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Left Ventricular Myocardial Remodeling and Contractile State in Chronic Aortic Regurgitation

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Summary

Background: In chronic aortic regurgitation, eccentric hypertrophy, with combined concentric hypertrophy of the left ventricle, is an important adaptive response to volume overload, which in itself is a compensatory mechanism for permitting the ventricle to normalize its afterload and to maintain normal ejection performance (physiologic hypertrophy). However, progressive dilatation of the left ventricle leads to depressed left ventricular (LV) contractility and myocardial structural changes, including cellular hypertrophy and interstitial fibrosis (pathological hypertrophy).

Hypothesis: The study was undertaken to determine the relationship between left ventricular myocardial structure and contractile function in 14 patients with chronic aortic regurgitation by cardiac catheterization and endomyocardial biopsies.

Methods: Myocardial cell diameter and percent interstitial fibrosis were obtained from biopsy samples. Contractile function was evaluated from the ratio of end-systolic wall stress to end-systolic volume index (ESS/ESVI) and the ejection fraction–end-systolic stress (EF–ESS) relationship, which was obtained from 30 normal control subjects.

Results: Myocardial cell diameter correlated significantly with the ESVI ($r = 0.72$, $p<0.005$), ejection fraction ($r = -0.58$, $p<0.05$), and ESS/ESVI ($r = -0.58$, $p<0.05$). The percent interstitial fibrosis also correlated inversely with ESS/ESVI ($r = -0.71$, $p<0.005$). Compared with very few patients with an ESVI <70 ml/m^2, the majority of patients with ESVI $\geqq 70$ ml/m^2 had a cell diameter of $\geqq 30$ μm and a percent interstitial fibrosis of $\geqq 10\%$. The nine patients who had depressed contractile function, as assessed from the EF–ESS relationship, had a higher percent interstitial fibrosis ($p<0.05$) than five patients showing a normal EF–ESS relationship, despite the fact that there was no significant difference in myocardial cell diameter between them. Thus, advanced cellular hypertrophy and excessive interstitial fibrosis were significantly and independently associated with myocardial contractile dysfunction and appeared to be responsible for ventricular remodeling.

Conclusion: Our findings suggest that in many patients with aortic regurgitation, eccentric hypertrophy changes its nature from physiologic to nonphysiologic during the earlier stages in the course of the disease rather than during the stage described previously.

Key words: aortic regurgitation, myocardial structure, contractile function, left ventricular hypertrophy, myocardial fibrosis, ventricular remodeling

Introduction

In chronic aortic regurgitation, eccentric hypertrophy, with combined concentric hypertrophy of the left ventricle, is an important adaptive response to volume overload, which in itself is a compensatory mechanism for permitting the ventricle to normalize its afterload and to maintain normal ejection performance (physiologic hypertrophy).[1, 2] However, progressive dilatation of the left ventricle leads to depressed left ventricular (LV) contractility[3, 4] and myocardial structural changes, including cellular hypertrophy and interstitial fibrosis (pathologic hypertrophy).[5–8] In clinical studies of this disease, however, only limited information is available on the relationship between structural remodeling and contractile dysfunction of the hypertrophied myocardium.

Previous studies have suggested that excessive myocardial cellular hypertrophy, but not interstitial fibrosis, is the major factor associated with depressed contractile function.[8, 9]

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However, recent experimental studies have indicated that other aspects of myocardial structure, specifically an abnormal accumulation of connective tissue (interstitial fibrosis), can also impair the contractility of the myocardium.[10–12]

The purpose of the present study was to reevaluate the relation between LV myocardial structure and contractile function and to clarify the transition stage from adaptive, physiologic hypertrophy to pathologic hypertrophy with a disproportionate increase in interstitial fibrosis and depressed myocardial contractility.

