD]; $P < .001$), as well as perpendicular to the free edge ($43.2\% \pm 19.4\%$ vs $17.3\% \pm 6.7\%$ radial strain; $P < .001$). Myxoid leaflets were less stiff circumferentially (4.0 ± 1.6 vs 6.1 ± 1.4 kN/m; $P < .001$) and radially (4.5 ± 1.1 vs 6.1 ± 1.4 kN/m; $P < .001$) than normal leaflets. Leaflet strength, however, was similar in both groups.

Conclusions: Myxomatous mitral valve leaflets are physically and mechanically different from normal mitral valve leaflets. They are more extensible and less stiff. Compared with chordae examined previously, however, they are affected much less. Myxomatous mitral valve disease may therefore affect the collagen in the chordae more severely than that in the leaflets.

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Myxomatous changes in mitral valve tissue are the leading cause of leaflet prolapse and mitral regurgitation in the United States.¹ Although leaflet prolapse is a common diagnosis, not all patients have severe mitral regurgitation and require an operation. For patients who require surgical intervention, the optimal approach is valve repair.² This involves removal of the redundant portion of the prolapsed leaflet and support of the repaired valve with an annuloplasty ring.³ Valve repair has been highly successful and has been shown to preserve left ventricular function more than valve replacement.^{3,4} An ongoing concern in its use, however, is the long-term durability of the repair, given that the valve tissue itself is diseased and likely mechanically compromised.

Although the clinical, echocardiographic, and pathologic abnormalities in myxomatous valve disease have been described,⁵ the biomechanical changes that occur in the myxoid leaflets have not been well characterized. Previous work has focused mainly on the mechanics of normal mitral valve tissue.⁶⁻¹⁵ Kunzelman and Cochran¹¹⁻¹⁵ have studied the mechanics of the mitral apparatus extensively and surveyed the differences between anterior and posterior leaflets and between basal and marginal chordae. However, they did not test human tissues or the effects of myxoid degeneration. We have previously reported on the physical and mechanical properties of myxomatous mitral valve chordae and have found them to be very different from those of normal chordae.¹⁶

Figure 1. Normal mitral valve (A) and myxomatous mitral valve tissue (B and C). Note the extended chordae, the hooding of the free edge of the valve, and the increased thickness of the chordae in the myxoid tissue compared with that in the normal valve. Myxomatous mitral valve resections such as these are usually taken from the posterior leaflet.

Because mitral valve prolapse is diagnosed primarily from the appearance and function of the leaflets, a separate study on myxoid leaflet tissues was conducted. We were specifically interested in determining whether leaflets from myxomatous mitral valves had mechanical properties significantly different from those of normal valves and whether these differences could help explain the mechanism of leaflet prolapse.

TABLE 1. Distribution of test samples (and valves) used in the biomechanical study of myxoid and normal mitral valves

Leaflets, No. of samples from (n) valves		
Myxoid	Anterior circumferential	5 (4)
	Posterior circumferential	82 (77)
	Anterior radial	5 (4)
	Posterior radial	84 (74)
Normal	Anterior circumferential	17 (14)
	Posterior circumferential	8 (7)
	Anterior radial	16 (11)
	Posterior radial	2 (2)

Note that most specimens in the myxoid group were from the posterior leaflet.

Methods

Tissue Procurement

Whole normal mitral valves, with no visible evidence of disease, were obtained at autopsy from individuals who had died of non-cardiac causes. These valves were harvested less than 24 hours after death, placed in physiologic saline (Hanks solution with 0.002% germicide-algicide), and taken to the laboratory. Valves from subjects between 16 and 70 years of age were included in the normal group.

Portions of myxomatous mitral valve leaflets (Figure 1) were obtained from patients undergoing either mitral valve repair or replacement for severe mitral regurgitation ($\geq 3+$ on color Doppler echocardiography) for primary myxomatous mitral valve prolapse. At the time of the operation, all excised valvular tissue was placed in saline solution in a sealed plastic container and sent to the surgical pathology department for routine gross examination. Such samples were collected each day by the investigators, examined grossly to confirm myxomatous features, placed in saline solution, and stored at 4°C for up to 5 days before testing.

