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RESEARCH ARTICLE

Echocardiographic assessment of morphofunctional and hemodynamic changes of rheumatic mitral valve dysfunction in the young.

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ABSTRACT

Background- Rheumatic fever and its sequel rheumatic heart disease remain a major health problem across the globe. This investigation aims to analyse the mitral valve morphofunctional changes, stratified by severity, and the magnitude of the mitral regurgitation and stenosis through a simplified echocardiographic scoring system in patients with rheumatic heart disease.

Methods- As cross-sectional echocardiographic study was carried out in 98 consecutive patients with confirmed rheumatic heart disease. Patients undergoing outpatient clinical care over an 18-month period (mean follow-up period of 9,7±2,9 years) were selected for echocardiographic investigation. After a double-blind echocardiograms review, the inter-rater reliability was calculated (Kappa=0.875 (0.775- 0.974; CI 95%). The morphofunctional data of mitral apparatus were scored on a rating scale from one to fifteen, encompassing three categories (1-5: mild; 6-10: moderate; 10-15: severe) to quantify the degrees of severity. Pearson's Chi-squared test with Yates' continuity correction were performed for comparative analysis and the Wilcoxon test and the Cliff's Delta effect size was calculated to examine differences related to morphological features.

Results- The majority of patients had rheumatic heart disease with clinical evidence and twenty patients (20,4%) had subclinical disease.The thickening of both mitral valve leaflets and the restrictive motion of the posterior leaflet were most frequently found in contrast with the low percentage of chordal and/or commissural fusion. The degree of the anterior mitral valve leaflet thickening was proportional to the magnitude of the mitral valve regurgitation (p=0.021). The higher degrees of mitral valve dysfunction were associated with more severe carditis (mitral valve regurgitation, p: 0.000; mitral valve stenosis, p: 0.031). No association was found between the severity of valvular lesions and patient age or length of the disease (p=0.320). The presence of beading was only observed in the acute phase (p=0,000); coaptation defect of the mitral valve was associated with significant left ventricle enlargement (p=0.000). The morphofunctional score of mitral apparatus, stratified by severity, was associated with the magnitude of mitral valve regurgitation (p=0,000) and of mitral valve stenosis (p=0,031) also quantified by severity. The highest scores were observed in patients with the most severe degrees of carditis (p=0,000); however, no association was found with either, the patients' age (p=0.373) or the duration of the disease (p=0.361).

Conclusions- In the analysis of severity of the mitral apparatus deformities and the resulting valve dysfunction, the morphofunctional score stratification was highly associated with the magnitude of mitral regurgitation and stenosis. In this young cohort, the higher scores were associated to severe carditis, but not to the patients' age or the duration of the disease. Taking into account the low prevalence of severe valve dysfunctions, these results highlight the importance of early intervention and adequate prevention.

Keywords: rheumatic heart disease; acute rheumatic fever; screening; echocardiography; valve dysfunction.

Introduction:

Technological progress and advances in the diagnosis and treatment of congenital and acquired heart diseases in children are becoming more intense and extensive, but neglected diseases continue to be a major challenge for those involved in providing health care[1]. Acute rheumatic fever (RF) and its sequel, rheumatic heart disease (RHD), remain a significant health problem across the globe. The frequency of RF and RHD has been markedly reduced in high-income countries since the 1950s. Although preventable, the disease still persists in low- and middle-income countries and represents the most common acquired heart disease in children and young adults under 25 years[2]. Recent estimates include up to 40.5 million prevalent cases, loss of >10 million disability-adjusted life-years and 306,000 deaths yearly worldwide[3,4]. The REMEDY study encompassing children and adults with RHD from 14 low-and-middle-income countries has shown high morbidity and mortality. In spite of their young age, a high prevalence of major cardiovascular complications was seen among the patients enrolled in the investigation. The mortality rate in the first 12 months was 116.3/1000 patient-years with a median age at the time of death of 28.7 years[5].

Estimated rates of progression from RF to RHD range from 60 to 70% of the cases[6-8]. The primary episode of RF is almost always seen in childhood; however, the cardiac sequels involve all age groups with its clinical and social repercussions. The economic impact of clinical and surgical treatments, in addition to loss of productivity are a consequence of a disability acquired at an early age. In this regard, an important determinant of disease progression, if not the main one, is the recurrence of acute episodes resulting from lack of prophylactic intervention and environmental risk factors. The worsening of previous valvar lesions or the appearance of new ones is expected with each recurrent episode. In most patients, the primordial episode is not recognized. In these cases, as mild and moderate valve dysfunction in young people are more often asymptomatic, which can also sometimes occur even in severe valvar lesions, the diagnosis is frequently made when advanced RHD has already developed. Therefore, accurate diagnosis in the early stages of the disease and the introduction of secondary prophylaxis prior to the advanced stages of the disease are essential strategies to reduce morbidity and mortality.

