Journal of Clinical & Experimental Cardiology
ISSN: 2155-9880

Mahfouz et al., J Clin Exp Cardiolog 2016, 7:10
DOI: 10.4172/2155-9880.1000472

Review Article OMICS International

Utility of Left Atrial Stiffness in Children with Acute Rheumatic Fever: A Speckle Tracking Echocardiography

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Abstract

Objective: We aimed to investigate the changes in left atrial stiffness (LASt) in children with acute rheumatic fever (ARF) and its impact on clinical outcome.

Patients and methods: 64 children presented with first attack of ARF, were enrolled and studied, using standard, tissue Doppler and speckle tracking echocardiography. They were compared with 36 matched controls. Left atrial (LA) volumes, mitral annular velocities, and global longitudinal LA strain were measured. The ratio of E/e′ to LA strain was used as an index of LA stiffness.

Results: LA maximal, minimal and pre-A volume indexes were significantly higher in children with ARF compared to controls (P<0.001). The E/e" ratio was significantly elevated (P<0.001), whilst the global LA strain was significantly decreased (P<0.001). LASt was greater in children with ARF than in the controls (p<0.001). Follow-up data showed that children with adverse clinical outcomes had a significantly greater LASt (P<0.003). ROC analysis showed that the predictive value of LASt in predicting adverse clinical outcome in children with ARF is corresponding to a good test with a cut off value ≥ 0.63 with area under the curve = 0.91 (P<0.0001), with a sensitivity of 81.5% and a specificity of 94.7%.

Conclusions: Children with first attack ARF have increased LASt in comparison with that of the matched controls. Meanwhile LASt is a good predictor adverse events of children of first attack of ARF. LASt could be a valuable parameter of subclinical carditis and ARF risk stratification.

Keywords: Atrial stiffness; Rheumatic fever; Echocardiography

Introduction

Acute rheumatic fever (ARF) is an inflammatory and autoimmune disease, occurs as a sequel of delayed group A β-hemolytic streptococcal pharyngitis [1]. The exact pathophysiologic and genetic determinants of ARF and rheumatic heart disease remain undefined. The autoimmune-like reaction on exposure to group A *Streptococci*, leads to myocarditis and endocarditis with eventually rheumatic heart disease. The antigenic mimicry hypothesis was claimed to be the underlying cause of autoimmune reaction [2].

Spite of advances in preventing medicine ARF remains a major and endemic health problem, among school-age children in developing nations. The initial attack of ARF is usually associated with nearly 50% of cardiac involvement. This serious sequel may affect endocardium, myocardium and rarely pericardium [3].

Left atrial myocardial functional changes can be detected early with the assessment of deformation profiles utilizing speckle tracking echocardiographic assessment. Left atrial stiffness is correlated with left atrial remodeling and indicates left atrial functional deterioration [4-6].

We hypothesized that left atrial myocardium, like left ventricle and cardiac valves is exposed to the inflammatory process of acute rheumatic fever and became stiff and according may have a significant impact on the future outcome of children with acute rheumatic fever.

We aimed to study the left atrial stiffness in children with acute rheumatic fever in comparison with control children and to investigate its impact on clinical outcome.

Subjects and Methods

This was conducted and initiated on approval from the Hospital Ethics Committee. Sixty four children with acute rheumatic fever for the first time (35 male, 29 female) were being followed-up at the Zagazig University hospital, in cardiology clinic with an age range (6-18). The diagnosis of all patients included was made according to Jones and World Health Organization criteria [7]. A control group of 36 age matched healthy children (20 male, 16 female) were included in the study.

Children with ARF were classified to a group with carditis (22 children) and another group without carditis (42 children), based on the presence or absence of clinical and or echocardiographic evidence of carditis. Mitral regurgitation was present in 22 children (grade II in 15, grade III in 6 and grade VI in one child), whilst aortic regurgitation was present in 9 patients (grade II in 8 and grade II in only one patient). Along the period of follow-up all children were receiving long acting penicillin every 21 days.

