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Does rheumatic myocarditis really exists? Systematic study with echocardiography and cardiac troponin I blood levels

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Aims Revised guidelines for diagnosis of rheumatic fever indicate that rheumatic myocarditis may 'contribute' to the genesis of congestive heart failure. Our objective was to assess non-invasively the presence of non-clinical markers of myocardial involvement in acute rheumatic fever.
Methods Echocardiography and assessment of cardiac troponin I (cTnI) blood levels were systematically performed in 95 consecutive patients with acute rheumatic fever, who were divided into three groups. Group 1: patients without carditis (n=22); group 2: patients with carditis and without congestive heart failure (n=59); group 3: patients with carditis and congestive heart failure (n=14).
Results Left ventricular ejection fraction was normal in all patients and did not differ between groups (group 1: 0.72±0.08, group 2: 0.69±0.06, and group 3: 0.66±0.07, p=0.09). Left ventricular diameters tend to be larger in group 3, but all patients had severe mitral and/or aortic regurgitation. Mean cTnI was 0.077±0.017 ng/ml (normal <0.1 ng/ml), did not differ between groups (p=0.45), and only 13 patients (seven with pericardial effusion) had detectable levels (0.2–0.4 ng/ml).
Conclusions Our study neither detected cTnI elevations nor echocardiographic abnormalities suggesting significant myocardial involvement during rheumatic fever. Congestive heart failure was always associated to severe valve regurgitation.

Introduction

Revised guidelines for the diagnosis of rheumatic fever[1] indicate that when rheumatic fever affects the heart, it usually involves the endocardium, myocardium, and pericardium to varying degrees. These guidelines also indicate that rheumatic myocarditis, although 'uncommon' in the absence of severe valvular damage, 'may contribute' to the genesis of heart failure during rheumatic fever.

However, the existence of a specific primary myocardial involvement contributing to the occurrence of heart failure during rheumatic fever is

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controversial. Interstitial myocardial infiltrates and Aschoff nodules have been observed in the ventricular myocardium of patients with rheumatic carditis, but significant myocyte necrosis is usually absent, even in patients with congestive heart failure;[2] therefore, with respect to the Dallas criteria,[3,4] the term 'rheumatic myocarditis' seems inappropriate. Several studies using echocardiography in patients with rheumatic fever[5–7] demonstrated that the major factor determining the occurrence of congestive heart failure during rheumatic fever is the extent of valvular lesions, as opposed to a myocardial factor. These data are in accordance with the observation that postoperative left ventricular function may normalise after valve replacement surgery in patients who had congestive heart failure during the acute stage of rheumatic fever.[5]

Cardiac troponin I (cTnI) and cardiac troponin T have recently emerged as very specific and sensitive markers of myocardial damage.[8–10] They are released by the cardiac cells in the proportion to the degree of cardiac injury. The cTnI and cTnT elevations have been reported in various types of non-ischaemic related myocardial injury and myocarditis, in adults and children.[10–12]

We performed a prospective study using Doppler echocardiography and cTnI in all the patients admitted to our institution for rheumatic fever, in order to detect non-invasively non-clinical markers of myocardial involvement during rheumatic fever, and determine whether a myocardial factor plays any clinically significant role in the genesis of heart failure during rheumatic fever.

Methods

Study population

All the patients admitted to our institution for acute rheumatic fever, who fulfilled the revised Jones criteria for diagnosis,[1] were systematically prospectively studied. Within 24 h of admission, before any treatment was administered, patients had cTnI, and standard Doppler echocardiography.

The diagnosis of rheumatic carditis was established clinically, with respect to revised guidelines.[1] The predominant effect of rheumatic carditis is valve involvement, and rheumatic carditis is defined by a new or modified cardiac murmur. Patients were divided into three groups, according to the severity of cardiac involvement: group 1 included patients without clinical sign of rheumatic carditis; group 2 included patients with clinical signs of rheumatic carditis, but without signs of congestive heart failure (mild to moderate carditis); and group 3 included patients with clinical signs of rheumatic carditis and signs of congestive heart failure (severe carditis: 'pancarditis').

