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Isolated Chronic Mitral Regurgitation With Preserved Systolic Left Ventricular Function and Severe Pulmonary Hypertension

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Pulmonary hypertension in chronic mitral valve disease has been related most commonly to left ventricular dysfunction or mitral stenosis; its association with chronic, isolated mitral regurgitation and preserved left ventricular systolic function is unclear. In 41 catheterized patients with chronic mitral regurgitation (known history of mitral regurgitation for >18 months) and preserved left ventricular systolic function (ejection fraction >0.55), historic, electrocardiographic, echocardiographic and hemodynamic variables were analyzed. Ten patients (Group I) had normal pulmonary artery systolic pressure (<30 mm Hg), whereas 31 patients had pulmonary hypertension. Pulmonary artery systolic pressure was mildly increased (30 to 49 mm Hg) in 13 patients (Group II) and was ≥50 mm Hg in 18 patients (Group III).

Univariate analysis showed the more frequent occurrence of male gender and ruptured chordae tendineae in the groups with pulmonary hypertension. Mean pulmonary capillary wedge pressure, size of the *V* wave in pulmonary capillary wedge pressure and pulmonary arteriole resistance were higher, whereas cardiac index was lower in the hypertension groups. Multivariate stepwise analysis revealed higher mean pulmonary capillary wedge pressure and pulmonary arteriole resistance as the only variables independently differing among groups.

In conclusion, pulmonary hypertension occurs frequently (76% of cases) in patients with chronic, isolated mitral regurgitation with preserved left ventricular systolic function. In these patients, a severe increase in pulmonary capillary wedge pressure is associated with elevation in pulmonary artery resistance, a finding similar to that in mitral stenosis.

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Isolated mitral regurgitation has been associated with increased left atrial, pulmonary capillary wedge and pulmonary artery pressures (1,2). These hemodynamic findings are observed in most patients with acute mitral regurgitation (3) and in some patients with chronic mitral regurgitation and impaired left ventricular systolic function (4). However, we have observed that significant pulmonary hypertension occurs in a few patients who have chronic, isolated mitral regurgitation with no apparent left ventricular systolic dysfunction. The purpose of this study was to 1) define the prevalence of pulmonary hypertension in isolated, chronic mitral regurgitation in the presence of preserved left ventricular systolic function; and 2) describe the clinical, echocardiographic and hemodynamic findings associated with this entity.

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Methods

Selection of patients. All patients with the diagnosis of chronic, isolated mitral regurgitation who underwent cardiac catheterization in our laboratory between January 1983 and April 1988 were retrospectively considered for inclusion in this study. Only patients with significant mitral regurgitation as determined by angiographic criteria (3+ and 4+) (5) were studied. Exclusion criteria were 1) left ventricular dysfunction (ejection fraction <0.55 measured angiographically in the right anterior oblique projection with the area-length method [6]); 2) acute mitral regurgitation (acute or recent [within 18 months] onset of symptoms or signs of mitral regurgitation); 3) concomitant significant disease of the aortic valve (>1+ aortic regurgitation or greater than mild aortic stenosis with valve area ≤1.5 cm^2) or mitral stenosis; 4) previous valvular heart surgery; 5) hypertrophic cardio-

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myopathy or concentric left ventricular hypertrophy (interventricular septum or posterior wall >12 mm); 6) congenital heart disease; and 7) acute myocardial infarction or unstable angina.

Hospital records were analyzed for all historic, electrocardiographic (ECG) and echocardiographic data. When these were not available, the patient's private physicians were contacted. Historic data included age, gender, predominant symptoms and their duration, New York Heart Association functional class, smoking status, lung disease, thromboembolism and presumed etiology of the mitral regurgitation. Electrocardiograms were analyzed for the presence of atrial fibrillation, left atrial enlargement (7) and left ventricular hypertrophy (8). Echocardiographic left atrial size and left ventricular dimensions as well as end-diastolic radius/wall thickness ratio as an index of volume/mass ratio were calculated (9). The echocardiographic presence of ruptured mitral valve chordae tendineae was also recorded.

All analyzed patients underwent right and left heart catheterization performed by either the Judkins or the Sones technique. Pressures were measured with fluid-filled catheters connected to Statham model P23-ID transducers that were independently calibrated against a mercury column with zero reference at the level of the midaxillary line. Cardiac output was measured with either the thermodilution or the Fick method. Pulmonary arteriole resistance was calculated as (mean pulmonary artery pressure − mean pulmonary capillary wedge pressure)/cardiac index and measured in Wood units.

