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Evidence Against a Myocardial Factor as the Cause of Left Ventricular Dilation in Active Rheumatic Carditis

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Objectives. **The aim of this study was to determine whether left ventricular dilation and congestive heart failure in patients with acute rheumatic fever with carditis are accompanied by left ventricular contractile dysfunction.**

Background. **Acute rheumatic fever with carditis involves both the myocardium and endocardium, with consequent valvular regurgitation. The relative contribution of volume overload induced by valvular regurgitation and myocardial dysfunction due to rheumatic myocarditis to the overall degree of left ventricular dilation and congestive heart failure in these patients is unknown.**

Methods. **To investigate this, we evaluated 32 patients (15 male, 17 female, mean age 14 ± 3 years) with documented active carditis and congestive heart failure. All 32 patients were found to have significant isolated mitral regurgitation or combined mitral and aortic regurgitation. Echocardiographic analysis of left ventricular dimensions and systolic performance was performed before and after isolated mitral or combined mitral and aortic valve replacement and the results were compared with those in 19 control subjects matched for age, gender and body surface area.**

Results. **Both preoperative left ventricular end-diastolic diameter and percent fractional shortening were significantly increased in patients compared with control subjects (57 ± 7 vs. 43 ± 3 mm, $p < 0.001$, and 38 ± 6% vs. 33 ± 1%, $p < 0.001$, respectively). After valve replacement, left ventricular end-diastolic diameter decreased significantly (57 ± 7 to 47 ± 6 mm, $p < 0.001$). Although percent fractional shortening decreased significantly postoperatively (38 ± 6% to 32 ± 6%, $p < 0.001$), the postoperative percent fractional shortening did not differ from that in control subjects (32 ± 6% vs. 33 ± 1%, p = NS).**

Conclusions. **The results of this study indicate that left ventricular dilation and heart failure in patients with acute rheumatic carditis rarely occur in the absence of hemodynamically significant regurgitant valve lesions. Furthermore, rapid reduction in left ventricular dimensions and preservation of fractional shortening after isolated mitral or combined mitral and aortic valve replacement suggest that rheumatic carditis is not accompanied by any significant degree of myocardial contractile dysfunction.**

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Current opinion suggests a putative role for myocarditis in the pathogenesis of left ventricular dilation and congestive heart failure during active rheumatic carditis (1). In the more severe form of the disease, a "toxic rheumatic myocarditis" has been incriminated (2). Although histologic evidence of myocarditis is present in 32% to 95% of autopsy cases (3), and was reported in every patient undergoing endomyocardial biopsy during the active phase of the disease, it is not clear that these features are related to abnormalities of left ventricular contractile function. It is our experience (4) and that of others (5) that left ventricular dilation and heart failure rarely occur in the absence of hemodynamically significant mitral regurgitation with or without accompanying aortic regurgitation. In patients with active rheumatic carditis presenting with overt heart failure, functionally severe mitral regurgitation and its anatomic correlate of annular dilation, chordal elongation and prolapse of the anterior mitral leaflet have been observed sufficiently frequently by us (6) to be regarded as a pathoanatomic hallmark of the disease. To clarify the relative contribution of volume overload induced by valvular regurgitation and myocardial dysfunction due to rheumatic myocarditis to the overall degree of left ventricular dilation, we analyzed left ventricular dimensions and function noninvasively in a group of young patients with documented active rheumatic carditis before and after successful isolated mitral or combined mitral and aortic valve replacement.

Methods

Patient selection. Over a 3-year period, 43 patients with documented active rheumatic carditis and congestive heart failure were seen at the Baragwanath Hospital. All 43 patients were found to have hemodynamically compromising mitral regurgitation with or without aortic regurgitation for which single- or double-prosthetic valve implantation was performed. Thirty-two of these patients had preoperative

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Table 1. Left Ventricular Internal Dimensions in Systole and Diastole and Fractional Shortening Measured Preoperatively and 3 Months Postoperatively in Study Group and in Normal Control Subjects

	Control Group	Study Group		Control Group Versus Study Group (p Value)		Pre Versus Post (p Value)
		Pre	Post	Pre	Post	
EDD (mm)	43 ± 3	57 ± 7	47 ± 6	< 0.001	< 0.001	< 0.001
ESD (mm)	29 ± 2	36 ± 6	32 ± 6	< 0.001	0.08	< 0.001
FS (%)	33 ± 1	38 ± 6	32 ± 6	< 0.001	0.68	< 0.001

EDD = left ventricular end-diastolic diameter; ESD = left ventricular end-systolic diameter; FS = fractional shortening; Post, Pre = after and before, respectively, isolated mitral or combined mitral/aortic valve replacement.

