Pattern of rheumatic valvular involvement and its contribution towards valvular malfunction in young adults

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Abstract

Objective To study the different patterns of valvular malfunction in rheumatic heart disease (RHD) and assess the factors contributing towards it.

Methods This is an observational study among patients with chronic RHD. One hundred patients (female 81 and 19 males) within ages 12 to 40 years (Mean age 27.3) were analyzed. A relevant clinical history including that of an initial episode of acute rheumatic fever (ARF) and recurrent episodes was obtained. 2D echo assessment of the cardiac valves was performed with an estimation of Wilkins score for the mitral valve (MV).

Results Among the study population female: male ratio was 4:1. 30% had recurrent episodes of ARF. Only 60% had at least some evidence of ARF at any time in their life. The posterior mitral valve appears to be affected more than the anterior leaflet giving an average Wilkins score of 9.7 and 6.7 respectively. The total score had a positive correlation with Mitral stenosis (MS) (p<0.05). MV involvement was noted in 97%. 44% had significant mitral valve prolapse (MVP) but no statistical correlation was noted with mitral regurgitation (MR) (p>0.05). A regurgitant grade of 2 or more was found in 41%. High sensitive C reactive protein of more than 1mg/dl was noted in 55% of patients.

Conclusion Chronic rheumatic MV disease can exist as MS, MR, MVP or simply an elevated valve score. Apart from recurrent streptococcal infections and chronic subclinical inflammation, a number of different components of valve damage contribute towards the end result.

Introduction

RHD is still a disease, causing significant mortality and morbidity in the developing world. It has been estimated that there are 15.6 million people affected by RHD. And every year 23300 deaths occur attributed to RHD [1-3]. Rheumatic fever is a multisystemic autoimmune disease resulting from infection with group A streptococcus. Morbidity and mortality vary from region to region worldwide, and is high in Asia [2] including Sri Lanka. Chronic RHD cause significant valvular damage needing valve replacement and most often valve intervention. Persistent inflammatory damage and hemodynamic injury to the valve leaflets are the main contributors towards the gradual progression of the disease [4]. Key anatomic abnormalities are leaflet thickening, nodularity, calcification, and commissural fusion, although all of these eventually result in narrowing of the valve orifice, their degree of contribution may not be the same. MS progresses much more rapidly in the background of severe or recurrent infections [5]. There are several studies describing the mechanisms and manifestations of valve damage in ARF but only limited studies look into chronic RHD. There are no studies looked at the factors that favor the type of valvular damage, and only a few studies assess the pattern of valvular involvement in chronic RHD. We designed this study to identify the different types of valvular malfunctions in chronic RHD. We also looked into non-valvular and valvular factors which could influence the degree of valvular malfunction.

Valve damage was objectively assessed by means of 2D Echocardiography. Factors already known to cause or take part in progression of valve damage according to available literature were also assessed.
Methodology

Study design and setting

This is a cross-sectional study, performed over the period of March 2016 to November 2017. Participants were diagnosed RHD patients aged above 12 years and not more than 40 years of age, following the Rheumatic Clinic at the Cardiology Unit, Teaching Hospital, Batticaloa, Sri Lanka. The sample size was one hundred. The size was determined according to similar studies done in the past. Patients with other co-morbid diseases, those with acute rheumatic fever and patients who had undergone valve replacement were excluded.

Data Collection

Data collection is done by a Consultant Cardiologist, Medical Officers, and Research Assistant. Information regarding demographic details, clinical history and follow up data was collected via an interviewer-administered questionnaire, clinic notes and laboratory investigations. A 2D echocardiogram was done by a Consultant Cardiologist and recorded. Wilkins score was calculated based on an assessment of leaflet mobility, valve thickening, calcification, and sub-valvular involvement. Scores relating to the anterior mitral valve leaflet (AMVL) and the posterior mitral leaflet (PMVL) were calculated separately. Each component was graded from 0 to 4. A normal valve score will be “9” in contrast a severely damaged valve will carry a maximum score of “16”. The average of both leaflet scores was taken as the final MV score. MV area was determined according to similar studies done under data was collected via an interviewer-administered questionnaire, clinic notes and laboratory investigations. A 2D echocardiogram was done by a Consultant Cardiologist and recorded. Wilkins score was calculated based on an assessment of leaflet mobility, valve thickening, calcification, and sub-valvular involvement. Among the patients with a history of an acute episode of RHD, the prevalence of joint involvement (73.3%) and fever (71.7%) were the common clinical findings. Only one patient had documented subcutaneous nodules with fever and sore throat at presentation. Two patients had abnormal body movements suggestive of chorea, one patient didn’t have any described symptoms or signs. Forty percent of the population had no history of ARF. Around 30% of the population had evidence of recurrent episodes of ARF. Nine of them had recurrences while on penicillin prophylaxis.