Methods

Fourteen consecutive patients (10 men, 4 women, aged 15 to 60 years [mean 41 ± 12 years]) with chronic aortic regurgitation were studied using cardiac catheterization and LV endomyocardial biopsy. Patients with aortic stenosis, mitral lesions, or coronary artery disease were excluded from the study. The purpose of the study and the invasive nature of the cardiac catheterization and endomyocardial biopsy were explained to each patient, and those who gave informed consent underwent the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Ten patients were asymptomatic or minimally symptomatic (in functional class I or II of the New York Heart Association classification), and 4 patients were moderately to severely symptomatic (in class III or IV). Eleven patients later underwent aortic valve replacement with a Bjork-Shiley prosthetic valve. In the remaining three patients, their clinical course has been under observation.

Cardiac Catheterization and Cineangiography

Our catheterization technique has been described previously.[4] Briefly, all medications were withheld for at least 24 h before catheterization. Right and left heart catheterizations were performed through the femoral approach in the fasting state. After measurements of pressure and cardiac output with the dye-dilution method, left ventriculography and aortic root angiography were performed. Aortic pressure and LV pressure were measured using a well-flushed, fluid-filled catheter connected to a transducer immediately before left ventriculography. Pressure tracings were recorded at a paper speed of 100 mm/s. Left ventriculography was carried out using biplane cineangiography (30° right anterior oblique and 60° left anterior oblique projections) at a film speed of 60 frames/s. Aortic root angiography was performed in all patients to estimate the degree of aortic regurgitation. All patients > 40 years underwent coronary arteriography. All coronary arteriograms were normal.

Left ventricular measurements: Volumes were computed using the area-length method and a regression equation. Extrasystolic and postextrasystolic beats were excluded. End-diastolic volume (EDV) and end-systolic volume (ESV) were determined, and the ejection fraction (EF) was calculated from (EDV − ESV)/EDV. Wall thickness was measured at the midportion of the right anterior oblique ventriculogram at end diastole. Left ventricular mass (LVM) was calculated using the method of Rackley *et al.*[13] Volume and mass were indexed for body surface area (EDVI, ESVI, and LVMI).

End-systolic circumferential stress (ESS) was calculated using Mirsky's formula[14] as

$$1332 \times (Pb/h)(1 - b^2/2a^2 - h/2b + h^2/8a^2$$

where P is the aortic dicrotic notch pressure, h is end-systolic wall thickness, and a and b are end-systolic semi-major and semi-minor axes, respectively, at the mid-wall. End-systolic wall thickness was calculated from ESV and LVM, which was assumed to be constant, according to the method of Hugenholtz *et al.*[15]

Myocardial contractile function was assessed from the ratio of end-systolic stress to end-systolic volume index (ESS/ESVI)[16] and also evaluated using the ejection fraction–end-systolic stress (EF–ESS) relation.[3,4] Assessment of myocardial contractility in patients with aortic regurgitation has been difficult because of the lack of a load-independent index of contractile function. As the end-systolic–stress-volume relation is shifted to the right with normal contractility in the setting of chronic volume overload, the ESS/ESVI should underestimate contractile function in aortic regurgitation. However, the EF–ESS relation takes afterload into account, but is affected by the level of preload. Therefore, contractile function may be slightly overestimated by this measure in the setting of aortic regurgitation and an augmented preload.

Endomyocardial Biopsy

At the end of catheterization, a percutaneous endomyocardial biopsy was performed in all 14 patients. An 8F long sheath was retrogradely inserted into the left ventricle through the right femoral artery. In each patient, three or four biopsies were taken, mainly from the lateral portion of the left ventricle using a disposable 7.5F Cordis forceps biotome (Cordis Corp., Miami Lakes, Fla., USA). Some premature ventricular arrhythmias occurred during the biopsy, but there were no serious complications in any of the 14 patients. Immediately after biopsy, the specimens were fixed in 10% neutral formaldehyde, dehydrated in alcohol, and embedded in paraffin.