From January 1999 to December 2000, 95 patients admitted to our institution for rheumatic fever were included in our study (54 males and 41 females). Their mean age was 13.4±1.2 years (4–31 years); mean body surface area (BSA) was 1.48±0.08 m^2. For 90 patients, the episode was the first reported episode of rheumatic fever, while five patients previously had one or several documented episodes of rheumatic fever. The mean delay between the first symptoms of rheumatic fever (usually fever or arthritis), and hospital admission was 11±2 days.

Twenty-two patients (23%) had no carditis (group 1), 58 patients (61%) had mild to moderate carditis (group 2), and 14 patients (16%) had severe carditis.

Troponin I blood levels

The assessment of cTnI blood levels was performed with Chiron Bayer ACS 180 chemiluminescent diagnostic test. This test is characterised by a high sensitivity, with a lower limit of detectability of 0.03 ng/ml. The upper limit of the normal cTnI value is 0.1 ng/ml.

Echocardiography

Doppler echocardiography was performed with Hewlett Packard HP 5000 machine, equipped with 2.5–5 MHz transducers. A standardised cross-sectional and Doppler echocardiographic examination was performed with multiple orthogonal parasternal, apical, and sub-costal views; particular attention was given to bidimensional and TM evaluation of segmental and global left ventricular function; left ventricular end-diastolic and end-systolic volumes were calculated according to the method proposed by Teicholz et al.[13] Mitral and aortic regurgitation were quantified using standard echocardiographic criteria, and were graded from 0 (absent) to 4 (severe). All echocardiographic studies were interpreted by experienced echocardiographists. The observers were blinded to the results of cTnI measurement.

Statistical analysis

All results were expressed as mean±standard deviation. The clinical features of the three groups of patients and their baseline echocardiographic recordings were compared with the H Kruskal and

Table 1 Clinical and biological characteristics of the population

	RF without carditis (group 1, *n*=22)	RF with carditis without signs of CHF (group 2, *n*=59)	RF with carditis and signs of CHF (group 3, *n*=14)	*p*
Age (years)	12.70±4.90	13.30±6.25	14.60±5.62	0.63
Body surface (m^2)	1.48±0.37	1.45±0.42	1.60±0.46	0.47
Hospital admission (days)	9.10±10.60	10.40±12	11.80±10.30	0.79
Body temperature (°C)	37.97±0.94	37.65±0.60	37.64±0.85	0.40
CRP (mg/ml)	8.93±5.49	8.93±6.67	13.48±9.25	0.18
Fibrin (g/l)	7.11±2.52	6.66±2.07	7.87±2.13	0.15
SR (mm)	58.17±26.14	60.70±24.64	67.15±24.65	0.37
ASTO (UI)	211.11±104.82	262.32±145.87	276.92±136.34	0.28
Anti-Dnase B (UI)	1093.15±610.86	1037.77±617.39	1170.77±652.31	0.70

RF=rheumatic fever; CHF=congestive heart failure; CRP=C-reactive protein; SR=sedimentation rate; ASTO=antistreptolysin-O.

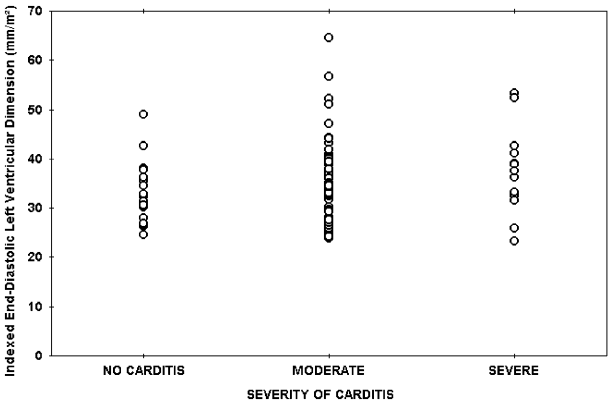

Fig. 1 Distribution of the indexed left ventricular end-diastolic dimension between the three groups

Wallis test. A *p* value of <0.05 was considered to be statistically significant.

Results

There was no significant difference concerning age, sex, BSA, delay of admission, body temperature, antistreptolysin-O (ASTO), anti-deoxyribonuclease B (Anti-Dnase B), sedimentation rate (SR), C-reactive protein (CRP) and fibrin between groups 1, 2, and 3 (Table 1).