Echocardiographic examination

Echocardiographic examinations utilizing (A Vivid 7 pro; GE, Horten, Norway, 3-MHz transducer) were performed to assess left ventricular ejection fraction , left atrial dimension and volumes as well as assessment of the presence and severity of mitral and aortic regurgitation (MR and AR). Pathologic regurgitation was distinguished from physiologic regurgitation according to The World Health Organization (WHO) recommendations: (1) color jet 1 cm, (2) color

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Received September 12, 2016; **Accepted** October 13, 2016; **Published** October 20, 2016

Citation: Mahfouz RA, Dewedar A, Mostafa TM (2016) Utility of Left Atrial Stiffness in Children with Acute Rheumatic Fever: A Speckle Tracking Echocardiography. J Clin Exp Cardiolog 7: 472. doi:10.4172/2155-9880.1000472

jet evident in at least two imaging planes, (3) color jet mosaic with peak velocity 2.5 m/s, and (4) Doppler signal holosystolic for MR and holodiastolic for AR [8,9]. Clinical and echocardiographic follow-up was performed regularly every three months and or at any time of a new event develops.

Assessment of the LA function by 2D STE

Gray scale image of apical 4-chamber views was obtained with the frame rates of 50–80 Hz or at least 40% of the heart rate to enhance the feasibility of the frame-to-frame tracking technique. Three consecutive heart cycles were recorded and averaged. Recordings were processed using an acoustic-tracking software incorporated in the Vivid Nine system (Echo Pac; GE Vingmed), allowing offline semiautomated analysis of speckle-based strain.

To calculate LA strain, the atrial endocardium was first traced manually. The epicardial surface was calculated automatically, and after manually reducing the region of interest to the atrial thickness, the software automatically divided each wall of the apical four-chamber ‚septal and lateral wall' and two-chamber ‚anterior and inferior wall' views into three segments: the apical, the mid, and the basal segments; we took the average of this wall and the average of the view, and repeated these steps in each wall of both apical four-chamber and two-chamber views. Once the longitudinal atrial strain curves were obtained, measurement of the peak atrial strain was taken. To obtain a noninvasive dimensionless parameter, the ratio of E/e' to LA peak strain was used to estimate the LA stiffness [10-12].

Statistical analysis

Statistical analysis was performed using the SPSS software package for windows, version 15.0 (SPSS, Chicago, IL, USA). Data were analyzed using nonparametric methods and reported as the mean ± standard deviation. Associations between parameters were assessed using Spearman's rank correlation test. Receiver operating curve (ROC) was used to assess the cut-off value of LASt in predicting adverse clinical outcome in children with ARF.

Results

Table 1 shows that LVEDd, LVEDs, LAD, ejection fraction and E/e" ratio were significantly greater in children with ARF compared to control children, whilst the other demographic and conventional echocardiographic characteristic were comparable.

	ARF (64)	Controls (36)	P value
Age (years)	13.5 ± 3.8	12.6 ± 3.5	0.69
BMI (kg/m^2)	21.4 ± 1.7	20.8 ± 1.9	0.82
SBP (mm Hg)	112 ± 7	109 ± 7	0.82
DBP (mm Hg)	65 ± 4	66 ± 5	0.15
IVSd (mm)	9.5 ± 1.9	8.1 ± 1.3	0.33
LVIDd (mm)	46.5 ± 6.2	38.5 ± 5.9	0.001
LVPWd (mm)	8.9 ± 1.4	8.5 ± 1.5	0.41
IVSs (mm)	12.8 ± 2.2	12.3 ± 1.9	0.18
LVIDs (mm)	30.6 ± 4.9	23.5 ± 4.3	0.001
EF	61.4 ± 6.1	69.5 ± 6.7	<0.05
LAD(mm)	34.6 ± 6.5	26.5 ± 4.2	<0.05
Mitral E (cm/s)	66.2 ± 15.3	62.5 ± 11.p	0.15
Mitral A (cm/s)	55.8 ± 12.5	55.2 ± 9.5	0.63
E/A ratio	1.15 ± 0.3	1.10 ±0.2	0.82
e' (cm/s)	6.8 ± 1.2	11.2 ± 1.6	<0.01
a' (cm/s)	7.9 ± 1.3	8.4 ± 1.5	0.09
E/e' ratio	9.9 ± 2.6	5.7 ± 1.8	<0.001

Table 1: Clinical and conventional echocardiographic data in children with acute rheumatic fever and controls.