Histologic measurements: Eight serial sections were obtained from each specimen embedded in paraffin and stained with hematoxylin-eosin and Masson-trichrome for light microscopic evaluation. The myocardial cell diameter was determined from more than 100 measurements of cross-sectioned myocytes at the exact level of the nucleus and calculated with the aid of an image analysis system (a personal computer and a pen digitizer) using the methods of Chalkley *et al.*[17] and Arai *et al.*[18] According to this method, even if the muscle fiber was cut obliquely at a 30° angle across the longitudinal axis, the error in the calculated cellular diameter is estimated at only 3%, which can be ignored.

Interstitial fibrosis was evaluated using the point-counting method.[19–21] A special ocular with a grid with vertical and horizontal lines providing 100 intersection points was used to determine the amount of fibrous tissue. The total number of in-

tersection points was regarded as 100%, and the points counted in the fibrous areas were expressed as percent of the entire tissue within the limits of the grid. Areas with arterioles and perivascular tissue were excluded. Interstitial fibrosis was determined from eight sections with Masson-trichrome stain. Typically, 1,000 intersection points were counted for the estimation of the average interstitial fibrosis in each patient. Fibrous content of the left ventricle was calculated as LVMI × IF/100, where LVMI was the LV mass index (g/m^2) and IF was the percent interstitial fibrosis (%).

All histologic measurements were analyzed independently by one co-worker (T.K.) who was blinded to the details of the patient's hemodynamic measurements. Left ventricular measurements were obtained by another co-worker (K.T.).

Normal Subjects

Normal values for quantitative angiographic and LV function were obtained from 30 normal subjects who had undergone catheterization for atypical chest pain.[4] Five normal subjects had undergone LV endomyocardial biopsy. In these subjects, the myocardial cell diameter was < 20 μm and the percent fibrosis was < 5%.

Statistics

Values were given as mean ± standard deviation. The correlation between two variables was made using Pearson's correlation coefficient r. A p value of < 0.05 was considered significant. Unmatched variables were compared using the Mann-Whitney test. Linear regression by least square was performed to obtain the relationship of EF to ESS for the 30 normal subjects. Then, 95% confidence limits were obtained.

TABLE I Histologic data in the 14 patients with aortic regurgitation

Patient number	Myocardial cell diameter (μm)	Interstitial fibrosis (%)	Fibrous content (g/m^2)
1	25.6	0.6	1.5
2	29.3	4.0	5.1
3	38.0	18.9	45.2
4	45.0	15.6	56.3
5	31.0	14.0	38.9
6	40.2	11.0	33.4
7	30.2	12.0	19.2
8	28.9	13.2	17.8
9	28.5	20.2	40.8
10	33.4	14.7	21.6
11	38.1	8.0	11.7
12	35.3	9.8	37.8
13	38.8	16.5	58.9
14	23.7	7.3	9.7
Mean	33.3	11.8	28.4
± SD	6.1	5.5	18.6

Abbreviation: SD = standard deviation.

Results

Myocardial Structure, Left Ventricular Volume, and Mass

The histologic and LV function measurements in the 14 patients with aortic regurgitation are shown in Tables I and II. Myocardial cell diameter ranged from 23.7 to 45.0 μm (mean, 33 ± 6 μm) and percent fibrosis, from 0.6 to 20.2% (mean, 11.8 ± 5.5%). Fibrous content ranged from 2 to 59 g/m^2 (mean, 28 ± 19 g/m^2). There was no significant correlation between myocardial cell diameter and percent fibrosis, whereas cell diameter was significantly related to fibrous content ($r = 0.69$, $p < 0.01$).

Myocardial cell diameter was significantly related to ESVI, EDVI, and LVMI, whereas percent fibrosis showed no significant correlation with these variables. In contrast, fibrous content showed a good correlation with ESVI, EDVI, and LVMI (Table III).

