

Comparison of Echocardiographic Variables Between Systemic Lupus Erythematosus Patients and a Control Group

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Background: Cardiovascular diseases increase morbidity and mortality in patients with systemic lupus erythematosus (SLE). The cardiac involvement could be silent. Echocardiography can be used as a noninvasive tool for the assessment of the ventricular function.

Objectives: We sought to evaluate different echocardiographic parameters via tissue Doppler imaging and speckle-tracking echocardiography (STE) in addition to conventional echocardiography.

Patients and Methods: This case-control study was conducted in 45 SLE patients (88% female; mean age = 31.2 ± 8.2 years) and 25 healthy controls (87% female; mean age = 30.3 ± 7.7 years), matched in terms of age and sex. Both groups had no clinical signs and symptoms of cardiac problems or risk factors for cardiovascular diseases. Both SLE and control groups underwent echocardiography for the assessment of the ventricular function and the sizes and diameters of the chambers. Two-dimensional STE was used for the measurement of the left ventricular (LV) global longitudinal systolic strain.

Results: The mean duration of SLE was 5.5 ± 3.4 years in our patients. No significant difference was found between the two groups concerning the LV and left atrium size, LV ejection fraction, right ventricular (RV) systolic function, RV and LV diastolic function, and pulmonary artery pressure. The LV global longitudinal strain was less in the SLE patients ($-18.56 \pm 2.50\%$ vs. $-19.89 \pm 1.94\%$; $P = 0.028$). The LV mass was greater, though not statistically significant, in the SLE patients (111 ± 29.54 g vs. 104.37 ± 27.39 g; $P = 0.468$). The interventricular septal diameter was thicker in the SLE patients (0.79 ± 0.15 cm vs. 0.77 ± 0.10 cm; $P = 0.046$).

Conclusions: Silent ventricular systolic dysfunction was more common in the patients with SLE than in the control group. Newer echocardiographic techniques such as two-dimensional STE provide an earlier chance for the detection of subclinical LV systolic dysfunction. Our findings were independent of the traditional risk factors.

Keywords: Systemic Lupus Erythematosus; Echocardiography; Left Ventricle

1. Background

Systemic lupus erythematosus (SLE) is an autoimmune disease occurring at any age. Cardiovascular diseases could increase morbidity and mortality in SLE patients (1). Recently, coronary heart disease and stroke have been reported more frequently than before in SLE patients. Research has shown that, in contrast to control groups, controlling the Framingham risk factors alone cannot decrease coronary heart disease and stroke in patients with SLE (2, 3). Chronic inflammation and the drugs used to treat it (e.g. corticosteroids) may have a role in increasing the frequency of cardiovascular diseases. The use of glucocorticoids has decreased death due to infection and active disease, but the persisting cardiovascular etiology could play a leading role in decreasing SLE survival. Recently, Huang et al. (4) used three-dimensional (3D) speckle-tracking echocardiography (STE) and suggested that SLE was an independent factor for the left ventricular (LV) systolic

function. In two other studies, myocardial involvement was seen in as many as 40% - 50% of the SLE patients in autopsy (5), while myocardial injury was found clinically in only 7% - 10% of the SLE patients (6). The LV diastolic dysfunction, albeit clinically silent, has also been reported in SLE patients (7). The precise estimation of myocardial status in SLE patients is important for patient management.

For the screening and diagnosis of subclinical heart diseases, noninvasive techniques such as echocardiography are relatively simple and universally available; the reported results have, however, been conflicting. The present study used STE in addition to conventional echocardiography and tissue Doppler imaging (TDI) in Iranian SLE patients to assess multiple variables of systolic and diastolic ventricular function. Moreover, given the dearth of data on the right ventricle (RV) in SLE, this cardiac chamber was assessed as well.

2. Objectives

STE has been widely used in different cardiovascular disorders to define even subtle myocardial dysfunction. Our aim was to determine whether this technique could add any further information to conventional echocardiographic imaging modalities such as two-dimensional (2D) echocardiography and TDI.

3. Patients and Methods

Forty-five patients with a diagnosis of SLE confirmed by an expert rheumatologist were recruited in this case-control study, conducted between 2011 and 2013. The subjects were selected consecutively from the patients visiting a rheumatologic clinic (Imam Reza Hospital). The included SLE patients did not have any clinical signs or symptoms of cardiac problems, history of heart disease, or conventional risk factors for atherosclerosis (i.e. hypertension, hyperlipidemia, diabetes mellitus, and cigarette smoking). Also enrolled were 25 healthy volunteer subjects, who were the colleagues or family members of the study author and had no clinical evidence of cardiac or systemic disorders. Having an age range and sex ratio similar to those in the SLE group was considered while selecting the controls.

