Mitral valve stiffening in end-stage heart failure: Evidence of an organic contribution to functional mitral regurgitation

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Objective: Mitral regurgitation is a complication for many patients with congestive heart failure. Although this regurgitation is considered purely functional, we hypothesize that the alterations in cardiac geometry and function induce dysfunctional remodeling of the mitral valve, which can be demonstrated by alterations in the material behavior of the leaflets and chordae.

Methods: Mitral leaflets and chordae from 23 valves from transplant recipient hearts (11 with dilated and 12 with ischemic cardiomyopathy) and from 21 normal valves (from autopsy) were mechanically tested.

Results: Radially oriented anterior mitral leaflet strips from failing hearts were 61% stiffer and 23% less viscous on average than those from autopsy control hearts. The mean stiffness of circumferentially oriented anterior leaflet strips was 50% higher than that of control hearts. Leaflet extensibility was reduced 35% overall. Likewise, the failing heart chordae were an average of 16% stiffer (all $P \leq .05$).

Conclusions: Mitral valves in congestive heart failure have significantly altered mechanics that suggest that the tissue is permanently distended and fibrotic and might be unable to stretch sufficiently to cover the valve orifice. These material changes in the valve tissues accompany the biochemical alterations in extracellular matrix composition that we have previously reported. Our finding of leaflet and chordal remodeling suggests that mitral regurgitation in patients experiencing heart failure might not be purely functional and that these mitral valves should not be considered normal. Moreover, there are implications for strategies of mitral valve surgery or percutaneous approaches in this patient population.

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Mitral valve dysfunction occurs in 55% to 75% of patients with congestive heart failure (CHF) presenting as ischemic or idiopathic dilated cardiomyopathy.¹⁻⁴ The prognosis is poor for all patients with CHF but is especially poor for patients with mitral regurgitation (MR), who have significantly more complications^{1,3} and survival 2-fold^{1,5} to 10-fold³ lower than that of patients without MR. Survival of patients with even mild MR is only half that of patients with no MR.¹ The occurrence of MR in these patients has long been perceived to be primarily a functional consequence of the altered cardiac geometry.^{6,7} The explanation is that there is nothing wrong with the valve itself but that it is being distorted by the dilatation of the ventricles, the valve annulus, or both. This interpretation has largely been based on observations that the mitral valves appear qualitatively normal on echocardiographic and gross morphologic examinations. In animal models, however, sustained alteration of the normal valvular loading patterns was shown to affect the valvular microstructure,⁸⁻¹⁰ resulting in regurgitation that might have been partly organic, as opposed to purely functional. On the basis of these previous studies, our hypothesis is that the alterations in cardiac geometry and function found in CHF will disturb the normal mitral valve loading and consequently induce

TABLE 1. Subject characteristics

Group	Subjects	Sex, F/M	Age, y*
Control specimens	21	7/14	48 ± 18
Transplant specimens	23	7/16	50 ± 15
Dilated	11	5/6	49 ± 15
Ischemic	12	2/10	51 ± 16

*Mean ± standard deviation.

dysfunctional remodeling of the valve. Although our hypothesis is but one possible interpretation, we believe that such remodeling changes in valvular microstructure and extracellular matrix composition would be indirectly demonstrated by abnormal material behavior of the valve leaflets and chordae. Therefore, this study investigated the possibility for valvular dysfunctional remodeling by measuring the material properties of mitral valves from the explanted hearts of transplant recipients.

Methods

Subjects

Mitral valves were obtained from the recipient hearts of 23 patients undergoing heart transplantation (Table 1). The use of these tissues was approved by the institutional review board. These patients were previously given diagnoses of CHF on the basis of severe left ventricular systolic dysfunction and either severe left ventricular dilatation or a history of atherosclerosis, coronary artery disease, or myocardial infarction. Ischemic cardiomyopathy (ICM; n = 12) was distinguished from dilated cardiomyopathy (DCM; n = 11) on the basis of the presence of segmental wall motion abnormalities and significant obstructive coronary disease. Other than these distinguishing characteristics, there were no significant differences in cardiac geometry or functional parameters between subjects with ICM and subjects with DCM. All patients demonstrated typical characteristics of CHF,⁵ with a mean MR severity of 2.4 ± 1.0 (Table 2). Patients who had mitral valve surgery before transplantation were excluded from the study. Normal control mitral valves were obtained from autopsy from 21 persons who died of causes other than cardiovascular or cardiac disease. The autopsy control specimens were selected according to the least time be-

tween death and arrival at the morgue to minimize the differences between the harvesting of valves from the control and transplant groups. There were no significant differences in age between the CHF and control groups.

