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Original Article (Pages: 8561-8578)

Doppler Tissue Echocardiography and Electrocardiography in Children with Celiac Disease Compared to Controls

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Abstract

Background
Celiac disease (CD) is an autoimmune mediated gluten sensitive enteropathy and characterized by a wide range of clinical manifestations. The study aimed to compare Doppler tissue echocardiography findings between children with celiac disease and healthy children.

Materials and Methods
This case-control study was performed on 186 celiac and healthy children aged 6- 19 years. Celiac diagnosed by clinical findings and laboratory's tests (tTGIgA) confirmed by intestinal biopsy. Controls consisted of voluntary individuals free of any diseases. Echocardiography performed on participants. Data analyzed utilizing SPSS software version 20.0.

Results
Left Peak A, left S', right ICT', right IRT', right S', EF, FS, left ET', left IRT', right E'/A' left S' were higher in case when Right ET was lower. Patients with left S' < 8 were lower in left A', higher in right ICT', lower level in right S', higher in left E/E'. Patients with Left E/E' ≥9, were higher in Left Peak E velocity, lower in IVSD, higher in right E/E', lower in left S' and lower in left E' (P<0.05).

Conclusion
Almost all heart findings were higher in celiac patients except a few. Patients with left S' <8 were in lower level of left A' and right S', and in higher level of right ICT', left E/E'. Patients with Left E/E' ≥9, were higher in Left Peak E velocity and E/E', lower in IVSD, left and left S'.

Key Words: Children, Celiac disease, Tissue Doppler Echocardiography.

*Please cite this article as: Noori NM, Teimouri A, Shahramian I, Shahraki T. Doppler Tissue Echocardiography and Electrocardiography in Children with Celiac Disease Compared to Controls. Int J Pediatr 2018; 6(11): 8561-78. DOI: **10.22038/ijp.2018.32405.2855**

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Received date: Apr.12, 2018; Accepted date: Jun.22, 2018

1- INTRODUCTION

Celiac disease (CD) is an immune system interceded gluten delicate enteropathy and it happens in hereditarily predisposed people (1). It also is a systemic disorder of immune-mediated which is caused by a lasting intolerance to gluten, which is found in wheat, rye and grain. It described by an extensive variety of clinical appearances and its prevalence varied from 0.3% in Germany to 2.4% in Finland. In which is higher 1.5 to 2 times in females than males and it influences around 0.6 to 1.0%, of total population (2, 3). CD is frequently associated with iron deficiency anemia, dermatitis herpetiformis, thyroid disorders, diabetes mellitus, metabolic bone disease, peripheral neuropathy, endothelial dysfunction, infertility and various connective tissue disorders. The incidence of CD increases in patients with primary and secondary cardiomyopathy (2).

One of its most prevalence signs that directed to the secondary cardiomyopathy is chronic malabsorption. An intestinal variation from the norm in patients with CD caused myocardial harm through insusceptible interceded components that are perhaps because of increment the foundational assimilation of different luminal antigens or infectious agents (4). Myocardial contribution can have the capacity to be auxiliary to a safe reaction that coordinated against an antigen exhibit in both the myocardium and the small digestive tract (2, 3, 5). In chronic provocative sicknesses like connective tissue issue, the heart contribution is normal. In this way, in Disc, cardiovascular inclusion is normal like in other constant incendiary sicknesses. Another turmoil that as often as possible related with Compact disc is idiopathic expanded cardiomyopathy. An immunologic acquainted component and an expanded predominance of Album in patients who have idiopathic widened cardiomyopathy have been illustrated (1, 6). Furthermore, a few reports have recommended that both CD and idiopathic expanded cardiomyopathy have an insusceptible procedure as for the heart and digestive system (2, 7, 8). Found that there is an association between Congenital Heart Defect (CHD) and CD in two cases with Coarctation of the aorta (CoA or CoAo) (9, 10). There are a few information proposing an expanding risk of cardiovascular events and stroke in patients with CD. For example, in two based population studies, an expanded risk of atrial fibrillation (AF) has been accounted in patients with CD (11, 12).

It is likewise conceivable that cardiac rhythm disturbances such as, AF might be related with the observed increment in the danger of stroke. The part of foundational irritation being developed of AF due to fibrotic changes in the chamber has been already settled (12). Doppler tissue echocardiography (DTE) evaluation is helpful instrument to get confirmation of subclinical hindrance of ventricular capacity amid clinical dependability in patients with CD (13). Akin et al. performed a study on DTE and conventional echocardiography to evaluate the impairment of myocardial diastolic functions in patients with CD. They received to the conclusion that DTE is more accurate and reliable (13). The aim of the present study is to investigate cardiac functions in patients with celiac disease by using DTE to identify myocardial dysfunctions in patients with celiac disease compared to healthy individuals. Akin et al., played out an investigation on DTE and conventional echocardiography to assess the impairment of myocardial diastolic capacities in patients with CD. They got to the conclusion that DTE is more precise and dependable (13). The present study aimed to investigate cardiac functions in patients with celiac disease compared to healthy individuals utilizing DTE.

