Mitral valve prolapse in patients with prior rheumatic fever

NICHOLAS J. LEMBO, M.D., LOUIS J. DELL’ITALIA, M.D., MICHAEL H. CRAWFORD, M.D., JACELYN F. MILLER, R.D.M.S., KENT L. RICHARDS, M.D., AND ROBERT A. O’ROURKE, M.D.

ABSTRACT  It is known that rheumatic heart disease frequently results in isolated mitral regurgitation without concomitant mitral stenosis, especially in countries with a high prevalence of rheumatic fever. However, more recent surgical pathologic data also have demonstrated a high incidence of mitral valve prolapse in cases of rheumatic heart disease, which suggests that rheumatic fever may be a cause of mitral valve prolapse. To determine whether this association of mitral valve prolapse and rheumatic heart disease is present in a stable clinic population, we studied 30 patients who had an apical systolic murmur and a well-documented history of rheumatic fever with dynamic auscultation, two-dimensional echocardiography, and pulsed Doppler examinations. Twenty of the 30 patients (67%) had findings on physical examination consistent with isolated mitral regurgitation and 25 patients (84%) had mitral regurgitation by Doppler examination. Echocardiography demonstrated mitral valve prolapse in 24 patients (80%), whereas only one of the total study group had echocardiographic findings consistent with mitral stenosis. We conclude that (1) the presence of an isolated systolic murmur in patients with a history of rheumatic fever frequently represents pure mitral regurgitation secondary to mitral valve prolapse and (2) postinflammatory changes in valvular tissue resulting from rheumatic fever may be the etiology of mitral valve prolapse in these patients.


RHEUMATIC HEART DISEASE was considered a major cause of isolated mitral regurgitation in the United States when rheumatic fever was a major health hazard,1–5 and this remains the predominant valvular sequela today in countries where rheumatic fever is still prevalent.6,7 This contrasts with a current series from Waller et al.8 who report nonrheumatic conditions as the cause of isolated mitral regurgitation in 97% of patients requiring mitral valve replacement. Because of this observation and the declining incidence of rheumatic fever in the United States over the past 20 years, rheumatic heart disease is now considered a very rare cause of mitral regurgitation unless associated with mitral stenosis or aortic valve dysfunction.9 However, Tomaru et al.10 and Marcus et al.11 have recently reported that valvular regurgitation caused by mitral valve prolapse may result from postinflammatory changes, including those after rheumatic fever.

We noted an isolated apical systolic murmur in many of our clinic patients who had a well-documented history of rheumatic fever and were receiving monthly prophylaxis with penicillin G benzathine (Bicillin). This physical examination finding was suggestive of mitral regurgitation and appeared consistent with the reports from the older literature in the United States1–5 and with recent data from countries with a high incidence of rheumatic fever.6,7 However, of greater interest was the potential role of mitral valve prolapse in the etiology of mitral regurgitation in patients with a history of rheumatic fever.10,11 Accordingly, we evaluated patients who had a well-documented history of rheumatic fever and an isolated apical systolic murmur by means of dynamic auscultation, echocardiography, and Doppler examinations to determine whether mitral valve prolapse was the source of these murmurs.

Methods

Patients. The study population consisted of 30 patients with a well-documented history of rheumatic fever as determined by chart review, including 23 women and seven men, ages 19 to 54 years (mean 31). This group of patients was identified from a total of 120 clinic patients who were receiving monthly pro-
phylaxis with intramuscular penicillin for rheumatic fever. These patients were chosen because they had only an apical systolic murmur on physical examination. The apical systolic murmur was pansystolic in nine patients and early, mid, or late systolic in 21 patients. No patient had a diastolic murmur, and therefore patients with evidence on physical examination of mitral stenosis and aortic regurgitation were excluded from the study.