A questionnaire on the systemic lupus erythematosus disease activity index (SLEDAI) was employed to evaluate the disease severity (8).

This study was carried out in accordance with the code of ethics of the World Medical Association (declaration of Helsinki) for experiments involving humans and obtained the approval of the Research Ethics Committee of Mashhad University of Medical Sciences (Registration # 2271). An informed written consent was obtained from each participant.

Both SLE and control groups underwent echocardiography (conventional, TDI, and 2D-STE).

3.1. Echocardiographic Assessment

Echocardiography was done for both groups using a Vivid 7 Dimension ultrasound scanner (GE Vingmed, Horten, Norway) with a 4-MHz transducer. Both linear and volumetric measurements of the LV size were done according to the recommended guideline (9). The left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal diameter (IVSD), and posterior wall thickness (PWT) were all measured in the parasternal long-axis view with the M-Mode tracing technique. The LV volumes (end-systolic and end-diastolic) and the ejection fraction (EF) were measured by the manual tracing of the endocardium in the apical four- and two-chamber views using the Biplane Simpson rule.

The LV mass was determined using the following formula (Equation 1) proposed by Devereux et al. (10):

$$(1) \quad LV \text{ mass} = 0.8 \times 1.04 \times \left[(\text{Septal thickness} + LV \text{ internal Diameter} + PWT)^3 - (LV \text{ internal diameter})^3 \right] + 0.6 \text{ g}$$

The LA volume was measured by the disk summation method using the single-plane approach (apical four-chamber view). The velocities of the E and A waves and the deceleration time were measured in the Doppler study of the mitral inflow. The peak systolic (S') and early diastolic (E') velocities of the mitral annulus at the septal and lateral sides were measured by pulsed Doppler tissue imaging. The region of interest was placed in the center of the imaging field parallel to the sector angle. Gain was minimized to allow clear tissue signal with minimal background noise. The frame rate was set at 100/sec. The E/A and E/e' ratios were determined.

The RV systolic function was assessed using multiple parameters, such as the right ventricular index of myocardial performance (RIMP) (Tei index), S' wave of the tricuspid annulus, and longitudinal systolic strain. The isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), and ejection time (ET) were measured from the tissue Doppler velocity of the lateral annulus of the tricuspid valve to calculate the RIMP using the relevant formula (Equation 2) (Figure 1A).

$$(2) \quad RIMP = \frac{IVRT + IVCT}{ET}$$

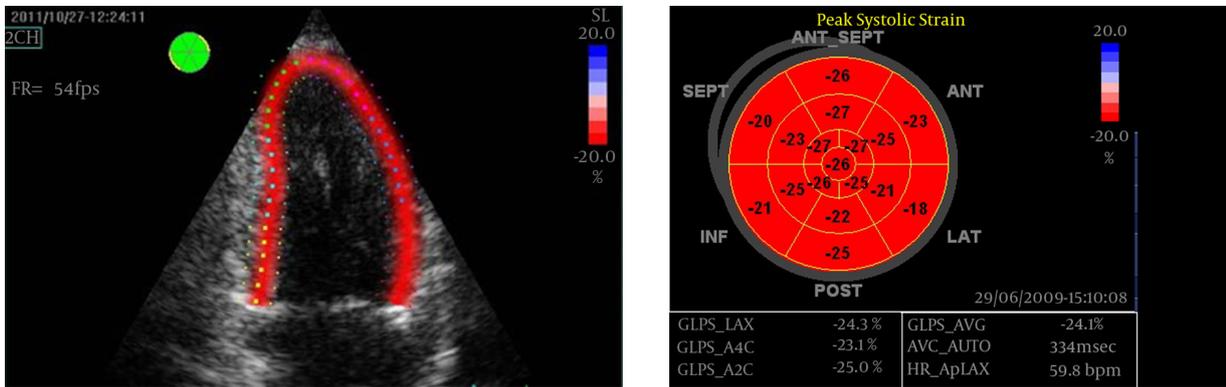
The S' velocity of the lateral annulus of the tricuspid valve, E' velocity, and atrial emptying wave (A') velocity were measured by TDI. Tissue-derived strain analysis was done to estimate the longitudinal strain in the mid segment of the RV free wall (Figure 1B). The E wave velocity of the tricuspid inflow was also measured. The E/A, E/E', and E'/A' ratios were calculated as echocardiographic parameters for the assessment of the RV diastolic function. Additionally, the pulmonary artery pressure was estimated using the tricuspid regurgitation peak pressure gradient.