The pooled prevalence of RHD detected by echocardiography is about seven to eight times higher than that detected by cardiac auscultation[9,10]. In this context, echocardiography has emerged as the most important tool for an accurate diagnosis of both RF and RHD and plays an invaluable role in recognizing the early stages of the disease, the subclinical rheumatic carditis, subclinical and mild clinical RHD. The World Heart Federation (WHF) has recently published an updated version of the criteria for echocardiographic diagnosis of RHD (2023 WHF guidelines)[11]. A new classification system for RHD based on echocardiographic findings and risks of the disease progression has been introduced. Additionally, a two-step updated set of echocardiographic criteria, screening and confirmatory criteria, has been developed to provide greater sensitivity. Two

morphological categories of the mitral apparatus pathological process, the thickening (leaflets and tendinous chords) and abnormal motion (restricted and excessive), have been included in the confirmatory criteria. Taking into account that mitral regurgitation is a non-specific lesion, the search for morphological changes in the diverse segments of the valve structure becomes essential for the definitive diagnosis of RHD on echocardiographic examination. The valvar morphological changes are a consequence of fibrous scaring and healing of the inflammatory process. Overall, they are represented by characteristic features such as the thickening of the components of the mitral valve (MV), abnormal motion of leaflets, abnormal tendinous chords length, commissural and chordal fusion, besides the coaptation defect.

In the scenario of early cardiovascular morbidity and mortality, we have witnessed over the last decade reinvigorated regional initiatives, directives from international institutions[12]. such as the World Health Organization, WHF, American Heart Association and the European Society of Cardiology, besides a renewed interest in research, a set of involvement and commitment actions to face the global burden of RHD. This investigation aims to analyse the morphofunctional changes of the mitral apparatus, stratified by severity, and the magnitude of the mitral regurgitation and stenosis through a simplified echocardiographic scoring system in patients with RHD.

Methods

PATIENTS, SETTING AND FOLLOW-UP

This cross-sectional echocardiographic study was carried out in 98 consecutive patients with confirmed diagnosis of RHD and regular compliance to the follow-up protocol. Since inclusion in the Programme of Prevention and Control of RF and RHD-Universidade Federal de Minas Gerais (UFMG), all patients were followed up on a regular basis every six months for at least 2 years after the diagnosis of RHD (mean follow-up period: 9,7 ± 2,9y) at the Paediatric Outpatients' Clinic of RF and RHD- Hospital das Clínicas (HC). This reference centre is integrated into the existing public health infrastructure for the state of Minas Gerais (Brazilian state with 0.59million km^2, 853 municipalities, and 19.6 million inhabitants)[13]. For admittance into the programme, it has been considered an age up to 18 years old and for the follow-up, the patients have been seen up to 24 years old when they are referred to the Adult Clinic, where the same medical record is used for the follow-up. Among the patients undergoing outpatient clinical care over an 18-month period those who met the inclusion criteria, were invited to participate in the echocardiographic investigation, regardless of the time and number of previous exams. Patients who underwent previous surgical interventions and those whose historical data could not be accessed were excluded. The diagnosis of recurrences was based on the revised Jones criteria[14]. Carditis was classified as mild, moderate and severe according to the protocol of the Division of Pediatric Cardiology/HC/UFMG[15]. Benzathine benzylpenicillin (BPG) for secondary prophylaxis was administered every 4 or 3 weeks, depending on the risks of recurrence or adverse consequences with a new acute episode. Written informed consent and assent were obtained from patients and/or families.

The study was approved by the UFMG Research Ethics Committee.

ECHOCARDIOGRAPHIC INVESTIGATION

Echocardiographic imaging was performed with Transthoracic Doppler Echocardiography (ACUSON Cypress Cardiovascular System PLUS 2010, portable and complete cardiovascular applications, with transducer V2c TTE, 2-4 MHz phased array).A standardised cross-sectional and Doppler echocardiographic examination was performed with multiple orthogonal parasternal, apical, and subcostal views. All echocardiograms were performed by a member of the paediatric cardiology team (Capuruço, C) and recorded for further analysis. The echocardiograms were reviewed and re-reported by two paediatric cardiologists with expertise in RHD (Mota, C and Meira, Z). Variables related to clinical assessment, historical data and demographic/ epidemiological information were included to characterize the study group. Echocardiographic analysis encompassed morphological, functional and hemodynamic variables. The anterior MV leaflet (AMVL) thickness measurements were performed in the parasternal long axis imaging, late diastole, with the leaflet at the maximal excursion and at the midpoint and tip, without harmonics. A thickness ≥ 3mm was defined as the cut-off value for pathological thickening. Due to the difficulties in obtaining accurate measurements, only a subjective evaluation has been made for the posterior MV leaflet (PMVL) and tendinous chords. Beading was defined as the focal nodules along the leaflets surface *presenting a beaded* appearance and irregular thickening as an irregular echo-dense aspect of the entire body of the leaflet, mainly at the tips. Considering the difficulties in obtaining accurate measurements of irregular valve thickening, a different number of patients were enrolled for specific assessments. The degree of severity of the MV regurgitation and stenosis, classified as absent, mild, moderate, or severe, were based on previously published recommendations[16,17]. All echocardiographic data were reviewed according to the WHF 2023 criteria[11] and previous exams and reports were also re-assessed. In addition to the classification of hemodynamic and functional data, a consensus was reached to quantify the severity of MV morphological changes in patients with RHD. The MV morphological and functional abnormalities, represented by enlarged left-side chambers and pulmonary hypertension, were scored on a rating scale from zero to fifteen, created especially for this investigation.

