

Comparative Study of Clinical and Doppler Echocardiographic Evaluations of the Progression of Valve Diseases in Children and Adolescents with Rheumatic Fever

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OBJECTIVE

Compare clinical and Doppler echocardiographic evaluations in assessing valvular diseases in children and adolescents with rheumatic fever, as well as assess the progression of the disease in light of these assessments.

METHODS

This is a longitudinal study of 258 children and adolescents diagnosed with rheumatic fever according to Jones' criteria. The follow-up period ranged from 2 to 15 years. The presence and quantification of valve diseases were determined by means of clinical and Doppler echocardiographic evaluations performed during the acute and chronic phases. The Kappa statistics method was used to estimate the degree of agreement between clinical and Doppler echocardiographic evaluations. Comparisons between clinical and Doppler echocardiographic findings on the progress of carditis and valvulitis, respectively, were made using chi-square test or Fisher's exact test, $p < 0.05$.

RESULTS

Of the 109 patients who underwent Doppler echocardiographic evaluation during the acute phase, 31 did not present clinical evidence of carditis, but the Doppler echocardiograms of 17 (54.8%) of them showed valve lesions (subclinical valvulitis). During the chronic phase, 153 of the 258 patients had normal cardiovascular examination results; however, Doppler echocardiograms showed that 81 of them (52.9%) had valve lesions (subclinical chronic valvular diseases). Involution of the valvular lesions, as shown by Doppler echocardiographic evaluations, was less frequent and occurred in 10 (25.0%) patients with mild valvulitis, in only one (2.5%) patient with moderate valvulitis, and in none of the patients with severe valvulitis.

CONCLUSION

The identification of rheumatic fever valve lesions can be enhanced when clinical evaluations are supplemented by Doppler echocardiographic examinations; also, clinical examinations are not as suitable to detect valvular lesion regression as the echocardiography. The diagnosis of subclinical valvulitis and valvulopathy influences the secondary prophylaxis of rheumatic fever and endocarditis.

KEY WORDS

rheumatic fever, Doppler echocardiography, valvulitis, rheumatic valvulopathy

Rheumatic fever (RF) is a leading cause of acquired cardiopathy among school children, adolescents and young adults in underdeveloped countries¹. RF increases expenditures with healthcare as it is a chronic disease requiring clinical follow-up and many times cardiac catheterization in order to approach the valvar lesions for balloon valvuloplasty, or surgical treatment to repair or replace the valve.

In the absence of carditis and/or recidivism of the disease, the prognosis is good with a smaller rate of progression to chronic valvulopathy. Generally speaking, patients without carditis will not develop significant chronic cardiopathy. However, the prognosis worsens according to the severity of carditis, and in the presence of heart failure in the initial episode of the disease, 60% showed evidence of cardiopathy after ten years². In view of the fact that the diagnosis of RF is the result of a composite of clinical-laboratorial manifestations, the rheumatic origin of subclinical valvulitis or chronic valvular disease should be analyzed in light of such criteria, not including Doppler echocardiographic findings³. Moreover, Doppler echocardiography, although extremely helpful in evidencing and quantifying cardiac abnormalities even in the absence of clinical signs, does not allow one to establish the etiology of the lesions⁴, even though it can suggest the etiology, since rheumatic valvular involvement abnormalities detected by Doppler echocardiogram are typical.

The advance in diagnostic methods with the introduction of Doppler echocardiography provided better means of evaluating *orovalvular* lesions (valve disease secondary to oral foci of infection). M-mode and two-dimensional images allow for a safe determination of the degree of ventricular dysfunction, presence of pericardial involvement, and alterations in the texture of valve tissue. Doppler analysis (pulsed, continuous, and color flow scanning,) enables the detection of valve dysfunction even without clinical evidence, as well as the classification of type and degree of valve lesion according to the regurgitation jet magnitude and valve area estimation⁵.

Bearing in mind the difference between clinical examinations and Doppler echocardiographic findings in defining the presence and degree of valve involvement, this study intends to quantify the degree of cardiac involvement in the acute and chronic phases of RF and to study the progression of the disease according to both assessments.