2- MATERIALS AND METHODS

2-1. Study design and samples

This case-control study was performed in a double-center of cardiology and gastroenterology clinics on patients aged from 6 to 19 years who matched in sex and age with healthy children from January to December 2017 after approval by the ethics committee of Zahedan University of Medical Sciences, Zahedan (ZaUMS), Iran. Consent form was obtained from the patients and controls guardians. Celiac disease diagnosed based on a combination of clinical findings and laboratory's tests (tTGIgA) with a cut point of 20 and confirmed by intestinal biopsy. After considering the exclusion criteria and confirmation by intestinal biopsy 92 patients with celiac disease were enrolled in the study. Control group consisted of 92 healthy voluntary individuals with the same age and gender free of any diseases.

2-2. Criteria

Patients with obvious valvular heart disease (VHD), rhythm abnormality, structural, congenital heart disease, active infection, malignancy, other systemic inflammatory diseases, diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease and hypertension excluded from the study. The same exclusion criteria were applied for the control subjects.

2.3- Measures and tools

The whole study population went under Electrocardiography (ECG), conventional echocardiography and Doppler tissue echocardiography by a cardiologist, using My Lab 60 instrument with 3-8-MHz transducers (made in Italy). ECG findings were as follow: QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; QTd (QT interval dispersion): different between max and min of QT; QTc (the corrected QT interval): QT/√(RR in seconds); QTcd (QTc dispersion): different between max and min of QTc. The values of all necessary echocardiographic parameters namely ejection fraction (EF), fractional shortening (FS), interventricular septal dimension in diastole (IVSD), interventricular septal dimension in systole (IVSS), left ventricular end-diastolic dimension (LVDD), and left ventricular end-systolic dimension (LVSD) posterior wall dimension in systole of the left ventricle (LVPWS), posterior wall dimension in diastole of the left ventricle (LVPWD), interventricular septal dimension in systole (IVSS), posterior wall dimension in systole (PWDS), and posterior wall dimension in diastole (PWD), were measured via M-mode echocardiography of the left side were estimated from three cardiac cycles.

The velocity of the blood flow through the heart valves, as well as the ejection time (ET), peak A velocity (A), peak E velocity (E), myocardial performance index (MPI), peak E (early mitral and tricuspid valve flow velocity) / peak A (late mitral and tricuspid valve flow velocity) velocity (E/A ratio), isovolumic relaxation time (IRT), isovolumic contraction time (ICT) of both sides were measured with pulsed Doppler echocardiography (14). The sample volume was positioned at the tips of the tricuspid and mitral valve leaflets in the apical four-chamber view to enable the measurement of (a): which is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow.

The sample volume was thereafter relocated to the left ventricular outflow tract just below the aortic valve (apical five-chamber view) so as to measure (b): which is the left ventricular ejection time. The right ventricular outflow velocity pattern was also recorded from the parasternal short-axis view with the Doppler sample volume positioned just distal to the pulmonary valve for the measurement of (b). Myocardial Performance Index (MPI/Tei Index) was calculated as a-b/b = (ICT + IRT)/ET.

The left ventricular mass index (LVMI) was also calculated by the following formula:

LVM (g) = 0.8 (1.04 (((LVEDD + PWTD + IVSTD)^3-LVEDD ^{3}))) + 0.6; and LVMI (g/m^2) = LVM / 2.7.

All the parameters in the above formula measured in the M-mode view and in diastole and utilized for left ventricular mass evaluation (14, 15). Relative Wall Thickness (RWT) was calculated as 2 times PWD divided by the LVEDD (16). Doppler tissue echocardiography (DTE) was another method that performed from the apical four-chamber view and 3 mm pulsed Doppler sample volume placed at the level of lateral mitral annulus. Myocardial velocity profiles of the lateral tricuspid annulus and lateral mitral annulus were obtained by placing the sample volume at the junction of the tricuspid annulus and the right ventricle (RV) free wall and at the junction of the mitral annulus and LV posterior wall, respectively. With this modality, the recorded values were the early (E), and late (A) diastolic mitral and tricuspid annular velocities, and the ratio of E/A. Right ventricle and left ventricle myocardial performance index (MPI) was obtained by dividing the sum of isovolumic relaxation time (IVRT) and isovolumetric contraction time (ICT) by the ejection time (ET) (MPI = (ICT + IRT)/ET) (**Figure.1**).

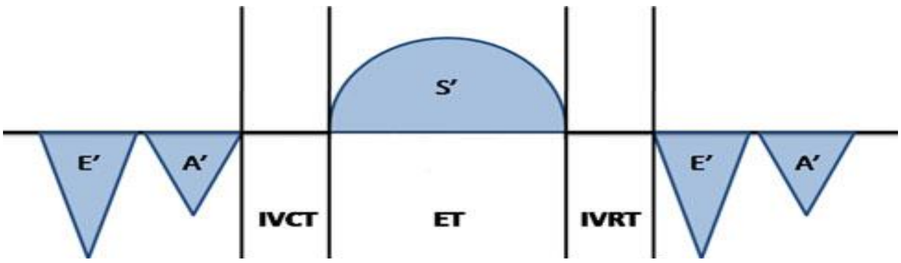

Fig.1: Diagram of Doppler Tissue Echocardiography waves: S', systolic wave; E', early diastolic wave; A', late diastolic wave (17).

Left and right S: Systolic myocardial velocity above the baseline in mitral and tricuspid. Left and right E: early diastolic myocardial relaxation velocity below the baseline in mitral and tricuspid. Left and right A: myocardial velocity associated with atrial contraction in mitral and tricuspid. Our participants weighted using RASA Mark made in Islamic Republic of Iran by error factor of 100 gr. In addition, their heights were measured in the standing position with a scale ruler.