Correlation between different parameters

Variables MVAT, MV pressure half time (MV P1/2t) and MV pressure gradient were transformed into normal distribution by using the logarithm of their value. Correlation between MVAT and mean pressure gradient across the mitral valve was found to have statistically significant correlation \(r = -0.755, P < 0.001\) Fig 3-B. MV P1/2t was positively correlated with MVAT \(r = 0.826, P < 0.001\), Fig. 3-A. Severity of MS detected by different means such as Trace MV area, Mean PG across MV, Pressure half time showed considerable variation in detection of severity (Fig 2). Correlation of mitral valve leaflet mobility \(r = 0.68, F(1,98) = 11.92, P < 0.001\), leaflet thickening \(r = 0.32, F(1,98) = 11.92, p < 0.005\), calcification \(r = 0.52, F(1,98) = 36.65 p < 0.001\), and sub-valvular thickening \(r = 0.66, F(1,98) = 77.51, p < 0.001\), were correlated with MVAT. Among all, immobility and sub-valvular thickening possessed the strongest correlation with MS severity. On linear regression the average mitral valve score had negative correlation with MVA Trace \(r = -0.662, p < 0.001\), and severity of MR \(r = 0.076, P > 0.05\). A Kendall’s tau-b correlation was run to determine the relationship between the average mitral
valve score and the presence of mitral valve prolapse. The relationship was weak and not statistically significant \( \tau_b = -0.077, P=0.364 \). There was a significant positive correlation noted between average valve score and severity of MS but not with MR.

The association between the presence of MVP and MR was not statistically significant \( P>0.05 \). No relationship has been observed for the presence of MVP with PMVL score or PMVL mobility among participants \( P>0.05 \).

Among the sample 94 of them had some degree of MR but only 41 of them had significant MR (Grade ≥II), 68 participants had MS, 20 participants had significant MR without MS. Patients undergoing PTMC had a statistically positive correlation with valve score \( r_s = 0.489, P<0.005 \).

**Table 1. Complete 2D Echocardiogram findings with frequencies/ percentage**

| Findings                          | n/% |
|----------------------------------|-----|
| **Severity of mitral stenosis**   |     |
| None                             | 33  |
| Mild                             | 41  |
| Moderate                         | 17  |
| Severe                           | 9   |
| **Severity of mitral regurgitation** |   |
| None                             | 6   |
| Grade I                          | 53  |
| Grade II                         | 32  |
| Grade III                        | 8   |
| Grade IV                         | 1   |
| **Severity of aortic stenosis**  |     |
| None                             | 93  |
| Mild                             | 6   |
| Moderate                         | 1   |
| Severe                           | 0   |
| **Severity of aortic regurgitation** |   |
| None                             | 54  |
| Grade I                          | 31  |
| Grade II                         | 13  |
| Grade III                        | 2   |
| **Presence of mitral valve prolapse** | |
| Yes                              | 44  |
| No                               | 56  |
| **Lateral commissural fusion**   |     |
| Not fused                        | 43  |
| Partially fused                  | 31  |
| Fused                            | 26  |
| **Medial commissural fusion**    |     |
| Not fused                        | 57  |
| Partially fused                  | 25  |
| Fused                            | 18  |
| **Tricuspid valve involvement**  |     |
| Yes                              | 10  |
| No                               | 90  |
| **Pulmonary hypertension**       |     |
| Significant TRPG                 | 33  |
| Non-significant TRPG             | 67  |
| **Presence of myxomatous mitral valve (n/%)** | |
| Involvement of heart valves in participants |   |
| MV involvement (n/%)             | 97  |
| AV involvement (n/%)             | 46  |

