Abstract

Objectives: Acute rheumatic fever (ARF) continues to affect millions of children in developing countries. Aim of the present study was to evaluate the role of myocardial dysfunction in the genesis of heart failure in patients with rheumatic carditis. There are limited studies on this subject.

Methods and Results: In this prospective study, 108 consecutive patients of ARF were evaluated by echocardiography and assay of cardiac troponin I blood levels. The patients were divided into three groups. Group A (n=30): patients with no evidence of carditis; Group B (n = 45): patients with first attack of carditis; and group C (n = 33): patients with recurrent attacks of carditis. Left ventricular dimensions tended to be larger in Group B and C patients. Left ventricular ejection fraction did not differ between the groups (Group A: 63±8.1%, Group B: 58±7.9%, Group C: 61.2±9%, p = ns). Heart failure was present in 37.7% patients of Group B, and in 60.6% patients of Group C (p = < 0.05). Ejection fraction was normal in majority of heart failure patients (75.7%). It was reduced in 29.4% of patients in Group B and in 20% of Group C patients with heart failure (p = ns). All patients with low ejection fraction had hemodynamically significant regurgitant valvular lesions. Mean cardiac troponin I values, an index of myocardial damage, did not differ between the three groups (Group A: 0.062±0.027 ng/ml, Group B: 0.068 ± 0.019 ng/ml, Group C: 0.071 ± 0.031 ng/ml, p = ns).

Conclusion: The present study did not demonstrate any echocardiographic abnormalities or cardiac troponin I elevation suggesting significant myocardial involvement during acute rheumatic fever. This lends credence to the view that myocardial involvement does not play any significant role in the genesis of heart failure in patients with rheumatic carditis.

INTRODUCTION

Acute rheumatic fever (ARF) results from an autoimmune response to infection with group A streptococcus. Although the acute illness causes considerable morbidity and some mortality, the major clinical and public health effects derive from the long term damage to heart valves - i.e. rheumatic heart disease (RHD).\(^1\) Over the past century, as living conditions and medical care have improved, ARF and RHD have become rare in developed countries. But the same does not hold true for developing countries like ours. Millions of children continue to suffer from the debilitating disease. There is marginal decline in the prevalence of ARF and RHD over the last two decades, as previously reported.\(^2\) According to WHO, at least 15.6 million people have RHD, 300000 of about 0.5 million who acquire ARF every year go on to develop RHD and 233000 deaths annually are attributable to ARF or RHD.\(^3\)

Though ARF and RHD are common, the aetiology and pathogenesis of the disease continue to remain elusive. Recent studies have unravelled to some extent the potential pathogenetic mechanisms by which the immune response against the Group A streptococcus attacks the cardiac valves.\(^4\) Revised guidelines for the diagnosis of rheumatic fever suggest that when the ARF affects the heart, it usually involves all the layers of the heart i.e. endocardium, myocardium and pericardium in varying degrees.\(^5\) However, the existence of a specific primary myocardial involvement contributing to the occurrence of heart failure during ARF is controversial.\(^6\) Observations that left ventricular function normalises after valve replacement surgery in ARF patients, who had congestive heart failure during acute stage, also puts a question mark on the very existence of myocarditis in such patients.\(^7\)

Aim of the present study was to determine whether a myocardial factor plays any role in the genesis of heart failure.
failure in ARF patients. Troponin I is a sensitive and specific marker of myocardial damage. Elevation of troponin I would indicate that myocardial injury does indeed exist in patients with ARF. In this study, troponin I estimation was done along with echocardiography in patients of ARF to detect noninvasively non-clinical markers of myocardial involvement and determine if myocardial factor plays any role.

**METHODS**

In this prospective study, 108 consecutive cases of ARF were enrolled during August 2004 to July 2006. The diagnosis of ARF was based on the revised Jones criteria. Routine blood count, antistreptolysin-O (ASO) titer, chest X-ray and ECG were obtained in all. Patients with ARF were divided into 3 groups based on the absence (Group A) or presence (Groups B and C) of carditis. Patients were included in Group B when they presented with first episode of ARF and clinical evidence of carditis. There was neither a history of ARF nor echocardiographic evidence of chronic valvular disease (such as mitral stenosis or aortic stenosis). Carditis, evidenced by the presence of murmurs suggestive of valvular regurgitation, constituted a major manifestation in all patients. In addition, few had heart failure (HF) and pericarditis. Group C comprised of patients with recurrence of ARF and clinical evidence of acute carditis. All these patients had either a history of a previous attack of ARF or had echocardiographic stigmata of chronic rheumatic valvular heart disease. The diagnosis of carditis was based on appearance of new murmur (in whom prior cardiac findings were available), clinical evidence of pericarditis, and unexplained acute onset of HF. Again, in addition to the major manifestations, all patients had elevated ASO titer along with the manifestations of ARF.

