Original Article

The Evaluation of Left Ventricular Functions with Tissue Doppler Echocardiography in Adults with Celiac Disease

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ABSTRACT

Background/Aim: The aim of this study was to investigate the effects of celiac disease on cardiac functions using tissue Doppler echocardiography (TDE). **Patients and Methods:** The study included 30 patients with celiac disease (CD) and 30 healthy volunteers. Echocardiographic examinations were assessed by conventional echocardiography and tissue Doppler imaging. The peak systolic velocity (S′m), early diastolic myocardial peak velocity (E′m), late diastolic myocardial peak velocity (A′m), E′m/A′m ratio, myocardial precontraction time (PCT′m), myocardial contraction time (CT′m), and myocardial isovolumetric relaxation time (IVRT′m), E to E′m ratio were measured. **Results:** In pulsed wave Doppler echocardiography, mitral late diastolic flow (A) velocity and E to E′m ratio were significantly higher (P = 0.02 and P = 0,017), E/A ratio was significantly lower (P = 0.008) and IVRT was significantly prolonged (P = 0.014) in patients with CD. In TDE, S′m, E′m, and E′m/A′m ratio were significantly lower, IVRT′m was longer (P = 0.009) from septal mitral annulus and S′m, E′m, E′m/A′m ratio were significantly lower, PCT′m, PCT/ET ratio, IVRT′m were longer, and MPI was higher from lateral mitral annulus in celiac group than controls. **Conclusion:** Our study confirms that patients with CD have impaired diastolic function. More importantly, we also demonstrated an impairment of myocardial systolic function in patients with CD by TDE. We recommend using TDE in addition to conventional echocardiography parameters for the cardiovascular risk assessment of patients with CD.

Key Words: Cardiac involvement, celiac disease, tissue Doppler echocardiography, ventricular functions

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Celiac disease (CD) is characterized by small intestinal inflammation in genetically susceptible individuals and may affect up to 1% of the population in some countries.[1] It is caused by a lasting intolerance to gluten, which is found in wheat, rye, and barley. Treatment consists of life-long gluten-free diet. However, recent data indicate that despite dietary compliance, mucosal inflammation may persist for many years.[2] CD is frequently associated with iron deficiency anemia, dermatitis herpetiformis, thyroid disorders, diabetes mellitus, and various connective tissue disorders. An increased incidence of CD in patients with idiopathic dilated cardiomyopathy (IDCM) as well as in patients with secondary cardiomyopathy[3-7] has been reported recently.

Routine echocardiographic assessment of regional left ventricular (LV) wall motion is subjective because it is determined by visual determination of endocardial excursion and wall thickening. Tissue doppler echocardiography (TDE) is an echocardiographic method that allows quantitative measurements of the myocardial contraction and relaxation velocities of a selected myocardial segment[8] is providing velocities of normal and pathologic myocardial structures during the cardiac cycle. The velocity of a moving tissue can be studied with pulse wave tissue Doppler sampling, which displays the peak velocities within a selected myocardial region against time, with high temporal resolution.[9] Assessment of myocardial wall velocities with respect to timing amplitude has been

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suggested for quantification of global and regional systolic and diastolic function.[10,11] TDE assessment may be useful to obtain evidence of subclinical impairment of ventricular function during clinical stability.

The aim of the present study was to investigate myocardial functions in patients with CD by using TDE to identify possible left ventricle myocardial involvement in relation to a reference population of healthy subjects.

PATIENTS AND METHODS

This study was performed in a single center, in collaboration with gastroenterology and cardiology clinics between July 2012 and August 2013. Following the approval of this study by the ethics committee of the Ankara Atatürk Education and Research Hospital, Turkey, the study was conducted in the Department of Gastroenterology, and the Department of Cardiology. Written informed consent was obtained from patients and controls. All celiac patients were diagnosed based on a combination of clinical findings and intestinal biopsy results, and all patients were referred to a skilled dietitian with experience in CD. Patients were re-evaluated for compliance to the gluten-free diet in the follow-up examinations. All patients underwent echocardiographic examination after the establishment of the dietary compliance by clinical examination.

Study population

Thirty patients (4 males and 26 female; mean age 30.7 ± 11 years), who were previously diagnosed as having CD, were enrolled in the present study. Control group consisted of 30 healthy voluntary individuals, free of any disease, matched for age, gender, body mass index, smoking, coronary artery disease risk factors (family history, hyperlipidemia, hypertension) with both the study groups.

The exclusion criteria were patients with obvious valvular disease (moderate or serious), ejection fraction, rhythm abnormality, structural or congenital heart disease (HCMP, ASD, VSD, and so on), coronary heart disease, active infection, malignancy, pregnancy, other systemic inflammatory diseases, diabetes mellitus, and uncontrolled hypertension. The same exclusion criteria were applied to the control subjects as well.

Echocardiography

All echocardiographic images were obtained with a scanner (Vingmed System 7; Vivid 7 Pro; Horten, Norway) using a 2.5–3.5 MHz probe. Echocardiographic measurements were taken with patients in the left lateral decubitis position. All measurements were the average of values obtained from 3 to 5 beats. The echocardiographic study was performed by an experienced operator who was blinded to the clinical status of the subject.

