Ventricular remodeling and mitral valve modifications in dilated cardiomyopathy: New insights from anatomic study

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Objective: The purpose of this study was to analyze the behavior of the mitral valve ring and the left ventricle in dilated cardiomyopathy.

Methods: We analyzed 68 fixed adult human hearts, divided into 48 hearts with dilated cardiomyopathy of ischemic or idiopathic origin and 20 hearts free of pathologic heart conditions. Digital images of the mitral ring perimeter, attachment of the anterior and posterior leaflets, and fibrous and muscular portions were collected. We also measured the internal perimeter of the left ventricle, the distance from the septum to the anterior and posterior papillary muscles, the distance between the papillary muscles, and the extension of inter-ventricular septum.

Results: The analysis of the results showed proportional distribution of the ring's fibrous portion ($r^2 = 0.98$) and muscular portion ($r^2 = 0.99$) according to the degree of mitral valve dilation. Linear regression revealed that the perimeters of anterior and posterior leaflet attachments ($r^2 = 0.96$ and $r^2 = 0.98$, respectively) also had a proportional relation. We did not observe proportionality between the degree of dilation of the mitral ring and the left ventricle. It was observed that dilation of the left ventricle takes place globally in its segments.

Conclusion: Differently from what was thought, in ischemic or idiopathic dilated cardiomyopathy, dilation of mitral ring is proportional and does not exclusively affect the posterior portion. The degree of left ventricular dilation does not determine the degree of dilation of the mitral ring because they are independent processes. These observations shed new light on the techniques used to correct mitral valve insufficiency in dilated cardiomyopathy.

The analysis of the mitral anulus dimensions in dilated cardiomyopathy (DCM) is of paramount importance in understanding the genesis of valvular dysfunction. It is assumed that the valvular dysfunction observed in DCM is related to dilation of the left ventricle (LV) and left atrium, mitral annular dilation, tearing of the chordae tendineae, and abnormal papillary muscle and LV wall contraction.¹ Valvular regurgitation in patients with ischemic or idiopathic DCM is a predic-

tive factor of poor prognosis² and a frequent complication at the final stage of cardiomyopathy, contributing to aggravation of heart failure and leading to unfavorable progression.³ The introduction of echocardiography was timely, and it has provided important data to understand the mechanisms that lead to the mitral valvular regurgitation observed in DCM. On the other hand, echocardiography has limited the anatomic studies needed to support the observations found.^{4,5}

Echocardiographic analysis in patients with DCM with and without mitral regurgitation has demonstrated that dilation of the mitral annulus occurs only in some patients and is not proportional to the degree of LV dilation. Thus valvular regurgitation associated with LV dilation has a mechanism of dilation independent of that of the mitral annulus, such as loss of sphincter action of the annulus or poor alignment of the papillary muscles.⁶

Anatomic studies of the mitral annulus in hearts from patients with DCM and in normal hearts have demonstrated that mitral dilation alone is usually not responsible for valvular regurgitation. There must be also a deformation in the fibrous skeleton to dilate the annulus and cause valvular regurgitation.⁷ Observations in LV experimental models have shown that mitral regurgitation only occurs when the annulus is more than 1.75-fold more dilated, or 1.50-fold dilated with an apical displacement of the posterolateral papillary muscle, indicating that the mitral valve compensates for annular dilation because of the wide surface of its leaflets.⁸ Knowledge of mitral valvular apparatus alterations may be applied to improve several surgical repair techniques involving the annulus, leaflets, chordae tendineae, and papillary muscles, together or separately, thus justifying its anatomic study in DCM.^{9,10}

Material and Methods

Hearts

Sixty-eight adult human hearts, fixed in 10% formaldehyde and well preserved, were grouped as follows. The first two groups together consisted of 48 hearts with DCM of ischemic or idiopathic origin, with 43 (89.5%) from male individuals. The age range of the subjects was 19 to 79 years, with a mean of 56.8 years; the weight range of the hearts was 400 to 1200 g, with a mean of 743.8 g. There were 48 hearts with DCM, which were subdivided into two groups: hearts from patients with ischemic DCM ($n = 24$) and those from patients with idiopathic DCM ($n = 24$). The following criteria were used to characterize hearts from patients with DCM¹⁰⁻¹²: diameter of at least 5.5 cm, as measured in the internal LV wall at half anterior papillary muscle body height, and perimeter of at least 15.0 cm, as measured in the internal LV wall at half anterior papillary muscle body height. Hearts with DCM were obtained from patients who died with advanced heart failure, and all subjects had clinical attendance and multiple hospitalization. Antemortem data in the medical registry were used to clarify the origins of the cardiomyopathy. The third (control) group consisted of 20 hearts with no cardiomyopathy, with 18 (90%) from male individuals. The age range of the subjects was 19 to 56 years,