STATISTICAL ANALYSIS

All data were systematically recorded in preformed data collection form. The statistical analysis was performed using the SPSS 21 software. Continuous variables were expressed as means with standard deviations or as medians and categorical variables as frequencies and percentages, reported with a 95% CI. Cohen's kappa (κ) statistics was used to evaluate the inter-rater reliability. Pearson's Chi-squared test with Yates' continuity correction was performed to test the association between the MV morphofunctional score and the following variables: severity of MV dysfunction, severity of carditis, patient age and the duration of the disease, defined as the period of time between the first acute episode and the echocardiographic screening. A Wilcoxon test was performed and Cliff's

Delta effect size was calculated to examine differences in BMI and age in relation to the severity of valvular dysfunctions. A *P* value <0.05 was considered statistically significant.

Results

Out of 298 consecutive patients (782 appointments) seen in the Outpatients' Clinic of RF and RHD during a period of 18 months, 98 patients met the criteria for participation in this study and were selected for echocardiographic investigation. The patients were followed by the same team of paediatric cardiologists over a period ranging from 2.0 to 13.1 years (mean: 9, 70 ± 2, 9 years). The age at the echocardiographic screening ranged from 5.2 to 21,0 years old (mean: 11.2± 2.7 years).

Table 1- Clinical and epidemiological information according to the historical data (n=98)

First episode (mean age)	9.2 ± 2.9 years
Duration of the disease (mean: 8.00 ± 5.8years)	n (%)
1-5 years	39 (39.8)
6-10 years	29 (29.6)
> 10 years	30 (30.6)
Recurrences	7 (7.1)
Distribution according to the clinical evidence	
RHD (clinical evidence)	71 (72.5)
RHD (clinical evidence and recurrence)	7 (7.1)
Subclinical RHD	20 (20.4)

Male: 50.9%; Female: 49.1

At the time of echocardiographic screening, out of 98 patients, 68 (69.4%) had less than 10 years of evolution since the first acute episode. Twenty patients (20.4%) had subclinical RHD. The group RHD with clinical evidence encompassed 7 patients with recurrences, 3 of which occurred during the period of selection for echocardiographic screening (Table 1). Out of the 5 patients who underwent valvular surgery, 4 had already presented recurrences prior to admission to the Prevention Program, and all of them were excluded from this study.

Isolated or mixed MV dysfunction was seen in 94.8% of patients. Concerning the pattern of distribution of the valvar lesions, isolated mitral regurgitation was the most prevalent (47, 5%) and aortic regurgitation was most often found concurrently with the involvement of the MV (45,2%). Association of MV stenosis and regurgitation did not represent a common finding in our cohort (6.3%). Mild aortic stenosis was found in one 16-year-old patient. Regarding the classification of the degree of valve dysfunction, 16.1% of patients had severe valve lesions. No association was

found between the severity of valvar lesions and patient age or the duration of the disease as stratified in three periods (p= 0.320). The higher degrees of MV dysfunction in the chronic phase were associated with a more severe cardiac involvement during the acute phase (MR, p: 0.000; MS, p: 0.031).