Specimen Preparation

The transplant recipient hearts were obtained immediately after transplantation and pathologic inspection. The mitral valve was dissected from the heart and stored in fresh Hanks balanced saline solution at 4°C for up to 5 days before testing. Our laboratory has previously determined that valves kept at 4°C retain their mechanical properties for up to 5 days.¹¹ This finding also justifies our use of autopsy valves, which were harvested less than 24 hours post-mortem from cadavers kept in cold storage (4°C) as suitable and valid control specimens for the transplant valves.

All chordae longer than 10 mm were cut from the leaflet for testing. After removing the remainder of the chordae, the leaflets were cut into strips (10 × 14 mm) oriented circumferentially or radially (parallel or orthogonal to the annular edge, respectively; Figure 1). Test specimens were noted as originating from either the posterior or anterior leaflet, and chordal insertions were characterized as marginal or basal. Several specimens were available from each valve (Table 3). It was not possible to obtain a circumferential and a radial sample from the same anterior leaflet. Only about half of the posterior leaflets had suitable tissue area to cut circumferential specimens. In addition, a small percentage of the valves (both transplant and control valves) were missing either the anterior or posterior leaflet because they were either retained by the pathologists or damaged during the ventricular transection. Finally, none of the control valves (unlike the transplant valves) had posterior leaflets large enough to cut radially oriented strips, and therefore differences in radial material properties of the posterior leaflets could not be tested.

Mechanical Testing

Mechanical testing was performed as previously described by Barber and colleagues.^{12,13} Briefly, leaflet strip thickness was measured with a digital indicator (Mitutoyo, Tokyo, Japan) and used to calculate the leaflet cross-sectional area. The average chordal cross-sectional area was calculated from their weight, length, and assumed density of 1.01 g/mL (on the basis of their buoyancy in Hanks saline) measured after testing.¹³ Specimens

TABLE 2. Cardiac chamber dimensions and functional parameters

Measurement	Subjects	DCM	Subjects	ICM
MV annular diameter (4C), cm	9	4.90 ± 0.40	11	4.59 ± 0.56
LVISD, cm	10	6.50 ± 1.21	10	6.14 ± 1.18
LVIDD, cm	10	7.22 ± 1.19	10	6.91 ± 1.03
IVS thickness, cm	10	0.93 ± 0.19	10	0.93 ± 0.28
PW thickness, cm	10	1.08 ± 0.29	10	0.93 ± 0.20
LA diameter, cm	10	4.65 ± 0.78	11	5.05 ± 0.59
MR, grade 0-4	10	2.15 ± 1.16	11	2.55 ± 0.91
Ejection fraction, %	10	18.0 ± 5.21	12	21.1 ± 8.75

Data are presented as means ± standard deviation. DCM, Dilated cardiomyopathy; ICM, ischemic cardiomyopathy; MV, mitral valve; 4C, 4-chamber; LVISD, left ventricular internal systolic diameter; LVIDD, left ventricular internal diastolic diameter; IVS, intraventricular septum; PW, posterior wall; LA, left atrial; MR, mitral regurgitation.

Normal (Autopsy Controls)

CHF (Transplant Recipients)

Figure 1. Mitral valves removed from heart transplant recipients (*lower*) show gross similarity to normal mitral valves obtained from autopsies (*upper*). The circumferential and radial directions of the valve are also indicated.

were gripped at both ends and placed in a servohydraulic tester (Model 8511; Instron, Canton, Mass). During testing, specimens were immersed in Hanks saline (37°C). Tissue was preconditioned until the load-displacement curves were repeatable (approximately 10 cycles). Immediately after preconditioning, one load-elongation cycle was recorded. After a stress-relaxation test (100 seconds) was performed to assess viscoelasticity, the specimens were stretched to failure.