with a mean of 32.6 years; the weight range of the hearts was 203 to 313 g, with a mean of 257.3 g. This group contained 20 formaldehyde-fixed cadaveric hearts from individuals with no history of cardiomyopathy and whose cause of death was trauma.

The exclusion criteria for idiopathic DCM were as follows: age younger than 18 years, ischemic coronary disease, congenital cardiac abnormalities, valvular anomalies, interventricular or interatrial septal anomalies or patent foramen ovale, infiltrative myocardial disease (such as amyloidosis), total atrioventricular block, hypertensive disease with systolic pressure greater than 200 mm Hg, correlation with puerperal period, positive Machado Guerreiro complement fixation test result (Chagas disease), LV cavity deformities, and surgical treatment of ventricular cavities or atrioventricular or semilunar valves. The same exclusion criteria for idiopathic DCM were used to characterize hearts with ischemic DCM, with an exception made for ischemic heart disease. In this case the inclusion criteria for ischemic DCM were the presence of coronary lesion of 70% of the vascular lumen in one or more coronary arteries and the presence of myocardial infarction in the histologic analyses. The inclusion criteria for the 20 cadaveric hearts with no previous cardiomyopathy in group 2 were as follows: absence of macroscopic cardiac alterations (particularly valvular lesions) and age older than 18 years and younger than 70 years.

Heart Preparation and Fixation Methods

After selection and identification of the specimens, we introduced cotton flakes and jelly foam to fill ventricular and atrial cavities, so that the heart would be molded and could return to its form in diastole. Subsequently, hearts were stored for 30 days in formaldehyde so that they could be dissected and prepared.

The great vasa were sectioned at the level of the valvular commissures, the vena cava and pulmonary veins were sectioned in their junction with the atria, and the right and left atria were sectioned at the atrioventricular junction, which enabled visualization of the left and right atrioventricular valves. The LV and right ventricular walls were cross-sectioned at half anterior papillary muscle body height (Figure 1).

Measurements

The measurements were obtained through digital photographs analyzed by a computer. To measure mitral annular and ventricular cavity perimeters, heart images were processed by a software to obtain more precise results that could be reproduced. The hearts were placed on a table with a digital camera support, and a graduated ruler was used to calibrate images of atrioventricular valves and ventricular cavities. These images were digitized and distances, and perimeters of mitral valve and LV cavity were analyzed by software.

The following were analyzed in the LV cavity: (1) distance between the interventricular septum and the posterior papillary muscle, (2) distance between the papillary muscles, (3) distance between the interventricular septum and the anterior papillary muscle, (4) extension of the interventricular septum, and (5) internal LV perimeter (as the sum of these variables; Figure 2). The mitral annulus was analyzed as follows: (1) insertion perimeter of anterior leaflet, (2) insertion perimeter of the posterior leaflet, (3)

Figure 1. *Left*, Heart with DCM after section of atrial cavities showing left and right atrioventricular valves. *Right*, Heart with DCM sectioned at half anterior papillary muscle height; LV and right ventricular cavities could be observed.

Figure 2. *Left*, Photograph of ventricular cavities sectioned at half anterior papillary muscle height. *Right*, Diagram demonstrates following variables: 1, distance between interventricular septum and posterior papillary muscle; 2, distance between papillary muscles; 3, distance between interventricular septum and anterior papillary muscle; and 4, extension of interventricular septum and internal LV perimeter LV by adding up measures.

Figure 3. *Left*, Photograph of base of heart and mitral valve. *Right*, Diagram demonstrates following variables: A-B, shorter perimeter distance between fibrous trigones (fibrous portion); B-A, longer perimeter distance between fibrous trigones (muscular portion); A-C, insertion perimeter of anterior leaflet; and C-A, insertion perimeter of posterior leaflet.

shorter perimeter distance between fibrous trigones (fibrous portion), (4) longer perimeter distance between fibrous trigones (muscular portion), and (5) mitral annular perimeter (as the sum of these variables; Figure 3).

