

Acute Severe Mitral Regurgitation During First Attacks of Rheumatic Fever: Clinical Spectrum, Mechanisms and Prognostic Factors

Joél Kamblock, Lam N'Guyen, Bruno Pagis, Philippe Costes, Christophe Le Goanvic, Philippe Lionet, Benoit Maheu, Gérard Papouin

Centre de Cardiologie du Taaone, Tahiti, French Polynesia

Background and aim of the study: The study aim was to describe the clinical spectrum and mechanism of acute severe mitral regurgitation (MR) observed during first episodes of rheumatic fever (RF), and to identify prognostic factors related to the short-term outcome.

Methods: Since 1990, 44 patients (mean age 9.2 ± 0.1 years; range: 4-17 years) have been admitted to the authors' institution with severe MR related to a first episode of RF, fulfilling revised Jones' criteria. Twenty-three patients admitted between 1995 and 2002 were included prospectively, and 21 admitted before 1994 were studied retrospectively.

Results: Left ventricular end-diastolic and end-systolic dimensions were 51 ± 2 mm (46 ± 3 mm/m² BSA) and 32 ± 2 mm (28 ± 2 mm/m² BSA), respectively; mean fractional shortening of the left ventricle was $39.0 \pm 1.0\%$ (range: 31-52%); Doppler-derived pulmonary arterial systolic pressure (PAPS) was 51 ± 6 mm (range: 27-90 mm). The mitral valve annulus was enlarged in all patients (mean diameter 31 ± 2 mm; 27 ± 4 mm/m² BSA). MR resulted from prolapse of the anterior mitral valve leaflet (P of AMVL) in 16 patients (36%), and from prolapse of the posterior mitral valve leaflet (P of PMVL) in nine (20%); the other 19 patients (43%) had restrictive motion of the PMVL, with normal motion of the AMVL, resulting in a 'false prolapse' of the AMVL (FP of AMVL). During the six-month interval following the RF episode, mitral valve surgery was required in 11

patients (25%); three patients (7%) died from cardiogenic shock before they could undergo surgery, while the other 30 patients were stabilized under medical treatment. Using univariate analysis, death or mitral valve surgery was associated with PAPS >50 mm (OR = 1.7, $p = 0.04$), male gender (OR = 1.88, $p = 0.008$), clinical signs of congestive heart failure at admission (OR = 2.7, $p < 10^{-4}$), and prolapse of the PMVL (OR = 5.2, $p = 0.01$). Death occurred, or mitral valve surgery was necessary, in eight patients with P of PMVL (89%), in four with P of AMVL (25%), and in two with FP of AMVL (11%) ($p < 0.001$). Despite limitations due to co-linearities and small sample size, multivariate analysis identified P of PMVL as the most potent predictor of adverse outcome. The long-term follow up (mean 6.3 years) of patients without P of PMVL, alive and not operated on during the first six-month interval after an RF episode, demonstrated a sharp decrease in the mean severity of MR (from grade 4 to 1.7; range: 1-3).

Conclusion: In contrast to previous reports of chronic rheumatic MR, acute severe MR due to RF is more frequently related to P of AMVL or P of PMVL, than to FP of AMVL. Patients with P of AMVL or FP of AMVL tend to improve with medical treatment; however, those with P of PMVL carry a poor medical prognosis, and most often require early mitral valve surgery.

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Mitral regurgitation (MR) is the most frequent valvular lesion resulting from active rheumatic carditis during episodes of rheumatic fever (1-3). However, the consequences of rheumatic carditis on the mitral valve

apparatus are highly variable (4). In some patients, rheumatic activity results in mild MR, which may frequently regress or disappear during long-term follow up, at least clinically (5). In some patients however, a single episode of rheumatic fever may result in severe MR, with congestive heart failure (CHF) and cardiogenic shock (6).

The medical treatment of acute active episodes of rheumatic fever with severe MR is empirically based on a combination of steroids or non-steroidal agents,

Address for correspondence:

Joél Kamblock, Centre de Cardiologie du Taaone, Tahiti, French Polynesia

Tel: (689) 772277

Fax: (689) 464617

e-mail: kamblock@mail.pf

diuretics, digitalis, angiotensin-converting enzyme (ACE) inhibitors and vasodilatory agents (6,7). However, to date, no prospective study has established the long-term prognosis of severely affected patients receiving medical treatment.