3.2. Global Left Ventricular Longitudinal Strain

The global left ventricular longitudinal strain (GLS) was assessed via the automated functional imaging method. Three apical views were recorded in each patient (apical long-axis and four- and two-chamber views) in gray scale with a frame rate of at least 50 per second. The mitral annulus and the LV apex were defined in each view. The endocardial, mid-myocardial, and epicardial borders were traced automatically (Figure 2A), whereas the region of interest was adjusted manually if necessary. The myocardial motion was evaluated via STE in each region of interest.

The peak systolic longitudinal strain was calculated in each ventricular segment, and the final data were gathered in a bull's-eye template (a 17-segment model) (Figure 2B). The mean longitudinal strain in all the 17 segments was identified as the average global longitudinal peak systolic strain for the whole LV. A larger longitudinal systolic strain was presented by a larger negative value. All the subjects with a poor endocardial definition were excluded from the study. The strain analyses were done on an offline basis. The echocardiographic data were gathered and interpreted blind to the subjects' clinical status.

Figure 1. Two-Dimensional Speckle Tracking for the Measurement of the Global Longitudinal Strain in the Left Ventricle (LV)



A, Automatic endocardial tracing in the two-chamber view. The same process is done in the four-chamber and apical long-axis views. The final result is shown as a Bull's-eye template; B, global longitudinal strain was -24.1% in this case.

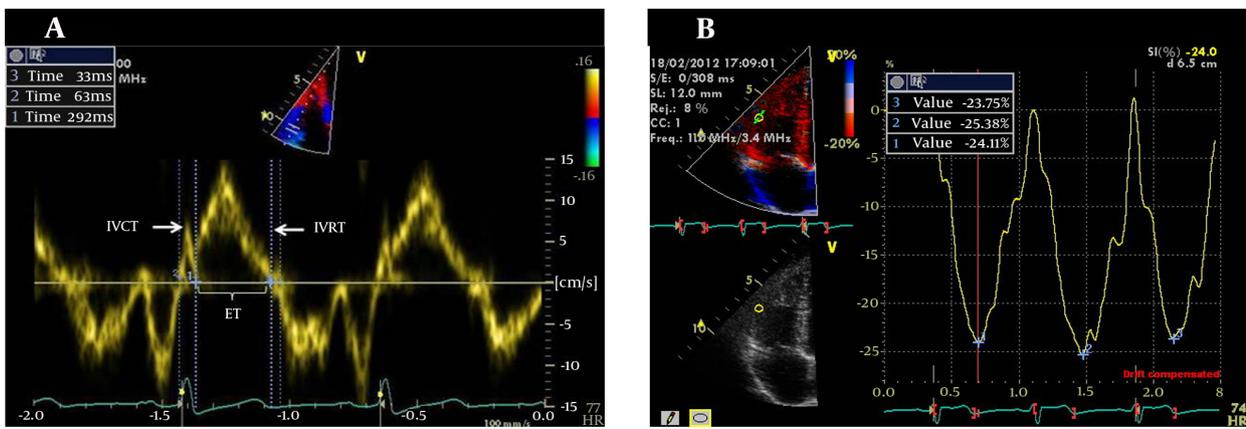


Figure 2. A, Tissue Doppler Imaging Used for Calculating the Right Ventricular Myocardial Performance Index (RV MPI). B, Tissue Doppler-Derived Strain Imaging for the Measurement of the Longitudinal Strain in the Mid Segment of the Free Wall.

3.3. Observer Variability

The interobserver variability was assessed in 10 randomly selected SLE patients via an analysis of the echocardiographic data measured by two separate observers. The GLS, RV strain, and RIMP were considered for this assessment. The interobserver agreement was also tested for these data.