Statistical Analysis

The many parameters analyzed were compared by single-factor variance analysis, and the differences between the groups were discriminated by the Bonferroni *t* test. Correlation among variables

Figure 4. Fibrous and muscular portions of mitral annulus (in centimeters).

was analyzed through linear regression. Data were shown as mean and standard deviation.

Results

The variables from the three groups (hearts with ischemic DCM, hearts with idiopathic DCM, and normal hearts) were distributed as follows: analysis of mitral annular and LV variables, comparison between mitral annular and LV perimeters in hearts with ischemic and idiopathic DCM, and comparison among mitral annular variables in normal hearts and hearts with DCM.

Analysis of Mitral Annular and Left Ventricular Variables

In comparing the normal heart group with the combined group of hearts with DCM, the results showed increases with DCM in mitral valve perimeter, mitral valve area, mitral leaflet area, perimeter distances between fibrous trigones, and insertion perimeter of posterior mitral leaflet ($P < .0001$; Table 1). The measurements of hearts with idiopathic DCM were greater than those of hearts with ischemic DCM. Table 2 shows P values comparing hearts with ischemic DCM, hearts with idiopathic DCM, and normal hearts and demonstrates significant differences among the groups. Figure 4 shows the proportional growth of the fibrous portion in relation to the muscular portion of the mitral annulus. The analysis of LV variables (Table 3), such as LV perimeter, distance between papillary muscle and septum, interpapillary distance, distance between anterior papillary muscle and septum, and septal extension, in normal hearts versus hearts with idiopathic and ischemic DCM, revealed that increases in different variables had similar behavior. That is, increases were global and spherical (Figure 5). Measurements in hearts with idiopathic DCM were

greater than those in hearts with ischemic DCM. There was a statistical difference in all variables ($P < .05$) between normal hearts and all hearts with DCM.

Comparison Between Mitral Annular and LV Perimeters in Hearts With Ischemic and Idiopathic Dilated Cardiomyopathy

Progressive increases in LV perimeter and mitral valve perimeter were observed when normal hearts and hearts with ischemic or idiopathic DCM were compared. In linear regression, it was observed in hearts with both ischemic and idiopathic DCM that LV perimeter was not linearly proportional with mitral valve perimeter. That is, the degree of LV dilation was not related to that of mitral annular dilation (Figure 6).

Comparison Among Mitral Annular Variables in Normal Hearts and Hearts With Dilated Cardiomyopathy

Analysis of the mitral annular variables in normal hearts and hearts with DCM and plotting in a linear regression chart showed that the distances between fibrous trigones were proportional to the degree of mitral annular dilation in both the fibrous portion ($r^2 = 0.986$, β error = 0.993, SE = 0.06) and the muscular portion of the annulus ($r^2 = 0.999$, β error = .999, SE = 0.006). It is noteworthy that increased intertrigonal distance was proportionally similar (Figure 7). The fibrous portion involved 21.5% of the annular perimeter in normal hearts and 24.8% in hearts with DCM. The insertion perimeter of the anterior leaflet involved 43% of the annulus in the normal hearts and 39% in the hearts with DCM. Because the insertion perimeters of the mitral annular anterior and posterior leaflets involved the annular perimeter in a more homogeneous manner, these variables were

TABLE 1. Measures related to mitral annulus in normal hearts and hearts with ischemic and idiopathic DCM

Variable	Normal hearts (n = 20)	Ischemic DCM (n = 24)	Idiopathic DCM (n = 24)	P value
Mitral annular perimeter	8.80 ± 0.87	10.30 ± 1.05	11.28 ± 1.28	<.0001
Total mitral area	6.12 ± 1.30	7.69 ± 1.72	9.30 ± 2.16	<.0001
Anterior and posterior leaflet area	6.12 ± 1.30	7.58 ± 1.63	9.15 ± 1.96	<.0001
Shorter perimeter distance between fibrous trigones (fibrous portion)	1.90 ± 0.24	2.62 ± 0.32	2.74 ± 0.42	<.0001
Longer perimeter distance between fibrous trigones (muscular portion)	6.90 ± 0.75	7.68 ± 0.89	8.54 ± 1.05	<.0001
Insertion perimeter of anterior leaflet	3.79 ± 0.67	4.06 ± 0.89	4.56 ± 0.86	<.05
Insertion perimeter of posterior leaflet	5.01 ± 0.85	6.24 ± 1.11	6.72 ± 1.38	<.0001

All figures are mean ± SD in centimeters.