Data and Statistical Analysis

All data were examined in customized Mathematica programs (Wolfram Research, Champaign, Ill) to obtain stiffness, extensibility, stress relaxation, and failure parameters, as described previously.^{12,13} Stiffness was the slope of the elongation curve, expressed both as elastic modulus (kiloPascals; normalized to measured tissue cross-sectional area) and as tension (Newtons per meter; normalized to idealized tissue width of leaflet strips [10 mm] or chordae [1 mm]). Extensibility was determined as the tissue strain before the collagen fibers became fully uncrimped and the tissue stiffened. The slope of the stress-relaxation curve (load vs log time) was calculated to measure tissue viscosity.

Descriptive summary statistics are presented as means and standard deviations. Group comparisons of patient characteristics were made by using the χ^2 and Wilcoxon rank sum tests. Repeated-measures analyses were performed (SAS PROC MIXED; SAS Institute, Inc, Cary, NC) to account for the lack of independence from multiple specimens evaluated from the same valve. Univariate models were initially formed to test group differences (ICM, DCM, and control) within leaflet and chordal subgroups. Thereafter, multivariable mixed models were developed for overall leaflet and chordae groups to evaluate group effects and interactions while adjusting for confounders (diagnosis, leaflet origin, chordal insertion, and test strip orientation). Within the CHF group, patient characteristics of age, sex, diabetes, extent of CAD, and cholesterol, as well as heart weight, posterior wall thickness, and grade of MR, were also considered for a propensity analysis. Adjusted *P* values have been provided. All statistical testing was 2-tailed, with a significance level of .05, and was performed with SAS version 8.2 (Cary, NC).

Results

Propensity Analysis

The 2 CHF groups (ICM and DCM) did not differ with respect to any of the explanatory factors that were considered, and there was little predictive value from the multivariable model. Therefore, propensity adjustments were not included in further mixed-model analyses that are presented here. Among all CHF valves, however, advanced age (*P* = .009) and diabetes (*P* = .02) were related to increased leaflet thickness. Posterior wall thickness had an inverse association with leaflet thickness (*P* = .007) and a positive association with elastic modulus (*P* = .04).

Physical Properties

Leaflet strips cut from the CHF valves were thinner than control anterior and posterior leaflets (Tables 3 and 4). Anterior leaflet strips from patients with DCM were thinnest (*P* = .02), with a mean thickness 10% less than that for ICM anterior leaflets. Likewise, chordae from the CHF hearts also had slightly smaller cross-sectional areas than normal control chordae (*P* = .08, Table 3).

Material Properties

Radially and circumferentially oriented anterior leaflet strips from CHF hearts were significantly stiffer (stiffness