Table 2 shows that LA minimal volume index, pre-A volume index and maximal volume index were significantly greater in children with ARF than in the control children (P<0.001 for all). While the global LA strain was significantly decreased (P<0.001) on the other hand the LASt was significantly increased in children with ARF compared to control children (P<0.001).

The results showed that children with carditis had a significant lower global left atrial peak strain% (P<0.05) and a significant greater left atrial stiffness (P<0.03) compared to those without carditis (Table 3).

Along the period of follow-up 31 (48%) children developed an adverse clinical outcomes. The adverse outcomes are summarized in (Table 4). Comparison of the patients with cardiac events versus those without events (Table 5) shows that LA minimal volume index, pre-A

	Patients (n = 64)	Controls (n = 36)	P value
LA minimal volume index (mL/m^2)	17.6 ± 2.8	11.3 ± 1.8	<0.001
LA pre-A volume index (mL/m^2)	21.9 ± 2.2	13.8 ± 2.3	<0.001
LA maximal volume index (mL/m^2)	29.1 ± 4.2	19.3 ± 3.1	<0.001
Global LA peak strain (%)	22.5 ± 4.5	39.2 ± 6.3	<0.001
LA stiffness	0.58 ± 0.16	0.28 ± 0.07	<0.001

Table 2: Comparison of left atrial (LA) volumes, stiffness and strain parameters of children with acute rheumatic fever and controls.

	ARF with cardidis N=22	ARF without carditis N=42	P value
LA minimal volume index (mL/m^2)	15.2 ± 2.6	18.1 ± 2.5	<0.05
LA pre-A volume index (mL/m^2)	18.5 ± 2.1	22.4 ± 2.5	<0.05
LA maximal volume index (mL/m^2)	26.1 ± 3.5	31.2 ± 4.5	<0.05
Global LA peak strain (%)	20.8 ± 4.6	25.5 ± 3.8	<0.05
LA stiffness	0.69 ± 0.19	0.56 ± 0.08	<0.05

Table 3: Comparison of left atrial (LA) volumes, stiffness and strain parameters of children with cute rheumatic fever with versus without carditis.

	Number of events	Percentage
Recurrent ARF	13	20.3
Heart failure	5	7.8
Atrial Fibrillation	11	17.2
Chronic RHD		
– MS	9	14.0
– MR	7	10.9
– MS+MR	3	4.7
– AR	1	1.5
– AR+MS	2	3.1
Death	1	1.5

Table 4: Cardiac events along the follow-up of children with acute rheumatic fever along the period of follow-up.

	Children with Events (n = 31)	Children without events (n = 33)	P value
LA minimal volume index (mL/m^2)	21.6 ± 2.9	15.1 ± 2.4	<0.03
LA pre-A volume index (mL/m^2)	25.5 ± 2.7	17.1 ± 2.5	<0.03
LA maximal volume index (mL/m^2)	33.5 ± 4.8	26.8 ± 4.2	<0.03
Global LA peak strain (%)	17.3 ± 3.7	28.6 ± 5.5	<0.001
LA stiffness	0.67 ± 0.25	0.41 ± 0.09	<0.003

Table 5: Comparison of left atrial (LA) volumes, stiffness and strain parameters of children with and without events during follow-up.

volume index and maximal volume index were significantly greater in children with events during follow-up than in children without events (P<0.03 for all). Furthermore, the global LA strain was significantly lower in children with events compared to those without events (P<0.01). On the other hand LASt was significantly increased in children with events compared to children without events (P<0.003). The data showed that there was a positive correlation between LASt and left ventricular filling pressure in children with ARF (r=0.79; p<0.001) (Figure 1), age (r=0.35, p<0.03), whereas there was a negative correlation between LASt and ejection fraction (r=-0.32, p<0.03).

