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Left Ventricular Shape Is the Primary Determinant of Functional Mitral Regurgitation in Heart Failure

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Objectives. The aim of this study was to examine the temporal association between the onset of functional mitral regurgitation and the development of changes in left ventricular shape, chamber enlargement, mitral annulus dilation and regional wall motion abnormalities during the course of evolving heart failure.

Background. Despite extensive characterization, the exact etiology of functional mitral regurgitation in patients with chronic heart failure remains unknown.

Methods. Heart failure was produced in seven dogs by multiple sequential intracoronary microembolizations. Serial changes in left ventricular chamber volume and shape were evaluated from ventriculograms. Changes in mitral annulus diameter and ventricular regional wall motion abnormalities were evaluated echocardiographically. The presence and severity of mitral regurgitation were determined with Doppler color flow mapping. Measurements were obtained at baseline and then biweekly until mitral regurgitation was first observed.

Results. No dog had mitral regurgitation at baseline but all developed mild to moderate regurgitation 12 ± 1 weeks after the first embolization. The onset of mitral regurgitation was not associated with an increase in left ventricular end-diastolic volume relative to baseline (58 ± 3 vs. 62 ± 3 ml), mitral annulus diameter (2.4 ± 0.1 vs. 2.4 ± 0.1 cm) or wall motion abnormalities of left ventricular wall segments overlying the papillary muscles. In contrast, the onset of mitral regurgitation was accompanied by significant changes in global left ventricular shape evidenced by increased end-systolic chamber sphericity index (0.22 ± 0.02 vs. 0.30 ± 0.01) ($p < 0.01$) and decreased end-systolic major axis/minor axis ratio (1.71 ± 0.05 vs. 1.43 ± 0.04) ($p < 0.001$).

Conclusions. These data indicate that transformation of left ventricular shape (increased chamber sphericity) is the most likely substrate for the development of functional mitral regurgitation.

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Functional mitral regurgitation often develops in patients with heart failure and, depending on its severity, can considerably reduce the effective stroke output of the failing left ventricle. Recognition of the etiology of this valvular incompetence may be helpful in identifying treatment that will improve ventricular pumping capability. Despite extensive characterization, the exact etiologic factors in functional mitral regurgitation remain uncertain, although four specific anatomic abnormalities of the left ventricle have been proposed. These are chamber enlargement (1), mitral anulus dilation (2), wall motion abnormalities of segments overlying the papillary muscles (3) and changes in ventricular shape (4). However, these abnormalities often coexist in the failing heart, making it difficult if not impossible to identify the precise abnormality responsible for the mitral regurgitation. One potential solution to this problem is to identify which of these four abnormalities is present when functional mitral regurgitation is first manifested during the course of evolving heart failure. However, temporal studies of this nature are not likely to be accomplished in patients because of the difficulties encountered in establishing a precise period during which functional mitral regurgitation is first manifested. In the present study, a canine model of chronic heart failure that manifests functional mitral regurgitation (5) was used to examine this temporal association. Specifically, the model was used to explore which of the four left ventricular chamber abnormalities—namely, mitral anulus dilation, chamber enlargement, regional wall motion abnormalities and shape changes—occur coincident with the onset of mitral regurgitation.

Methods

The canine model of chronic heart failure used in this study has been described in detail (5). In this model, heart failure is produced by multiple sequential intracoronary embolizations with microspheres that lead to the loss of viable myocardium. The model manifests many of the sequelae of heart failure observed in patients, including marked and sustained depression of left ventricular systolic and diastolic function, left ventricular hypertrophy and dilation, reduced cardiac output, increased systemic vascular resistance and activation of the sympathetic nervous

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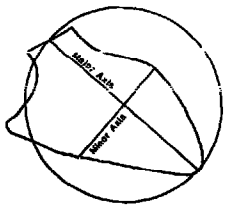

Figure 1. Diagram of the techniques used in the quantitation of global left ventricular shape. An angiographic left ventricular silhouette is shown with depiction of the major and minor axes. The circle, whose diameter is equal to the major axis of the ventricle, represents the sphere used to calculate the sphericity index.

system (5). In the present study, seven healthy mongrel dogs weighing 23 to 35 kg underwent a series of cardiac catheterizations and coronary embolizations to produce chronic heart failure. The protocol was approved by the institution's Care of Experimental Animals Committee. All cardiac catheterizations were performed with the chest closed and under general anesthesia and sterile conditions. Dogs were anesthetized with an intravenous injection of 0.1 mg/kg body weight Innovat-Vet (droperidol, 2.0 mg/kg, and fentanyl citrate, 0.04 mg/kg) followed by an intravenous injection of 7.5 mg/kg of pentobarbital sodium. The protocol for microsphere embolizations and the type of microspheres used for this purpose were previously described (5). In brief, polystyrene latex microspheres, 77 to 102 μm in diameter, were injected in alternating fashion into the left anterior descending and circumflex coronary arteries during subselective coronary catheterization. Each dog underwent five to nine embolizations 2 to 3 weeks apart. Embolizations were discontinued when left ventricular ejection fraction, determined angiographically, was ≤35%.