Mean left ventricular end-diastolic and end-systolic dimensions were respectively 48.6±1.5 mm (34.6±1.6 mm/m^2 BSA) and 29.5±1.1 mm (20.9±0.9 mm/m^2 BSA) (Fig. 1; Table 2). No patient had abnormal left ventricular function as assessed by echocardiography. Mean fractional shortening was 0.39±0.01 (0.28–0.55) and mean ejection fraction was 0.69±0.01 (0.52–0.86) (Fig. 2). No patient had segmental hypokinesis. Five patients in group 3 and two patients in group 2 had pericardial effusion, but none of them had depressed left ventricular function.

All the patients in group 3 had moderate to severe aortic and/or mitral regurgitation (Fig. 3). Congestive heart failure was never observed without the presence of grade 3 or 4 aortic and/or mitral regurgitation.

Mean cTnI value was 0.077±0.017 ng/ml and 13 patients (group 1: *n*=2; group 2: *n*=7; group 3: *n*=4) had detectable amounts of cTnI, between 0.2 and 0.4 ng/ml. Only four of the 13 patients with detectable cTnI had congestive heart failure. Of these 13 patients, two in group 2, and all the four in group 4 had pericardial effusion detected with echocardiography. Maximal cTnI value was 0.4 ng/dl and was observed in two patients with pericardial effusion (one in group 2, and one in group 3). There was no statistically significant difference for cTnI levels between the three groups, with mean values of 0.064±0.028 ng/ml in group 1, 0.076±0.021 ng/ml in group 2, and 0.100±0.061 ng/ml in group 3, respectively (p=0.45).

Correlation between cTnI levels and the time of admittance to the hospital (in days) was weak and not significant (r=0.13, p=0.21), with a tendency to the increase of the cTnI with the delay in admittance (Fig. 4). The patients who had high rates of troponin I were not the patients for whom delay in admittance were the shortest. There was no significant correlation between SR and cTnI (r=−0.06, p=0.63), there was a tendency to the decrease of the troponin with the importance of the inflammatory syndrome.

There was no correlation between cTnI levels and the levels of ASTO (r=0.050, p=0.70) and Anti-Dnase B (r=0.16, p=0.15) suggesting that blood levels of cTnI are not influenced by the immune response during acute rheumatic fever.

Table 2 Echocardiographic dimensions of the three groups

Echocardiographic dimensions	RF without carditis (group 1, *n*=22)	RF with carditis without signs of CHF (group 2, *n*=59)	RF with carditis and signs of CHF (group 3, *n*=14)	*p*
LV end-diastolic dimension (M-mode)	46±12.3	47.5±12.3	57.4±18.3	<0.001
LV end-systolic dimension (M-mode)	27.1±5.5	28.9±8.3	35.9±6.9	<0.001
Left atria (M-mode)	33.5±6.5	32.5±6.1	40.6±1	0.03
LV end-diastolic dimension index, mm/m^2 (M-mode)	32.3±6.1	34.7±8.4	37.8±8.6	0.13
LV end-systolic dimension index, mm/m^2 (M-mode)	18.8±.3.7	21±4.8	23.4±4.9	<0.02
Left atrial (M-mode) index mm/m^2	23.2±3.8	23.6±5.7	26.2±5	0.17
Fractional shortening	0.41±0.13	0.39±0.10	0.38±0.11	0.22
LV ejection fraction (Teicholtz)	0.72±0.08	0.69±0.06	0.66±0.07	0.09

M-mode=motion mode; RF=rheumatic fever; CHF=congestive heart failure.

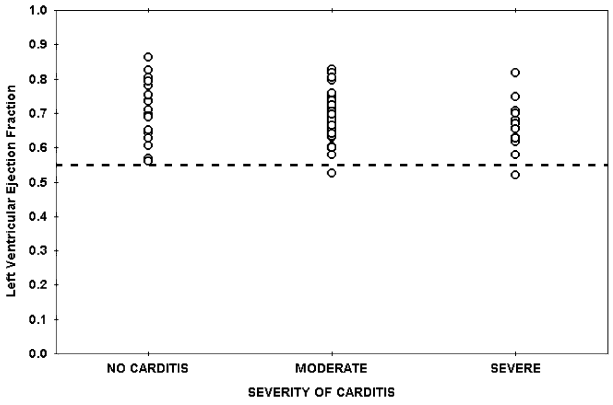

Fig. 2 Distribution of ejection fraction between the three groups.