METHODS

A longitudinal study was conducted, with retrospective data on 258 patients diagnosed with RF, as per Jones' criteria (1992)⁶, who were seen and treated at our institution between August 1983 and December 1998. Subjects were selected among the 392 patients being followed in outpatient clinics specific for the treatment of RF. The presence and quantification of valve diseases

in acute and chronic phases were determined by means of clinical and Doppler echocardiographic assessments. Of the 258 patients, 109 underwent Doppler echocardiography during the acute phase. During the chronic phase, considered as the persistence of the disease after at least two years, all patients had the degree of their cardiac involvement determined by clinical and Doppler echocardiographic evaluations.

The determination of the degree of cardiac involvement was made in the acute and chronic phases within a period of three months, at the most, between the clinical classification and Doppler echocardiography. According to the patient's clinical history, the onset of clinical manifestations and the characterization of major and minor manifestations were defined, as per Jones' criteria. The acute phase was defined as the period between the onset of symptoms and signs and the end of the 12th week of the disease, or earlier, with the normalization of laboratory tests that represent acute-phase serum reactions.

From 1994 on, all patients with acute rheumatic fever (ARF) treated at our institution, even without clinical manifestations of cardiac involvement, were also submitted to Doppler echocardiography, besides clinical, radiological and electrocardiography examinations. Doppler echocardiographic examinations, including the four modes – M-mode, two-dimensional, pulsed, continuous and color flow mapping – were performed with Siemens CF PLUS and Hewlett-Packard (HP) echocardiography equipment, version 1.500, with 2.5, 3.5 and 5.5 MHz waves.

The left chambers size determination was obtained in M-mode via the parasternal short axis view. Values obtained were compared to normal reference values, according to the weight. The ejection fraction (EF) was evaluated according to the Teichholz method (1964)⁵. The criteria used to quantify valve regurgitations were based on the color flow mapping. The mitral regurgitation jet area was used to determine the degree of mitral regurgitation. Mitral regurgitation was considered physiological under the following conditions: valves with normal morphology and texture; normal-sized cardiac chambers; and small regurgitation jet of less than 1 cm of the valve closing level, according to Doppler color flow mapping analysis; regurgitation jet occupying less than 50% of the systole according to Doppler continuous analysis. Aortic regurgitation was quantified by the ratio between the extent of the regurgitation jet and the left ventricular outflow tract width⁷. In obstructive lesions, mitral valve area was determined by means of a Doppler technique based on pressure half-time (PHT), absence of significant aortic regurgitation, and by two-dimensional planimetry. Mitral stenosis was quantified based on the valve area, estimated by the PHT and planimetry, and maximum and medium diastolic gradients between the left atrium (LA) and the left ventricle (LV).

Clinical classifications of the degree of cardiac

involvement were made during the acute and chronic phases. During the acute phase, classification of the cardiac involvement, known as carditis, was conducted according to institution protocol based on the classification described by Décourt⁸ and Markowitz & Gordis⁹. Four degrees of carditis were considered: absent, mild, moderate and severe. In the chronic phase, the presence and degree of cardiac involvement, chronic cardiopathy, were determined by parameters similar to those of the acute phase, and stratified in absent, mild, moderate, and severe categories. For the Doppler classification of the degree of cardiac involvement in the acute and chronic phases, the valve lesion degree and heart chambers size according to previously established echocardiographic patterns were the only aspects considered^{5,7,10,11}. Doppler echocardiographic classifications of the degree of valve involvement in the acute and chronic phases, valvulitis and chronic valvulopathy, respectively, were also divided into four degrees: absent, mild, moderate and severe.

The term 'valvulopathy' used here is restricted solely to the exclusive Doppler echocardiographic analysis of mitral and/or aortic lesions in the chronic phase of RF. In this study, the determination of lesions in the tricuspid and pulmonary valves was not performed. The valve lesions classified as mild-to-moderate were included in 'moderate involvement', and those classified as moderate-to-severe were analyzed as severe.

The research protocol was approved by the hospital's Research Ethics Committee. Data obtained were analyzed using EPI-Info 6 software. A comparative study of the clinical progression of patients with RF was performed in light of clinical evaluations, including electrocardiography and chest X-ray findings, as well as the four classifications of valvar lesions according to Doppler echocardiographic criteria. To estimate the agreement among the classifications, Kappa statistics were used, with calculations of non-weighted Kappa (K) values. The conventional interpretation of K values is as follows: Kappa above 75% – excellent level of agreement; between 40% and 75% – reasonable-to-good level of agreement; under 40% – poor level of agreement. The progression of the disease according to clinical and Doppler echocardiographic findings for carditis and valvulitis, respectively, was compared by means of the chi-square test (χ^2) or Fisher's exact test. The statistical significance level was set at 5% ($p < 0.05$).