Evaluation of left ventricular shape. Changes in global left ventricular shape were evaluated from ventriculograms performed with the dog placed on its right side. Ventriculograms were recorded on 35-mm cine film, at 30 frames/s, during the injection of 20 ml of contrast material (RENO-M-60, Squibb Diagnostics). Correction for image magnification was made with a calibrated grid placed at the level of the left ventricle. Left ventricular chamber volumes at end-systole and end-diastole were calculated with the area-length method (6) and were used to determine the ejection fraction. Premature beats and postextrasystolic beats were excluded from the analysis.

Two methods were used to quantitate global left ventricular shape. *In method 1*, ventricular shape was quantitated from angiographic silhouettes based on the major axis/minor axis ratio calculated at end-systole and end-diastole (7) (Fig. 1). The major axis was drawn from the apex of the ventricle to the midpoint of the plane of the aortic valve. The minor axis was drawn perpendicular to the major axis at its midpoint. As this ratio decreases (approaches unity), the shape of the left ventricle approaches that of a sphere. *Method 2* was an adaptation of the sphericity index described by Lamas et al. (8). The sphericity index was calculated at end-systole and end-diastole as the volume of the left ventricle divided by the volume of a sphere with a diameter equal to the major axis of the left ventricle (Fig. 1). As this ratio increases, the shape of the ventricle approaches that of a sphere.

Echocardiographic measurements. Echocardiographic studies were performed by using a Hewlett-Packard model 77020A ultrasound imaging system with a 2.5-MHz transducer. All echocardiographic measurements were made with the dog placed in the right lateral decubitus position. Echocardiograms were recorded on a Panasonic 6300 VHS recorder for subsequent evaluation. Mitral anulus diameter was quantitated by averaging three measurements obtained from three separate echocardiographic projections—a parasternal long-axis view and apical two- and four-chamber views. The mitral anulus diameter was measured during diastole just before atrial contraction and during midsystole. These two measurements were chosen because the mitral anulus diameter is maximal and minimal at these respective times during the cardiac cycle (9). The apical four-chamber view was used to calculate the perpendicular distance D between the point of coaptation of the mitral leaflets and the mitral anulus plane at end-systole as previously described (2). Regional wall motion of the left ventricular segments overlying the anterolateral and posteromedial papillary muscles was quantitated by using the papillary level short-axis view (2). The fractional area of shortening of each of these segments was calculated as described by Boltwood et al. (2).

Quantitation of mitral regurgitation. The presence or absence of mitral regurgitation was determined with the use of Doppler color flow mapping. The severity of regurgitation was quantitated from the area of the regurgitant jet/area of the left atrium ratio (10). The severity of mitral regurgitation, calculated from the apical two- and four-chamber views, was averaged to obtain a single representative measure of the severity of regurgitation.

Study protocol. Echocardiographic, angiographic and Doppler color flow measurements were made at baseline, before any embolizations, and were repeated biweekly until functional mitral regurgitation was first observed. A final set of measurements was obtained an average of 3 months after the onset of functional mitral regurgitation. During the course of coronary embolizations, measurements were always obtained a minimum of 2 weeks after each embolization to avoid the immediate effects of coronary embolization.

Data analysis. Temporal changes of echocardiographic, angiographic and Doppler color flow measurements were examined by using repeated measures analysis of variance (ANOVA) with the level of significance set at alpha = 0.05. If significance was attained, pairwise comparisons were then

JACC Vol. 20, No. 7
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Table 1. Echocardiographic, Angiographic and Doppler Color Flow Measurements During the Course of Evolving Heart Failure