2-4. Statistical analysis

Data were analyzed using SPSS software version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The continuous variables expressed as mean ± standard deviation (SD) and categorical variables expressed as number and percentages. The normal distribution of variables verified with the Kolmogorov-Smirnov (K-S) test; while the distribution was normal, Student's t-test applied for comparisons between the groups other than the Mann-Whitney U. The values were accepted as significant when P<0.05.

3- RESULTS

The present examination performed to look at DTI measures in celiac and controls children. **Table.1** shown normally distribution of the major variables. The majority of the variables were free in distribution except Left a, Left ET, LVDD, ET', right A', Left MPI, Right MPI, Left MPI', Right MPI' that were normal (p>0.05) (*please see the table at the end of paper*). **Table.2** shown sex distribution of participants and patients in groups of left S' and left E/E' levels. Observed that from 92 patients, 54 (58.7%), and 38 (41.3%) were female and male respectively. From 92 healthy children 44 (47.8%), and 48 (52.2%) were female and male in the order given. The analysis showed that the sex distribution was same (Pearson X^2= 2.183, and P= 0.140) in case and control. In the case of E/E' as a dysfunction, the severity defined with higher mean level and the table showed that from the 9 patients who had E/E' higher than cut-off, the sex distribution was 5 and 4 for female and male, respectively. Similar pattern observed in left S'<8 so that from the patients who had the level of left S' lower than 8, 53.3% were females (*please see the table at the end of paper*).

Table.3 shown the mean of normal variables in case and control. All the variables were different significantly in case and control except am and LVDD (p>0.05). Left MPI, right MPI, left MPI', right MPI' and right A' were higher in case and right ET' (p<0.001), and left ET (p<0.001) were higher in controls significantly (*please see the table at the end of paper*). **Table.4** shown that the mean age of case and controls were 10.33±3.12 and 10.25±4.09 years, respectively (p>0.05). All the anthropomorphic indices of weight (p<0.001), height (p<0.001) and BMI (p<0.001) were lower in case significantly. Left Peak A (58.68±14.09 vs. 53.68±10.51), left S' (9.29±1.27 vs. 8.91±1.63), right ICT' (79.98±14.43 vs. 74.76±15.37), right IRT' (112.33±20.89 vs. 101.69±19.89), right S' (11.66±2.37 vs. 32.14±28.38), EF (0.74±0.65 vs. 29.31±37.63), FS (0.43±0.57 vs. 16.84±22.23), left ET' (242.21±21.46 vs. 320.26±66.49), left IRT' (110.56±18.53 vs. 88.76±24.52), right E'/A' (1.79±0.64 vs. 2.10±0.76), left S' (1.84±0.37 vs. 1.70±0.46) were significantly higher in case when, right ET was higher in control (248.74±24.51 vs. 267.41±31.58) (*please see the table at the end of paper*).

Table.5 shown heart findings in patients' groups based on S'=8 and E/E'=9. In terms of left S' cut-off point, the patients who had left S' < 8 were in lower level of left A' (6.49±1.13 compared to 7.31±1.61), and right S' (10.45±1.90 compared to 11.90±2.39), and were higher level of right ICT' (86.60±13.07 compared to 78.69±14.41), and left E/E' (7.63±1.55 compared to 6.39±1.50), significantly. In terms of left E/E' cut-off, the patients who had left E/E' ≥ 9, were in higher levels of left Peak E velocity (114.56±15.53 compared to 98.06±16.69), and right E/E' (5.88±3.62 compared to 4.69±1.31) significantly; when the patients had lower level of IVSD (0.54±0.13 compared to 0.63±0.11), left S' (8.40±0.96 compared to 9.38±1.27), and left E' (11.94±1.72 compared to 17.65±17.87), significantly (*please see the table at the end of paper*).

4- DISCUSSION

From the present investigation resulted that heart complication of left A, left S', right ICT', right IRT', right S', EF, FS, left ET', left IRT', right E'/A', left S' were higher on the off chance that and right ET was higher in charge. Karadas et al. (18) led an investigation on kids with CD to survey the subclinical impact on heart. They examined DTE measures and estimated that E/E' was varied significantly from case to controls dissimilar with the present study outcome. Saylan et al. (19) in a study on children aged from 5 months to 19 years reported a significant difference on weight and height between the participants' categorization of case and control. Regarding age and anthropometric indices the present study was confirmed by Saylan et al.'s results. This study resulted that IVSD and LVDD parameters were different between case and control significantly dissimilar with present results. Be that as it may, in present examination EF and FS which are generally utilizing to evaluate left ventricle (LV) systolic capacity were similar in case and controls in same line with this study results that the parameters measured utilizing conventional echocardiography.