Twenty-eight of the 30 patients (93%) had a history of acute rheumatic fever documented by review of admission charts and by strict application of the Jones criteria: (1) at least two major criteria (n = 26) or (2) one major and two minor (n = 2). In addition, all 28 patients had supporting evidence of a preceding streptococcal infection documented by rising antistreptolysin O (ASO) titers and/or a positive throat culture for group A β-hemolytic streptococci and/or recent scarlet fever (table 1). In the remaining two patients, admitted in 1938 and 1949, the hospital laboratory records could not be located. However, the patient admitted in 1938 presented with carditis, polyarthritis, and fever and developed chorea during her hospitalization. The patient admitted in 1949 had polyarthritis, erythema marginatum, subcutaneous nodules, and fever documented during hospitalization. Thus both patients had three major and one minor criteria and, although supporting evidence of a preceding streptococcal infection could not be documented secondary to lost laboratory records, we believe that both patients had acute rheumatic fever. The mean age of the patient group was 13 years when the diagnosis of acute rheumatic fever was made. Thus the time from diagnosis of acute rheumatic fever to study date averaged 18 years. All study patients were on monthly prophylaxis with intramuscular benzathine penicillin and none was on cardiac medications. No patients had a history of prior endocarditis and none had a history of angina pectoris or electrocardiographic evidence of myocardial infarction. All 30 patients gave written consent to participate in the study on a form approved by our institutional review board.

Physical examination. Physical examination was performed independently by two staff cardiologists who were blinded to the results of echocardiography and Doppler studies. Physical examination was accomplished by having the patient and the auscultators in separate rooms and by having an independent observer place an electronic stethoscope (Andries Stethoscope, Andries Tek, Austin, TX) on the chest wall and direct the various maneuvers. Systolic murmurs were graded from I to VI with the patients resting in the left lateral decubitus position. Subsequently, commonly used bedside maneuvers were used to determine the origin of the systolic murmur. These included isometric handgrip, amyl nitrite inhalation, respiration, Valsalva maneuver, squatting and standing, leg elevation, cycle length changes, and transient arterial occlusion. Mitral regurgitation was diagnosed when the murmur intensity decreased with amyl nitrite, increased with transient arterial occlusion, and increased with isometric handgrip. Forward flow murmurs were identified when murmur intensity increased with amyl nitrite, increased after long cycle lengths, and did not change with transient arterial occlusion. Difficulties arose in the case of mitral regurgitation secondary to mitral valve prolapse where murmur intensity may increase after amyl nitrite inhalation and during isometric handgrip, thereby yielding a false diagnosis of a forward flow murmur. In this instance the responses to leg elevation, transient arterial occlusion, and cycle length changes were deciding factors in determining etiology of the murmurs.

Echocardiography. After the physical examination, complete two-dimensional echocardiography was performed in each patient. Echocardiography was performed with the patient at rest and in the absence of tachycardia or systolic hypertension at the time of the study. All standard echocardiographic views were obtained, including parasternal long- and short-axis views as well as apical four- and two-chamber views. Visualization of all four cardiac valves was attempted, and careful assessment of each cardiac valve was made to evaluate for stenosis or prolapse. The two criteria required for the diagnosis of mitral valve prolapse on two-dimensional echocardiography were (1) systolic displacement of the coaptation point of the anterior and posterior leaflets posterior to the mitral annular plane in the parasternal or apical long-axis views and (2) similar displacement in the apical four-chamber view. Posterior displacement of the lateral aspects of the mitral leaflets in the apical four-chamber view was not considered adequate for the diagnosis of prolapse, since this may be caused by a nonplanar anulus configuration. The echocardiogram was evaluated by a cardiologist blinded to the results of the physical examination and Doppler study.

Doppler examination. Each individual was examined with a commercially available duplex pulsed Doppler ultrasonoscope (ATL Mark 600 or Ultramark 8) with 2.25 or 3.00 MHz transducers. Since the goal of examination was to identify the presence of mitral regurgitation and exclude the presence of other lesions, a standard approach was used. Mitral regurgitation was identified by the presence of abnormal systolic velocities in the left atrium adjacent to the mitral valve leaflets. Transient systolic velocities that were detected only in early systole and that were confined in the left atrium within 1 cm of the mitral leaflets were considered within normal limits. Mitral regurgitation was defined as present if abnormal systolic velocities were detected greater than 1 cm from the mitral leaflets and were pansystolic or were present in mid to late systole. The apical four-chamber view was used to exclude mitral stenosis, aortic regurgitation, and aortic stenosis. Right-sided valve lesions and ventricular septal defect were excluded by criteria described by Hatle and Angelsen. The Doppler echocardiogram was evaluated by an experienced cardiologist who did not know the results of clinical examination.