Table 2- Abnormal morphological features of mitral valve (n=67)

Morphological features	n	%
AMVL diffuse thickening (≥3mm)	47	92.2
PMVL diffuse thickening	38	74.5
AMVL and/or PMVL focal or irregular thickening (≥3mm)	25	49.0
Beading	2	3.9
Restrictive motion*	39	76.5
Dog leg	24	47.0
Chordal thickening	19	37.0
Chordal lengthening**	13	25.5
Chordal and/or commissural fusion	2	3.9
Chordal rupture /flail	2	3.9
Coaptation defect	5	9.8

AMVL: anterior mitral valve leaflet PMVL: posterior mitral valve leaflet

*Anterior or posterior leaflet (diastole)

** Excessive anterior leaflet tip motion (systole)

Table 3- AMVL thickness according to the degree of mitral regurgitation (n=67)

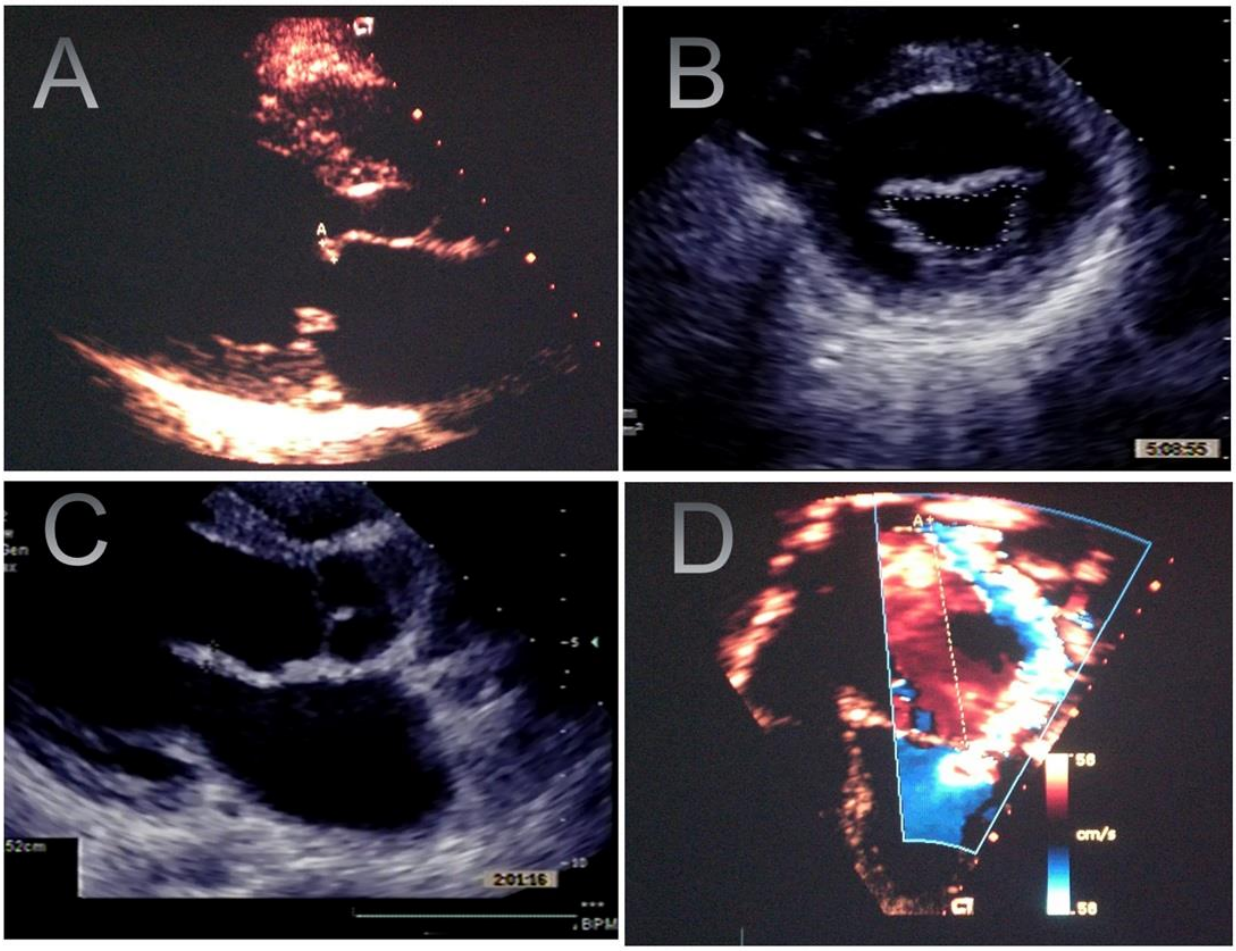
AMVL Thickness (mm)	Total	Absent	Mild	Moderate	Severe
mm)	n (%)	n(%)	n(%)	n(%)	n(%)
< 3,0	3 (4.5)	-	3 (4.5)	0	0
3,0 < 4,0	28 (41.8)	1 (3.6)	20 (71.4)	7 (25.0)	0
4,0 - 6,0	29 (43.3)	0	15 (51.7)	8 (27.6)	6 (20.7)
>6,0	7 (10.4)	0	0	1 (14.3)	6 (85.7)

p =0.021 AMVL thickness: mean= 4.4 ± 1.3mm (median: 4.2mm)