and 3-month postoperative echocardiographic evaluation data available for analysis and constitute the study group. The severity of valvular regurgitation was corroborated on clinical evaluation, chest roentgenograms and Doppler echocardiographic evaluation and confirmed on intraoperative hemodynamic assessment in all patients. Diagnostic criteria for active rheumatic carditis included the modified Jones criteria (7), macroscopic appearance of the heart tissues at the time of surgery (8,9) and light microscopic features of active carditis (9,10) in tissues submitted for histologic study. Of the 32 patients who constituted the study group, 19 underwent mitral valve replacement only and 13 underwent combined mitral and aortic valve replacement. Nineteen normal subjects matched for age, gender and body surface area served as the control group.

Data collection. Hospital records were analyzed for all historical, echocardiographic, roentgenographic and operative data. Historical data included age, gender, New York Heart Association functional class and duration of symptoms. Body surface area was computed for each patient. Two-dimensional echocardiography with two-dimensional targeted M-mode echocardiography was performed in all patients in the left decubitus position immediately before and 3 months after valve replacement. Left ventricular internal dimensions in diastole and systole were measured in the parasternal short-axis view at the level of the tips of the papillary muscles and fractional shortening was calculated. All studies were performed using a high resolution cardiac imaging system (Ultramark 8 ATL) coupled to 2.5- or 5-MHz mechanical transducers.

Valve implantation using St. Jude Medical or Medtronic Hall prostheses was performed using standard cardiopulmonary bypass and surgical techniques. Myocardial preservation was achieved using cold potassium crystalloid cardioplegia, topical hypothermia and low flow systemic hypothermia uniformly. The submitral apparatus was resected in all patients. Postoperative management included routine anticoagulation with warfarin sodium and dipyridamole to maintain a target international normalized ratio of 2 to 2.5 and standard rheumatic fever prophylaxis. Diuretic agents and angiotensin-converting enzyme inhibitors were used routinely preoperatively and continued in the same dose postoperatively in all patients.

Statistical analysis. Data are presented as mean value ± SD and comparisons made using two-way repeated measures analysis of variance. Differences were considered significant at $p < 0.05$.

Results

Baseline clinical characteristics. Thirty-two patients and 19 control subjects were entered into the study. Both groups were well matched for age and body surface area (14 ± 3 vs. 14 ± 1.8 years, p = NS, and 1.2 ± 0.2 vs. 1.3 ± 0.2 m^2, p = NS, respectively). Of the 32 patients none were >19 years old, and 28 (87%) were ≤16 years old. There were 15 male and 17 female patients. All patients had clinically decompensated heart failure and 16 (50%) pulmonary edema. By clinical evaluation, 19 (59%) had predominant mitral regurgitation and 13 (41%) severe combined mitral and aortic regurgitation.

Evidence for rheumatic activity. All 32 patients met the prerequisite modified Jones criteria for rheumatic fever. Carditis was uniformly present. Macroscopic features of active rheumatic carditis, including fibrinous pericarditis, noninfected verrucous vegetations on the free edge of the mitral or aortic leaflets and nonspecific signs of acute inflammation, were seen in 27 patients (84%). Light microscopic examination of surgically resected cardiac tissue showed diagnostic histologic features of active rheumatic carditis (Aschoff nodules and fibrinoid necrosis) in 13 (41%) of patients and a nonspecific polymorphonuclear inflammatory response in 21 (66%). One or both of the aforementioned histologic features were documented in every patient. Characteristic abnormalities on two-dimensional echocardiography (6), including mitral annular dilation, chordal elongation and anterior leaflet prolapse, were present in all 32 (100%) of the patients.

Left ventricular dimensions and fractional shortening (Table 1). At baseline, patients in the carditis group had significantly increased left ventricular end-diastolic diameter and percent fractional shortening compared with values in control subjects (57 ± 7 vs. 43 ± 3 mm, $p < 0.001$ and 38 ± 6% vs. 33 ± 1%, $p < 0.001$, respectively). After valve replacement, left ventricular end-diastolic diameter decreased significantly (57 ± 7 to 47 ± 6 mm, $p < 0.001$).

Although percent fractional shortening decreased significantly postoperatively (38± 6% to 32 ± 6%, $p < 0.001$), the postoperative value did not differ from that in control subjects (32 ± 6% vs. 33 ± 1%, p = NS).