As shown in Figure 1, in five patients with ESVI < 70 ml/m^2, the mean value of myocardial cell diameter was 29 ± 5 μm. In four of five patients, the cell diameter was < 30 μm. However, in nine patients with an ESVI ≧ 70 ml/m^2, the average cell diameter was 36 ± 5 μm, and in eight of nine patients, the cell diameter was ≧ 30 μm, suggesting advanced cellular hypertrophy. In addition, in four of the patients with an ESVI < 70 ml/m^2, the interstitial fibrosis was < 10%, whereas in all but one patient with an ESVI ≧ 70 ml/m^2, percent fibrosis was ≧ 10%, suggesting severe myocardial fibrosis. In two patients with an ESVI < 60 ml/m^2, interstitial fibrosis was not significant (percent fibrosis < 5%).

TABLE II Left ventricular function data in the 14 patients with aortic regurgitation

Patient number	EDVI (ml/m^2)	ESVI (ml/m^2)	LVMI (g/m^2)	EF	ESS/ESVI (kdyn/cm^2/ml/m^2)
1	147	59	256	0.60	3.5
2	130	55	128	0.58	3.2
3	207	89	239	0.57	2.0
4	334	228	361	0.32	1.0
5	152	81	278	0.47	2.0
6	267	147	304	0.45	1.2
7	201	115	160	0.43	1.3
8	129	67	135	0.48	2.1
9	226	122	202	0.46	1.6
10	186	102	147	0.45	1.9
11	144	68	146	0.53	3.7
12	178	114	296	0.36	1.4
13	357	239	330	0.27	1.3
14	138	61	133	0.55	4.4
Mean	200	111	221	0.47	2.2
± SD	74	59	80	0.10	1.1

Abbreviations: EDVI = end-diastolic volume index, ESVI = end-systolic volume index, LVMI = left ventricular mass index, EF = ejection fraction, ESS = end-systolic wall stress, SD = standard deviation.

TABLE III Correlation between histologic data and left ventricular volume, mass, and ejection fraction in the 14 patients with aortic regurgitation

	Myocardial cell diameter	Interstitial fibrosis	Fibrous content
EDVI	r = 0.71 (p < 0.005)	r = 0.53 (p = NS)	r = 0.81 (p < 0.001)
ESVI	r = 0.72 (p < 0.005)	r = 0.53 (p = NS)	r = 0.82 (p < 0.001)
LVMI	r = 0.63 (p < 0.01)	r = 0.27 (p = NS)	r = 0.76 (p < 0.002)
EF	r = −0.58 (p < 0.05)	r = −0.51 (p = NS)	r = −0.76 (p < 0.002)

Abbreviation: NS = not significant. Other abbreviations as in Table II.

The relationship between the amount of myocardial fibrosis and enlargement of the left ventricle was also seen in the relation between fibrous content and ESVI (Fig. 2).

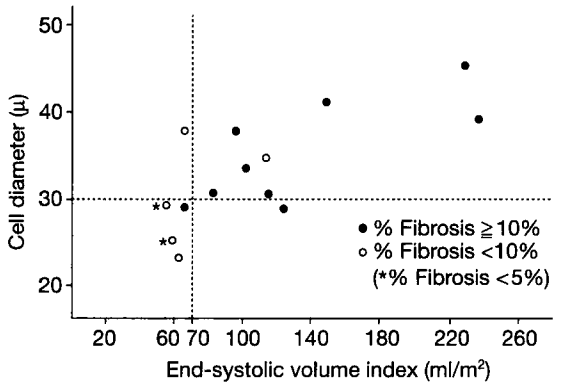

FIG. 1 Relation between myocardial cell diameter and end-systolic volume index (ESVI), and percent fibrosis in the 14 patients with aortic regurgitation. Myocardial cellular hypertrophy was relatively mild in patients with ESVI < 70 mlm², and percent fibrosis was generally < 10%. In two patients with ESVI < 60 ml/m², interstitial fibrosis was not observed. However, cellular hypertrophy was severe in patients with ESVI ≧ 70 ml/m², and myocardial fibrosis was significant.