Control group. Fifty-one control subjects with normal findings on physical examination were evaluated to determine the incidence of mitral valve prolapse on echocardiography at our institution. The group consisted of 44 normal volunteers and seven patients from our clinic population receiving prophylaxis
with penicillin for well-documented rheumatic fever. Of these seven patients, five had a completely normal findings on physical examination and two had a grade I/VI early systolic murmur at the left sternal border identified as a flow murmur after dynamic auscultation. The echocardiographer was blinded to the history in this control group. Mitral valve prolapse was diagnosed in three of the 51 subjects (6%) by the same echocardiographic criteria described above. None of the seven patients with a history of rheumatic fever had mitral valve prolapse on echocardiography. However, one patient had a thickened anterior and posterior leaflet of the mitral valve without evidence of mitral stenosis or regurgitation by Doppler examination.

Results

Physical examination. Cardiac auscultation by both cardiologists confirmed that all 30 patients had apical systolic murmurs without the presence of diastolic murmurs. The murmur was judged to be grade I/VI in 10 patients (33%), grade II/VI in 12 patients (40%), and grade III/VI in eight patients (27%). Origin of the murmur as determined by dynamic auscultation is depicted in figure 1. Twenty of the 30 patients (67%) were diagnosed as having a murmur compatible with mitral regurgitation: nine were holosystolic murmurs, two early systolic, four mid-systolic, and five late systolic. Three of these patients had mid-systolic clicks: one with a holosystolic murmur, one with a mid-systolic murmur, and one with a late systolic murmur. In nine patients (30%) the murmur was attributed to aortic outflow turbulence; five of these patients had early peaking systolic murmurs and the remaining four patients had mid-peaking systolic murmurs. Only one patient (3%) had a right-sided murmur, which increased with inspiration.

Echocardiography. The results from echocardiography are indicated in figure 2. Twenty-four of the 30 patients (80%) had echocardiographic evidence of mitral valve prolapse without concomitant mitral stenosis or other valvular disease. Six of these 24 patients had mild thickening of one or both of the mitral valve leaflets, but no diastolic doming. Only one of the 30 patients (3%) with mitral valve prolapse had mild thickening of both mitral valve leaflets with doming consistent with mild mitral stenosis. This patient also had thickening of the aortic valve leaflets but no evidence of aortic stenosis at cardiac catheterization. Only five patients (17%) had normal echocardiograms.

Doppler examination. Pulsed Doppler examination demonstrated isolated mild-to-moderate (detected in the mid-left atrium) mitral regurgitation in 25 of the 30 patients (84%) (figure 3). One patient had moderate tricuspid regurgitation (3%). Four patients (13%) had normal findings on Doppler examination, without evidence of regurgitant or stenotic valvular lesions and ventricular or atrial septal defects. The one patient who had evidence of mild mitral stenosis on two-dimensional echocardiography had mitral valve orifice velocities at the upper limit of normal and had normal aortic valve orifice velocity.

Combined results of physical examination, echocardiography, and Doppler studies. The combined results of physical examination, echocardiography, and Doppler studies are shown in figure 4. Mitral regurgitation was diagnosed by physical examination in 20 patients and by Doppler in 25 patients. Echocardiography demonstrated mitral valve prolapse without mitral stenosis or other valvular disease in 24 patients. Fifteen patients with mitral regurgitation diagnosed both by physical examination and Doppler had mitral valve prolapse on echocardiography. Twenty-two of 24 patients (92%) with mitral valve prolapse on echocardiography had mitral regurgitation present by physical examination and/or Doppler. Examples of representative two-dimensional and Doppler echocardiograms are provided in figure 5.
with a good prognosis barring recurrent rheumatic fever or bacterial endocarditis. Other investigators have reported a similar benign prognosis for patients with a history of rheumatic mitral regurgitation. However, all of these studies were based on physical examination findings and did not include cardiac catheterization, echocardiography, or Doppler confirmation.