TABLE 3. Physical and mechanical properties

	Anterior leaflet		Posterior leaflet:	Chordae
	Circumferential	Radial	Circumferential	
No. of specimens (no. of valves)				
Control	13 (10)	19 (11)	13 (11)	82 (13)
All transplants	12 (10)	15 (10)	14 (11)	124 (21)
Dilated	7 (6)	7 (5)	6 (4)	56 (9)
Ischemic	5 (4)	8 (5)	8 (7)	68 (12)
Thickness, mm (cross-sectional area for chordae, mm ²)				
Control	2.15 ± 1.14	1.80 ± 0.38	1.77 ± 0.39	3.16 ± 3.12
All transplants	1.39 ± 0.36	1.33 ± 0.37*	1.57 ± 0.49	1.70 ± 1.76
Dilated	1.32 ± 0.28	1.28 ± 0.49	1.57 ± 0.45	1.39 ± 1.24
Ischemic	1.49 ± 0.47	1.37 ± 0.25	1.56 ± 0.55	2.24 ± 2.29
Extensibility, % strain				
Control	23.7 ± 15.5	22.5 ± 9.6	38.4 ± 14.7	12.3 ± 8.8
All transplants	16.8 ± 9.1	16.0 ± 10.7	30.9 ± 15.0	9.7 ± 8.8
Dilated	16.0 ± 10.3	14.7 ± 5.9	33.0 ± 14.1	9.1 ± 10.5
Ischemic	18.0 ± 8.1	17.2 ± 14.0	29.3 ± 16.4	10.1 ± 7.3
Stiffness, N/m (N/mm for chordae)				
Control	6070 ± 2140	3840 ± 907	5510 ± 1460	52.3 ± 14.7
All transplants	9090 ± 2280*	6170 ± 1620*	6250 ± 1910	60.8 ± 27.9*
Dilated	9010 ± 1700	7100 ± 1780	5760 ± 1370	58.8 ± 16.7
Ischemic	9200 ± 3160	5360 ± 958	6630 ± 2250	62.4 ± 3.46
Elastic modulus, kPa (MPa for chordae)				
Control	3550 ± 2050	2292 ± 827	3390 ± 1660	67.4 ± 116.9
All transplants	7150 ± 3360*	5031 ± 1918*	4340 ± 1900	80.4 ± 73.1
Dilated	7210 ± 2530	6092 ± 1941	3930 ± 1560	85.6 ± 72.2
Ischemic	7060 ± 4640	4103 ± 1422	4640 ± 2160	72.3 ± 74.9
Relaxation slope, N/(m log [time])				
Control	11.87 ± 3.54	12.53 ± 3.01	10.19 ± 2.46	7.16 ± 3.19
All transplants	10.32 ± 2.95	9.70 ± 2.61*	11.18 ± 1.97	6.63 ± 2.36
Dilated	10.44 ± 3.24	10.15 ± 2.99	10.97 ± 1.38	7.25 ± 2.81
Ischemic	10.15 ± 2.86	9.32 ± 2.37	11.34 ± 2.4	6.26 ± 1.99
Failure strain, % strain				
Control	39.3 ± 18.7	56.5 ± 19.2	60.4 ± 17.1	32.3 ± 12.3
All transplants	36.8 ± 11.6	42.5 ± 23.4	53.9 ± 15.7	31.8 ± 13.2
Dilated	39.2 ± 13.8	40.4 ± 16.1	55.2 ± 9.2	32.3 ± 15.4
Ischemic	33.3 ± 7.8	44.3 ± 29.5	52.9 ± 19.4	31.5 ± 11.3
Failure load, g				
Control	1550 ± 795	1090 ± 697	741 ± 252	1320 ± 781
All transplants	1880 ± 900	1240 ± 441	823 ± 379	1420 ± 822
Dilated	1785 ± 739	1430 ± 499	704 ± 367	1318 ± 820
Ischemic	2010 ± 1170	1040 ± 290	913 ± 386	1510 ± 818
Failure tension, N/m (N/mm for chordae)				
Control	1520 ± 780	1070 ± 684	727 ± 248	12.94 ± 7.67
All transplants	1840 ± 883	1210 ± 433	808 ± 372	13.96 ± 8.06
Dilated	1751 ± 725	1404 ± 490	691 ± 360	12.93 ± 8.05
Ischemic	1970 ± 115	1023 ± 285	896 ± 379	14.81 ± 8.03
Failure stress, kPa (MPa for chordae)				
Control	881 ± 592	661 ± 402	450 ± 278	14.4 ± 26.7
All transplants	1400 ± 798	978 ± 419	541 ± 271	17.2 ± 16.4
Dilated	1380 ± 634	1170 ± 464	449 ± 186	17.4 ± 15.5
Ischemic	1430 ± 1070	791 ± 303	609 ± 315	16.9 ± 17.9

Data are presented as means ± standard deviation. **P* < .05, congestive heart failure combined versus autopsy control.

TABLE 4. Mixed model effects for physical and mechanical leaflet properties

Thickness			
Effect	Estimate	Standard error	P value
Intercept	1.938	0.151	<.0001
Dx- ICM	−0.399	0.220	.08
Dx- DCM	−0.542	0.220	.02
Anterior leaflet	−0.118	0.139	.40
Radial	0.033	0.152	.82
Extensibility			
Effect	Estimate	Standard error	P value
Intercept	38.420	2.891	<.0001
Dx- ICM	−7.759	3.869	.05
Dx- DCM	−8.180	3.890	.04
Anterior leaflet	−15.215	3.253	<.0001
Radial	−0.253	3.315	.94
Stiffness			
Effect	Estimate	Standard error	P value
Intercept	4730	412	<.0001
Dx- ICM	1960	522	.0006
Dx- DCM	2390	525	<.0001
Anterior leaflet	1840	491	.0005
Radial	−2720	483	<.0001
Elastic modulus			
Effect	Estimate	Standard error	P value
Intercept	2470	506	<.0001
Dx- ICM	2190	641	.0016
Dx- DCM	2990	645	<.0001
Anterior leaflet	1760	584	.005
Radial	−1940	585	.002
Relaxation slope			
Effect	Estimate	Standard error	P value
Intercept	10.419	0.555	<.0001
Dx- ICM			
& anterior	−2.548	1.009	.016
Dx- DCM			
& anterior	−1.803	0.997	.07
Anterior leaflet	1.613	0.854	.07
Radial	0.493	0.781	.53
Failure strain			
Effect	Estimate	Standard error	P value
Intercept	61.200	4.313	<.0001
Dx- ICM	−7.972	5.500	.15
Dx- DCM	−7.705	5.527	.17
Anterior leaflet	−20.074	5.102	.0003
Radial	13.814	5.046	.0090