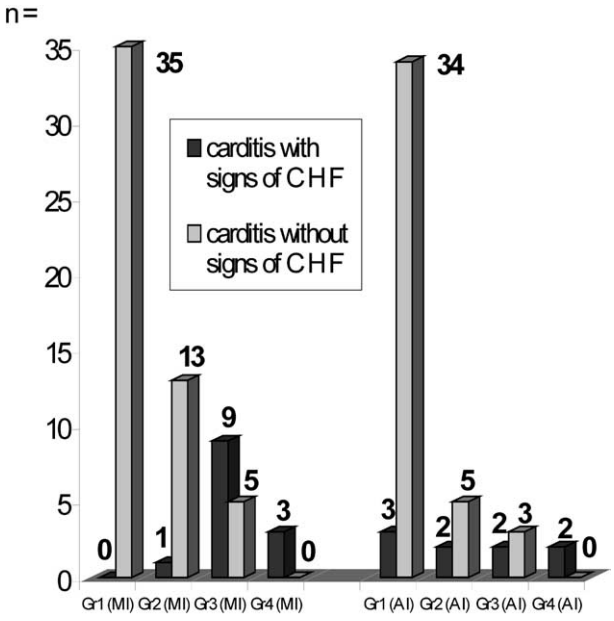

Fig. 3 Distribution of valve regurgitations in the three groups. CHF=congestive heart failure; AI=aortic insufficiency; MI=mitral insufficiency; Gr=regurgitation grade.

Discussion

In our prospective systematic study of 95 consecutive patients with rheumatic fever, we could not find any echocardiographic or biochemical sign suggesting significant myocardial involvement, even in a group of 14 patients with severe carditis and heart failure (five of whom also had pericardial effusion). In our study, the occurrence of congestive heart failure was never the consequence of left ventricular dysfunction, but always associated to severe valvular regurgitations caused by rheumatic endocarditis.

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 both endocardium, pericardium, and myocardium. Revised guidelines[1] for the diagnosis of rheumatic fever indicate 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, in disagreement with this long standing view point, most clinical studies[5–7,14] performed in patients with rheumatic fever failed to disclose signs

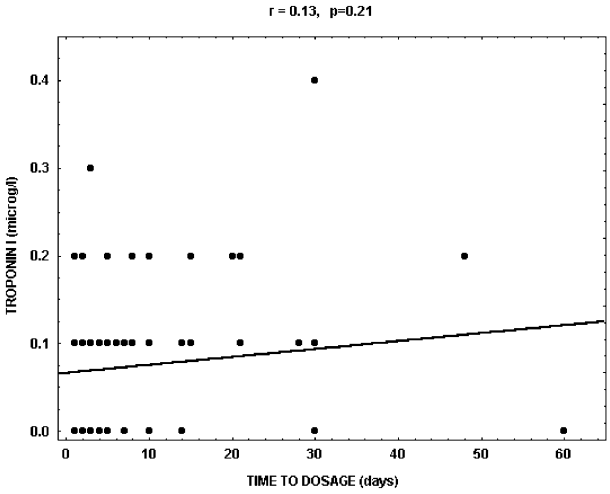

Fig. 4 Correlation between cTnI levels and the time of admittance to the hospital.

suggesting the existence of a specific rheumatic myocardial involvement.

Aschoff nodules are the histological hallmark of rheumatic fever, and have been identified in left atrial appendages[15] and ventricular myocardium of patients with rheumatic fever and rheumatic heart disease. However, the presence of Aschoff nodules in the ventricular myocardium does not signify that they play a role in the genesis of congestive heart failure during the acute stage of the disease. Rather, these nodules are mature lesions, usually observed only during the secondary phase of rheumatic fever, 2 or 3 weeks after the beginning of cardiac symptoms. In our study, the mean delay between the first symptoms of rheumatic fever and cTnI blood levels was 11 days, this being significantly shorter than the time interval usually reported for Aschoff nodules to be detected.