Selzer and Katayama in 1972 reported the first large series of 230 consecutive cases of isolated mitral regurgitation in which the majority of patients (92%) were evaluated with cardiac catheterization. They reported that 88 (39%) of the 230 patients had mitral regurgitation secondary to a rheumatic etiology. The identification of a rheumatic etiology was based on description of the valve on surgical inspection in 61 (69%) of the 88 patients and on a history of rheumatic fever in the remaining 27 patients (31%). Other investigators also report a very high incidence of pure mitral regurgitation in children in Mexico and India, where rheumatic fever remains a major health hazard. This contrasts with recent studies by Waller et al., who reported their findings in 97 patients over 30 years of age undergoing mitral valve replacement for isolated severe mitral regurgitation. Their analysis of the excised mitral valves included measured mitral valve area and annular circumference. In this series mitral valve prolapse with or without ruptured chordae was considered the most common etiology, accounting for 60% of isolated severe mitral regurgitation requiring valve replace-

**FIGURE 4.** Combined results of physical examination, echocardiography, and pulsed Doppler studies.

**Discussion**

Historically, there has been considerable controversy regarding isolated mitral regurgitation in patients with a history of rheumatic fever. Many of the initial pathologic and clinical studies concluded that isolated mitral regurgitation of rheumatic origin was exceedingly rare unless accompanied by mitral stenosis. However, as early as 1926, Sprague and White challenged this view and suggested that isolated mitral regurgitation of rheumatic origin was a distinct clinical entity, indicating that it was not a necropsy finding because it was rarely if ever fatal. In 1960, Jhaveri et al. reported that 56 of 300 adult patients (18.6%) with a history of rheumatic fever had isolated mitral regurgitation on physical examination. These patients remained asymptomatic for a mean follow-up of 18 years. The authors concluded that patients with a history of rheumatic fever and only apical systolic murmurs have a benign type of mitral regurgitation

**FIGURE 5.** Example of an echocardiogram showing mitral valve prolapse (A) and a Doppler recording showing mitral regurgitation (B) from an asymptomatic 19-year-old man. He had acute rheumatic fever at the age of 7 years, manifested by a new mitral regurgitation murmur, marked cardiomegaly on chest x-ray, and both right- and left-sided heart failure. He also had polyarthritis, fever, first-degree atrioventricular block, and a positive throat culture for group A β-hemolytic streptococci. Currently on physical examination, he has a grade II/VI holosystolic murmur at the apex, which radiates to the axilla.
Coronary artery disease accounted for 30%, followed by infective endocarditis (5%) and rheumatic heart disease (3%). Thus they concluded that nonrheumatic conditions accounted for 97% of patients requiring mitral valve replacement for isolated severe mitral regurgitation. However, five of the 60 patients defined as having mitral valve prolapse had prior histories of acute rheumatic fever but were not classified as having mitral regurgitation secondary to a rheumatic etiology. More importantly, microscopic examination was not performed to determine whether myxomatous proliferative changes were present.

The microscopic diagnosis of mitral valve prolapse due to myxomatous proliferation requires that the spongiosa extend into the replace part of the fibrosa. This results in a loss of fibrous tissue and accumulation of mucopolysaccharides that weakens the central portion of the fibrosa and enables cusp expansion and chordal elongation to occur. However, there are multiple causes of mitral valve prolapse that are not related to myxomatous proliferation, such as ischemia, trauma, hypertrophic cardiomyopathy, and bacterial endocarditis.

Tomaru et al. recently described a new entity of postinflammatory mitral valve prolapse. They evaluated 27 patients with mitral valve prolapse who required mitral valve replacement for valvular regurgitation. Thirteen of the 27 (48%) excised mitral valves on microscopic examination revealed classic myxomatous changes. However, the remaining 14 valves (52%) demonstrated fibrosis with vascularization and scattered infiltration of round cells, including lymphocytes and plasmacytes without prominent myxomatous proliferation of the spongiosa. They postulated that these changes were caused by a postinflammatory process associated with chronic inflammation. Furthermore, there was a history of rheumatic fever only in patients with this inflammatory type of mitral valve prolapse and in none of the patients with myxomatous prolapse. They concluded that mitral valve prolapse is produced not only by myxomatous changes but also by postinflammatory changes resulting from rheumatic fever. In addition, gross inspection of the valves demonstrated a greater mean surface area of anterior and posterior valve leaflets and a larger mitral annular dimension in both myxomatous and postinflammatory prolapse when compared with normal hearts. This finding questions the validity of the conclusions of Waller et al. that attribute the majority of surgical mitral regurgitation to myxomatous changes based on gross valvular inspection without microscopic examination.