TABLE 4. Continued

Failure load			
Effect	Estimate	Standard error	P value
Intercept	652	145	<.0001
Dx- ICM	173	186	.36
Dx- DCM	210	184	.26
Anterior leaflet	992	173	<.0001
Radial	−603	171	.0010
Failure tension			
Effect	Estimate	Standard error	P value
Intercept	639	142	<.0001
Dx- ICM	170	183	.36
Dx- DCM	206	181	.26
Anterior leaflet	973	169	<.0001
Radial	−593	167	.0010
Failure stress			
Effect	Estimate	Standard error	P value
Intercept	310	119	.013
Dx- ICM	251	151	.10
Dx- DCM	375	149	.016
Anterior leaflet	708	138	<.0001
Radial	−384	138	.008

Effects are ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM) versus control, anterior versus posterior, and radial versus circumferential. Dx, Diagnosis.

and elastic modulus, both $P \leq .001$) than autopsy control leaflets (Figure 2 and Tables 3 and 4). In the ICM diagnosis group, the leaflets were also less viscous ($P = .02$) than control leaflets. CHF leaflets required slightly less strain to failure, although this was not statistically significant either as a combined group ($P = .08$) or as subgroups ($P = .15$, ICM; $P = .17$, DCM; Table 4). Extensibility was lower in CHF hearts than in control hearts ($P = .05$, ICM; $P = .04$, DCM) for each leaflet test strip orientation analyzed. The leaflets from patients with DCM seemed affected the most, although there were no statistical differences found between the CHF groups; compared with the patients with ICM, the mean anterior radial stiffness was 32% higher, the mean radial elastic modulus was 48% higher, and the mean radial failure stress was 47% higher for the patients with DCM.

As found in leaflets, the mitral valve chordae from transplant hearts were slightly less extensible and more stiff ($P = .05$) than that chordae from autopsy control hearts (Figure 2 and Table 3). In particular, the mean stiffness of basal chordae from transplant hearts was 17% higher than that from normal hearts ($P = .02$). Although the elastic modulus, like the stiffness, was higher for the CHF chordae than for control chordae, the wide variation in the chordal cross-sectional area prevented the modulus difference from reaching statistical significance. There was also no difference in

Figure 2. A, Illustration of the material properties calculated from the load-deformation data, as explained in the text. B, Representative load-strain curves from radially and circumferentially oriented leaflet strips. C, Representative stress-relaxation curves from radially oriented leaflet strips. D, Representative load-strain curves from chordae. B through D contain specimen curves most closely matching the average material properties of Table 4.

failure characteristics between the transplant and control groups. The differential diagnoses of CHF (ICM and DCM) demonstrated similar chordal mechanics.

Discussion

This study demonstrates that mitral valves from patients with CHF (whether ICM or DCM) had significantly altered material properties compared with those from a control group with the same mean age. These valves were stiffer, less extensible, and less viscous, which we believe is due to a dysfunctional remodeling response to the altered valvular loading patterns in CHF. To our knowledge, this is the first report of altered mechanics in these valves for 2 reasons. First, the MR often found in these patients is largely presumed to be functional, as opposed to organic.⁶ Second, these heart valves have been used as normal control valves for studies of valve biology or other valve diseases. The altered mechanics reported here contradict both of these assumptions. Furthermore, these changes appear to represent a fibrotic remodeling response that has some notable

differences from the remodeling found in myxomatous^{12,13} or rheumatic valve disease.