It has been shown that, during rheumatic carditis, CHF does not result from rheumatic myocarditis (8), but is rather closely related to the extent of valvular lesions (9). Therefore, mitral valve surgery is frequently indicated in patients with severe acute rheumatic MR, and refractory CHF (10-16).

In the young population affected by rheumatic fever, mitral valve repair is usually strongly preferred to mitral valve replacement. Good long-term results of mitral valve repair for rheumatic mitral valve disease have indeed been reported in large series (16,17). However, the short-term deterioration of surgical repair has been reported when patients needed to be operated on immediately after, or even during, ongoing active rheumatic carditis (17).

Although echocardiography is still not approved in the diagnosis of rheumatic carditis (18-20), it has been shown to define accurately the mechanisms of acute severe rheumatic MR (4,6). In the landmark study of Marcus et al. (6), severe acute rheumatic MR was most often related to mitral annulus dilatation and anterior mitral valve leaflet prolapse. However, this study - which was limited by a selection bias inherent to any surgical report - provided no information about patients with severe MR who were not operated on, for those who died before surgery, or who refused to undergo surgery.

In French Polynesia, rheumatic fever and rheumatic heart disease represent major health problems. The annual incidence of rheumatic fever is still in the range of 100 per 100,000 of the school-aged population, while the prevalence of rheumatic valvular disease among the general population is 2% (21). A computer-based network has been integrated into the public health prevention program of rheumatic fever, allowing the collection of extensive epidemiological data and the regular complete long-term follow up of almost all affected patients (22).

The aims of the present study were to report a series of consecutive patients admitted to the authors' institution over a 12-year period for severe acute rheumatic MR resulting from active carditis during a first episode of rheumatic fever. An additional aim was to describe the mechanisms of MR as defined by echocardiography, and to identify prognostic factors related to both the short-term and long-term outcomes.

Clinical material and methods

Study population

Between January 1990 and December 2002, a total of

1,389 patients had a first episode of rheumatic fever and were admitted to the authors' institution. Among these patients, 44 (12 males, 32 females) with acute severe rheumatic MR and active carditis formed the study population. Those patients presenting with a recurrence of rheumatic fever were excluded; consequently, 23 patients admitted between 1996 and 2002 were studied prospectively, and 21 patients admitted between 1990 and 1995 were analyzed retrospectively.

Rheumatic fever was diagnosed in agreement with revised Jones' criteria (18,19). All patients had negative blood cultures, and particular attention was given to exclude the diagnosis of infective endocarditis or of congenital mitral valve prolapse. Severe MR was defined with standard clinical and echocardiographic criteria (22-26). All patients were followed up at six-month intervals, with clinical examination and Doppler echocardiography. All were treated with a combination of steroids (starting dose 1 mg/kg) for six to eight weeks, diuretics, digitalis and ACE inhibitors; the alpha-blocker prazosin was given to 10 patients. Secondary prophylaxis of rheumatic fever was performed every three weeks with intramuscular injections of benzathine penicillin.

Echocardiography

Echocardiographic imaging was performed by two experienced observers using Hewlett Packard 2500 and 4500 machines, equipped with 3.5- and 5-MHz transducers. A standardized cross-sectional and Doppler echocardiographic examination was performed with multiple orthogonal parasternal, apical and subcostal views. M-mode and bidimensional dimensions were indexed to body surface area (27,28). The structure of the annulus, valves, leaflets and subvalvular apparatus were carefully evaluated. Leaflet motion was graded as excessive, normal or restricted, according to whether the location of maximal systolic excursion of any portion of the mitral leaflet extended beyond, to, or below the mitral annular plane. Prolapse of the mitral valve was defined as systolic displacement of the coaptation point of mitral valve leaflets posterior to the plane of the mitral valve annulus into the left atrium in the parasternal long-axis and apical four-chamber views (29). Displacement of the mitral valve leaflets noted only on the apical four-chamber view was not accepted as prolapse (30). The severity of MR was graded from 0 to 4 according to standard criteria (22-26). The mechanism of MR was determined on the basis of the presence or absence of leaflet prolapse, annular dilatation, restriction of leaflet mobility and direction of the jet of MR (31).

Statistical analysis

A chi-square test, *t*-test and logistic regression were used for the statistical analysis. The hazard ratios (HR)

were calculated for prognostic analysis using logistic regression. A p -value <0.05 was considered to be statistically significant. Commercially available software was used to perform the statistical analyses (Epi Info 6.04 cfr and Statistica 5.1; Statsoft Inc., Tulsa, USA).