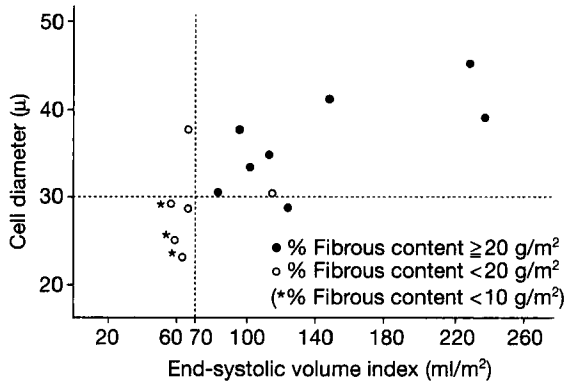

FIG. 2 Relation between myocardial cell diameter and end-systolic volume index (ESVI), and fibrous content in the 14 patients with aortic regurgitation. In patients with ESVI < 70 ml/m², fibrous content was < 20 g/m². In contrast, in all but one patient with ESVI ≧ 70 ml/m², fibrous content was ≧ 20 g/m².

Myocardial Structure and Left Ventricular Ejection Fraction

Myocardial cell diameter showed a significant inverse correlation with EF, whereas percent fibrosis was not related to EF. Fibrous content showed a significant correlation with EF (Table III).

Myocardial Structure and Left Ventricular Contractile Function

Both myocardial cell diameter and percent fibrosis showed a significant inverse correlation with the ESS/ESVI (Fig. 3). Fibrous content also showed a highly significant correlation with the ESS/ESVI (Fig. 3).

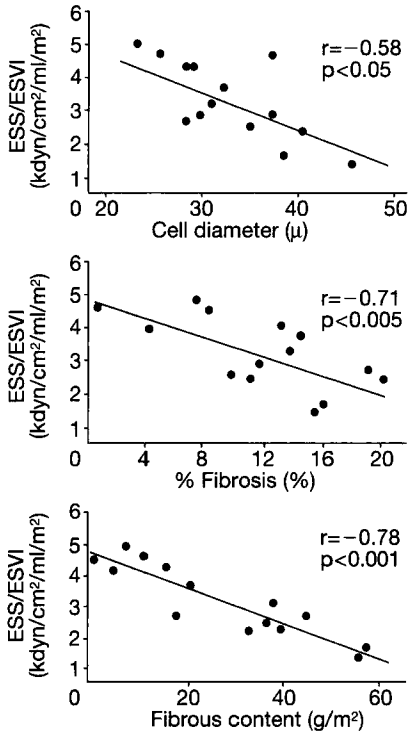

FIG. 3 Correlation between myocardial structural changes and left ventricular contractility as assessed by the end-systolic stress/end-systolic volume index (ESS/ESVI) in the 14 patients with aortic regurgitation.

For further confirmation of the relationship between interstitial fibrosis and LV contractile function, we evaluated the contractile state using the EF–ESS relation in all 14 patients and compared the degree of structural changes between the patients with normal contractility and those with depressed contractility. As shown in Figure 4, 5 patients (Group 1) had values that fell within the 95% confidence interval of the normal EF–ESS relation, indicating normal contractility. The remaining nine patients (Group 2) had abnormal relations of EF to ESS that fell below the lower 95% confidence limit, indicating depressed contractility. The mean value of percent fibrosis, but not myocardial cell diameter, showed a statistically significant difference between the two groups.

The ESVI in the five patients of Group 1 averaged 66 ± 13 ml/m^2. For four of these patients, the ESVI was < 70 ml/m^2. However, the ESVI for the nine patients of Group 2 averaged 139 ± 61 ml/m^2. For eight of nine patients, the value was ≧ 70 ml/m^2.