Inter-reviewer agreement of diagnosing definitive RHD and the specific assessment to the morphological changes was almost perfect with a κ (inter)=0.875 (0.75- 0.974 CI 95%). The diffuse or irregular thickening of both MV leaflets and the restrictive motion of

the PMVL were most frequently observed (Figures 1). Out of the 38 patients presenting mild mitral and aortic valves regurgitation, the AMVL measurement in 3 (7.9%) of them showed normal values. Another patient with aortic regurgitation presented AMVL thickening but no mitral valve regurgitation. The higher frequency of chordal thickening and excessive movement of the AMVL tip contrasted with the low percentage of chordal and/or commissural fusion (Figures 1 and 2). In half of the patients an irregular thickening with echo-dense aspect was observed. Comparing the AMVL thickness with the severity of MV dysfunction, the degree of the leaflet thickening was significantly associated with the magnitude of the regurgitation (Table 2 e 3).

Figure 1- Echocardiographic images of morphological changes of mitral valve apparatus and mitral regurgitation in rheumatic heart disease.



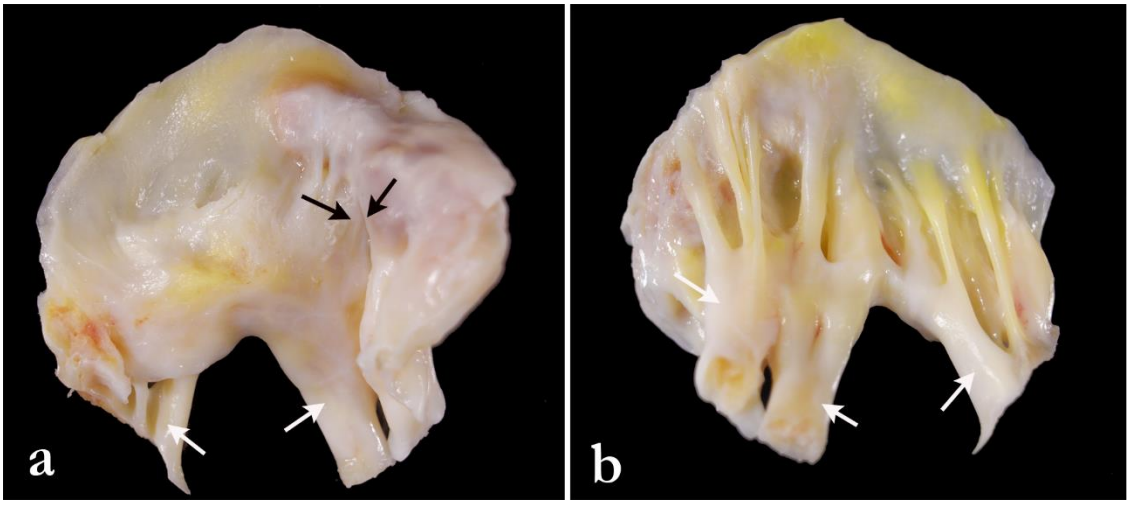
A- The parasternal long-axis view shows thickening of both mitral leaflets, fixed posterior leaflet and fusion of tendinous chords.

B- The parasternal short view shows beading on the atrial surface of mitral valve in a 9-year-old patient with rheumatic heart disease and recurrent acute episode.

C- The parasternal long-axis view shows irregular thickening of mitral leaflets and tendinous chords.

D- The apical four-chamber view shows dilatation of left-sided chambers, mitral regurgitation and Coanda effect on color Doppler jet.

Figure 2-Illustrative gross view of a surgical specimen from a patient with chronic rheumatic mitral valvar disease.



On panel a) we see the atrial aspect of the valve, showing the anterior leaflet and part of the mural one with diffuse and irregular thickening and commissural fusion (between black arrows). Panel b) shows the ventricular aspect of the valve, with shortened and fused cords (white arrows). The cordal alterations are also appreciated in panel a) (white arrows).

Taking into account the distribution of patients into three categories as shown in Table 1– RHD subclinical (1), RHD with clinical evidence with (2) and without recurrences (3) – beading was seen in two patients included in category 2, both in the acute phase, during recurrences (Figure 1). Pericardial effusion was more frequent during the acute episodes than in the chronic phase (p=0,000). A normal ejection fraction was seen in all patients. In the evaluation of 36 patients with an enlarged left ventricle, stratified into three categories –mild, moderate and severe – the presence of coaptation defect of the MV was highly associated with significant degree of the left ventricle enlargement (p=0,000).