Results

The mean age of patients was 9.2 ± 0.1 years (range: 4 to 17 years). Previous symptoms evocative of pharyngitis were reported in 11 patients (25%). Arthritis and fever were present in 17 (38%) and 31 (70%) patients, respectively. Clinical signs of CHF were observed in 20 patients (45%). An elevation of the biological markers of inflammation (erythrocyte sedimentation rate and/or C-reactive protein) and of anti-streptolysin O (ASO) titers was observed in all patients. Normal sinus rhythm was present in all cases.

Echocardiographic findings

Echocardiography demonstrated enlargement of the left cardiac structures in all patients. The mean left atrial dimension was 39 ± 2 mm, mean left ventricular (LV) end-diastolic and LV end-systolic dimensions were 51 ± 2 mm (46 mm/m^2 body surface area, BSA; normal value 38.5 mm/m^2 BSA) (28) and 31 ± 2 mm (28 mm/m^2 BSA; normal value 24.4 mm/m^2 BSA) (28), respectively. The mean diameter of the mitral valve annulus was 31 ± 2 mm (27 mm/m^2 BSA); LV fractional shortening and LV ejection fraction were $39.0 \pm 1.0\%$ (range: 31 to 52%) and $68.0 \pm 1.0\%$ (range: 58 to 82%), respectively. The mean systolic pulmonary artery pressure (PAPS) was estimated as 51 ± 6 mm (range: 27 to 90 mm). Pericardial effusion was present in eight patients, but none of these required pericardial drainage. Significant aortic regurgitation was noted in five patients (mild to moderate in three patients and severe in two). The mechanism of MR was identified using echocardiography in all patients; prolapse of the anterior mitral valve leaflet (AMVL) was observed in 16 patients (36%), and of the posterior mitral valve leaflet (PMVL) in nine (20%). Nineteen patients (43%) had a posteriorly directed MR jet resulting from normal motion of the AMVL associated with restrictive motion of the PMVL ('false prolapse' of the AMVL). The mechanism of MR as described by echocardiography was confirmed during surgery in all operated patients, except for one patient who was misdiagnosed by echocardiography as having prolapse of the AMVL, and was subsequently proved during surgical examination to have a false prolapse of the AMVL. Chordal rupture was diagnosed during surgical examination in all seven of the operated patients with prolapse of the PMVL, and in two of the three with prolapse of the AMVL.

Short-term prognosis analysis

During the six-month interval following hospital admission, mitral valve surgery was required by 11 patients (25%), on the basis of persistence of severe symptoms, major LV dilatation or pulmonary hypertension. Three patients (7%) died from refractory cardiogenic shock before they could be transferred from Tahiti to New Zealand for emergency cardiac surgery; 30 patients (68%) were stabilized with medical treatment. With univariate analysis, four prognostic factors for early death or cardiac surgery were identified: PAPS >50 mm (HR: 1.7, $p = 0.04$); male gender (HR: 1.88, $p = 0.008$); clinical signs of CHF at admission (HR: 2.7, $p < 0.0001$); and prolapse of the PMVL (HR: 5.2, $p = 0.01$). Patient age, the presence of aortic regurgitation, left atrial and LV dimension and alpha-blocker therapy were not associated with the short-term prognosis of patients. Multivariate analysis was limited by the small size of the patient population, and by co-linearities. However, prolapse of the PMVL emerged as the most potent predictor of death or surgery: death occurred or surgery was required in two of the 19 patients with false prolapse of the AMVL (11%), in four of the 16 with prolapse of the AMVL (25%), and in eight of the nine with prolapse of the PMVL (89%) ($p < 0.001$).

Long-term prognosis of unoperated patients

The mean follow up of the 29 patients who were alive and not operated on during the six-month interval following the first episode of rheumatic fever was 6.3 years. No patient was lost to follow up, while only one patient had a recurrence of rheumatic fever. Mitral regurgitation was evaluated clinically and with echocardiography twice each year; a sharp decrease in the severity of MR was demonstrated, from a mean grade of 4 (at admission) to 1.7 (range: 1 to 3; $p < 0.001$) at follow up. No patient developed significant mitral stenosis. The indexed LV end-systolic and end-diastolic dimensions were significantly reduced, from 43.95 ± 3.63 to $30.61 \pm 1.08 \text{ mm/m}^2$ BSA, and from 27.02 ± 2.60 to $18.96 \pm 0.98 \text{ mm/m}^2$ BSA, respectively ($p < 0.01$), while LV fractional shortening remained unchanged (39 ± 1.7 versus $38.1 \pm 2.2\%$).