Specimens were prepared by first trimming away all chordae and then cutting the leaflets into rectangular strips oriented in either the circumferential or radial direction. The circumferential direction was defined as parallel to the free edge, and the radial direction was defined as from the free edge to the basal attachment to the anulus (Figure 2). All leaflet test strips were 10 mm wide and at least 14 mm long, and radial and circumferential strips were analyzed separately because of expected anisotropy of the tissue.¹³

A total of 113 myxomatous and 33 normal mitral valve specimens were obtained. From the myxoid valves, we obtained 87 circumferential and 89 radial leaflet strips (Table 1). From the normal valves, we obtained 25 circumferential and 18 radial leaflet strips. In the myxoid population there were 85 male and 28 female subjects. In the normal population there were 18 male and 12 female subjects and 3 subjects whose sex was unknown. Inclusion into the myxoid group was based on pathologic examination (thickened central layer¹⁷) and echocardiographic findings (thickened, redundant leaflets and dilated anulus¹⁸). Tissues from patients with Marfan syndrome and ischemic heart disease were excluded. The average patient age was 57 ± 12 years in the myxoid group and 37 ± 14 years in the normal group.

Figure 2. Normal mitral valve depicting the orientation of circumferential and radial samples, as well as basal and marginal chordae. Note that although radial and circumferential specimens were taken from different locations from each valve, their orientation with respect to the valve was maintained.

Tensile Testing

Tissue specimens were gripped at both ends with 2-piece Delrin clamps lined with sandpaper and secured in an Instron servohydraulic testing machine (model 8511; Instron, Canton, Mass). Specimens were immersed in a bath of Hanks solution heated to 37°C during all mechanical tests. The grips were first moved 1 to 2 mm closer together to slightly wrinkle the tissue and to ensure no preload. The tissue was then preconditioned by continuously loading and unloading at 4 mm/s to a predetermined load (between 200 and 400 g) until the load-displacement curve was repeatable. The last load-elongation cycle was recorded for analysis. The stiffness and extensibility of the tissue were calculated from this load-elongation curve (Figure 3). To measure stress relaxation, the tissue was stretched at 4 mm/s to the preconditioning load and held for 100 seconds while the decay of the load over time was recorded. A curve of load versus log time was plotted, and the stress-relaxation slope was calculated. Finally, the tissue was loaded at 4 mm/s until it failed, and the failure strength and failure strain were recorded (Figure 3). Other parameters (eg, volume, weight, and cross-sectional area) were measured for each of the specimens after mechanical testing was completed.

Data Analysis

All data were examined by means of customized software programs written in Mathematica (Wolfram Research, Champaign, Ill). Comparisons of mechanical properties between normal and myxoid tissues were performed by means of a *t* test or Mann-Whitney rank sum test.

In the ideal case, comparisons between the myxoid and normal tissues should be done between like specimens (ie, myxoid anterior leaflets cut in the radial direction vs normal anterior leaflets cut in the radial direction). Unfortunately, such perfectly matched speci-

Figure 3. Typical load-elongation curve showing how mechanical properties are calculated. First, load in grams is converted into tension (newtons per meter) by expressing load as force (newtons) and normalizing for specimen width. Elongation is converted to strain by normalizing for specimen length. From the resulting tension-versus-strain curve, stiffness is computed as the slope of the linear range, and extensibility is obtained from the intersection of the stiffness tangent with the strain axis. Failure strength and strain are measured at the peak of the curve.

mens were not always available. Repair of the regurgitant myxoid mitral valve usually involves the removal of a portion of the posterior leaflet. The anterior leaflet is usually left intact. Thus, most myxoid tissues available for study were mainly from the posterior leaflet (Table 1). Comparisons between myxoid and normal tissues were therefore reported only for those data obtained from the posterior leaflet. The normal posterior leaflet, however, is extremely small, making it difficult to cut 10 mm-wide strips of tissue from

Figure 4. Representative histologic sections of picosirius red-stained myxoid chordae viewed under polarized light microscopy. Note the fibrous tissue that appears to surround the original chords. *Inset* is a typical image of a normal chorda. *C*, Collagen core; *S*, fibrous sheath.