In another recent report, Marcus et al. presented their findings in 61 patients with active rheumatic carditis requiring surgical correction of severe mitral regurgitation. Fifty-seven of these patients (93%) had marked prolapse of the anterior mitral valve leaflet on echocardiography, and at surgery mitral valve prolapse was found in all 57 patients. Among these 57, mitral annular dilatation was found in 54 (95%), chordal elongation in 50 (88%), and chordal rupture in four (17%). Fibrosis and retraction of the mitral leaflet tissue was noted in only eight of the 61 patients (13%) at surgery. The authors concluded that anterior mitral valve leaflet prolapse is the most common valvular abnormality in patients with severe mitral regurgitation caused by active rheumatic carditis. These results agree with the findings of Chauvaud et al. in children from Mediterranean countries and Northern Africa, where rheumatic fever is still prevalent.

In the present investigation, the diagnosis of mitral regurgitation on physical examination was based on the results of dynamic auscultation. In most cases Doppler examination corroborated the physical examination findings; however, Doppler studies detected mitral regurgitation more often than the physical examination. This was not surprising, since the murmur of mitral regurgitation secondary to mitral valve prolapse may behave similarly to an aortic outflow murmur during dynamic auscultation. Specifically, the apical systolic murmur of mitral valve prolapse may increase in response to amyl nitrite inhalation, leading to a false diagnosis of a flow murmur especially when a click is not present. This may explain the more frequent diagnosis of mitral regurgitation by Doppler examination when compared with the physical examination. Also, Doppler may be more sensitive for the detection of mitral regurgitation. Therefore our findings are consistent with those of Steinfield et al., who reported that 34 of 184 patients with acute rheumatic fever had evidence on physical examination of a mid-to-late systolic murmur or a click during their follow-up, which did not include an echocardiographic or Doppler examination.

In the present investigation, the results of echocardiography provide complementary data to the recent surgical pathologic series. These studies cannot be directly compared because they include patients with severe mitral regurgitation in the surgical series and patients with mild-to-moderate mitral regurgitation in our study. Nonetheless, we found mitral valve prolapse, adhering to strict echocardiographic criteria, in 22 of 28 patients with mitral regurgitation documented by physical examination or Doppler in the absence of stenosis or other valvular
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disease. In addition, the majority of cases in our series involved the anterior leaflet of the mitral valve, which was also consistent with the recent surgical series. However, the mean age of our study group was younger (31 years) than that of the group reported by Tomaru et al.\textsuperscript{10} (43 years). Our patients may represent a subgroup with early mitral regurgitation caused by rheumatic heart disease. It is also feasible that they may have gained some protective effect from regular monthly prophylaxis with penicillin. At this time, it is unknown whether long-term prophylaxis for rheumatic fever will prevent further valvular inflammation in this subset of patients as suggested by Tomkins et al.\textsuperscript{27}

There are several potential limitations to the present investigation. Hemodynamic and angiographic assessments are lacking because all of our patients were asymptomatic, and this would have exposed these patients to unnecessary risks. However, echocardiography combined with Doppler has a very high sensitivity and specificity in the detection of mitral regurgitation in patients with valvular heart disease.\textsuperscript{28} In the present study, 23 of the 30 patients were women, which is not surprising because rheumatic mitral valve disease and clinical evidence of mitral valve prolapse are more common in women. In a control population with normal findings on physical examination, including both normal volunteers and patients with a well-documented history of rheumatic fever, the echocardiographic incidence of mitral valve prolapse was only 6%. Therefore we do not believe that the high incidence of prolapse in the study group was attributable to a low echocardiographic threshold for identifying prolapse. Whether these patients had mitral valve prolapse before their attack of acute rheumatic fever is an issue that cannot be resolved completely without surgical pathologic documentation ruling out myxomatous proliferation within the valve. However, the common echocardiographic findings of thickened valve leaflets with prolapse of the anterior rather than posterior leaflet are more consistent with the surgical description in the recent reports as opposed to myxomatous mitral valve prolapse.

The results of the present investigation are consistent with those of numerous other studies, showing that the presence of a systolic murmur in patients with a past history of rheumatic fever frequently represents isolated mitral regurgitation without mitral stenosis. However, the cause of mitral regurgitation in this patient population is often mitral valve prolapse. Our findings support the theory of an inflammatory etiology of mitral valve prolapse proposed by Tomaru et al.\textsuperscript{10} and Marcus et al.\textsuperscript{11} in patients with a history of rheumatic fever. Whether long-term prophylaxis for rheumatic fever will prevent further valvular inflammation in these patients is currently unknown. We plan to follow these patients on a long-term basis to determine the progression of prolapse and regurgitation, as well as the development of mitral stenosis.

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