3.4. Statistical Analysis

All the statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 16.0. The continuous variables were presented as mean \pm standard deviation (SD). Normality tests (i.e. Kolmogorov-Smirnov and Shapiro-Wilk) were used to assess the distribution pattern of the variables. The t-test and chi-square test were utilized for the analysis of the quantitative and qualitative variables, respectively. In case the data were not normally distributed, non-parametric tests were employed for comparison. The level of significance was set at 0.05.

4. Results

The study population was comprised of 45 SLE patients including 38 (84.4%) females at a mean age of 31.38 ± 8.09 years and 25 healthy individuals as the control group including 19 (76%) females at a mean age of 30.20 ± 7.74 years. Both groups were matched in terms of age ($P = 0.555$) and sex ($P = 0.391$). Neither the SLE patients nor the control group had risk factors for cardiovascular diseases, including hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking, and family history of cardiovascular diseases.

The SLEDAI score was 8.3 ± 5.1 in the SLE patients. The SLE duration was 5.5 ± 3.4 years. The disease severity was estimated as mild to moderate according to the calculated score. All the patients were on corticosteroid therapy, but the total daily dose of prednisolone was not high (less than 30 mg).

All the measured echocardiographic variables are depicted in Table 1.

Table 1. Echocardiographic Variables in the Systemic Lupus Erythematosus Patients and the Control Group (by Conventional Study, Tissue Doppler Imaging, and Speckle Tracking) ^{a,b,c}

Echocardiographic Parameters	SLE Patients (N = 45)	Normal Group (N = 25)	P Value
RV systolic function			
TDI-derived MPI ^d	0.27 ± 0.08	0.28 ± 0.07	0.788
Tricuspid annulus S', cm/s ^d	11.85 ± 1.66	12.16 ± 1.62	0.275
RV longitudinal strain, % ^d	-33.20 ± 9.11	-33.47 ± 8.05	0.641
RV diastolic function			
Tricuspid E velocity, m/s ^d	0.49 ± 0.12	0.47 ± 0.11	0.791
Tricuspid annulus E' ^d	11.92 ± 2.56	13.32 ± 2.86	0.245
Tricuspid deceleration time, ms	176.28 ± 33.68	174.11 ± 26.76	0.164
Tricuspid E/E' ratio ^d	4.15 ± 1.46	4.30 ± 1.55	0.322
Tricuspid E/A ratio	1.45 ± 0.38	1.56 ± 0.34	0.884
Tricuspid E'/A' ratio ^d	1.12 ± 0.55	1.09 ± 0.62	0.228
LA volume, cc	46.12 ± 15.78	41.14 ± 13.01	0.606
PAP, mmHg	24.42 ± 5.24	22.52 ± 4.07	0.142
LV size			
IVSd, cm	0.79 ± 0.15	0.77 ± 0.10	0.046
LVIDd, cm	4.47 ± 0.47	4.55 ± 0.45	0.748
LVIDs, cm	3.03 ± 0.39	2.88 ± 0.57	0.222
LVPWt, cm	0.75 ± 0.15	0.68 ± 0.12	0.156
LV mass, gr	111 ± 29.54	104.37 ± 27.39	0.468
LVEDV, cc	93.88 ± 20.14	90.71 ± 17.81	0.579
LVESV, cc	40.14 ± 9.54	37.29 ± 8.34	0.410
LV systolic function			
LVEF	57.21 ± 4.90	58.98 ± 3.72	0.152
Mitral annulus S' ^d	6.92 ± 1.17	7.04 ± 1.01	0.680
GLS average	-18.56 ± 2.50	-19.89 ± 1.94	0.028
LV diastolic function			
Mitral E velocity, m/s	0.75 ± 0.16	0.77 ± 0.13	0.729
Mitral A velocity, m/s	0.57 ± 0.15	0.57 ± 0.16	0.955
Mitral E/A ratio	1.40 ± 0.45	1.44 ± 0.44	0.588
Mitral deceleration time, ms	176.42 ± 36.84	167.22 ± 29.82	0.143
Mitral septal E', cm/s ^d	9.92 ± 2.09	11.08 ± 2.10	0.933
Mitral lateral E', cm/s ^d	13.42 ± 3.21	14.14 ± 2.79	0.488
Septal E/E' ratio ^d	7.77 ± 1.70	7.17 ± 1.35	0.359

^a Abbreviations: GLS, Global longitudinal strain; IVSd, Interventricular septum diameter in diastole; LV, Left ventricle; LVIDd, Left ventricular internal diameter in diastole; LVIDs, Left ventricular internal diameter in systole; LVEDV, Left ventricular end-diastolic volume; LVEF, Left ventricular ejection fraction; LVESV, Left ventricular end-systolic volume; LVPWt, Left ventricular posterior wall thickness; MPI, Myocardial performance index; and SLE, Systemic lupus erythematosus.