TABLE 2. Analysis of mitral annulus variables comparing normal hearts and hearts with DCM

Variable	P values		
	Ischemic DCM versus idiopathic DCM	Ischemic DCM versus normal hearts	Idiopathic DCM versus normal hearts
Mitral annular perimeter	<.05	<.05	<.05
Total mitral area	<.05	<.05	<.05
Anterior and posterior leaflet area	<.05	<.05	<.05
Shorter perimeter distance between fibrous trigones (fibrous portion)	NS	<.05	<.05
Longer perimeter distance between fibrous trigones (muscular portion)	<.05	<.05	<.05
Insertion perimeter of anterior leaflet	NS	NS	<.05
Insertion perimeter of posterior leaflet	NS	<.05	<.05

All figures are mean ± SD in centimeters. NS, Not significant.

TABLE 3. LV variables in normal hearts and hearts with ischemic and idiopathic DCM

Variable	Normal hearts (n = 20)	Ischemic DCM (n = 24)	Idiopathic DCM (n = 24)	P value
LV perimeter	13.26 ± 1.83	19.16 ± 1.84	21.28 ± 1.84	<.0001
Distance between interventricular septum and posterior papillary muscle	1.88 ± 0.45	3.49 ± 0.72	3.96 ± 0.90	<.0001
Distance between anterior and posterior papillary muscles	3.20 ± 0.70	4.76 ± 0.79	5.40 ± 0.80	<.0001
Distance between interventricular septum and anterior papillary muscle	3.26 ± 0.89	4.80 ± 1.19	5.35 ± 1.04	<.0001
Interventricular septal extension	4.92 ± 0.78	6.11 ± 1.13	6.56 ± 0.85	<.0001

All figures are mean ± SD in centimeters.

also analyzed in relation to valve perimeter. Linear regression analysis revealed that the insertion perimeters of the anterior ($r^2 = 0.964$, β error = 0.982, SE = 0.057) and posterior ($r^2 = 0.983$, β error = 0.992, SE = 0.026) leaflets were proportional to mitral annular dilation (Figure 8). When we compared the mitral leaflet area with the mitral valve area, we observed a linear correlation between them ($r^2 = 0.9842$, β error = 0.992, SE = 0.06), which demonstrates that when there is growth of the ring, there is also growth of the leaflets.

Discussion

The closure mechanism of the left atrioventricular valve has not been completely explained yet. Considered inert for many years, the annulus not only serves as a support for leaflet insertion but also decreases its circumference during systole and reduces the valvular orifice area to be closed.¹³

Mitral insufficiency is common in patients with ischemic and idiopathic DCM. Although the real mechanism of functional insufficiency has not been completely understood, one could suppose that some concurrent factors, such as

PERCENTAGE OF LEFT VENTRICLE VARIABLES OCCUPATION
(NORMAL HEARTS)

PERCENTAGE OF LEFT VENTRICLE VARIABLES OCCUPATION
(DILATED CARDIOMYOPATHY)

Figure 5. Percentage of LV variables analyzed in normal hearts (*left*) and hearts with DCM (*right*).

Figure 6. LV and mitral annular perimeters in ischemic and idiopathic DCM.

displacement of the papillary muscles, valvular insertion traction in the fibrous annulus, and decreased contractile force in the LV leading to decreased transvalvular pressure, are among the probable etiologic factors.¹⁴

Anatomic studies⁷ have demonstrated that mitral annular dilation rarely causes regurgitation. Therefore there must be some abnormality in the fibrous skeleton of the heart to make the annulus dilate and cause mitral regurgitation. The mitral annulus comprises two fibrous structures—the right and left fibrous trigones—that are in an anterior position. However, its posterior segment has no fibrous structures that could theoretically dilated.

Glasson and colleagues¹⁵ used radiopaque markers and

biplane videofluoroscopy and found the mitral annulus to be a dynamic structure that may undergo changes in shape and size of all its segments, both in the posterior and anterior portions. The dynamics of the anterior leaflet thus could be a much more active component in the left atrioventricular valvular apparatus than previously thought.

Our study analyzed valves in situ with software and made assessment of insertion perimeters of the leaflets and of the distances between fibrous trigones of the mitral annulus possible. Analysis of these perimeters with the excised valve may interfere in its evaluation. Kunzelman and colleagues¹⁶ compared the mitral valve perimeter and the extension of the insertion of each leaflet in situ and after

Figure 7. Fibrous and muscular portions in relation to mitral valve perimeter.