RESULTS

Of the 258 patients enrolled in the study, 132 (51.2%) were men and 126 (48.8%) were women; patient age at the first bout varied from 3.2 years and 16.5 years, mean age 9.0 ± 2.6 years and median age 9.0 years. Taking into account only the follow-up period of 258 patients at this institution, total patient-years were 1,383.

In the distribution of patients according to Jones's criteria, arthritis, carditis and chorea were common

manifestations in the ARF medical condition affecting 65.5%, 56.6% and 24.0% of patients, respectively. Among the most common important clinical manifestations related to the presentation of ARF, the association between arthritis and carditis was the most frequent, affecting 29.8% of the 258 patients in the first bout. Only 2.7% of the patients had carditis, arthritis, and chorea combined, and the concomitance of arthritis and chorea was also uncommon (4.3%).

The main Doppler echocardiographic findings of the 109 patients evaluated at our institution during the first bout are listed on Table I. In most cases (99.1%), the left ventricular contractile function was within the limits of normality, and just one patient, with an ejection fraction of 0.52, showed decreased contractility. Fifty-eight patients (53.2%) had one or more enlarged cardiac chambers, and the combined enlargement of LA and LV was more frequent than the isolated or global enlargement of the four chambers. Whether isolated or associated with other lesions, mitral regurgitation was present in 92 (84.4%) patients and aortic regurgitation, in 53 (48.6%). However, aortic regurgitation was recorded separately in just three (2.7%) patients and no obstructive valve lesions were observed. Pericardial fluid effusion was uncommon, having only been observed in four (3.7%) examinations.

The 'diagonal' reading analysis of Table II shows that both in the acute phase and in the chronic phase the clinical evaluation tended to underestimate the degree of cardiac involvement, as compared to the valve lesion degree classification by Doppler echocardiography

Table I – Distribution of frequency of Doppler echocardiographic findings in the first bout of rheumatic fever (n = 109)

Parameters analyzed	n	%
Absence of abnormalities	14	12.8
LV contractile function alteration	3	2.7
↑ LA	10	9.2
↑ LV	7	6.4
↑ LA and LV	38	34.9
↑ Global	3	2.7
Pericardial effusion	4	3.7
Isolated mitral regurgitation	42	38.5
Isolated aortic regurgitation	3	2.7
Mitral and aortic regurgitation	50	45.9

parameters. In the acute phase, seventeen (54.8%) of the 31 patients with no evidence of cardiac involvement according to clinical evaluation showed valvar lesion upon Doppler echocardiography (subclinical valvulitis). Similarly, in the chronic phase, 81 (52.9%) of the 153 patients with no clinical evidence of valve lesions and with normal ECGs and chest X-rays had valve alterations detected by the Doppler echocardiographic examination (subclinical chronic valvulopathy). All patients clinically identified as cardiopathic, however, showed valvulopathy upon Doppler echocardiographic evaluation. Both

evaluations were in agreement on the diagnosis of the degree of valve lesion in those patients with cardiac involvement classified as moderate or severe, both in the acute and chronic phases.

The analysis of the progression of cardiac involvement from the acute phase to the chronic phase, according to clinical evaluation aided by electrocardiography and chest X-ray studies, showed that the percentage of valve lesion regressions was greater when the carditis degree was mild (59.4%), lower in moderate degree carditis (15.2%), and there was no record of involution in cases of severe carditis. In the group of patients with no clinical evidence of carditis, eight (7.1%) had cardiac alterations in the clinical evaluation performed during the chronic phase (table III).

Taking into consideration the degree of cardiac involvement assessed by Doppler echocardiography both

in the acute phase and chronic phase, the absence of valvulitis indicated a greater likelihood of normality in the chronic phase; just one (7.1%) patient without a valve lesion in the acute phase evidenced a mild valve lesion in the chronic phase (Table IV).

As shown, valve lesion involution assessed by Doppler echocardiographic evaluation was less common than in clinical evaluations, occurring in ten (25.0%) patients with mild valve lesion ($p = 0.0013$) and only one (2.5%) patient with moderate valvulitis ($p = 0.0526$). Moreover, severe valvulitis did not retreat to normal Doppler echocardiographic values (Table V).