Discussion

In patients with acute rheumatic fever and carditis, the distinction between left ventricular dilation and congestive heart failure arising as a consequence of contractile dysfunction due to rheumatic myocarditis or volume overloading associated with valvular regurgitation has important clinical implications. This study represents the first clinical evaluation of left ventricular function in a well categorized group of patients with documented active rheumatic carditis. Two major findings of this study are that 1) heart failure in this disease rarely occurs in the absence of hemodynamically significant valvular regurgitant lesions, and 2) prompt reduction in left ventricular dimensions and preservation of fractional shortening after isolated mitral or combined mitral and aortic valve replacement provide good evidence that rheumatic carditis is not accompanied by myocardial contractile dysfunction to any significant degree.

The presence of significant regurgitant lesions in every patient with acute rheumatic fever and heart failure in this consecutive analysis of 32 patients is consonant with our previous experience (4). Furthermore, our documentation of the mechanism of mitral regurgitation (6) and, more recently, of aortic regurgitation (11) provides further evidence for the pivotal role of valvular regurgitation in this disease.

Because the first episode of rheumatic fever is often asymptomatic, and severe episodes may represent the cumulative effect of several previous attacks, it is difficult to determine the duration of valvular regurgitation in our patients. Nevertheless, the presence of substantial left ventricular dilation would imply subacute or chronic regurgitation. Kontos et al. (12) showed the inability of left ventricular volumes to discriminate between subacute and chronic regurgitation. Although the precise duration of regurgitation may not be certain, on the basis of clinical, echocardiographic and intraoperative observations, its severity is unquestionable. This is underscored by the marked increase in end-diastolic diameter (57 ± 7 mm), which becomes even more significant when one considers that the mean body surface area in this group of patients was only 1.2 ± 0.2 m^2. But the most compelling evidence that left ventricular dilation and heart failure were largely the result of valvular regurgitation is the rapid and significant reduction in heart size after single- or double-valve replacement.

Contractile function. Fractional shortening is an ejection phase index of left ventricular performance that is dependent on contractility, preload and afterload. Preload is increased in mitral regurgitation, enhancing ejection performance (13,14). In subacute or chronic mitral regurgitation, afterload is usually normal (15). Thus, in mitral regurgitation augmented preload and normal afterload enhance ejection performance and raise it to the high normal range (16). Zile et al. (17) found that a supernormal shortening fraction >32% usually predicted a good postoperative result. Using a relatively load-independent index of contractility, Wisenbaugh (18) found an ejection fraction of 0.6 to be predictive of normal left ventricular contractile function in patients with chronic severe mitral regurgitation. After mitral valve replacement, most patients experience a decline in ejection performance; however, in patients with good contractile reserve this decline is small and reflects the adverse postoperative loading conditions (19). Both the supernormal preoperative fractional shortening and the nonsignificant postoperative decline in fractional shortening in our patients are consistent with relatively well preserved contractile function. Chordal resection during mitral valve survery has been demonstrated to adversely affect postoperative left ventricular performance (20,21). Preservation of ejection performance, despite chordal resection in all of our patients, further argues against the presence of any substantial preoperative contractile dysfunction. The decline in end-systolic diameter after valve replacement also suggests that if there was any increase in afterload after valve replacement, it was not present at follow-up. It would appear therefore that histologic rheumatic myocarditis, unlike viral myocarditis, has no functional consequence in terms of contractile dysfunction.

Therapeutic implications. Documentation of significant valvular regurgitation and absence of left ventricular contractile dysfunction has critical therapeutic implications in patients with acute rheumatic fever and heart failure. In those who do not respond to inotropic and vasodilator therapy, restoring mitral or aortic valve competence becomes a priority. Despite the disadvantages of prosthetic valve implantation in this young group of patients, it is our experience (4) and that of others (22) that this treatment may be lifesaving and has a reasonably low mortality rate (0% to 4%) in experienced centers. Furthermore, the results of this study suggest that corticosteroids may be inappropriate therapy for heart failure in this group of patients.

The absence of contractile dysfuction, even during the phase of fulminant rheumatic carditis, as the results of our study suggest, argues against any significant long-term contribution to systolic dysfunction that is sometimes seen in patients with chronic rheumatic heart disease. Using a load-independent index of left ventricular function, our observation that a low ejection fraction in patients with mitral stenosis is related to increased afterload with no identifiable contractile dysfunction (23) further supports this conclusion. The left ventricular dysfunction seen in patients with long-standing severe rheumatic mitral regurgitation is probably related to chronic volume overload, which is also seen in patients with nonrheumatic mitral regurgitation.

Summary. The results of this study indicate that the pathogenetic basis of left ventricular dilation and heart failure in patients with acute rheumatic fever is severe isolated mitral regurgitation or combined mitral and aortic

regurgitation. Despite the presence of rheumatic myocarditis, left ventricular contractile function is unimpaired. These data provide a rational basis for aggressive surgical intervention in this group of patients.

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