Study patients. Within the study period, 237 patients with a diagnosis of significant mitral regurgitation underwent cardiac catheterization. Of these patients, 196 were excluded because of concomitant valvular disease (n = 94), associated left ventricular dysfunction (n = 74), acute mitral regurgitation, previous valvular heart surgery, hypertrophic cardiomyopathy or congenital heart disease (n = 26). Pulmonary hypertension (pulmonary artery systolic pressure ≥30 mm Hg) was present in 86% of excluded patients. In excluded patients with normal systolic left ventricular function, pulmonary hypertension occurred in 83% of cases.

Of the 41 patients who constituted the study group, 10 had normal pulmonary artery systolic pressure (<30 mm Hg) (Group I). The remaining 31 patients (76%) had pulmonary hypertension: pulmonary artery systolic pressure was mildly increased (30 to 49 mm Hg) in 13 patients (Group II) and ≥50 mm Hg in 18 (Group III). Seven (17%) of the 41 patients exhibited significant elevation (>70 mm Hg) in pulmonary artery systolic pressure.

Statistical analysis. Univariate analysis was used to define differences of continuous variables among the three groups according to pulmonary artery systolic pressure. One-way analysis of variance and chi-square testing were used for continuous and discrete variables, respectively. Variables that varied significantly among groups by the univariate analysis were further analyzed with a multivariate stepwise analysis using the SAS statistical package (10). All values were expressed as mean values ± 1 SD. A p value <0.05 was considered significant.

Table 1. Variables Differing Significantly Among the 41 Patients With Mitral Regurgitation

	Group			
	I (n = 10)	II (n = 13)	III (n = 18)	p Value
Gender (male)	3	3	12	<0.05
Ruptured chordae	1	3	11	<0.03
PCWM (mm Hg)	8 ± 3	20 ± 3	27 ± 9	<0.001
PCWV (mm Hg)	15 ± 8	35 ± 8	46 ± 14	<0.001
PAR (Wood units)	0.9 ± 0.3	1.3 ± 0.7	2.8 ± 2.1	<0.002
CI (liters/min)	2.9 ± 0.6	2.3 ± 0.5	2.1 ± 0.5	<0.001

CI = cardiac index; PAR = pulmonary arteriole resistance; PCWM = pulmonary capillary wedge pressure (mean); PCWV = pulmonary capillary wedge pressure *V* wave.

Results

Clinical features. Left ventricular ejection fraction was similar among Groups I, II and III: 0.69 ± 0.11, 0.70 ± 0.09 and 0.74 ± 0.08, respectively. Univariate analysis of the studied variables among groups (Table 1) showed male gender and echocardiographic or operative presence of ruptured mitral valve chordae tendineae to be more frequent in Group III. Mean pulmonary capillary wedge pressure, size of the *V* wave in the pulmonary capillary wedge pressure and pulmonary arteriole resistance were higher whereas cardiac index was lower in the pulmonary hypertension groups. Other hemodynamic variables including left ventricular end-diastolic pressure, incidence of pulmonary disease, smoking history and etiology did not differ among groups. A >5 year history of symptoms or signs of mitral regurgitation was present in 7 of 10, 12 of 13 and 14 of 18 patients in Groups I, II and III, respectively. In the remaining eight patients signs and symptoms had been present for 18 months to 5 years. These differences among groups were not significant. There was no statistically significant difference in the incidence of atrial fibrillation among groups: Group I (n = 3; 30%), Group II (n = 8; 61%) and Group III (n = 7; 39%). Echocardiographic findings are presented in Table 2; there were no significant differences among groups.

Multivariate stepwise analysis revealed mean pulmonary capillary wedge pressure and pulmonary arteriole resistance to be the only variables independently differing among groups ($p < 0.0001$, $p < 0.05$, respectively).

Discussion

Comparison with previous studies. It has been recognized for >30 years that significant pulmonary hypertension can

Table 2. Echocardiographic Variables in the Three Study Groups

	Group		
	I	II	III
Left atrial diameter (cm)	4.8 ± 0.6	5.1 ± 1.3	5.2 ± 0.9
Left ventricular diameter (systolic) (cm)	3.5 ± 0.8	3.9 ± 1.1	3.5 ± 0.8
Left ventricular diameter (diastolic) (cm)	5.9 ± 0.9	5.9 ± 1.1	5.8 ± 0.6
Radius/wall thickness ratio	2.8 ± 0.7	3.1 ± 0.4	2.6 ± 0.4

There were no significant differences among groups.

complicate chronic, isolated mitral regurgitation. Bentivoglio et al. (1) reported four cases of chronic, isolated mitral regurgitation with pulmonary hypertension, right ventricular enlargement and pathologic changes in pulmonary vasculature; even though their patients had no previous left ventricular enlargement or failure, left ventricular function was not assessed. Ross et al. (4) similarly described six patients with chronic, isolated mitral regurgitation and pulmonary hypertension, but most of their patients had left ventricular dysfunction. Since that time it has been commonly believed that severe pulmonary hypertension is much less frequent in chronic isolated mitral regurgitation than in mitral stenosis. This belief is probably related to the increased compliance of an enlarged left atrium, which would tend to prevent a significant persistent increase in pulmonary venous pressure, vascular resistance and artery pressure (11).