**Discussion**

Our study showed MS, MR, MVP, AS and AR are the usual forms of valvular malfunction in RHD. There are already known factors which could influence the progression of valve damage also noted in our study. Factors like female predominance, rural and sub urban population, where internal overcrowding is common were prominent in our population too. These were known risk factors in ARF and RHD [6,7]. Recurrent infections were documented in 30% of the population similar to previous studies [11,12]. Among these patients, the majority gives the history of defaulting penicillin prophylaxis.

A significant number of patients (40%) had no clinical event indicating a history of acute rheumatic fever in the past. This shows that these patients probably had a clinically silent acute episode. Mild or even asymptomatic ARF has been reported in the literature but not to this extent [8,9]. Clinically silent Chronic RHD is well documented [10]. Because secondary prevention is the most important factor to prevent the progression of RHD, present criteria to identify ARF needs significant amendment to detect these clinically silent patients. Our findings are also not consistent with the opinion that less severe ARF does not cause cardiac involvement [11]. In fact, there could be a lot more people within the community with Chronic RHD especially when they have clinically silent disease. Effective measures need to be proposed such as population-based 2D echocardiographic screening to identify these people for secondary prophylaxis [10].

**2D Echocardiographic pattern of valvular involvement**

Forty-six patients (46%) had AV involvement. Among these AS was detected only in 7 patients. There were no cases of severe AS. Fifteen patients had significant AR of more than Gr II (Table 1). These findings are similar to previous studies [10, 13].

As the mitral valve is the commonest target for RHD, the focus of this study was an in depth assessment of the mitral valve. MS with commissural fusion and MR were the clinically important end results of MV involvement. Since MVP is also a known feature of chronic RHD [14], MVP and its impact on MR was also assessed. Wilkins score was used to assess the severity of MV involvement [15], even though the Wilkins score was originally...
formulated to assess the suitability of percutaneous mitral commissurotomy (PTMC), we considered it reasonable to use this score as it covers the major anatomical features of valvular involvement.

We found that the PMVL encountered significant damage when compared to the AMVL (Average score of AMVL: PMVL = 6.7:9.7), (Fig 1). This could be due to the different morphology of the PMVL compared to AMVL, at the same time predilection of PMVL compared to the AMVL in RHD cannot be excluded. MS is a well-documented sequel of RHD. The majority had only mild or moderate MS (58%) in the study group. This could be due to the fact that, patients with severe MS had undergone PTMC, Mitral valve replacement or died due to complications of severe valve involvement.

While assessing the severity of MS usually the trace MV area is considered more accurate than MV P1/2t or PG. Among both of these measurements, we found that MV P1/2t (r = 0.826) correlated better with traced values than PG (r = 0.755). In situations where tracing the valve became difficult such as poor windows, severely fibrosed or calcified valves where edges are too difficult to define, MV P1/2t is more desirable than PG (Fig 3).

More than half of the population had partially or completely fused commissures and this was one of the significant factors which promote clinically significant valvular damage in the form of MS. Immobility and sub-valvular thickening had a strong correlation with severity of MS. Both these parameters should be given more weight on predicting future MS. There was also a significant positive correlation noted between the average valve score and severity of MS but not with MR. There could be several other anatomical factors involved in the manifestation of MR not merely a severity of the valve damage. Isolated MR in patients with a history of RHD is well documented in the literature [16, 17]. Significant MR (Grade ≥II) alone without MS was detected in 20 patients. Only one had very severe MR (Grade IV). Severe regurgitation (Grade III, IV) is much low compared to severe MS. MR is a prominent finding in acute RF than MS. Mainly due to annular dilatation and MVP [22].

We found a significant population with MVP(44%), (Table 1) of AMVL. This could be due to immobility of PMVL, shortening of the PMVL chordae, and possibly due to elongation of AMVL chordae as in ARF [22]. They might progress to MR later years. Follow-up studies are needed to assess the fate of MVP. But in our study no statistically significant relationship of MVP and the presence of MR was noted (P>0.05) unlike in ARF [22]. This could be due to the fact that with time AMVL prolapse is reduced due to shortening of chordae so the MR simply could be due to mal-coaptation rather than MVP in chronic RHD patients. Progressive PMVL damage could be a causative factor for MVP, and MVP does not appear to be responsible for or act as a precursor of progressive MV damage.