Discussion

To the best of the present authors' knowledge, this study is the first to report clinical, echocardiographic and prognostic factors in a homogeneous group of consecutive patients with acute severe rheumatic MR observed during the first attacks of rheumatic fever. The results underline several important concepts concerning the pathophysiology of severe acute rheumatic MR, and suggest practical bedside recommenda-

tions for the management of this severe complication of rheumatic fever.

Acute severe MR is a rare, but serious, complication of the first episodes of rheumatic fever, occurring in only 44 of 1,389 patients (3%) during a 12-year period. Mortality from refractory cardiogenic shock was 7% within the first few days following hospital admission, and despite intensive medical treatment, mitral valvular surgery was required in 11 patients (25%) during the six-month period following the clinical episode. Within the perspective of primary prevention of this severe manifestation of rheumatic fever, it is clearly disappointing that previous pharyngeal symptoms were noted in only 25% of the patients.

Mechanism of MR and short-term prognosis

In agreement with the results of previous studies (4,6), mitral valve annulus dilatation and mitral valve prolapse or false prolapse was observed in all of the present patients with severe acute rheumatic MR. However, in contrast to previous reports, prolapse of the PMVL was identified in a significant proportion (20%) of patients with severe acute rheumatic MR. Prolapse of the PMVL was suspected by careful examination of mitral valve leaflet motion in the parasternal long-axis view, and confirmed in the presence of an anteriorly directed mitral regurgitant jet in color Doppler mode (31).

Based on the results of the present study, the observation of prolapse of the PMVL during active rheumatic carditis is of paramount importance, as it proved to be the most independent predictive factor of death or need for cardiac surgery during the six-month interval following the episode of rheumatic fever. Among the nine patients with prolapse of the PMVL, one patient died and seven underwent early cardiac surgery. In contrast, among 35 patients with prolapse or false prolapse of the AMVL, two deaths occurred and only two patients required early surgery ($p < 0.001$).

According to current knowledge of the mechanisms of acute rheumatic MR, it is difficult to explain the adverse prognostic value related to prolapse of the PMVL, compared to prolapse or false prolapse of the AMVL. However, the latter condition has been reported to be mostly determined by chordal elongation, without chordal rupture, in the vast majority of patients with active rheumatic severe MR (6,14,32-36). In the study of Marcus et al. (6), chordal rupture was observed in only 7% of patients exhibiting prolapse of the AMVL. These authors emphasized the characteristic self-aggravating nature of acute MR in these patients, whereby annular dilatation and chordal elongation aggravate each other, gradually increasing the severity of mitral valve incompetence. The present data support the hypothesis that, in patients with

severe MR due to prolapse or false prolapse of the AMVL, and in the absence of chordal rupture, an early and intensive medical treatment based on steroids (limiting valvular, annular and chordal inflammation) and a combination of digitalis, diuretics and ACE inhibitors would be expected to limit the self-aggravating process of acute rheumatic MR. Indeed, in the present study a strong decrease in the severity of MR was observed over both short-term and long-term follow up in patients without prolapse of the PMVL who received intensive medical treatment and regular secondary prophylaxis. In contrast, the data demonstrated that complete chordal rupture is most often present when acute rheumatic prolapse of the PMVL is observed. In the present study, chordal rupture was indeed confirmed during surgical examination in the seven patients with prolapse of the PMVL who underwent surgery. In those patients with severe MR due to complete chordal rupture, intensive medical treatment by itself would not be expected to decrease substantially the degree of MR. In fact, among the present patients a significant clinical improvement was observed under medical treatment in only one case with prolapse of the PMVL. Thus, the study results support the hypothesis that the presence of chordal rupture is characteristic of rheumatic prolapse of the PMVL, in contrast to chordal elongation, which is most frequently observed in patients with prolapse and false prolapse of the AMVL. Rather than prolapse location itself, the presence of chordal rupture in most patients with rheumatic prolapse of the PMVL forms the basis of an adverse immediate prognosis in these cases.

Long-term prognosis in unoperated patients

The present results demonstrated a strong trend towards a sharp decrease in the severity of MR caused by prolapse or false prolapse of the AMVL, and which were not operated on during the acute stage. With a mean follow up of 6.3 years, the severity of MR decreased from severe (grade 4) in all patients, to a mean of 1.7 (range: 1 to 3), with a normalization of LV end-diastolic and end-systolic dimensions.