There are likely both biochemical matrix remodeling and geometric causes for these material property changes in the CHF mitral valves. We recently reported that these valves have greater concentrations of collagen (15% higher) and cells (78% higher) and a 7% lower concentration of water.¹⁴ We propose that the greater concentration of cells indicates an upregulation of mitogenic activity, which could be accompanied by increased matrix synthesis. Because collagens are largely responsible for providing tissue with the strength to withstand high tensile loads,^{15,16} the accumulation of collagen in mitral valves would increase stiffness. The loss of water, which is a major component of the extracellular matrix and contributes to tissue viscoelasticity, is likely responsible for the reduced viscous relaxation. The reduced extensibility, on the other hand, suggests that the leaflet and chordal tissue has also become permanently distended and stretched. A permanent stretch of the valve tissues would effectively reduce the amount of tissue defor-

mation required before the collagen fibrils become uncrimped and begin to bear loads. Correspondingly, the altered material load-strain curves of the valve tissues show a leftward shift of the “crimped to uncrimped” transition region and a higher slope of the collagenous region (Figure 2). This material change is also not due to aging alone; valve stiffening¹⁷ and thickening¹⁸ are associated with aging, but our group of CHF valve test specimens was found to be thinner and yet stiffer than control specimens from the same age group.

These findings provide support for the theory that heart valves are not passive structures but are instead active tissues containing cells that adapt to loading or geometry outside of their normal range by remodeling the microstructural makeup of the tissue.^{8,9} Although this is only one possible interpretation of our data, we assert that the fibrotic change found in this study provides evidence for remodeling. Reports from clinical studies,¹⁴ animal models,⁸⁻¹⁰ and computer models¹⁹ provide additional support by showing that mitral valves exposed to chronic, acute, or simulated ventricular insults demonstrate upregulated DNA and collagen synthesis, as well as increased cell, collagen, and glycosaminoglycan concentrations and increased leaflet stresses. The resulting remodeled valves, however, might not be able to function normally in the long term.

These material property changes indicate that MR in patients with CHF might be partly organic in nature and might have serious clinical consequences. Our proposed mechanism for this MR is that because of the increased tissue stiffness, the valve cannot distend sufficiently in the radial direction to cover the valve orifice. This mechanism is consistent with a previous finite element model⁸ in which increased stiffness and reduced extensibility caused increased valve stresses and reduced coaptation, leading to MR. Although normal mitral valves have an inherent natural redundancy of leaflet size that enables some reduction of the coaptation region without valve leakage,⁸ in the setting of CHF, an enlarged valve annulus will compound the inability of the valve to stretch sufficiently. Furthermore, these abnormal material properties might also affect the valvular closing velocities and response to dp/dt . Thus mitral valve remodeling should be incorporated into the listing of potential causes of MR.⁶ The progressive cycle of abnormal valvular loading, regurgitation, and remodeling is likely a factor in the adverse patient prognoses that accompany MR^{1,3,5} and might have implications for the surgical or percutaneous approaches to manage this patient population. Annuloplasty techniques and even edge-to-edge repair have demonstrated a high return of 3+ or 4+ MR in patients with ischemic MR.^{20,21} Percutaneous approaches to treat this type of MR will be challenging, and chord-sparing mitral valve replacement might be required more often for surgically treated patients.²²

These findings of material property abnormalities in mitral valves from failing hearts also affect more basic science studies of heart valve disease. Although these valves were considered normal in such studies, their material properties, matrix, and cells are those of a remodeled tissue. Data resulting from their use should be interpreted in light of the valve origins.

This study had a number of limitations. One limitation was that due to the minimum specimen size requirements for mechanical testing, the smaller lateral scallops of the posterior leaflet could not be tested. In particular, P3, the leaflet region most likely affected by an ischemic event causing displacement of the papillary muscles,²³ was not tested. Most of the posterior leaflet specimens were taken from P2, the larger central scallop. Another limitation is that we cannot delineate the relative contributions of functional and organic MR to the total MR of the patients. This goal will likely require significant animal and computer modeling studies. Finally, we were limited by the amount of patient information available on the control specimens to use in further risk-adjusted analyses.

In conclusion, we have provided the first evidence that chronic dysfunction of the heart, geometric distortion of the heart, or both, affects the material behavior of the mitral valve. These material property changes would consequently impair valve function and might worsen any existing functional MR. Thus, the diagnosis of functional MR, which characterizes the valve as a solely passive structure, might not accurately depict the valve dysfunction in patients with CHF.

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