### Inflammation and valve damage

There is documented evidence to show that there is a progressive immune response in the chronic phase of RHD [18]. There is also evidence to say that oxidative stress, hsCRP could be involved in the pathogenesis of rheumatic heart valve disease [18, 19, 21]. Persistent elevations of CRP has been noted in chronic rheumatic heart valve disease [20].

Evidence of chronic inflammation was checked by measuring C-reactive protein (CRP) and hsCRP. High CRP or hsCRP (>1mg/L) was noted in 56.8% of subjects out of 88 patients in which hsCRP was measured. But no statistically significant correlation was found between the CRP and severity of MS(r = 0.172, P>0.05), presence of MVP (r = -0.07, P>0.05), presence of commissural fusion (Lateral commissure: r = 0.07, P>0.05, medial commissure; r = 0.12, P>0.05) or the total valve score. Effects of persistently elevated CRP and valve damage needs to be observed in long term follow-up.

Interestingly the level of hsCRP was significantly lower in patients who had undergone PTMC when compared to the rest of the population (Table 3). This favors the fact that turbulent flow due to a damaged valve could be the major factor, which leads to progressive fibrosis, thickening, and calcification. Hemodynamic turbulence could be the cause for the persistent subclinical inflammation, with PTMC gradient across MV is reduced significantly. hsCRP also appears significantly higher in patients with multi-valvular involvement indicating an excess of subclinical inflammation [20].

| Table 2. Presence of MVP and MR |
|---------------------------------|
| MR | No MR | Grade I | Grade II | Grade III | Grade IV |
|----|-------|---------|----------|-----------|----------|
| MVP present | 2 | 23 | 15 | 3 | 1 |
| No MVP | 4 | 30 | 17 | 5 | 0 |

| Table 3. PTMC vs CRP (PTMC – Percutaneous trans mitral commissurotomy; CRP – C reactive protein) |
|-----------------------------------------------|
| CRP/ hsCRP | <1mg/L | 1-3mg/L | 3-10mg/L | >10mg/L |
| PTMC Done | 8 | 8 | 4 | 0 |
| Not done | 30 | 16 | 17 | 6 |
Figure 1. Frequencies of mitral valve score. Left: AMVL (Anterior mitral valve) score, Right: PMVL (Posterior mitral valve) score, Bottom: Average MV (mitral valve) score.

Figure 2. The severity of MS (Mitral stenosis) detected via different techniques (Trace MV area, Mean Pressure Gradient across MV, Pressure half time (MV P1/2t)). Frequency of participants with A- Normal MVA (Mitral valve area), B- Mild MS, C- Moderate MS, D- Severe MS.
The statistically positive correlation of PTMC with valve score \( (r_{s} = 0.489, P < 0.005) \) could be the result of mechanical damage which heals by fibrosis and scarring without persistent inflammation. Usually, PTMC is attempted in patients with a Wilkins score of less than or equal to eight. Inflammatory markers just after PTMC might give a clue of post-PTMC healing and scaring.

In addition to factors like recurrent streptococcal infection, valvular changes identified by 2D echocardiography and subclinical inflammation have some influence on valvular malfunction. A detailed prospective study would shed more light on these issues.

**Conclusion**

The subclinical nature of the acute and chronic stage is the major challenge in identifying patients with RHD. One needs to consider MS, MR, MV score and MVP separately in assessing the severity of rheumatic MV disease. Relatively high score of PMVL, presence of MR, AR and MVP might help to identify the RHD patients in routine 2D Echocardiogram in the age group of 12 to 40 years. hsCRP would help as a blood investigation in this aspect. Commissural fusion, sub-valvular involvement, and immobility of leaflets are other factors which could predict future significant MS. Factors producing a MR in Chronic RHD needs further investigation.

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**Conflict of interests**

The are no conflicts of interest. No financial support was obtained for this study.

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