**Echocardiographic Evaluation**

All the patients underwent detailed echocardiographic examination within 24 to 48 hours of establishment of diagnosis of ARF and before the initiation of anti-inflammatory treatment. Echocardiographic imaging was performed with HDI1500 ATL machine having M-mode, 2 dimensional and colour Doppler echocardiographic facilities. A standardised cross sectional and Doppler echocardiographic evaluation was done with multiple orthogonal parasternal, apical and subcostal views with the patient in the left lateral decubitus position. All examinations were recorded on half inch videotape (VHS) for future analysis.

Particular attention was given to evaluation of global and segmental left ventricular function. Left ventricular end-diastolic and end-systolic volumes were calculated according to the Teicholz method. Ejection fraction (EF) <50% was regarded as reduced ejection fraction. Mitral and aortic regurgitation were quantified using standard echocardiographic criteria, and were graded from 0 (absent) to 4 (severe). Mitral regurgitation (MR) was considered moderate if there was a broad proximal jet filling half the left atrium (LA) or attenuation of systolic flow from the pulmonary veins to the LA. These criteria with addition of systolic flow reversal in pulmonary veins were required for the diagnosis of severe MR.

Aortic regurgitation (AR) was considered to be moderate if the diameter of the regurgitation jet was >20 - 30% of the diameter the left ventricular outflow tract, in association with diastolic flow reversal in the proximal thoracic descending aorta. In addition to these criteria, diastolic flow reversal in the abdominal descending aorta was required for the diagnosis of severe AR.

**Cardiac Troponin I (cTnI)**

The assessment of cTnI was performed with Aculite chemiluminescent diagnostic test. This test is characterised by a high sensitivity, with a lower limit of detectability of 0.03ng/ml. The upper limit of the normal cTnI value is ≤ 1.3 ng/ml.

**Statistical Analysis**

All results were expressed as mean ± standard deviation. The clinical features of the three groups of patients and their baseline echocardiographic measurements were compared by one-way Anova. Categorical data were compared by chi-square test. All reported probability values were two sided, and a probability value of less than 0.05 was considered to be statistically significant. Statistically analysis was done on SPSS 10.0 Version for Windows.

**RESULTS**

One hundred and eight patients suffering from ARF comprised the study group. Thirty patients (27.8%) had ARF without carditis (Group A), 45 (41.7%) had first attack of ARF with carditis (Group B), and 33 (30.5%) had recurrence of ARF with carditis (Group C). The mean delay between first symptoms of rheumatic fever (usually fever or arthritis) and presentation for medical examination was 12 ± 3 days.

There were no significant differences concerning age, sex, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) between groups A, B, and C (Table 1).

Left ventricular function was normal in all group A patients and in the majority of patients of group B and C. No significant differences were observed in the mean values of ejection fraction between the three groups of patients (Group A: 63 ± 8.1%, Group B: 58 ± 7.9%, Group C: 61.2 ± 9%) (Table 2). No patient had segmental hypokinesia. Heart failure (HF) was more common in patients with recurrent carditis (Group C, 60.6%, Group B, 37.7%; p = <0.05). All patients with HF had hemodynamically significant regurgitant lesions (moderate to severe MR and/or AR). Ejection fraction...
(EF) was reduced in 11 patients (5 in Group B and 6 in Group C, \( p = \text{ns} \)) (Table 3). Again, all these patients with reduced EF had significant regurgitant lesions. EF was normal in 24 (75.7%) out of 37 patients with HF (both group B and C included).

In both groups of patients, the LV dilatation was associated with significant valvular regurgitation. Mean indexed values of LV end-diastolic and end-systolic dimension did not differ significantly between Group B and C but were significantly more than the corresponding values for Group A (Table 2).

Pericarditis with mild pericardial effusion was present in 8 of group B and 12 of Group C patients. None of the patients of Group A had pericarditis or pericardial effusion.

Mean serum cTnI value were 0.062 ± 0.027 ng/ml in Group A, 0.068 ± 0.019 ng/ml in Group B, and 0.071 ± 0.031 ng/ml in Group C, respectively (\( p = \text{ns} \)). Only 5 patients had detectable amounts of cTnI, all of whom had pericarditis. There were no correlations between ESR and cTnI (\( r = -0.05, P = 0.61 \)) and between the levels of ASO titer and cTnI (\( r = 0.13, p = 0.20 \)). There was also no correlation between cTnI levels and time of presentation of the patients (\( r = 0.15, P = 0.32 \)).

**DISCUSSION**

The present study demonstrates that majority of patients with rheumatic carditis have normal left ventricular systolic function and normal cardiac troponin I values. Very few clinical studies have been done to unravel the mechanisms leading to development of heart failure in patients with rheumatic carditis.