The present study resulted that left and right myocardial performance index (MPI) was different in case and control similar with Saylan et al. study; they likewise received to the conclusion of significant differences in left E, left A and right', right MPI, left S, left ICT, right A, and right IRT utilizing DTE in case and control, when significant changes not observed in left IRT and left MPI. From the present examination resulted that left S', right ICT', right IRT', right S', left ET', left IRT', right E'/A', left S' were higher in case (19). Noori et al. (20) directed an investigation on celiac patients to evaluate cardiovascular associations by DTE and conventional echocardiography and came about that, with respect to DTE technique, ET, MPI and IRT in both left and right hearts were distinctive in case compared with controls. They additionally came about that left ICT was distinctive altogether in case and controls. The present investigation got to the comparative outcomes with the exception of ET that was not higher in both left and right heart and IRT that was higher in the right heart utilizing comparable method (DTE). Akin et al. (13) assessed left ventricular functions with utilizing of DTE and conventional techniques on patients. They found that LVDD, LVSD, PWD, IVSD, and EF parameters were not different in case and controls. With respect to the parameters in study, Noori et al. (20) resulted same outcomes aside from that discovered IVSD and EF were significant different in case and controls.

These results of the recent studies in same line with the conclusion of the present investigation. In Noori et al.'s study (20) left E'/A' was not significant that was similar with the results of the present examination, however, IRT' in left and right had same patterns with the results of the present investigation that it was confirmed also by Akin et al.'s results (13). Akin et al. (13) revealed any differences in MPI between the groups when Noori et al. (20), and the present found. Akin at al. (13) found that left S', left E ', and left E'/A' ratio were significant when was similar with the present study in left S'. Left IRT' was longer in patients like the present investigation. Sari et al. (6) utilized conventional echocardiography to evaluate cardiovascular finding in case and controls. In their investigation the findings such as: EF, IVSD, PWD, LVDD, LVSD, left E, left A were not significant. The outcomes are comparable with the present investigation aside from left peak A velocity that was significant in the present examination. The patient was divided into two groups regarding E/E' proportion and S'. The results of the present examination demonstrated that the patients who had S' <8 had bring down levels of left peak A' velocity and right S'. What's more, had larger amount of right ICT' and left E/E'. If there should be an occurrence of left E/E' ≥9, the patients had larger amounts of Left

Peak E velocity s and right E/E'. What's more, had bring down level of IVSD, left S' and left E'. Cremation's et al. (21) found A' and DT were same and E, E/A, had distinctive qualities in patients considering E/E'>9 in patients. In Noori et al.'s study (22) and Balkan et al.'s study (23) an expansion in the ratio of left E/E' causes diastolic dysfunctions in the case particularly when the level of E/E' is more than suspected level. Balkan et al. (23) detailed that echocardiographic assessment uncovered that E, LVES, LVED, LA measurement, LAVI, and LVMI esteems were fundamentally higher in E/E' proportion ≥ 9 than E/E' proportion < 9. The consequences of Noori et al.'s study (22) examine uncovered that thalassemia patients with low level of E/E' had low estimations of EF and FS in more aged patients.

The present study demonstrated that EF and FS were dissimilar in groups of thalassemia patients based on E/E' cutoff. Marcello Marc et al. (24) played out an examination on thalassemia patients to recognize early cardiac dysfunctions by DTE and came about that patients with S' < 8 cm/s had a lower estimation of left E' in contrast with patients with left S' > 8 cm/s. With comparative arrangement of left S', the Noori et al. (22) examine came about that left E' was comparable in the two groups of patients. It appeared that patients with S' < 8 cm/s likely have higher danger of cardiovascular associations in thalassemia patients.

Noori et al. (22) found that EF was not decreased in all age gatherings of patients with left S' < 8 cm/s essentially when Marcello et al. (24) and Akpinar et al. (25) found a huge contrast. The present investigation concluded that EF was comparable in patients with S' arrangements. In correlation, the present investigation was comparative with Noori at al. (22) and different with the said results about.

5- CONCLUSIONS

Our investigation demonstrated that TDE exhibit the weakness of myocardial diastolic capacity in patients with celiac disease. Presumed that all the heart discoveries were higher in celiac patients. Patients who had left S' <8 were in lower level of left A' and right S', and in higher of right ICT', left E/E'; patients who had Left E/E' ≥ 9, were in more elevated amount of Left Peak E velocity and E/E'. These outcomes showed that TDE is smarter and more accurate to recognize early heart changes in patients with CD. We prescribe to utilize TDE to recognize subclinical cardiovascular dysfunctions in celiac patients.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

The authors would like to thank all the participants' parents for their warm participation in the study.

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Table-1: The data normally distribution based on Kolmogorov-Smirnov test

Variables	K.S	P- value	Variables	K.S	P- value	Variables	K.S	P- value
Age	0.103	<0.001	EF	0.496	<0.001	QTcd	0.107	<0.001
Weight	0.077	0.010	FS	0.496	<0.001	Heart Rate	0.094	<0.001
Height	0.069	0.034	Left ET'	0.21	<0.001	Right E/E'	0.151	<0.001
Left a	0.061	0.095	Left ICT'	0.15	<0.001	Left E/E'	0.105	<0.001
Left peak E	0.082	0.004	Left IRT'	0.098	<0.001	Left E'/A'	0.311	<0.001
Left Peak A	0.104	<0.001	Left S'	0.075	0.013	Right E'/A'	0.127	<0.001
Right a	0.074	0.016	Left E'	0.342	<0.001	Left MPI	0.059	0.200[c]
Right peak E	0.097	<0.001	Left A'	0.07	0.027	Right MPI	0.063	0.071
Right peak A	0.100	<0.001	Right ET'	0.116	<0.001	Right MPI'	0.065	0.055
Right ET	0.083	0.004	Right ICT'	0.087	0.002	Left MPI'	0.055	0.200'
Left ET	0.066	0.051	Right IRT'	0.093	0.001	Left S'	0.475	<0.001
IVSD	0.106	<0.001	Right S'	0.406	. <0.001	BMI	0.117	<0.001
LVDD	0.051	0.200	Right E'	0.062	0.086	LVMI	0.1	<0.001
PWD	0.148	<0.001	Right A'	0.064	0.061	PWS	0.141	<0.001
IVSS	0.096	<0.001	QT	0.223	<0.001	QTd	0.369	<0.001
LVDS	0.153	<0.001	QTc	0.127	<0.001			