DISCUSSION

Considering that the tricuspid and pulmonary valves show (physiological) regurgitation in most normal children

Table II – Comparison of clinical and Doppler echocardiographic classifications of the degrees of cardiac involvement in acute and chronic phases of rheumatic fever

Analysis phases	Clinical evaluation: carditis / chronic cardiopathy (degrees)	Doppler echocardiographic evaluation: valvulitis / chronic valvulopathy (degrees)				Total n
		Absent n	Mild n	Moderate n	Severe n	
Acute	Absent	14	17	0	0	31
	Mild	0	23	13	0	36
	Moderate	0	0	27	6	33
	Severe	0	0	0	9	9
	Total	14	40	40	15	109
Chronic	Absent	72	79	2	0	153
	Mild	0	14	21	0	35
	Moderate	0	0	29	11	40
	Severe	0	0	0	30	30
	Total	72	93	52	41	258

Non-weighted Kappa statistics: acute phase = 0.50; chronic phase = 0.39

Table III – Rheumatic fever progression based on the degree of carditis

Carditis degrees Clinical evaluation	Chronic cardiopathy degrees – clinical evaluation				Total n
	Absent n	Mild n	Moderate n	Severe n	
Absent	104	5	3	0	112
Mild	38	16	7	3	64
Moderate	11	11	27	21	70
Severe	0	3	3	6	12
Total	153	35	40	30	258

Table IV – Progression analysis of rheumatic fever according to the degree of valvulitis

Valvulitis degrees: Doppler echocardiographic evaluation	Valvulopathy degrees: Doppler echocardiographic evaluation				Total n
	Absent n	Mild n	Moderate n	Severe n	
Absent	13	1	0	0	14
Mild	10	24	4	2	40
Moderate	1	16	18	5	40
Severe	0	1	6	8	15
Total	24	42	28	15	109

Table V – Distribution of patients according to the degree of carditis and valvulitis and frequency of regression of cardiac involvement

Cardiac involvement in the acute phase	Regression of cardiac involvement				p
	Yes		No		
	n	%	n	%	
Mild carditis	38	59.4	26	40.6	0.0013*
Mild valvulitis	10	25.0	30	75.0	
Moderate carditis	11	15.7	59	84.3	0.0526±
Moderate valvulitis	1	2.5	39	97.5	
Severe carditis	0	0	12	100	-
Severe valvulitis	0	0	15	100	

• $\chi^2 = 10.36$; ± Fisher's exact test

and adolescents^{12,13}, and that abnormal regurgitation jets may be due to pulmonary hypertension, the participation of these valves in RF was not evaluated in this study. Aortic regurgitation was not considered physiological in any of the patients. Only valve lesions were taken into consideration in determining the degree of cardiac involvement, even during the acute phase, bearing in mind that pericardial and/or myocardial involvement in ARF is generally mild and does not determine the severity of the rheumatic cardiac involvement^{14,15,16}.

There is no other study similar to this one in medical literature correlating the progression of RF and the degree of mitral and/or aortic valve lesions evidenced by clinical and Doppler echocardiographic assessments. The Kappa (K) test, commonly employed to measure the agreement between different evaluations made by investigators, has not been used in studies comparing clinical and Doppler echocardiographic classifications of valve lesions in RF. Reflecting the lower sensitivity of clinical examinations as compared to the Doppler echocardiographic analysis for detecting valvulitis and/or chronic rheumatic valvulopathy, Kappa values were interpreted as showing poor and moderate agreement, depending on the degree of cardiac involvement. In serious cases, clinical and Doppler echocardiographic assessments were in agreement.

In the analysis of the clinical presentation profile of RF documented in medical literature, the distribution of the frequency of the main major manifestations of RF is similar regarding the first bout^{14,17-19}. The distribution of major clinical manifestations in episodes that occurred in the 1980s and the late 1990s in some states of the United States, such as Utah^{20,21}, was similar to that observed among the patients enrolled in this study, e.g., chorea that affected 24% of the patients in our study and 28% of those in Utah, as were the low rates of association between Chorea and arthritis (4.0% and 4.3%, respectively). In the presence of carditis the diagnosis of RF is easier, especially if there is another major manifestation. One hundred and forty-

six patients (56.6%) [in this study] were affected by carditis, a percentage similar to that of other studies, regardless of their having been conducted in developed or developing countries^{17,22,23}.