Figure 8. Insertion perimeter of mitral annular anterior and posterior leaflets in relation to mitral valve perimeter.

excision of the valve and observed increases by 31% in posterior leaflet insertion and by 3.3% in the anterior leaflet insertion when leaflets were excised. Because there were many options, we decided to analyze seven mitral annular variables to check the behavior of the annulus in ischemic and idiopathic DCM: perimeter, area, leaflet area, fibrous and muscular portions of the annulus, and insertion perimeters of the anterior and posterior leaflets.

The increases of mitral valve area and leaflet area that were observed in ischemic and idiopathic DCM occurred in a linear pattern. Therefore, there is a compensatory mechanism of the leaflets related to their own condition of natural redundancy. This mechanism compensates for mitral regurgitation when the dilation of the ring occurs.

According to many authors,^{8,13,17,18} the short perimeter distance between fibrous trigones is an area that could not

be distended, because it is part of the fibrous heart skeleton. Our study compared normal hearts with hearts with DCM and demonstrated a proportional increase in the fibrous and muscular portions of the annulus relative to the degree of dilation of the mitral annulus. Because the fibrous portion involved only 21.5% of the mitral circumference, we also measured the insertion perimeter of the anterior leaflet, which involved 43% of the circumference. Both measures, the shorter perimeter distance between fibrous trigones representing the fibrous portion of the annulus and the insertion perimeter of the anterior leaflet, showed an increase proportional to that observed in the valvular annulus. These data are in disagreement with the literature, in which most reports do not consider the fibrous portion of the annulus to be increased,^{1,14,19} and with data from the authors previously cited,^{7,20,21} who accept a minimal increase.

In light of these data, we pose a question. If mitral annulus dilation were anatomically proportional, what would be the theoretic basis to perform asymmetric annuloplasty? According to the literature,¹⁹ anatomic studies have demonstrated that when annular dilation occurs, the distance between the fibrous trigones remains stable and dilation takes place along the insertion of the posterior leaflet. It is presumed that the anatomic reason that the anterior portion of the mitral annulus does not take part in annular dilation might be the continuity of the valve with the interventricular septum in its fibrous portion. This fact corroborates performance of annuloplasty involving the posterior portion exclusively.²²

On the basis of this assumption, several authors¹⁹⁻²¹ have used a metallic or polytetrafluoroethylene annulus, an autologous pericardial strip, or a simple suture as surgical techniques to repair mitral regurgitation. All techniques move the LV posterior wall, represented by the mitral valve posterior leaflet, toward the anterior leaflet. Carpentier²³ believed that asymmetric annuloplasty divides the forces on the left atrioventricular valvular annulus in an unequal manner, which was contrary to persistent annular dilation process, and proposed remodeling with a rigid polytetrafluoroethylene ring.

With respect to ventricular morphologic changes in DCM, many authors¹⁹⁻²⁴ have recently demonstrated some disadvantages of using the rigid annulus, including deformation of the natural geometry of the annulus and possible obstruction of the LV outflow tract. Thus there are different suggestions for several kinds of remodeling techniques involving reduction or reinforcement of only the posterior portion of the annulus. Duran and Ubago²⁵ developed a totally flexible annular ring to reconstruct the left atrioventricular valvular annulus, restoring the normal size and shape of the annulus and respecting valvular annulus changes during the cardiac cycle.

The ventricular variables analyzed demonstrated a global

and proportional dilation among the segments observed. According to Kono and associates,^{26,27} changes in the LV cavity occurring during the course of heart failure are manifested by increased chamber sphericity; that is, changes do not occur in segments but globally.

Our observations also demonstrated a lack of correlation between degrees of LV and mitral annular dilation. These data raise questions about the real determining factor for mitral insufficiency, because very large cavities do not lead to significant annular dilations. How then could the annuli be highly dilated if the ventricular cavities are not much dilated? The absence of correlation between LV and mitral annular dilation does not support the influence of these techniques on ventricular remodeling in patients with severe DCM.

On the other hand, it is clear from the data presented in this study that the dilation also occurs in the anterior portion of the ring in hearts with ischemic or idiopathic DCM. We therefore suggest that these anatomic data support the use of complete mitral annuloplasty techniques in DCM.

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