TABLE 2. Comparison of circumferential and radial leaflet test strips taken from the posterior leaflet of myxoid and normal mitral valves

	Circumferential	Radial	<i>P</i> value
Myxoid			
Extensibility (% strain)	37.2 (27.8-51.2)*	39.7 (29.0-52.5)	.405
Stiffness (kN/m)	3.9 (2.7-5.0)*	4.6 (3.8-5.2)	.008
Failure strain (% strain)	52.2 ± 16.1	62.0 ± 16.6	.001
Failure strength (N/m)	844 (630-1149)*	733 (597-975)	.077
Relaxation slope (% tension/log[s])	10.9 ± 5.0	12.3 ± 3.9	.120
Normal			
Extensibility (% strain)	15.5 ± 6.2	24.1 ± 4.0	.105
Stiffness (kN/m)	6.1 ± 1.6	6.4 ± 0.3	.777
Failure strain (% strain)	34.9 ± 8.5	35.6 ± 0.4	.915
Failure strength (N/m)	981 ± 373	657 ± 73.4	.274
Relaxation slope (% tension/log[s])	11.3 ± 2.8	9.2 ± 0.2	.353

Note that no significant differences were found between normal circumferential and normal radial test strips. All values are means ± SD.

*Median (25th-75th percentile) in instances where a rank sum test was performed.

the leaflet with the long axis oriented in the radial direction (from the annulus to the free edge). Most of the leaflet strips obtained from the normal posterior leaflets were therefore oriented circumferentially (along the margin of the posterior leaflet). Comparison of mechanical properties between radial and circumferential strips from the normal posterior leaflet revealed no significant differences between the two (Table 2). This allowed us to group the normal radial and normal circumferential test strips, thus increasing the sample size of the normal posterior leaflet strips. The grouped

radial and circumferential test strips from the normal posterior leaflet were then compared with radial myxoid posterior leaflets and with circumferential myxoid posterior leaflets.

Results

Myxoid posterior leaflet test strips were thicker ($P < .001$) and heavier ($P < .001$) than the test strips of tissue taken from normal posterior leaflets (Table 3). Myxoid posterior leaflets were significantly more extensible ($P < .001$) and less stiff ($P < .001$), both circumferentially and radially, than the normal posterior leaflets (Table 3). Although the myxoid posterior circumferential and radial strips had the same failure strength as the normal leaflets, their failure strain was 58% greater ($P = .005$) than that of the normal leaflets (Table 3).

There were no differences in the stress-relaxation data of the myxoid and normal groups. Histologic observations of representative specimens showed results consistent with those of previous reports. What is pertinent to the analysis of the mechanical properties is the observation of considerable fibrosis or sheath-like covering around the myxoid chordae, particularly near their insertion into the leaflets (Figure 4).

Discussion

Mechanical analyses of diseased mitral valve tissues have been relatively sparse. The work of Clark⁶ and of Ghista and Rao^{7,8} in the early 1970s, as well as more recent studies by Kunzelman and Cochran,¹³ have focused on normal mitral valve leaflets and chordae. Our results for normal human

Figure 5. Comparison of the relative changes that myxoid disease produces in the mechanics of leaflets and chordae. The chordal data were adapted from our previous article¹⁶ and are included here for comparison with that from the leaflets. Note that the failure strength of myxoid basal and marginal chordae were reduced by factors of 1.5 and 2.7, respectively, whereas the changes in leaflet strength were not significant. Factor changes were calculated by dividing the larger mean (either myxoid or normal) by the smaller mean. Statistical significance between normal and myxoid data is denoted by asterisks. The largest *P* value in any of these groups is .03. *Circ.*, Circumferential.