Narula et al.[2] studied rheumatic fever patients with endomyocardial biopsy, a very insensitive tool for the diagnosis of myocarditis. Aschoff nodules and interstitial infiltrates were observed in patients with rheumatic fever and congestive heart failure, but significant myocyte necrosis was not detected in any of these patients; the authors thus concluded that their observations argue 'against the use of the term myocarditis with reference to rheumatic fever, at least when the Dallas criteria[3,4] are applied'. Histological myocardial involvement during rheumatic fever is infrequent, limited to interstitial lesions without myocyte necrosis, and therefore has no consequence in terms of immediate contractile dysfunction and late sequelae, unlike viral myocarditis.[16]

Several echocardiographic studies[5–7,17–19] reported that left ventricular dilatation is frequently observed during rheumatic fever, and is associated with the presence of severe valvular lesions. On the other hand, isolated left ventricular dysfunction is reported to be very uncommon. In the study of Vasan et al.,[6] including 108 patients with rheumatic fever, only 10 had diminished fractional shortening, eight of whom also had haemodynamically significant regurgitant lesions. In our study, no patient had left ventricular dysfunction as assessed by echocardiography; shortening fraction and ejection fraction did not differ between patients without carditis, and patients with rheumatic carditis, whether or not they had congestive heart failure. Left ventricular enlargement was only observed in patients with severe valvular lesions, and congestive heart failure was never observed without the presence of significant mitral and/or aortic regurgitation.

To our knowledge, our study is the first prospective series reporting the systematic use of echocardiography and highly sensitive cTnI assessment during acute rheumatic fever. The cTnI blood level is now a well-established marker of myocardial injury, that has been validated in animal models of myocarditis,[20] and studied in various human clinical settings[9–12,21] (viral and toxic myocarditis). In our study, there was no significant difference for cTnI blood levels between patients without carditis and patients with rheumatic carditis, whether or not they had congestive heart failure. Maximal cTnI level observed in our study was only 0.4 ng/ml.

In 13 patients, however, detectable amounts of cTnI, between 0.2 and 0.4 ng/ml were observed in patients with and without carditis. These 13 patients did not differ significantly from the other 82 patients without cTnI elevations, with respect to clinical presentation, echocardiographic data, and severity of carditis. The very mild cTnI elevations (between 0.2 and 0.4 ng/ml) are well below cTnI values reported previously in patients with a definite diagnosis of myocarditis.[21] The cTnI release has been reported to occur in proportion to the degree of myocardial injury.[22,23] The very low detectable amounts of cTnI observed in our patients clearly reflect only minimal myocardial injury, and such minimal myocardial damage cannot explain or participate in the occurrence of congestive heart failure in any of our patients. This is consistent with the absence of congestive heart failure in nine of the 13 patients with detectable cTnI. Pericarditis may cause limited sub-epicardial myocardial cell damage resulting in mild cTnI elevation.[24] Mild pericardial effusion was detected by echocardiography in all four patients with severe carditis and detectable cTnI, and in two of the seven patients

with mild carditis and detectable cTnI. Limited pericarditis, undetected by echocardiography, may explain sub-epicardial myocyte damage with limited cTnI elevation.

Two recent retrospective studies did not find a significant increase in cTnI blood levels in patients with acute rheumatic fever.[25,26] There was no difference in repeated cTnI blood levels between 27 children with acute rheumatic fever and 23 healthy controls in the study by Oran et al.[25] Gupta et al.[26] recently studied the serum of 22 patients who had had acute rheumatic fever in 1944, including 14 with carditis, and nine patients with scarlet fever. There was a minimal, and not significant, degree of elevation of cTnI above normal levels in 18% of the patients with acute rheumatic fever and this was not significantly different from those with scarlet fever alone. The authors 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 specificity of cTnI elevation is nearly 100% for myocardial injury. However, mild false positive cTnI elevations have rarely been reported, and attributed to the presence of heterophilic antibodies, in young children after vaccinations.[27,28] In the context of huge immunologic response induced by streptococcal infection that characterises rheumatic fever, one might speculate that heterophilic antibodies[29,30] might have interfered with cTnI blood levels. In the present study, the absence of correlation between the levels of cTnI and ASTO and Anti-Dnase B suggests that the cTnI blood levels are not influenced by the immune response during acute rheumatic fever.