In our study group pulmonary hypertension in chronic, isolated mitral regurgitation was observed in the presence of preserved systolic left ventricular function. A very high proportion of our patients (31 of 41, 76%) had increased pulmonary artery pressure and 7 (17%) of 41 exhibited significant elevation (>70 mm Hg).

Possible pathogenetic mechanisms. The common occurrence of high pulmonary artery pressures in our study group could have been related to several of the following factors.

1) Reactive pulmonary hypertension. Selzer and Katayama (2) stated that in some cases of chronic mitral regurgitation, passive or even reactive pulmonary hypertension occurs. It seems likely that in some of our patients significant variability in response to the increase in left atrial pressure (12) may have led to the development of severe pulmonary hypertension. In these patients, overreactive pulmonary vessels responded to the left atrial pressure stimulus inappropriately with vasoconstriction and intimal hyperplasia or medial hypertrophy, or both (1). Because the compliance of the venous tissue varies widely from patient to patient (13), differences in the distensibility of the pulmonary vascular bed may also lead to the development of severe pulmonary hypertension (14,15) in the nondistensible vascular beds.

2) Decreased left atrial compliance. Even though we were unable to demonstrate a difference in left atrial size among groups, a decreased left atrial compliance may have contributed to the development of pulmonary hypertension in some of our patients. This is consistent with the observed higher pulmonary capillary wedge pressure found in our pulmonary hypertension group.

3) Severe grade of mitral regurgitation. It is possible that the development of pulmonary hypertension was simply related to more severe mitral regurgitation than is found in patients with normal pulmonary artery pressures. However, as quantitative techniques (that is, regurgitant index) were not applied in assessing the mitral regurgitation, this possibility cannot be verified.

4) Ruptured chordae. It has been suggested (16) that because patients with ruptured chordae tendineae as the cause of mitral regurgitation have an acute or subacute onset of regurgitation, their left atrium is smaller and stiffer than that in patients with rheumatic heart disease. This could have had an effect on the development of pulmonary hypertension. In our study we did find a more frequent incidence of ruptured chordae in the severe pulmonary hypertension group, even though we attempted to eliminate patients with acute onset of mitral regurgitation, and left atrial size, as previously mentioned, was similar between groups.

Of interest, atrial fibrillation did not differ significantly among groups. Because atrial fibrillation has been proposed as an index of chronicity and correlated with left atrial size and pressure (3), one would have expected a higher incidence of atrial fibrillation in Group III. Such differences were not supported by our findings.

Study limitations. There are several potential limitations to this study. The study was retrospective and the patient population was selected from those referred for cardiac catheterization. As patients catheterized tend to be more symptomatic, the exact incidence of pulmonary hypertension in less symptomatic patients with mitral regurgitation is unknown. Particular attention was paid to exclude patients with acute mitral regurgitation. However, an acute component superimposed on chronic mitral regurgitation leading to an exacerbation of symptoms and subsequent cardiac catheterization cannot be entirely excluded in some patients. Favorable loading and, mainly, unloading conditions of the left ventricle in mitral regurgitation may mask left ventricular dysfunction (17,18). The overestimation of left ventricular systolic function and the inclusion of patients with left ventricular dysfunction despite an ejection fraction >0.55 may have occurred in the study group. However, patients with significant pulmonary hypertension (Group III) had values for left ventricular ejection fraction, left ventricular diameters, left ventricular end-diastolic pressure and radius to wall thickness ratio similar to those of patients in Groups I and II. Although diastolic dysfunction cannot be entirely ruled out, the exclusion of patients with acute ischemia and significant left ventricular hypertrophy should have minimized its importance.

Conclusions. Pulmonary hypertension is frequently observed in chronic, isolated mitral regurgitation despite preserved left ventricular systolic function. In some patients very high pulmonary artery pressures are observed. These findings suggest that high pulmonary capillary wedge pressure can cause changes in pulmonary vascular resistance similar to those found in mitral stenosis. Whether these changes are permanent or reversible remains to be determined.

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