	Baseline	2 Weeks Before MR	Onset of MR	3 Months After Onset of MR
Ejection fraction (%)	55 ± 2	43 ± 3*	38 ± 3†	23 ± 2†
LV EDV (ml)	58 ± 3	62 ± 3	62 ± 3	75 ± 4*
LV ESV (ml)	26 ± 1	36 ± 3	38 ± 2†	57 ± 3†
Systolic MAD (cm)	2.4 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.7 ± 0.1†
Diastolic MAD (cm)	2.7 ± 0.1	2.7 ± 0.1	2.7 ± 0.1	2.9 ± 0.2*
ED axis ratio	1.54 ± 0.03	1.37 ± 0.05†	1.33 ± 0.04†	1.22 ± 0.04†
ES axis ratio	1.71 ± 0.05	1.54 ± 0.04*	1.43 ± 0.04†	1.22 ± 0.04†
ED sphericity index	0.28 ± 0.02	0.37 ± 0.03	0.38 ± 0.03*	0.48 ± 0.03†
ES sphericity index	0.22 ± 0.02	0.27 ± 0.01*	0.30 ± 0.01*	0.43 ± 0.03†
FAS, anterolateral (%)	53 ± 1	49 ± 1	47 ± 1	31 ± 1*
FAS, posteromedial (%)	53 ± 1	48 ± 1	46 ± 1	32 ± 1*
Distance D (cm)	0.5 ± 0.1	0.7 ± 0.1†	0.9 ± 0.2†	0.9 ± 0.1†
Severity of MR (%)	0	0	8 ± 1	15 ± 1

*$p < 0.01$, †$p < 0.001$ relative to baseline. ED = end-diastolic; EDV = end-diastolic volume; ES = end-systolic; ESV = end-systolic volume; FAS = fractional area of shortening; LV = left ventricular; MAD = mitral anulus diameter; MR = mitral regurgitation.

performed on the basis of a Student paired *t* test. An adjustment on the rejection levels of these individual tests was based on the method of Bonferroni. A probability value < 0.01 was considered significant. All data are reported as the mean value ± SEM.

Results

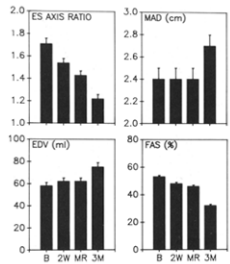
Mitral regurgitation. No dog studied had mitral regurgitation at baseline. However, all seven dogs developed functional mitral regurgitation a mean of 12 ± 1 weeks after the initial embolization. Once mitral regurgitation developed, it persisted to the end of the study. When regurgitation was first observed, its severity was 8 ± 1%; this value increased significantly to 15 ± 1% by 3 months after onset ($p < 0.001$) (Table 1).

Temporal changes in left ventricular chamber volumes. The changes in left ventricular end-systolic volume, end-diastolic volume and ejection fraction during the course of the study are shown in Table 1. Left ventricular end-diastolic volume was unchanged between the baseline measurement and the time of onset of mitral regurgitation. However, it was significantly increased at 3 months after the onset of regurgitation (Fig. 2). Left ventricular end-systolic volume increased significantly from the baseline value to the time of onset of mitral regurgitation. However, end-systolic volume measured 2 weeks before the onset of regurgitation did not differ from that measured at the time of onset (Fig. 2). End-systolic volume increased significantly by 3 months after the onset of mitral regurgitation.

Temporal changes in mitral anulus diameter (Table 1, Fig. 2). Mitral anulus diameter measured at baseline and at the time of onset of mitral regurgitation did not differ, but the value increased significantly at 3 months after the onset of regurgitation.

Temporal changes in regional wall motion (Table 1, Fig. 2). Neither the fractional area of shortening of the left ventricular segment overlying the anterolateral papillary muscle nor the fractional area of shortening of the segment overlying the posteromedial papillary muscle changed significantly between the baseline measurement and that at the time of onset of functional mitral regurgitation (Fig. 2). However, the fractional area of shortening of both segments was significantly reduced at 3 months after the onset of regurgitation.

Figure 2. Bar graphs (mean ± SEM) illustrating the temporal changes of left ventricular end-systolic (ES) major axis/minor axis ratio (**top left**), mitral anulus diameter (MAD) (**top right**), left ventricular end-diastolic volume (EDV) (**bottom left**) and fractional area of shortening (FAS) of the left ventricular segment overlying the posteromedial papillary muscle (**bottom right**). Data shown are values at baseline (B) and at 2 weeks before (2W), at the time of onset of (MR) and at 3 months (3M) after the onset of functional mitral regurgitation.



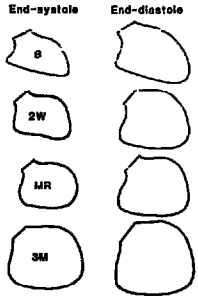


Figure 3. End-systolic (left) and end-diastolic (right) left ventricular silhouettes from a study dog. The silhouettes depict the changes of global left ventricular shape at baseline (B) and at 2 weeks before (2W), at the time of onset of (MR) and at 3 months after the onset of (3M) functional mitral regurgitation.