Table 4- Quantification of severity of the mitral valve morphological/functional features

ECHO features / score	1	2	3
AMVL and/or PMVL thickening	Mild	Moderate	Severe
Restrictive and/ or excessive motion of leaflets	Mild	Moderate	Severe
Chordal and /or Commissural abnormalities	Chordal thickening ECHO-dense with irregular thickening	Commissural and/or chordal fusion	Chordal rupture / flail
Deformity of leaflets		Dog leg	Coaptation defect
Functional abnormalities (↑chambers – PH)	Mild	Moderate	Severe/ PH

Score: 1-5→mild; 6-10 → moderate; 10-15 → severe PH: pulmonary hypertension

The quantification of morphofunctional data included five groups of morphological and functional variables and three degrees of severity: mild (score 1, 1st column), moderate (score 2, 2nd column) and severe (score 3, 3rd column) as showed in Table 4.

Table 5- Morphofunctional score, stratified by severity, according to the degree of the mitral regurgitation (n=93)

Score	n(%)	Mitral regurgitation [n (%)]			
		Absent	Mild	Moderate	Severe
ZERO	6 (5.5)	3 (50.0)	3 (50.0)	0	0
1-5	63 (67.7)	1 (1.8)	47 (74.5)	15 (23.7)	0
6-10	13 (14.0)	0	2 (15.4)	7 (53.8)	4 (30.8)
>10	11 (11.8)	0	0	0	11 (100)

p=0,000 Score: 1-5→mild; 6-10 → moderate; 10-15 → severe

Table 6- Morphofunctional score, stratified by severity, according to the degree of the mitral valve stenosis (n=93)

Score	Total n(%)	Mitral stenosis [n (%)]		
		Absent	Mild	Moderate
ZERO	6 (5.5)	6 (100.0)	0	0
1-5	63 (67.7)	62 (98.4)	1 (1.6)	0
6-10	13 (14.0)	11 (84.4)	1 (7.8)	1 (7.8)
>10	11 (11.8)	7 (66.7)	3 (25.0)	1 (8.3)

p=0,022 Score: 1-5→mild; 6-10 → moderate;10-15 → severe

Mild and moderate degrees of MV regurgitation were seen in 83.9% and mild and moderate MV stenosis in 7.2% of the patients. No patient showed severe MV stenosis. The degree of the morphofunctional score was associated with the magnitude of MV regurgitation (p=0.000) and stenosis (p=0.022), both quantified by severity (Tables 5 and 6). The morphofunctional score, stratified by the severity of changes in the chronic phase (RHD), was also compared to the degrees of cardiac involvement during the acute phase (RF), classified as absent, mild, moderate and severe carditis. As the previously mentioned association between significant valve dysfunction and severe carditis, the highest scores were highly associated with the most severe degrees of carditis (p=0,000). Likewise, no association of the score was observed with either, the patient age (p=0,373) or the length of the disease (p=0,361).

Discussion

The process of valve deformation which might ultimately lead to valvar dysfunction in patients with RHD take time to develop. It is a pathological consequence of inflammation but the underlying mechanisms are not fully understood. The inflammatory process remains active even in the late course of valvular dysfunction and presents a dynamic pattern of progression according to the duration of the disease. On the other hand, it

should also be considered that mild and moderate valvular lesions in patients undergoing intervention may regress or stabilize. Therefore, according to the methodological approach of this cross-sectional study and taking into account the aims of this investigation, the characterization of the clinical profile of the study group, in addition to demographic and epidemiological aspects, resulted in exclusion of a large number of patients before proceeding with the analysis of morphological changes in VM and their interconnections.

CHARACTERIZATION OF THE CLINICAL PROFILE OF THE STUDY GROUP

In this cohort, characterized by the inclusion of young individuals, 69.4% of patients presented less than 10 years of evolution after the primary episode (mean length of the disease: 8,0± 5,8 years) and 83.9% had mild or moderate valvar lesions; however, the RHD classification in patients with moderate-grade obstructive valvar lesions should be considered significant from a prognostic point of view. In contrast to the absence of severe MV stenosis, a mild aortic stenosis associated with mitral and aortic regurgitation was found in one 16-year-old patient. Another local investigation encompassing 702 patients followed up at the Outpatients' Clinic of RF and RHD, HC-UFMG, did not find any patients with aortic stenosis[13]. Like the involvement of MV, the aortic valve disease in the young is also characterized by regurgitation, while mixed aortic lesions become more common by the second decade of life. Nonetheless, a more accelerated course with severe mitral and aortic valvar stenosis has been reported in sub-Saharan and Indian regions in patients under 16 years old[18- 20]. Several causes have been suggested to explain this rapid progression, such as inadequate secondary prophylaxis and repeated recurrences, besides persistence of predisposing factors to RF.