Nosanchuk et al.[31] showed that cTnI rate might be elevated in case of incomplete serum centrifugation. Indeed, it is possible that the antibodies can bind non-specifically to fibrin or that the indicator enzyme is physically trapped by the fibrin in the separation matrix. Because incomplete separation of serum can leave fibrin in the sample, a false increase of cTnI concentration can result. He recommends the use of the plasma rather than serum or the centrifugation of serum long enough to ensure a complete separation of the fibrin (for example on 2000×*g* during 10 min).

Study limitations

In the present study, the detection of myocardial involvement was assessed with cTnI blood levels, whose sensitivity is reported to be in the range of 0.34–0.53 for the diagnosis of myocarditis.[20] Low sensitivity is the main limitation of all the clinical studies performed in the field of myocarditis; for example, the sensitivity of endomyocardial biopsy has been estimated to be in the range of 0.20–0.30.[2]

However, we used a much more sensitive cTnI assessment than the ones used in previous studies of myocarditis; for example, the lower limit of detection and upper limit of the reference range of the assay used in the study of Lauer et al.[21] were 2.2 and 0.1 ng/ml respectively, versus 0.03 and 0.1 ng/ml in our study. The sensitivity of cTnI elevation for the diagnosis of myocarditis has also been demonstrated to be a time-dependant phenomenon, with higher sensitivity when dosages are performed early in the course of the disease, before the first month of evolution. In our study, the mean delay between symptoms onset and cTnI blood level sampling was 11 days only. We therefore believe that the sensitivity of cTnI assessment performed in our study was high; hence, the negative predictive accuracy of cTnI assessment is not expected to have significantly limited the validity of our results.

Fractional shortening and left ventricular ejection fraction are load-dependent indexes of left ventricular function. In the presence of severe valvular lesions causing significant alterations in preload and afterload, the sensitivity and specificity of left ventricular ejection and fractional shortening as markers of left ventricular dysfunction may be questioned. However, this shortcoming issue was overcome recently by Gentles et al.,[7] who studied stress—velocity index which is an afterload-adjusted and preload-independent index of myocardial contractility. This study performed in 55 patients with acute rheumatic fever demonstrated the presence of subtle degree of left ventricular contractile dysfunction in patients with severe carditis, but this was closely related to the mechanical factors, i.e. valvular lesions caused by rheumatic endocarditis, as opposed to a myocardial factor. In the rare reported patients with apparent contractile dysfunction during rheumatic fever,[5] surgical correction of valvular lesions whereby normalising preload and afterload, led to post-operative normalisation of load-dependant and load-independent indexes of left ventricular function, further confirming the absence of a significant role of a myocardial factor during rheumatic fever.

Finally, from a methodological point of view, as in any negative study, the fact that we did not observe signs of myocardial injury in our study does not strictly imply that rheumatic myocarditis does not exist. The clinical presentation of rheumatic

fever is reported to be more severe in areas of high incidence. However, the incidence of rheumatic fever in French Polynesia is one of the highest in the world,[32] and therefore, the clinical presentation of rheumatic fever in French Polynesia is expected to resemble the conditions described in the developed countries several decades ago. From our data, myocardial involvement during rheumatic fever appears to be at least very rare, and clinically irrelevant in the determinism of congestive heart failure during rheumatic fever.

Clinical implications

Our results suggest that there is no clinically relevant myocardial involvement during rheumatic fever, even in patients with severe carditis and congestive heart failure, usually diagnosed as presenting 'pancarditis' This confirms that heart failure is related only to the extent of valvular lesions. For patients with refractory congestive heart failure, valvular surgery, as opposed to inotropic support, must be considered. Chauvaud et al.[33] showed the good long-term (29 years) results of reconstructive surgery in rheumatic mitral valve insufficiency. The conservative surgery has a low hospital mortality rate and an acceptable rate of re-operation. The results are excellent regarding the minimal risk of thromboembolic events.

Long standing sub-clinical unrecognised rheumatic myocarditis[34–37] has been evoked to explain the occurrence of left ventricular dysfunction in patients with chronic rheumatic heart disease; in the absence of significant myocyte necrosis during the acute stage of rheumatic fever, our results demonstrate that this hypothesis is unlikely.

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