K.S: Kolmogorov-Smirnov, a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, AT: Acceleration time, Dt: deceleration time, Peak E: early mitral and tricuspid valve flow velocity, Peak A: late mitral and tricuspid valve flow velocity, ET: ejection Time, Aod: Diameter of Aorta in Diastole, LAd: Diameter of LA in Diastole, Aos: Diameter of Aorta in Systole, LAs: Diameter of LA in Systole, IVSD: interventricular septal dimension in Diastole, LVDD: left ventricular end-diastolic dimension, PWD: posterior wall dimension in diastole, IVSS: interventricular septal dimension in systole, LVDS: Left ventricular diameter at systole, PWS: posterior wall dimension in systole, EF: ejection fraction, FS: fractional shortening, QT: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, QTc: QT / √ RR, NFQTc: new formula for QTc in which is equal to 2qt/(1+RR), QTd: the difference between the maximum and minimum QT values. QTcd: the difference between the maximum and minimum QTc values.

Table-2: The sex distribution of participants in groups of S' and E/E'

Groups	Female	Male
	Number (%)	Number (%)
Case	54(58.7%)	38(41.3%)
Control	44(47.8%)	48(52.2%)
Left E/E'< 9	49(59.0%)	34(41.0%)
Left E/E'>=9	5(55.6%)	4(44.4%)
Left S'< 8	8(53.3%)	7(46.7%)
Left S'>=8	46(59.7)	31(40.3%)

Table-3: The comparison of normal distributed heart findings in case and controls

Variables	Participants	Mean	SD	T- value	P- value
Left a	Case	420.83	43.54	0.70	0.483
	Control	416.40	41.73		
Left ET	Case	244.21	21.44	-4.58	<0.001
	Control	263.12	33.29		
LVDD	Case	3.75	0.49	-0.38	0.704
	Control	3.78	0.66		
Right Et'	Case	243.66	22.32	-8.06	<0.001
	Control	286.46	45.74		
Right A’	Case	8.97	2.46	3.38	0.001
	Control	7.82	2.18		
Left MPI	Case	0.73	0.15	4.62	<0.001
	Control	0.60	0.21		
RMPI	Case	0.74	0.18	3.11	0.002
	Control	0.65	0.20		
Right MPI’	Case	0.79	0.12	9.90	<0.001
	Control	0.62	0.11		
Left MPI’	Case	0.78	0.11	14.36	<0.001
	Control	0.55	0.11		

SD: Standard deviation, LVDD: Left ventricular end-diastolic dimension, ET': ejection Time, Left MPI: Myocardial Performance index, RMPI: radionuclide myocardial perfusion imaging.

Table-4: Comparison of heart findings and anthropomorphic indices in free distribution in case and controls

Variables	Groups	Mean	SD	Mean Rank	Sum of Ranks	MW.U	P- value	Variables	mean	SD	Mean Rank	Sum of Ranks	MW.U	P- value
Age	Case	10.33	3.12	92.89	8545.5	4196.5	0.921	Left S'	9.29	1.27	101.57	9344	3398	0.021
	Control	10.25	4.09	92.11	8474.5				8.91	1.63	83.43	7676		
Weight	Case	25.11	7.69	72.56	6675.5	2397.5	<0.001	Left E'	17.08	17.05	96.46	8874.5	3867.5	0.313
	Control	34.46	13.38	112.44	10345				14.92	2.72	88.54	8145.5		
Height	Case	123.67	13.46	74.63	6866	2588	<0.001	Left A'	7.17	1.57	97.49	8969.5	3772.5	0.203
	Control	137.01	21.97	110.37	10154				6.71	1.58	87.51	8050.5		
Left peak E	Case	99.67	17.21	94.85	8726.5	4015.5	0.549	Right ICT'	79.98	14.43	102.13	9395.5	3346.5	0.014
	Control	99.32	15.32	90.15	8293.5				74.76	15.37	82.88	7624.5		
Left PeakA	Case	58.68	14.09	101.77	9363	3379	0.018	Right IRT'	112.34	20.81	105.33	9690.5	3051.5	0.001
	Control	53.98	10.51	83.23	7657				101.70	19.90	79.67	7329.5		
Right a	Case	432.26	52.17	92.6	8519.5	4222.5	0.979	Right S'	11.66	2.37	75.01	6901	2623	<0.001
	Control	438.47	46.44	92.4	8500.5				32.14	28.39	109.99	10119		
Right peak E	Case	69.47	16.33	92.11	8474.5	4196.5	0.922	QT	0.36	0.03	92.78	8535.5	4206.5	0.942
	Control	69.18	12.43	92.89	8545.5				0.36	0.03	92.22	8484.5		
Right peakA	Case	49.21	12.06	88.98	8186	3908	0.369	QTc	0.44	0.04	85.15	7833.5	3555.5	0.060
	Control	50.27	11.36	96.02	8834				0.45	0.04	99.85	9186.5		
Right ET	Case	248.74	24.51	78.97	7265.5	2987.5	0.001	QTd	38.80	7.12	87.77	8074.5	3796.5	0.136
	Control	267.41	31.58	106.03	9754.5				40.27	6.52	97.23	8945.5		
IVSD	Case	0.62	0.11	88.26	8119.5	3841.5	0.278	QTcd	47.96	10.00	86.4	7948.5	3670.5	0.120
	Control	0.65	0.11	96.74	8900.5				50.23	9.13	98.6	9071.5		
PWD	Case	0.35	0.06	92.22	8484	4206	0.942	Hear Rate	93.14	17.95	88.26	8119.5	3841.5	0.279
	Control	0.36	0.05	92.78	8536				97.21	22.65	96.74	8900.5		
IVSS	Case	0.86	0.14	91.09	8380.5	4102.5	0.72	Right	4.81	1.68	89.33	8218.5	3940.5	0.42