No association was found between severe valvar dysfunction and patient age or length of the disease. Although this investigation encompassed young patients, other factors should be considered in this analysis as the regular follow-up (mean: 9, 7 ± 2,9 years) with close monitoring and high compliance to prophylaxis resulting in low frequency of recurrences. Additionally, more severe degrees of MV regurgitation and stenosis (RHD) were associated with severe carditis (RF) in our cohort. The control of recurrent acute episodes by means of high BPG adherence has been reported to be effective in reducing the risk of progression and improving outcomes[13,21-23]. From this perspective, the asymptomatic patients diagnosed as mild to moderate RHD are those who will be more favoured by penicillin prophylaxis[24]. Early RHD has shown a dynamic and heterogeneous evolution and important data on the risk factors for its progression have been gathered in longitudinal studies[6,23-28]. According to the 2023 WHF guidelines, mild RHD are classified as "Stage B". On the basis of risk score, these patients are at moderate or high risk of disease progression and at risk of developing symptoms[11]. Several factors such as a higher duration of the disease from diagnosis, increasing age and administration of secondary prophylaxis besides the presence of aortic and mitral valves abnormalities were described as determinants for the stability or progression of the RHD[26,29]. In this context, patients with mild disease are the most stable

and approximately two thirds of the valvar lesions remain mild over the time. The group with moderate RHD is the most dynamic and the evolution is equally distributed for regression, stability or progression of the disease[6]. These conditions warrant prospective investigation, as questions regarding their long-term outcome remain to be answered.

On the other side, greater progression rates and poorer outcomes have been reported in patients with moderate to severe RHD in comparison to those with mild disease[6,7,8,25,30]. RHD usually develops in the years after the acute RF, but previous acute episodes are recognized only in 30 to 50% of cases, probably due to subclinical or undetected mild clinical disease[10]. After having been undiagnosed for long, patients often seek medical attention with symptoms due to significant valve dysfunction. In these circumstances, the opportunity for an early prophylactic intervention is missed. Advanced RHD usually results from cumulative valvar damage related to recurrent acute episodes and also from hemodynamic compromise as a consequence of the distorted valvar anatomy. In addition, severe carditis has been considered a risk factor for the progression of RHD to more advanced stages. No regression of severe RHD has been observed in patients with a significant cardiac involvement during the acute phase[8]. More severe carditis has been seen in recurrences than in primary episodes, and they have also been pointed out as a risk factor for more significant cardiac sequels [13]. Regarding the association between the higher degrees of MV dysfunction and more severe cardiac involvement during the acute phase, the morphofunctional score was also applied in this analysis and demonstrated good performance with similar results. The highest scores were found in patients with the most severe degrees of carditis.

MORPHOLOGICAL CHANGES OF MITRAL VALVE AND INTERCONNECTIONS

Within the concept of an ordered cascade of events, the morphological changes are progressive and interconnected with functional and hemodynamic disturbances throughout the evolution of the disease. From this perspective, the morphofunctional score, stratified by severity, may be a potential tool to add information in categorizing the severity of RHD throughout patient follow-up. Dysfunction of the MV may also represent specific conditions, such as congenital anomalies, annular calcification, bicuspid aortic valve and non-specific lesions, secondary to various diseases. In this context, the changes in the valvar morphology, according the 2023 WHF guidelines became a condition for the confirmatory echocardiographic diagnosis of RHD[11]. The morphological features are the expression of valvar deformity which in turn results from the underlying inflammatory process during the acute phase (Figure 1 and 2). Nonetheless, the intralesional mononuclear cells produce inflammatory cytokines even in the chronic phase[31]. After an acute episode, the damage initiated at the line of closure of the leaflets may extend to the tendinous chords. Throughout the progression of the disease, the morphological changes can occur simultaneously in the same segment or co-occur in more than one segment of the valve apparatus. The continuous process of scarring and deformation leads to valve dysfunction. In patients with RHD, the MV leaflets usually

show a diffuse thickening, dense fibrosis and neovascularization[15]. Diffuse thickening of the MV leaflets was described as a universal feature in patients with an established RHD and in 40% of those with a first episode of carditis[32]. The PMVL retraction can be seen at the early stage of regurgitation[15]. After dilatation of the posterior annulus and functional retraction of the stretched PMVL, the area of apposition of the valvar leaflets decreases[33]. Rheumatic mitral regurgitation results from incomplete coaptation caused by thickening of leaflets and chordal shortening that leads to restrictive movement of leaflets in systole[34]. Diffuse thickening of the leaflets and PMVL restrictive movement were the most observed changes in the present study, which are similar findings to the ones that have already been described[10,32,34,35]. Morphological changes observed in MV regurgitation such as thickening, calcification, shortening of chords, coaptation defect and restriction of valve movement were described in three-dimensional echocardiographic examination; thickening and calcification of the mitral apparatus in addition to commissural fusion have been listed as the most characteristic features of mitral stenosis in adults[34]. The AMVL thickness showed a median of 4.2mm. Measurements smaller than 4mm were found in 46.3% of the patients enrolled in this investigation which means that if a cut-off ≥4, 0 mm had been defined for pathological thickening instead of ≥3 mm, in almost half of the our patients, this frequent morphological feature would not have been used to support the diagnosis.The uppermost measurement of 2.9 mm for both AMVL tip and midpoint was reported in an investigation carried on in healthy school-age children from New Zealand [36]. Regarding the different presentation patterns of mild RHD on echocardiographic exam, one patient presented mild valve dysfunction but no leaflet thickening and another a mild leaflet thickening but without valve dysfunction, both with aortic regurgitation. These patterns may reflect the dynamics of the progression or regression process of the disease. Furthermore, mild RHD can progress with mild valve dysfunction, without morphological changes (Table 3).