Discussion

Although there have been numerous studies on the natural history, pre- and postoperative LV performance, and indications for valve replacement in patients with chronic severe aortic regurgitation,[22] the relation between LV contractile function and myocardial structural changes has not fully been elucidated.[6, 8, 9, 20, 21, 23] Krayenbuehl *et al.*[8] found that in patients with aortic regurgitation the myocardial cell diameter correlated weakly and inversely with measures of LV contractile function (EF and peak velocity of contractile element shortening), whereas percent interstitial fibrosis did not correlate with any of these variables. From these findings, they concluded that advanced cellular hypertrophy, but not excessive interstitial fibrosis, appeared to be the major cause for depressed contractile function.[8]

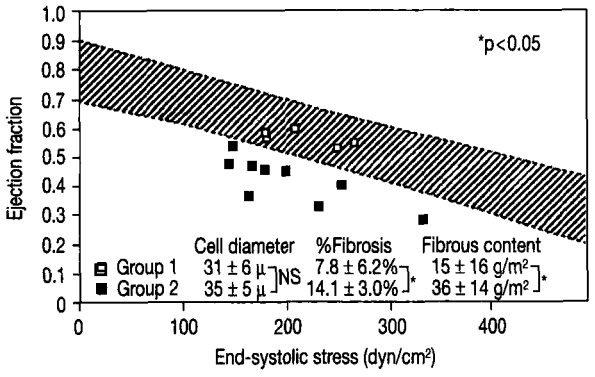

FIG. 4 Relation between ejection fraction (EF) and end-systolic stress (ESS) for the 14 patients with aortic regurgitation, and comparisons of myocardial structural changes between the five patients with normal left ventricular contractility and the nine patients with depressed contractility, as assessed from the EF–ESS relationship. The shaded area represents the 95% confidence interval for the EF–ESS relationship in 30 normal subjects.[4]

However, recent experimental investigations have demonstrated that myocardial fibrosis initially adversely alters LV diastolic function and ultimately impairs LV contractile function,[12, 24, 25] and have also suggested that the disproportionate increase in interstitial fibrosis represents an important determinant of pathologic hypertrophy.[10–12]

A major finding of the present study was a strong correlation between percent interstitial fibrosis and ESS/ESVI. This finding suggests that myocardial fibrosis is significantly associated with the reduction in contractility of the hypertrophied myocardium. Another important finding was that a disproportionate increment in interstitial fibrosis emerged when the left ventricle enlarged about twofold or greater its normal volume and LV pump performance was still preserved.

Interrelations between Myocardial Cellular Hypertrophy and Interstitial Fibrosis

No significant correlation was found between myocardial cell diameter and percent fibrosis. This apparently contradicts the hypothesis that myocardial fibrosis is a concomitant or sequel to progressive cellular hypertrophy. However, significant fibrosis (percent fibrosis ≧ 10%) was observed in most of the present patients in whom the cell diameter was ≧ 30 μm. Moreover, interstitial fibrosis was very slight (percent fibrosis < 5%) in two patients with relatively mild hypertrophy. Therefore, this suggested that myocardial fibrosis accelerates when cell diameter exceeds 25–30 μm. In the present study, the majority of patients showed severe hypertrophy, with a cell diameter of ≧ 30 μm, including a few patients with slight hypertrophy. This appears to be one reason to explain the lack of correlation between myocardial cell diameter and percent fibrosis. Another possibility was that the relevant factors responsible for the development of cellular hypertrophy and the proliferation of interstitial fibrosis were independent of each other.[10]

Myocardial Structure and Left Ventricular Volume

A significant positive correlation was observed between myocardial cell diameter and LV volume, indicating that myocardial cellular hypertrophy advances with enlargement of the left ventricle. Of importance is the fact that a disproportionate amount of interstitial fibrosis emerged when the ESVI exceeded 70 ml/m^2, which is double its normal value (Fig. 1). The association between the proliferation of myocardial fibrosis and enlargement of the left ventricle was more clearly shown in the relation between fibrous content and ESVI (Fig. 2). In view of the fact that the normal LVMI is about 80–120 g/m^2,[4] it can be suggested that a significant amount of the myocardium was lost in patients with a fibrous content ≧ 20 g/m^2, in whom the ESVI was ≧ 70 ml/m^2. From a morphologic point of view, these findings indicated that LV hypertrophy changed its nature from being physiologic to nonphysiologic at this stage.