Temporal changes in left ventricular shape (Table 1, Fig. 2 and 3). Both the end-diastolic and the end-systolic left ventricular major axis/minor axis ratio decreased significantly between baseline and the time of onset of functional mitral regurgitation, indicating increased left ventricular chamber sphericity (Fig. 2). Both ratios were further reduced at 3 months after the onset of regurgitation. Similarly, both the end-systolic and end-diastolic sphericity indexes were significantly increased between baseline and the time of onset of functional mitral regurgitation. Both indexes were further increased at 3 months after the onset of regurgitation. A typical example of the shape changes of the left ventricle during the course of the study is shown in Figure 3.

Temporal changes of the perpendicular distance D (Table 1). The changes in the perpendicular distance D between the mitral anulus plane and the coaptation point of the mitral leaflets during the course of the study are shown in Table 1. This distance increased significantly from baseline to the time of onset of mitral regurgitation. There was no further increase in this distance 3 months after the onset of regurgitation.

Discussion

Our results clearly indicate that the onset of functional mitral regurgitation during the course of evolving heart failure is associated with changes in left ventricular shape manifested by increased chamber sphericity. Neither mitral anulus dilation, left ventricular chamber enlargement nor abnormalities of left ventricular wall motion were present when mitral regurgitation was first manifested. Therefore, these three abnormalities cannot be considered as integral components of the etiology of functional mitral regurgitation. Instead, transformation of left ventricular shape appears to be the most likely determinant of this functional valvular incompetence.

Mitral regurgitation and left ventricular shape. The mechanism by which alterations of left ventricular shape can lead to the development of functional mitral regurgitation is not fully understood. In the present study the onset of mitral regurgitation was associated with an increase in the perpendicular distance between the mitral anulus plane and the coaptation point of the mitral valve leaflets. An increase in this distance indicates retraction of the mitral valve leaflets toward the ventricular apex leading to incomplete mitral valve closure during systole. The means by which increased left ventricular chamber sphericity can induce this type of mitral leaflet retraction can be found in the postulate delineated by Perloff and Roberts (11,12). In the normally ellipsoid left ventricle, the position of the papillary muscles permits their contraction to exert a vertical force on the chordae tendineae. Application of this force moves the mitral valve leaflets together during isovolumetric contraction and restrains their motion during ventricular ejection (11,12). In a more spheric ventricle, the papillary muscles may undergo lateral migration and, therefore, may not be vertically aligned with the mitral anulus. In this situation, the forces exerted on the leaflets through the chordae tendineae become more lateral than vertical. This lateral tension prevents apposition of the leaflets and renders the valve incompetent (11,12).

Factors influencing the severity of regurgitation. In the present study, the development of profound left ventricular dysfunction by 3 months after the onset of mitral regurgitation was accompanied by a further increase in left ventricular sphericity, significant mitral anulus dilation, marked left ventricular chamber enlargement and severe hypokinesia of the left ventricular wall segments overlying the papillary muscles. The development of profound left ventricular dysfunction was also associated with a marked increase in the severity of functional mitral regurgitation. Even though mitral anulus dilation, left ventricular enlargement and left ventricular wall motion abnormalities may not be factors in the etiology of functional mitral regurgitation, at present, we cannot exclude the possibility that all of these abnormalities, once manifested, act in concert to influence the severity of the regurgitation. It is also possible that once initiated, mitral regurgitation may itself exert a reinforcing influence such that "mitral regurgitation begets mitral regurgitation" (11). Finally, recent studies have shown that angiotensin-converting enzyme inhibitors can prevent changes in left ventricular shape (increased sphericity) in patients after myocardial infarction (13) and, therefore, may be useful in limiting the degree of functional mitral regurgitation.

Conclusions. Our results indicate that the onset of functional mitral regurgitation during the course of evolving heart failure is not associated with mitral anulus dilation, left

ventricular chamber enlargement or regional left ventricular wall motion abnormalities. These abnormalities, therefore, cannot be viewed as integral components in the etiology of functional valvular incompetence. In contrast, the onset of functional mitral regurgitation was accompanied by changes in left ventricular shape manifested by increased sphericity. This observation suggests that the transformation of left ventricular shape is the most likely substrate for the development of functional mitral regurgitation in the course of evolving left ventricular failure.

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