When analysing the balance between morphological and functional/ hemodynamic changes both, the degree and the extent of the structures involved in the continuous pathological process must be considered. Thus, when comparing the AMVL thickness with the severity of the valve dysfunction in the present study, the degree of leaflet thickening was highly associated with the magnitude of mitral regurgitation. Chordal elongation with AMVL tip motion was observed in one quarter of cases. This morphological change can lead to an eccentric regurgitant jet and the so-called Coanda effect (Figure 1). The more mobile AMVL overrode the restricted PMVL and the tendency of the posteriorly directed regurgitant jet is to align its trajectory with the convex surface of the left atrium. Chordal elongation with excessive AMVL motion is also seen in acute episodes of the disease, when can be associated with annular dilatation, chordal rupture, and beading[10]. This acute small fibrin vegetations are seen along the line of closure of leaflets on the atrial valvar surface but they also can be found on the surface of the tendinous chords[10,15,32,34]. Their presence was observed in two patients during recurrences

(Figure1). In this circumstance, they may be useful to support the diagnosis of recurrent acute episodes in patients with established RHD.

As the disease progresses, commissural fusion, coaptation defects of the MV leaflets and, in severe cases, obliteration of the interchordal spaces may occur. Deposition of calcium may be found in children with accelerated progression of RHD[15]. Coaptation defect of the MV leaflets was associated with a significant degree of the left ventricle enlargement. The severity of valvar lesions and the dilation of the left heart chambers are interrelated and overlapped as a consequence of the unique process of valve deformity. In this setting, abnormal coaptation could also be due not only to cordal fusion or shortening but also to left ventricle dilatation, which could modify the orientation and position of the papillary muscles. The typical ''hockey-stick'' appearance is due to the AMVL restricted motion during diastole. Commissural and/or chordal fusion and coaptation defect, classified as severe changes in the score stratification, were uncommon among our patients. These results are in accordance with the distribution of the valvar lesions by severity in this investigation, which suggests stability in the dynamics of the evolutionary pattern. Overall, the best strategies for intervention must incorporate early and accurate diagnosis, prompt introduction of prevention measures, and surveillance throughout a close monitoring of the patients. These initiatives create the opportunity to change the course of RHD and improve the outcomes by preventing disease progression. As regards our best perspectives, there is the prospect of a vaccine for Group A Streptococcus in the horizon of prevention.

Limitations

The main limitation of this investigation was that, although the majority of patients has been followed up since the primary episode, others had already been diagnosed with an established RHD when they were enrolled in the program. In the last group, patients were excluded from this investigation as medical reports sometimes could not be proved to be either complete or comprehensive. We were unable to collect complete information of the past history or review the previous echocardiograms with the aim of characterizing the clinical profile of the study group and analyse the clinical correlation with the echocardiographic changes. The application of the score in patients with more advanced RHD could increase its usefulness through the inclusion of other morphological variables for investigating aortic disease and mitral stenosis, such as the measurements of the annulus and area.

Conclusions

In the analyse of severity of mitral valve deformities and the subsequent valvar dysfunction, the morphological score, stratified by severity, was associated with the magnitude of MV regurgitation and stenosis. The echocardiographic score may be a potential tool to add information for categorising the RHD severity. In this young cohort, the higher morphofunctional scores were associated with severe carditis, but not with the patients' age or the duration of the disease. Taking into account the low prevalence of severe valvar dysfunctions, the results highlight the importance of early intervention and adequate prevention.

Conflict of Interest:

None

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Disclosure

None.

Authors' contributions

CCCM conceived and designed the project and participated in the analysis and interpretation of data; wrote the draft manuscript and reviewed the echocardiogram reports according to the 2023 WHF criteria. The CABC performed all echocardiograms and the statistical analysis and synthesized the data. VDA analyzed the results and critically revised successive drafts of the manuscript. LCV and AAC participated in acquiring relevant information from historical and echocardiographic data and from previous echocardiograms. All authors were involved in critically reviewing the manuscript for intellectual content and approved the submitted version.

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