Myocardial Structure and Left Ventricular Ejection Performance

In the present study, we observed a significant correlation between myocardial cell diameter and EF, but not between

percent fibrosis and EF, which was consistent with the findings of Krayenbuehl *et al.*[8] In addition, we found a strong inverse correlation between fibrous content and EF. Fibrous content was obtained as a product of percent fibrosis and LVMI. The correlation coefficient between fibrous content and EF ($r = -0.76$) was high compared with that between LVMI and EF ($r = -0.57$). This suggests that the increase in interstitial fibrosis plays an important role in the reduction in ejection performance. Nevertheless, it remained unclear from the finding described above whether the reduction in ejection performance was caused by either the depressed contractile state or the impairment of diastolic function or both.

Myocardial Structure and Left Ventricular Contractility

In this study, there was a weak but significant inverse correlation between myocardial cell diameter and ESS/ESVI, an index for estimating LV contractility. Furthermore, we found a strong inverse correlation between percent fibrosis and ESS/ESVI. Thus, the present study provides evidence that the development of interstitial fibrosis is an important factor for the reduction in contractility of the hypertrophied myocardium. The higher correlation coefficient between fibrous content and ESS/ESVI may suggest a synergistic effect of cellular hypertrophy and interstitial fibrosis on the reduction in LV contractility.

The relationship between interstitial fibrosis and reduction in contractility was more clearly shown in the EF–ESS relation, another method for assessing myocardial contractility. The patients with reduced contractility generally had more severe interstitial fibrosis than did those with normal contractility. However, there was no statistical difference in myocardial cell diameter between patients with reduced contractility and those with normal contractility. This suggests that interstitial fibrosis is related to the reduction in contractility independent from myocardial cellular hypertrophy. Thus, the present study revealed that interstitial fibrosis, which had heretofore been considered to have few detrimental effects on LV function, plays a major role in the reduction in myocardial contractility.

Study Limitations

In the present study, we evaluated structural changes of the left ventricle as a whole using biopsies collected from the endomyocardium of the left ventricle and examined its relation to LV function. It is not known whether the LV myocardial tissue changes uniformly throughout.[26] However, Schoen *et al.*[27] reported that in patients with aortic valve disease morphologic changes in the myocardium appeared uniformly distributed over the whole ventricle, and two to three biopsy samples should adequately reflect LV endomyocardial structure in this setting.

The number of patients evaluated in this study was relatively small, and further investigations are required to permit more confident evaluation, interpretation, and corroboration of our findings.

Conclusions

Identifying the transitional stage from physiologic to pathologic hypertrophy with irreversible myocardial damage and depressed function has important implications in determining the timing of therapeutic[11, 28, 29] as well as surgical interventions for aortic regurgitation.[2, 22, 30] In the present study, (1) both advanced cellular hypertrophy and excessive interstitial fibrosis were associated significantly and independently with myocardial contractile dysfunction, and (2) such myocardial structural changes (remodeling) emerged when the left ventricle was enlarged to approximately double or greater its normal volume (i.e., ESVI $\geqq 70 ml/m^2$) and the ejection performance was still preserved. Our findings indicate that in a number of patients with aortic regurgitation, eccentric hypertrophy of the left ventricle changes its nature from physiologic to pathologic at an earlier stage of the natural history than the stage previously described.[31–34] The relationship between LV myocardial structure and function would provide new insights into the management strategies for patients with chronic severe aortic regurgitation.

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