TABLE 3. Comparison of the mechanical properties of normal leaflets (circumferential and radial test strips grouped) with myxoid circumferential and myxoid radial test strips

	Normal (circ and rad)	Myxoid (circ)	Myxoid (rad)	Circ <i>P</i> value	Rad <i>P</i> value
Weight (mg)	146 ± 86.5	337 ± 147	361 ± 135	.001	.001
Cross-sectional area (mm ²)	10.5 ± 3.4	24.4 ± 8.4	26.7 ± 8.8	.001	.001
Volume (cm ³)	0.151 ± 0.09	0.257 ± 0.09	0.289 ± 0.09	.006	.001
Extensibility (% strain)	17.3 ± 6.7	41.2 ± 18.5	43.2 ± 19.4	.001	.001
Stiffness (kN/m)	6.1 ± 1.4	4.0 ± 1.6	4.5 ± 1.1	.001	.001
Failure strain (% strain)	35.0 ± 7.5	55.4 ± 22.0	62.0 ± 16.6	.005	.001
Failure strength (N/m)	801 (665-1091)*	844 (630-1149)	733 (597-975)	.972	.472
Relaxation slope (% tension/log[s])	10.8 ± 2.6	10.9 ± 5.0	12.3 ± 3.9	.966	.288

Note that myxoid leaflet test strips have the same failure strength as normal leaflet test strips. All values are means ± SD. *circ*, Circumferential; *rad*, radial. *Median (25th-75th percentile) in the instances where a rank sum test was performed.

mitral valves are similar to those of Kunzelman and Cochran, who tested porcine mitral valves. However, because of differences in testing methods, more specific comparisons are difficult to make. In reviewing the literature we did not find a single published article describing the mechanics of myxomatous mitral valves other than our previous report on myxomatous mitral valve chordae.¹⁶ The

only similar publication is from 1983,¹⁹ reporting on the mechanics of myxoid tricuspid chordae. In one of the few quantitative ultrastructural studies in print, Whittaker and colleagues²⁰ have shown that collagen from myxoid mitral valve chordae has a lower intrinsic birefringence than normal collagen, indicative of a less highly organized material at the molecular level. Accordingly, we found gross

Figure 6. Diagram demonstrating how an increase in thickness may produce an increased cross-sectional area without altering the number of load-bearing collagen fibers within the leaflet segment. If the thickness is not accounted for in the analysis, the swelling will be perceived as a decrease in failure stress, even though the strength (in grams or newtons) of the leaflet is unaffected.

mechanical changes in myxoid tissues that are likely responsible for leaflet prolapse.

We conclude that myxoid mitral valve leaflets are more than twice as extensible and less stiff than normal leaflets (Figure 5). Similarly, integrating data from this study on leaflets and our previous work on chordae,¹⁶ myxoid chordae are more extensible, less stiff, and not as strong as normal chordae. The failure strength, in particular, is compromised much more in the chordae than it is in the leaflets (Figure 5). For example, in absolute terms the average failure loads of the myxoid marginal chordae were 62% lower (0.5 vs 1.3 kg) than those of normal chordae.¹⁶

It is only after accounting for the differences in tissue dimensions that the profound changes in tissue mechanics produced by the myxomatous process become fully apparent. Stiffness and failure strength are usually expressed in terms of stress, with the units being force per cross-sectional area of the specimen tested. Force is expressed in newtons, and cross-sectional area is expressed in square meters (Figure 6). These values are often presented in pascals, where 1 Pa is equal to 1 N/m². Because we anticipated that the bulk of the increase in the thickness of the myxoid leaflet was caused by an accumulation of glycosaminoglycans (and hence water), we chose to present the mechanics

of the leaflets in terms of membrane tension or force per unit width of the test strip (ie, newtons per meter). This method ignores thickness and avoids the effect of the swelling that adds bulk to the tissue without contributing any strength to the leaflet. The use of tension rather than stress as a measure of leaflet stiffness or of strength better reveals the effects of myxomatous disease on the mechanics of the collagen and elastin components. If one were to express the data in terms of stress, the increased water content would produce a misleading decrease in stiffness and failure strength. Accordingly, we found that the failure strength of the myxoid leaflets decreased very little, despite the more than 2-fold increase in cross-sectional area. This finding implies that the number of load-bearing fibers per unit width, or their strength, has changed very little.