Rheumatic myocarditis is usually believed to occur in the setting of pancarditis, the most severe form of rheumatic carditis, during which the rheumatic process is supposed to involve all the layers of heart i.e. endocardium, pericardium, and myocardium. Revised guidelines for the diagnosis of rheumatic fever also suggest that left ventricular dysfunction resulting from myocarditis, although ‘uncommon’ in the absence of severe valvular damage, may contribute to the genesis of heart failure. However, few clinical studies which have been done so far raise in serious question regarding role of

![Figure 1](https://www.japi.org/)

**Table 1**: Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ARF without carditis (Group-A, n-30)</th>
<th>ARF with carditis (Group-B, n-45)</th>
<th>ARF with carditis (recurrent) (Group-C, n-33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14.6 ± 5.7</td>
<td>12.9 ± 4</td>
<td>11.8 ± 5.3</td>
</tr>
<tr>
<td>Gender (Male:Female)</td>
<td>23:7</td>
<td>34:11</td>
<td>24:9</td>
</tr>
<tr>
<td>Day of presentation</td>
<td>10.4 ± 6</td>
<td>11.3 ± 5.6</td>
<td>10.7± 8</td>
</tr>
<tr>
<td>ESR (mm in 1 hr.)</td>
<td>64.2 ± 18.7</td>
<td>58.9 ± 17.6</td>
<td>67.1 ± 19.2</td>
</tr>
<tr>
<td>CRP (mg/ml)</td>
<td>13.5 ± 9.1</td>
<td>12.6 ± 8</td>
<td>11 ± 8.6</td>
</tr>
<tr>
<td>ASO titer (Todd unit)</td>
<td>276 ± 121.5</td>
<td>260 ± 135.9</td>
<td>258 ± 137</td>
</tr>
</tbody>
</table>

\( ^p \text{value} = \text{Not significant for each parameter, ARF = Acute Rheumatic Fever; ESR : Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein; ASO = Anti-streptolysin-O.} \)

**Table 2**: Echocardiographic parameters of the study population

<table>
<thead>
<tr>
<th>Echocardiographic Dimension</th>
<th>ARF without carditis (Group-A, n-30)</th>
<th>ARF with carditis (recurrent) (Group-C, n-33)</th>
<th>Gr. A Vs. Gr. B</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDDI (cm/m²)</td>
<td>3.2 ± 0.6</td>
<td>4.53 ± 1.3</td>
<td>4.61 ± 1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVESDI (cm/m²)</td>
<td>2.51 ± 0.32</td>
<td>2.91 ± 0.90</td>
<td>2.87 ± 0.81</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LA Index (cm/m²)</td>
<td>2.30 ± 0.41</td>
<td>3.11 ± 0.90</td>
<td>3.34 ± 10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EF (%)</td>
<td>63 ± 8.1</td>
<td>58 ± 7.9</td>
<td>61.2 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Low EF (%)</td>
<td>—</td>
<td>5 (11.1%)</td>
<td>6 (18.1%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Table 3**: Distribution of heart failure and ejection fraction in patients with rheumatic carditis

<table>
<thead>
<tr>
<th>Variable</th>
<th>ARF with carditis (Group-B, n-45)</th>
<th>ARF with carditis (recurrent) (Group-C, n-33)</th>
<th>’p’ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>17 (37.7%)</td>
<td>20 (60.6%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Reduced EF with HF</td>
<td>5 (29.4%)</td>
<td>4 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Reduced EF without HF</td>
<td>0 (0%)</td>
<td>2 (15.3%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

HF - Heart Failure; EF - Ejection Fraction; NA - Not Applicable

LVEDDI = Left Ventricular End-diastolic Dimension Index; LVESDI = Left Ventricular End-systolic Dimension Index, LA : Left Atrium; EF : Ejection fraction, NA : Not applicable
myocarditis in the setting of acute rheumatic carditis. Echocardiographic studies report that LV dilatation is frequently observed during ARF, and is associated with presence of severe valvular lesions.\textsuperscript{7,12,13} Isolated LV dysfunction is not common. In a landmark study, Vasan et al, who performed echocardiographic examinations in 108 consecutive patients with ARF, demonstrated that majority of patients with rheumatic carditis had normal LV systolic function.\textsuperscript{13} HF was invariably associated with presence of haemodynamically significant valvular lesions. The present study also could not find any difference in ejection fraction between patients without carditis and patients with carditis. LV dilatation was present only in patients with significant valve lesions. Those few patients who had HF and reduced EF had haemodynamically significant regurgitant valvular lesions.