The sensitivity and specificity of the left atrial stiffness in predicting adverse clinical outcome were investigated utilizing receiver operating characteristic curves. LASt ≥ 0.63 on initial attack of ARF had a sensitivity of 81.5% and specificity of 94.7%, respectively, in predicting adverse clinical outcome (recurrent attacks of rheumatic fever, heart failure, chronic rheumatic heart diseases and atrial fibrillation) (Figure 2).

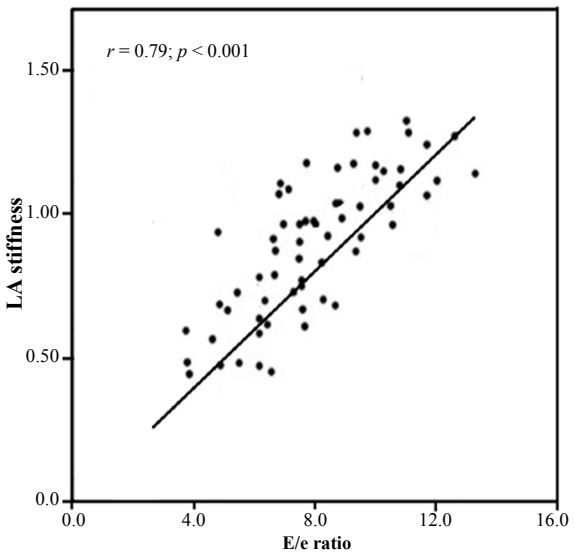

Figure 1: Correlation of left atrial stiffness to the left ventricular filling pressure (E/e) in children with acute rheumatic fever.

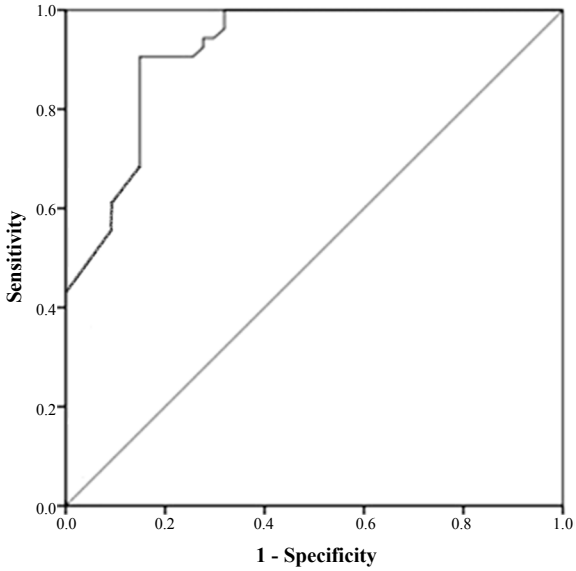

Figure 2: ROC analysis. The predictive value of left atrial stiffness in predicting adverse clinical outcome in children with acute rheumatic fever is corresponding to a good test with a cut off value >0.63 with area under the curve=0.91 (P<0.001), with a sensitivity of 81.5% and a specificity of 94.7%.

Discussion

We investigated the changes in the left atrial stiffness in children presented with first attack of acute rheumatic fever and the utility in clinical outcome of those children. In the current study, LASt was detected to be significantly greater in the children with ARF than in the control children. In addition, LASt was found to be significantly correlated with left ventricular filling pressure (E/e“) in the children with ARF, whilst it was inversely correlated with left ventricular ejection fraction. Likewise, it was found that LASt with a cut-off value ≥ 0.63 is a good predictor of developing adverse outcome (recurrent rheumatic activity, atrial fibrillation and chronic rheumatic heart disease), during follow-up.