	Control	0.87	0.15	93.91	8639.5			E/E’	4.93	1.55	95.67	8801.5		
LVDS	Case	2.14	0.44	94.22	8668	4074	0.662	Left E/E'	6.59	1.57	89.25	8211	3933	0.408
	Control	2.20	0.90	90.78	8352				6.94	2.18	95.75	8809		
PWS	Case	0.35	0.06	92.59	8518.5	4223.5	0.981	Left E/ A'	2.54	3.29	88.91	8179.5	3901.5	0.360
	Control	0.36	0.05	92.41	8501.5				2.36	0.74	96.09	8840.5		
EF	Case	0.74	0.06	86.76	7981.5	3703.5	0.143	Right E/ A'	1.79	0.64	82.34	7575.5	3297.5	0.010
	Control	0.76	0.07	98.24	9038.5				2.05	0.76	102.66	9444.5		
FS	Case	0.43	0.06	87.74	8072	3794	0.224	LVMI	16.72	5.07	88.09	8104.5	3826.5	0.262
	Control	0.44	0.07	97.26	8948				18.04	6.76	96.91	8915.5		
Left ET'	Case	242.21	21.46	52.48	4828.5	550.5	<0.001	Left S'	1.84	0.37	99	9108	3634	0.024
	Control	320.26	64.50	132.52	12192				1.70	0.46	86	7912		
Left ICT'	Case	78.05	15.16	88.08	8103	3825	0.257	BMI	15.97	1.80	75.51	6947	2669	<0.001
	Control	81.63	17.58	96.92	8917				17.55	2.48	109.49	10073		
Left IRT'	Case	110.57	18.53	116.16	10687	2055	<0.001							
	Control	88.76	24.52	68.84	6333									

M-W u=Mann-Whitney U, a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, AT: Acceleration time, Dt: deceleration time, Peak E: early mitral and tricuspid valve flow velocity, Peak A: late mitral and tricuspid valve flow velocity, ET: ejection Time, Aod: Diameter of Aorta in Diastole, LAd: Diameter of LA in Diastole, Aos: Diameter of Aorta in Systole, LAs: Diameter of LA in Systole, IVSD: interventricular septal dimension in Diastole, LVDD: left ventricular end-diastolic dimension, PWD: posterior wall dimension in diastole, IVSS: interventricular septal dimension in systole, LVDS: Left ventricular diameter at systole, PWS: posterior wall dimension in systole, EF: ejection fraction, FS: fractional shortening, QT: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, QTc: QT / √ RR, NFQTc : new formula for QTc in which is equal to 2qt/(1+RR), QTd: the difference between the maximum and minimum QT values, QTcd: the difference between the maximum and minimum QTc values, NFQTcd: new formula for QTcd in which is equal to 2qtd/(1+RR), R in v5: (R wave in V5) the amplitude of R wave in left Precordial, S in v1: (S wave in V1) the amplitude of S wave in right, HR: Heart Rate, Peak E /A: early mitral and tricuspid valve flow velocity / late mitral and tricuspid valve flow velocity, BMI: Body Mass Index, RWT: relative wall thickness, LA/AO in Diastole: Diameter of LA in Diastole/ Diameter of Aorta in Diastole, LA/AO in Systole: Diameter of in Systole / Diameter of Aorta in Systole, LVM: left ventricular mass, LVMI: left ventricular mass index, MPI: Myocardial performance index, BMI: body mass index.

Table-5: The comparison of heart findings in patients with severe hear complication based on S' and E/E' levels.