^b All the variables are presented as Mean ± standard deviation.

^c P values ≤ 0.05 are considered significant.

^d Echocardiographic parameters were gathered by tissue Doppler imaging measured by two-dimensional speckle-tracking echocardiography. The remaining parameters were measured by conventional study.

The LVEF, size and thickness of the chambers, pulmonary artery pressure, and mitral and tricuspid inflows were assessed by conventional echocardiography. TDI was used to measure the systolic and diastolic functions of the RV (TDI-derived RIMP and longitudinal strain and S' and E' velocities) and the systolic and diastolic functions of LV (S' and E' velocities). The GLS was the only parameter measured by 2D-STE.

The SLE patients had a lower EF (57.21 ± 4.90 vs. 58.98 ± 3.72; P = 0.152) and mitral annulus S' velocity (6.92 ± 1.17 cm/sec vs. 7.04 ± 1.01 cm/sec; P = 680); the difference however, did not constitute statistical significance. The GLS was significantly lower in the SLE patients than in the control group (-18.56 ± 2.50% vs. -19.89 ± 1.94%; P = 0.028).

As regards the LV diastolic dysfunction, the SLE patients did not show this condition more frequently than the controls.

The SLE patients had a greater LV mass (111 ± 29.54 g vs. 104.37 ± 27.39 g; P = 0.468) and interventricular septal thickness at end-diastole (0.79 ± 0.15 cm vs. 0.77 ± 0.10 cm; P = 0.046).

The minimum value of the tricuspid annulus was 8 cm/sec. The range for the deceleration time of the tricuspid inflow was 135 - 230 msec and the E/A and E/E' ratios were 0.88 - 2 and 2.14 - 6.25, respectively.

None of the subjects had evidence of the RV diastolic dysfunction considering the cut-off values suggested in the latest related guideline (9).

RIMP, tricuspid annulus S' velocity, and strain imaging (TDI-derived) were used for the assessment of the RV systolic function, which showed no significant differences between the two groups.

4.1. Inter- and Intraobserver Variability

The main echocardiographic parameter was the GLS, for which there was a high inter- and intraobserver agreement (inter-class correlation coefficient [ICC]: 0.95, 95% confidence interval [CI]: 0.8-0.98; P < 0.001 and ICC: 0.91, 95%CI: 0.67 to 0.98; P < 0.001, respectively). The intra- and interobserver agreement was worse in the assessment of

the RV strain than in the RIMP (ICC: 0.86, 95%CI: 0.46 to 0.96; P < 0.001 vs. ICC: 0.83, 95%CI: 0.32 to 0.96; P = 0.007, respectively) (Table 2).

5. Discussion

The present study confirmed the role of echocardiography in the early detection of cardiovascular dysfunction in SLE patients. We excluded patients with coronary heart disease risk factors because some studies have suggested that cardiovascular problems in patients with SLE could be attributable to the traditional coronary artery disease risk factors (such as hypertension, dyslipidemia, and diabetes mellitus), all of which may be provoked by corticosteroid therapy (11, 12). Nonetheless, the underlying disease may be atherogenic by itself through its chronic activation of the immune system (3).

The underlying inflammatory processes leading to subclinical vasculitis, myocarditis, or vascular stiffening could result in such changes in the ventricular structure as ventricular remodeling and subsequent hypertrophy (13). The greater septal thickness and LV mass (though insignificant in the latter) in SLE may be due to the increase in the afterload and systolic blood pressure. An increase in the LV mass can cause a rise in the end-diastolic volume because of the difficulty to stretch the myocardial fiber in a ventricle with reduced compliance (14).

Pieretti et al. (15) suggested that inflammation-mediated arterial stiffening was the underlying mechanism for the LV hypertrophy in SLE and that it was not exclusively a result of associated ischemic or valvular heart disease, renal failure, premature subclinical atherosclerosis, or hypertension. The increases in arterial stiffness, documented in SLE patients, seem to be directly related to the chronicity of the disease and the circulating markers of inflammation (16). The LV hypertrophy could result in stroke, coronary heart disease, congestive heart failure, and sudden cardiac death in different patient groups. Accordingly, the LV hypertrophy may be deemed a prognostic factor for cardiac morbidity and mortality in SLE patients (17). Our literature review yielded conflicting results vis-à-vis the ventricular size and function in SLE (18-25).