Acute rheumatic fever is an inflammatory process with multisystem affection. ARF is a delayed sequel to group A streptococcal pharyngitis. ARF in it serious form of carditis, may be associated with higher incidence of morbidity and mortality. Early stages of carditis may be associated with mitral regurgitation. If the compensatory mechanisms are insufficient, left ventricular systolic dysfunction occurs. Aortic regurgitation may occur during ARF in combination with mitral regurgitation or in isolation. Persistent or recurrent attacks of valvulitis usually lead to the development of mitral stenosis with bicommissural fusion. Chronic rheumatic heart diseases usually cause big health problems that may require percutaneous or surgical interventions. Other adverse outcomes may occur as heart failure, atrial fibrillation, infective endocarditis and embolic events [13].

Left atrial stiffness may be increased as a result of the inflammatory changes in atrial myocardium during ARF. Moreover LASt may be increased as a result of mitral valvular regurgitation in ARF early in the acute episode of carditis, and pathologic, hemodynamic, and functional changes are important determinants in the worsening of left atrial stiffness. It was observed that Doppler echocardiography is an important tool in diagnosing subclinical carditis and valvulitis, which are proposed to be major criteria in the diagnosis of ARF [14].

In patients with ARF we found that LASt was slightly greater in children with carditis than those without carditis, the difference was mildly significant (P<0.05). On the other hand LASt was much greater in children with ARF [either with or without carditis than in control subjects (P<0.00)].

The current study showed that children with ARF and greater LASt had a higher prevalence of adverse clinical outcomes. Meanwhile, a LASt ≥ 63 was the best cut-off value in predicting adverse sequel in children with acute rheumatic fever. Acute rheumatic fever may cause atrial myocardial fibrosis and consequently increasing left atrial stiffness. This fibrosis and stiffness may affect outcome of children with acute rheumatic, in predisposing atrial arrhythmias and may have a role in developing chronic rheumatic heart disease.

The abnormal left atrial volumes and strain could be explained by rheumatic myocardial insults on both atrial and ventricular myocardium. Moreover the left atrium may be exposed to the effects of increased left ventricular myocardial stiffness and abnormal function either due to regurgitant lesion or rheumatic myocarditis.

Leite-Moreira et al. [15] atria modulate ventricular filling by smoothing the transformation of the continuous venous return to the

intermittent filling pattern of the ventricles during diastole through three main components: a reservoir phase, occurs mainly during ventricular systole, a conduit and an active phases during ventricular diastole. Spite the dynamic role of atria in ventricular filling, atrial function and emptying pattern is, conversely, highly influenced by the ventricular diastolic wall stress, underlying the close connection observed between these chambers.

Alpert et al. [16] reported that rheumatic carditis usually leads to mitral valvulitis and atrial inflammation. A combination that may cause left atrial dilation, fibrosis of atrial myocardium associated disorganization of the atrial muscle bundles. As a result, electrical instability, incongruent velocities propagation, and inhomogeneous refractory periods within the atrial myocardium [17]. Furthermore, T-cell lymphocytes are activated leading to increase in inflammatory cytokines and consequently fibrotic valvular changes. Therefore, these lesions are not inactivated, and there is ongoing inflammation in these lesions [18]. Patients with rheumatic MS exhibit varying levels of inflammation. Moreover, the degree of inflammation and tachyarrhythmia's are closely associated in these patients [19,20].

Limitation

Study limitations include

First the sample size was small, second, there is no gold standard measurement for the left atrial function, third dedicated software for left atrial strain analysis was lack, so we used software for left ventricular analysis to assess the left atrial strain and stiffness. Further long-term prospective studies with clinical endpoints and repeated strain measurement over time are required to assess the effects of reverse atrial modeling on strain and stiffness.

Conclusion

In this study, left atrial stiffness was found to be greater in children with acute rheumatic fever than in healthy control subjects. Meanwhile LASt was significantly correlated with left ventricular filling pressure and has a significant impact on the clinical outcome in children with ARF with a cut-off value of ≥ 0.63 in predicting adverse sequel. Left atrial stiffness could be an important parameter in the diagnosis of rheumatic carditis, and in risk stratification of ARF, even in the absence of clinical or other echocardiographic manifestations.

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