Variables	Left S' levels	Mean	SD	t-value	P-value	Variables	E/E' ratio level	Mean	SD	t-value	P-value
Left a	S'<8	418.20	39.40	-0.25	0.800	Left a	E/E'<9	420.82	44.71	0.00	0.996
	S'>=8	421.34	44.52				E/E'>=9	420.89	32.70		
Left peak E	S'<8	99.13	13.79	-0.13	0.895	Left peak E	E/E'<9	98.06	16.69	-2.83	0.006
	S'>=8	99.78	17.88				E/E'>=9	114.56	15.53		
Left Peak A	S'<8	54.20	12.42	-1.35	0.180	Left Peak A	E/E'<9	58.96	14.09	0.57	0.568
	S'>=8	59.55	14.30				E/E'>=9	56.11	14.64		
Right a	S'<8	428.47	46.83	-0.31	0.760	Right a	E/E'<9	430.30	53.92	-1.84	0.085
	S'>=8	433.00	53.40				E/E'>=9	450.33	27.45		
Right peak E	S'<8	71.00	25.90	0.39	0.695	Right peak E	E/E'<9	68.40	14.11	-1.95	0.055
	S'>=8	69.18	13.98				E/E'>=9	79.39	29.53		
Right peak A	S'<8	52.80	14.95	1.26	0.210	Right peak A	E/E'<9	49.13	12.20	-0.19	0.849
	S'>=8	48.51	11.40				E/E'>=9	49.94	11.34		
Right ET	S'<8	242.00	19.68	-1.17	0.247	Right ET	E/E'<9	248.06	25.13	-0.81	0.423
	S'>=8	250.05	25.24				E/E'>=9	255.00	17.61		
Left ET	S'<8	244.40	20.79	0.04	0.970	Left ET	E/E'<9	243.92	22.05	-0.39	0.695
	S'>=8	244.17	21.69				E/E'>=9	246.89	15.26		
IVSD	S'<8	0.60	0.10	-1.01	0.317	IVSD	E/E'<9	0.63	0.11	2.29	0.025
	S'>=8	0.63	0.11				E/E'>=9	0.54	0.13		
LVDD	S'<8	3.72	0.28	-0.22	0.829	LVDD	E/E'<9	3.74	0.50	-0.32	0.749
	S'>=8	3.75	0.52				E/E'>=9	3.80	0.43		
PWD	S'<8	0.34	0.05	-0.86	0.393	PWD	E/E'<9	0.35	0.06	-0.35	0.730
	S'>=8	0.35	0.06				E/E'>=9	0.36	0.07		
IVSS	S'<8	0.83	0.17	-0.69	0.494	IVSS	E/E'<9	0.86	0.14	0.88	0.381
	S'>=8	0.86	0.14				E/E'>=9	0.82	0.14		
LVDS	S'<8	2.15	0.30	0.08	0.939	LVDS	E/E'<9	2.14	0.44	-0.13	0.897
	S'>=8	2.14	0.46				E/E'>=9	2.16	0.39		

PWS	S'<8	0.34	0.05	-1.02	0.310	PWS	E/E'<9	0.35	0.06	-0.23	0.816
	S'>=8	0.36	0.06				E/E'>=9	0.36	0.07		
EF	S'<8	0.74	0.06	-0.43	0.668	EF	E/E'<9	0.74	0.07	-0.25	0.803
	S'>=8	0.74	0.07				E/E'>=9	0.75	0.06		
FS	S'<8	0.42	0.06	-0.42	0.674	ES	E/E'<9	0.43	0.06	-0.36	0.719
	S'>=8	0.43	0.06				E/E'>=9	0.44	0.05		
Left ET’	S'<8	241.53	19.01	-0.13	0.895	Left ET'	E/E'<9	241.55	22.24	-0.88	0.379
	S'>=8	242.34	22.02				E/E'>=9	248.22	11.23		
Left ICT'	S'<8	77.07	17.79	-0.27	0.784	Left ICT'	E/E'<9	78.48	15.05	0.82	0.414
	S'>=8	78.25	14.72				E/E'>=9	74.11	16.51		
Left IRT'	S'<8	114.67	14.47	0.94	0.352	Left IRT'	E/E'<9	109.98	19.12	-0.93	0.357
	S'>=8	109.77	19.20				E/E'>=9	116.00	10.95		
Left A'	S'<8	6.49	1.13	-2.37	0.025	Left A'	E/E'<9	7.24	1.57	1.34	0.185
	S'>=8	7.31	1.61				E/E'>=9	6.51	1.54		
Right ET'	S'<8	246.47	20.65	0.53	0.598	Right ET'	E/E'<9	243.69	22.87	0.03	0.976
	S'>=8	243.12	22.72				E/E'>=9	243.44	17.49		
Right ICT'	S'<8	86.60	13.07	2.11	0.047	Right ICT'	E/E'<9	79.61	14.44	-0.73	0.466
	S'>=8	78.69	14.41				E/E'>=9	83.33	14.79		
Right IRT'	S'<8	116.13	18.09	0.77	0.443	Right IRT'	E/E'<9	111.87	21.23	-0.66	0.514
	S'>=8	111.60	21.33				E/E'>=9	116.67	16.77		
Right S'	S'<8	10.45	1.90	-2.58	0.017	Right S'	E/E'<9	11.69	2.38	0.33	0.741
	S'>=8	11.90	2.39				E/E'>=9	11.41	2.40		
Right E'	S'<8	14.19	2.12	-1.32	0.190	Right E'	E/E'<9	14.97	2.40	0.11	0.912
	S'>=8	15.12	2.54				E/E'>=9	14.88	3.35		
Right A'	S'<8	8.27	1.75	-1.22	0.227	Right A'	E/E'<9	9.08	2.48	1.29	0.199
	S'>=8	9.11	2.56		0.128		E/E'>=9	7.97	2.16		
QT	S'<8	0.36	0.02	-0.03	0.977	QT	E/E'<9	0.36	0.03	0.69	0.491
	S'>=8	0.36	0.03		0.971		E/E'>=9	0.35	0.02		
QTc	S'<8	0.44	0.03	0.07	0.945	QTc	E/E'<9	0.44	0.04	0.96	0.342