Several factors may explain this rather unexpected favorable long-term outcome. First, all of the patients were carefully followed up, and received intensive medical treatment with regular injections of benzathine penicillin every three weeks to prevent rheumatic fever recurrence. Indeed, only one patient had recurrence of rheumatic fever during follow up, and this led to severe MR and required mitral valve surgery. Another contributory factor may be represented by the natural trend towards a decrease in the severity of MR over the long-term follow up, as has been reported previously in patients with chordal elongation and annular dilatation, without chordal rupture

(35). Due to the characteristic fibrotic and retractile pattern of the chronic rheumatic process, the tissues of the annulus and of the subvalvular mitral apparatus were reported to change over a long period from an elongated and distended shape to a shorter form; in turn, this led to a spontaneous decrease in the degree of prolapse or false prolapse of the AMVL, and a decrease in the severity of MR. Over a longer follow up, significant mitral valve stenosis might be observed in some of these patients, though it was not seen in any of the present cases.

ACE inhibitor use in patients with severe rheumatic MR

The clinical benefit of ACE inhibitors in patients with MR remains unproven and controversial (37,38). On the basis of the favorable results reported in preliminary studies (39-45), the decision was taken by the present authors to administer ACE inhibitors to all patients admitted to their institution with severe rheumatic MR. Although the present study was not designed to determine the benefits of ACE inhibitors in patients with rheumatic MR, the good long-term results in the subgroup without prolapse of the PMVL tended to support this strategy. However, considering the recently reported deleterious effects of ACE axis manipulation in animal models of MR (46,47), it is believed that further randomized studies are needed to demonstrate the clinical benefits of ACE inhibitors in young patients with severe rheumatic MR.

Clinical implications

The study results suggest practical recommendations for the bedside management of patients with severe MR during the first episodes of active rheumatic carditis. Determination of the precise mechanism of MR with Doppler echocardiography plays a pivotal role in the risk stratification of patients presenting with acute severe MR during the first episodes of rheumatic fever. In patients with prolapse of the PMVL, chordal rupture is most frequently present, death frequently occurs, and immediate surgery is often required. Thus, these patients require very close clinical monitoring, and transfer to an institution where cardiac surgery is immediately available must be strongly considered. In contrast, in patients with prolapse or false prolapse of the AMVL, chordal rupture is rarely present. When the good long-term prognosis in this group of patients is balanced with long-term problems related to cardiac surgery in rheumatic MR for young patients (17,36), intensive medical treatment must be proposed for patients without prolapse of the PMVL, the aim being to avoid surgery at least during the first few months after the rheumatic fever episode.

Limitations of the study

The main limitations of the present study were related to its small sample size, and its mixed design, which combined prospective and retrospective data. However, all patients were evaluated by the same two experienced cardiologists during both periods of the study, while the computer-based network on rheumatic fever limited any selection bias for those patients who were analyzed retrospectively.

False prolapse of the AMVL was observed in 40% of the present patients, who were supposed to have a first clinical episode of rheumatic fever. False prolapse of the AMVL, which requires retraction of the PMVL subvalvular apparatus, is unlikely to develop within a few days of a first episode of rheumatic fever, however. Thus, it is possible that some of the present patients had suffered previous undetected episodes of rheumatic fever, before being admitted for the clinical rheumatic fever episode labeled as their 'first'.

In the present investigation, 20% of the patients with severe rheumatic MR had prolapse of the PMVL, a value which was significantly higher than reported elsewhere. However, the lower proportion of prolapse of the PMVL reported previously on rheumatic MR may result from referral bias, which is inherent to all the surgical reports, and provides no information regarding patients who did not undergo surgery. For example, the present data showed that death before surgery occurred more frequently in patients with prolapse of the PMVL, and this may have contributed to the lower rate of PMVL prolapse in the surgical series.

In conclusion, prolapse of the PMVL is observed in a significant proportion of patients presenting with acute severe MR during the first episodes of rheumatic fever, and represents an independent adverse predictor of a poor medical prognosis, due to the presence of chordal rupture in most of these patients. Early surgical treatment is frequently indicated in these cases, who require very close clinical monitoring. In contrast, patients with prolapse or false prolapse of the AMVL have an excellent long-term prognosis, provided that they receive intensive medical treatment and adequate prevention of rheumatic fever recurrence. In these patients, surgical treatment should be delayed as long as clinically possible.

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