Heart failure was also not observed without the presence of significant regurgitant lesions. Gentles et al reviewed echocardiogram and clinical data in 55 patients during ARF.\textsuperscript{12} They found markedly elevated LV size and decreased shortening fraction only in patients who had moderate to severe valvular regurgitation. They concluded that mechanical factors were most important contributor to myocardial damage during and after ARF. In another significant study, Narula et al. assessed the role of endomyocardial biopsy for evaluation of acute rheumatic carditis. They did not show any significant evidence of cellular infiltration or myocardial damage.\textsuperscript{14}

Again, studies which have assessed cTnI levels in patients with ARF are sparse. The development of sensitive and specific assay for cardiac troponins has markedly improved the diagnosis of myocardial injury.\textsuperscript{15} Fetal hearts contain two cTnI isoforms: the adult cardiac isoform and an isoform similar to that found in adult slow switch skeletal muscle.\textsuperscript{16} The slow switch isoform is gradually replaced so that at birth, only the adult cardiac isoform is detectable. This serves the basis for high specificity and sensitivity of serum cTnI as a marker for cardiac injury.

In the present study, there was no significant difference for cTnI blood levels between patients without carditis and patients with rheumatic carditis, whether or not they had HF. Only 5 patients had detectable levels of cTnI and all of them had pericarditis. Pericarditis is known to cause mild cTnI elevations because of limited subepicardial myocardial cell damage.\textsuperscript{17}

Oran et al enrolled 27 consecutive patients with rheumatic carditis and 23 healthy children to assess the level of cTnI in both the groups.\textsuperscript{18} They could not find any increase in its level in patients with rheumatic carditis. Gupta et al studied the serum of 22 patients who had ARF in 1944, including 14 with carditis, and nine patients with scarlet fever.\textsuperscript{19} There was a minimal and insignificant degree of elevation of cTnI above normal levels in 18% of the patients with ARF and this was not significantly different from those with scarlet fever alone. They concluded that the absence of significant cTnI elevation throughout the course of rheumatic fever, in particular during active carditis, argues against significant cardiomyocyte injury. The present study also could not demonstrate any significant elevation of cTnI in patients with rheumatic carditis.

Whatever the mechanisms leading to development of myocarditis are, there have been few clinical investigations supporting the hypothesis that rheumatic myocarditis less likely contributes to the clinical manifestation of rheumatic carditis.\textsuperscript{18} Many patients with active carditis who undergo surgery to restore valve competence have rapid improvement. Therefore varying degree of LV dysfunction encountered preoperatively may be a sequel of severe regurgitant valve lesion rather than of a rheumatic myocardial factor itself.\textsuperscript{7}

**LIMITATIONS OF STUDY**

In the present study, ejection fraction was used an index of LV systolic function. EF is load dependent. In the presence of severe valvular lesions causing significant alterations in preload and afterload, the sensitivity and specificity of parameter such as EF may be questioned. However, in patients with apparent contractile dysfunction during ARF, surgical correction for valvular lesions (thereby normalizing preload and afterload) led to post-operative normalization of load-dependent as well as load independent indexes of LV function.\textsuperscript{7} This confirms the absence of a significant role of a myocardial factor during rheumatic fever.

cTnI was estimated in the present study at one point of time. No serial estimation of cTnI could be done because of cost factor. However, Oran et al, who have done serial estimations of cTnI could not also demonstrate any rising titre of cTnI values.\textsuperscript{18} Thus, single point estimation of cTnI does not invalidate main results of this study.

**CONCLUSION**

Acute rheumatic fever may be a rarity in developed countries. But the disease continues to affect millions of children in developing counties causing considerable morbidity and mortality. Very few studies have been done in India to elucidate the role of myocardial factor in the setting of rheumatic fever. Amidst this backdrop, the present study has attempted to unravel the contribution of myocardial factor to the clinical spectrum of rheumatic carditis. This study found that there is no clinically relevant myocardial involvement during acute rheumatic fever, even in patients with severe carditis and heart failure. This finding is in concordance with latest observations expressed by others based on clinical, echocardiographic, and pathologic observations. This lends credence to the view
that significant cardiomyocyte injury does not play any role in the genesis of severe carditis and heart failure in patients with ARF.

REFERENCES

Announcement

Suggestions are invited from members, postgraduate students regarding the areas they would like to be discussed during APICON 2008.
Rush your suggestions by 31st May, 2007 to: Dr. YP Munjal, Dean, Indian College of Physicians and Chairman CME.
E-mail: ypmicp@yahoo.com

Announcement

Nominations are invited from members of API for the Post of Editori-in-Chief - API Textbook of Medicine.
The nominations alongwith seven copies of biodata should be proposed and seconded by two members and should reach the API Office, Dr. Sandhya Kamath, Hon. General Secretary, Unit No. 6 and 7, Turf Estate, Off. Dr. E Moses Road, Opp. Shakti Mill Compound; Mahalaxmi West, Mumbai 400 011 by 30th June 2007.

Dr. Sandhya Kamath
Hon. General Secretary