Table 2. Inter- and Intra-observer Agreement (n = 10) in the Three Main Measurements ^{a,b}

Measurements	Intraobserver Agreement			Interobserver Agreement		
	Degree of Correlation ^c	95% Confidence Interval	P Value	Degree of Correlation ^c	95% Confidence Interval	P Value
Longitudinal strain (for RV)	0.86	0.46 - 0.96	< 0.001	0.83	0.32 - 0.96	0.007
TDI-derived MPI (for RV)	0.96	0.87 - 0.99	< 0.001	0.90	0.65 - 0.97	< 0.001
GLS (for LV)	0.95	0.80 - 0.98	< 0.001	0.91	0.67 - 0.98	< 0.001

^a Abbreviations: GLS, Global longitudinal strain; LV, Left ventricle MPI, Myocardial performance index; RV, Right ventricle; and TDI, Tissue Doppler imaging.

^b Measurements were done in ten randomly selected systemic lupus erythematosus patients.

^c ICC, Interclass correlation coefficient.

We found no significant differences concerning the conventional measurements of the internal systolic and diastolic diameters and functions of the chambers. The LVEF was not significantly different between the SLE and control groups in our study, chiming in with the results of the studies by Nagueh et al. (21) and Enomoto et al. (22).

In a study on 104 SLE patients compared with 104 age- and sex-matched controls, the E/E', left atrial volume index, LV mass index, pulmonary artery pressure, and RV dimension were significantly higher in the patient group (25).

In a study by Buss et al. (23), the systolic and myocardial velocities defined by TDI were impaired in the 67 SLE patients compared to the control group; the results were confirmed by strain and strain rate imaging. In a case-control study by Wislowska et al. (24), there were no statistically significant differences in the systolic heart function between the SLE and control groups. The authors also reported that the EF was lower in the SLE patients but in the subgroups with a long disease duration. In addition, the diastolic function was impaired significantly, showing higher mitral A' velocity and lower E'/A' ratio, which is not compatible with our results (in both LV and RV).

There is a paucity of data on the RV function in SLE in the existing literature. In one of these few studies, Leal et al. (26) recently recruited 35 childhood-onset SLE patients and found a significant reduction in the RV longitudinal systolic strain (but not strain rate). The results of our study on an adult population showed that the systolic and diastolic function of the RV, assessed in terms of RIMP, S' velocity, and TDI-derived strain analysis, were not impaired. We conclude that the LV seems to be more vulnerable than the right heart in SLE patients.

As was previously mentioned, for all the research on the assessment of the ventricular function mostly targeting the LVEF, S' velocity, and TDI-derived strain, the data on 2d-STE are limited. Recently, Huang et al. (4) used 3D-STE and demonstrated that the peak systolic GLS was $-18.2 \pm 2.9\%$ in their SLE patients. All the patients were followed up for one year, and no cardiovascular events or symptoms necessitating further work-up were detected. Nevertheless, it seems that a longer follow-up duration is needed to define the clinical importance of the detected LV dysfunction in an otherwise asymptomatic SLE patient.

An abnormal LV function could be detected in SLE patients even in those without cardiac symptoms or coronary heart disease risk factors. STE is a valuable method for detecting such subclinical myocardial dysfunction and seems to be superior to conventional echocardiography.

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Authors' Contributions

Study concept and design: Hoorak Poorzand, Seyedeh Zahra Mirfeizi; Acquisition of data: Hoorak Poorzand,

Seyedeh Zahra Mirfeizi, Aida Javanbakht; Analysis and interpretation of data: Hoorak Poorzand, Seyedeh Zahra Mirfeizi, Aida Javanbakht; Drafting of the manuscript: Aida Javanbakht, Hoorak Poorzand, Hedieh Alimi; Critical revision of the manuscript for important intellectual content: Hoorak Poorzand; Statistical analysis: Aida Javanbakht, Hoorak Poorzand; Administrative, technical, and material support: Aida Javanbakht, Hoorak Poorzand, Seyedeh Zahra Mirfeizi, Hedieh Alimi; Study supervision: Seyedeh Zahra Mirfeizi, Hoorak Poorzand.

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