In this investigation, 87.2% of the 109 Doppler echocardiograms performed in the acute phase showed some kind of abnormality, whereas 17 (15.6%) of the patients did not have any abnormality upon cardiovascular examination. Ty & Ortiz²⁴ also documented abnormalities in 89.0% of 28 patients with ARF, five (17.9%) of them without any clinical evidence of carditis. Similarly, among the 258 patients submitted to Doppler echocardiographic examinations in the chronic phase, 190 (73.6%) were diagnosed with valve abnormalities, whereas in 85 (44.7%) patients the clinical examination was normal. Regarding the results of the Doppler echocardiographic study performed in the acute phase with 109 patients, the left ventricular contractile function was slightly affected in just one patient (0.9%), which coincides with the results found by Ty & Ortiz²⁴ who reported a decrease in the ejection fraction and the shortening fraction in one (3.6%) of the 28 patients evaluated in this phase. The authors attribute this fact to the use of anti-inflammatory agents and the low sensitivity of these parameters in detecting mild contractile function abnormalities.

Moreover, the left ventricular dilatation due to mitral and/or aortic valve dysfunctions tends to overestimate these measurements. The end-diastolic left ventricular chambers in M-mode were found to be enlarged in 53.2% of the acute phase echocardiograms. Mitral regurgitation was the predominant lesion, either isolated or in combination with other lesions in 84.4% of the cases, which is in agreement with the reports from medical literature^{20,25}. Aortic regurgitation was observed in 48.6% of the 109 patients in Doppler echocardiographic studies, but only fourteen (12.8%) patients had auscultation results consistent with aortic regurgitation.

Of the 258 patients evaluated during the chronic phase, 189 showed some type of mitral and/or aortic

valve lesion, with mitral regurgitation (isolate or combined) as the predominant lesion (97.9%), followed by aortic regurgitation combined with mitral lesions (49.2%), and mitral stenosis associated with mitral regurgitation (12.7%); no cases of aortic stenosis or isolated mitral stenosis were identified. These findings are in agreement with those documented in medical literature for investigations of patients in age groups similar to those in this study; and it was noted that obstructive lesions require more time to be established^{25,26}.

In his clinical experience with mild degree carditis patients, Décourt⁸ had already described that in approximately 80% of the cases cardiac manifestations vanished, and clinical progression left no residual valve disease. However, in cases of moderate or severe carditis, residual cardiopathy would be the most likely occurrence. Thomas²⁶ demonstrated that patients with no cardiac abnormalities during the acute phase continued to have clinical examinations considered normal during the follow-up period, whereas for those patients who had murmurs in the acute phase, the regression rate varied according to the intensity of the murmurs. Similarly, Majeed et al.²⁷ observed the development of residual cardiopathy in 49% of 29 children with carditis, whereas none of the children without carditis experienced chronic rheumatic cardiopathy (CRC).

The findings of the present investigation, in agreement

with the findings by former authors, showed that clinical progression to CRC varied according to the degree of carditis. Of the 64 patients who had mild carditis, 38 (59.4%) showed no further clinical evidence of valve involvement. However, of the 82 patients with moderate or severe carditis, 86.6% progressed to CRC and all of the cases of severe carditis (100.0%) manifested clinical evidences of CRC. The regression of valve lesions was less frequent, verified by Doppler echocardiographic evaluation in the acute and chronic phases. Only ten (25%) of the patients with a mild degree of valvulitis, one (2.5%) patient with moderate valvulitis, and none of the patients with severe carditis had normal Doppler echocardiographic examinations in the chronic phase.

This study demonstrated that the Doppler echocardiographic study is an important supplementary examination for identifying and classifying valve lesions, both in the acute and the chronic phases of RF. With Doppler echocardiographic assessments, the frequency of valve lesion identification is higher and valve lesion regression is smaller relative to the clinical evaluation. In the acute phase, the identification of subclinical valve lesions has implications for treatment regarding rest and close monitoring of the patient. In the chronic phase, it is important to define the timing for interrupting secondary prophylaxis and the indication of endocarditis prophylaxis.

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