	S'>=8	0.44	0.04		0.938		E/E'>=9	0.43	0.04		
QTd	S'<8	36.67	8.38	-1.27	0.206	QTd	E/E'<9	38.86	7.34	0.21	0.836
	S'>=8	39.22	6.84		0.282		E/E'>=9	38.33	5.00		
QTcd	S'<8	47.33	13.06	-0.26	0.794	QTcd	E/E'<9	48.06	10.34	0.30	0.764
	S'>=8	48.08	9.39				E/E'>=9	47.00	6.36		
Heart Rate	S'<8	91.40	13.07	-0.41	0.684	Heart Rate	E/E'<9	93.86	18.18	1.16	0.249
	S'>=8	93.48	18.80		0.607		E/E'>=9	86.56	14.96		
Right E/E'	S'<8	5.29	2.85	1.22	0.225	Right E/E'	E/E'<9	4.69	1.31	-2.06	0.043
	S'>=8	4.71	1.36		0.453		E/E'>=9	5.88	3.62		
Left E/E’	S'<8	7.63	1.55	2.94	0.004	Left S'	E/E'<9	9.38	1.27	2.82	0.016
	S'>=8	6.39	1.50		0.010		E/E'>=9	8.40	0.96		
Left E’/A'	S'<8	2.10	0.51	-0.57	0.571	Left E’/A'	E/E'<9	2.61	3.46	0.61	0.543
	S'>=8	2.63	3.59		0.221		E/E'>=9	1.90	0.43		
Right E’/A'	S'<8	1.77	0.34	-0.18	0.859	Right E'/A'	E/E'<9	1.77	0.63	-0.98	0.331
	S'>=8	1.80	0.69				E/E'>=9	1.99	0.72		
Left MPI	S'<8	0.72	0.16	-0.29	0.776	Left MPI	E/E'<9	0.73	0.15	0.47	0.643
	S'>=8	0.73	0.15				E/E'>=9	0.70	0.08		
Right MPI	S'<8	0.77	0.16	0.73	0.464	Right MPI	E/E'<9	0.74	0.19	-0.48	0.630
	S'>=8	0.74	0.18				E/E'>=9	0.77	0.10		
Right MPI'	S'<8	0.83	0.15	1.40	0.164	Right MPI'	E/E'<9	0.79	0.12	-0.96	0.341
	S'>=8	0.78	0.11				E/E'>=9	0.83	0.14		
Left MPI'	S'<8	0.80	0.11	0.63	0.532	Left MPI'	E/E'<9	0.78	0.11	0.40	0.689
	S'>=8	0.78	0.11		0.530		E/E'>=9	0.77	0.07		
Left E’/A'	S'<8	15.41	1.77	-1.32	0.189	Left E'/A'	E/E'<9	15.97	1.79	0.05	0.961
	S'>=8	16.07	1.79		0.196		E/E'>=9	15.94	1.92		
Left E’/A'	S'<8	15.57	2.93	-0.96	0.339	Left E'/A'	E/E'<9	16.88	5.23	0.90	0.369
	S'>=8	16.95	5.37				E/E'>=9	15.27	2.95		
Left E’/A'	S'<8	13.38	2.91	-0.92	0.361	Left E'/A'	E/E'<9	17.65	17.87	2.29	0.006
	S'>=8	17.81	18.53				E/E'>=9	11.94	1.72		

M-W u=Mann-Whitney U, a: is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow, AT: Acceleration time, Dt: deceleration time, Peak E: early mitral and tricuspid valve flow velocity, Peak A: late mitral and tricuspid valve flow velocity, ET: ejection Time, Aod: Diameter of Aorta in Diastole, LAd: Diameter of LA in Diastole, Aos: Diameter of Aorta in Systole, LAs: Diameter of LA in Systole, IVSD: interventricular septal dimension in Diastole, LVDD: left ventricular end-diastolic dimension, PWD: posterior wall dimension in diastole, IVSS: interventricular septal dimension in systole, LVDS: Left ventricular diameter at systole, PWS: posterior wall dimension in systole, EF: ejection fraction, FS: fractional shortening, QT: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, QTc: QT / √ RR, NFQTc : new formula for QTc in which is equal to 2qt/(1+RR), QTd: the difference between the maximum and minimum QT values, QTcd: the difference between the maximum and minimum QTc values, NFQTcd: new formula for QTcd in which is equal to 2qtd/(1+RR), R in v5: (R wave in V5) the amplitude of R wave in left Precordial, S in v1: (S wave in V1) the amplitude of S wave in right, HR: Heart Rate, Peak E /A: early mitral and tricuspid valve flow velocity / late mitral and tricuspid valve flow velocity, BMI: Body Mass Index, RWT: relative wall thickness, LA/AO in Diastole: Diameter of LA in Diastole/ Diameter of Aorta in Diastole, LA/AO in Systole: Diameter of in Systole / Diameter of Aorta in Systole, LVM: left ventricular mass, LVMI: left ventricular mass index, MPI: Myocardial performance index.