In comparing the relative differences between the changes that myxoid disease induces in leaflets versus in chordae, it should be noted that some of the differences observed in the chordae are geometry dependent. The 4-fold difference in failure strength between normal and myxoid chordae is largely due to the 2- to 3-fold increase in their cross-sectional area. Unlike the apparent swelling of myxoid leaflets caused by increased glycosaminoglycan content, the myxoid chordae increased their cross-sectional area through an accumulation of fibrous tissue around the original chords (Figure 4). Had this new fibrous overgrowth been composed of well-organized collagen, like the native chordae, then its relative strength (in newtons per square meters) would have remained the same, and in absolute terms (in newtons or kilograms), it would have increased. The fact that the strength was reduced 4-fold indicates that this new material played little or no role in reinforcing the chordae or providing additional strength. Indeed, in absolute terms the failure strength of the chordae dropped, despite the additional material. Not only did the new material not reinforce the chordae, but the native collagen in the interior lost some of its original strength. It is also interesting to note that disruption to the collagen, as reported in the literature,²¹ does not seem to affect the strength of the leaflets much but profoundly affects the strength of the chordae. Indeed, this was alluded to in the report by Whittaker and colleagues²⁰ of decreased birefringence in myxoid chordae. We therefore believe that myxomatous mitral valve disease, in terms of its effect on collagen, should be considered more of a disease of the chordae, rather than of the leaflets.

One factor that needs to be considered in the comparison is age. Because the patients in the myxoid group were roughly 20 years older than those in the normal group, it could be argued that the compromised mechanical properties of myxoid valves resulted from the age difference. It has been shown, however, that collagen in the elderly has less crimp than collagen in the middle aged.¹⁰ A reduction in crimp would decrease the extensibility (elasticity) of the tis-

sue and increase the stiffness. We found the opposite in the myxoid tissues from older patients. Our findings indicate that the compromised mechanics of myxoid valves are real and not just the result of age-related degeneration. Studies comparing properly age-matched groups may therefore demonstrate even greater differences in extensibility.

Another factor that should be taken into account is the nonuniform distribution of myxomatous changes in the valve tissues. The leaflet segments removed at the time of operation are usually those that are the most severely affected. Although this type of sampling may exaggerate the apparent severity of myxoid changes in the mitral apparatus as a whole, it is the presence of these localized myxoid changes that causes the severe clinical symptoms that require surgical intervention.

Mitral valve prolapse is a common diagnosis on echocardiography, but only a fraction of patients have mitral regurgitation. It therefore remains unclear whether the myxomatous changes observed in the mitral leaflets and chordae cause prolapse and regurgitation or are a consequence of the regurgitation. It is possible that some of the myxoid changes result from regurgitation, similar to the cusp-edge fibrosis that occurs in regurgitant aortic valves.¹⁷ Alteration in one component, through disease, may produce changes in the other component. However, the clearly abnormal chordal insertions into myxoid leaflets and the recent genetic evidence²² suggest that myxoid changes cannot be entirely acquired; genetic determinants are at least partly responsible.

In conclusion, this study has shown that myxoid leaflets are more extensible and less stiff than normal leaflets. Comparison of these data with those obtained for chordae¹⁶ suggest that myxomatous mitral valve disease affects the load-bearing capacity of the chordae more than it does the leaflets. Myxomatous mitral valve tissue is therefore clearly abnormal and may not function properly, even after successful mitral valve repair.

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