Left atrial diameter (LA; mm), left ventricle end diastolic diameter (LVEDD; mm), left ventricle end systolic diameter (LVESD; mm), interventricular septum diameter (IVSd; mm) at end diastole, and posterior wall diameter (PWd; mm) at end diastole were obtained from the M-mode echocardiographic tracing under the guide of two-dimensional imaging. Left ventricular ejection fraction was calculated with Simpson's method as (diastolic volume − systolic volume)/(diastolic volume).

The transmitral diastolic flow velocities were measured in the apical four-chamber view by using pulsed Doppler echocardiography with the sample volume sited at the tip of mitral leaflet. Mitral early diastolic flow (E) velocity and late diastolic flow (A) velocity, E/A ratio, deceleration time (DT), isovolumetric relaxation time (IVRT) were measured from an apical four-chamber view.

Tissue Doppler measurements were performed in the apical four-chamber view, and a 3 mm pulsed Doppler sample volume was placed at the level of septal mitral annulus and lateral mitral annulus. The peak systolic velocity (S'm; centimeters per second), early diastolic myocardial peak velocity (E'm; centimeters per second), late diastolic myocardial peak velocity (A'm; centimeters per second), E'm/A'm ratio, myocardial precontraction time (PCT'm; milliseconds; time interval between the onset of electrocardiograms QRS and onset of S'm), myocardial contraction time (CT'm; milliseconds; between onset and cessation of the S'm), and myocardial isovolumetric relaxation time (IVRT'm; milliseconds; from the end of S'm to the onset of E'm), E to E'm ratio (was the ratio between the E transmitral flow velocity and mean of the lateral and septal walls E'm velocity) were measured. PCT/ET ratio was calculated. Tissue Doppler MPI was calculated by dividing the sum of PCTm and IVRTm by ETm.

The parameters of systolic function assessed were: Left ventricular end-diastolic and end-systolic diameters, ejection fraction, septal Sm, and lateral Sm by pulsed TDE, IVCTm, IVCT, IVCTm/ETm, IVCT/ET, MPI by TDE.

Peak E and A wave velocities, DT, E/A ratio, IVRT, septal and lateral Em velocity, septal and lateral Am velocity, IVRTm, Em/Am ratio, and E/Em ratio were determined as LV diastolic function parameters.

Statistical analysis

Data were analyzed using SPSS 17 software package. The continuous variables are expressed as either mean ± standard deviation or median (minimum − maximum) and the nominal

variables are expressed as number and percentages (%). The normal distribution of variables was verified with the Shapiro–Wilk test. As the distribution was normal, Student's *t*-test was employed for comparisons between the groups. Paired *t*-test was used for comparisons within the groups. The nominal variables were analyzed using Chi-square test. The values were accepted as significant when $P<0.05$.

RESULTS

There was no statistically significant difference between celiac and the control group in terms of age, gender, weight, height, body mass index, systolic blood pressure, diastolic blood pressure, and heart rate. Demographic characteristics of patients and control subjects are listed in Table 1. Laboratory data of both the groups are listed in Table 2. No significant difference was detected between the two groups with respect to serum lipid parameters, fasting blood glucose, thyroid hormones, hemoglobin, iron, iron-binding capacity, vitamin B12, and folic acid.

Table 1: The demographic characteristics of the subjects in study groups

Patients characteristics	Patient group (*n*=30)	Control group (*n*=30)	*P* value
Gender (female/male)	26/4	25/5	
Age (years)	30.7±11.0	27.6±7.59	0.21
Height (cm)	161±7.3	164±6.7	0.11
Weight (kg)	58.0±12.4	58.5±12.6	0.87
Body mass index (kg/m^2)	22.2±4.31	21.5±3.7	0.53
Systolic blood pressure (mmHg)	109±8.2	108±8.3	0.75
Diastolic blood pressure (mmHg)	67.5±7.62	68.3±7.46	0.67
Heart rate (beats/min)	72.2±7.42	74.9±8.64	0.19

The data are given as mean ±SD

Table 2: The biochemical, hormonal, and hematological parameters of the celiac patients and control group

Laboratory values and normal ranges	Patient group	Control group	*P* value
Fasting glucose (mg/dL) (74-106)	89.0±10.7	91.3±8.1	0.36
Total cholesterol (mg/dL) (50-200)	163±36.3	152±35	0.25
LDL (mg/dL) (0-130)	99.8±23.6	100±28	0,95
HDL (mg/dL) (45-65)	49.7±5.8	51.4±13.1	0.52
Triglyceride (mg/dL) (0-200)	112±39.8	100±42.5	0.26
Hemoglobin (mg/dL) (12-16)	12.6±1.29	13.2±1.71	0.11
Iron (µg/dL) (33-193)	66.7±50.7	78±44.4	0.36
Iron-binding capacity (µg/dL) (168-585)	386.2±92.3	352.4±57.8	0.09
Free T3 (pg/mL) (1.8-4.6)	2.88±0.62	3.3±0.37	0.08
Free T4 (ng/mL) (0.9-1.7)	1.1±0.24	1.13±0.2	0.614
TSH (uIU/mL) (0.27-4.2)	1.89±0.5	1.57±0.91	0.1
Vitamin B12 (pg/mL) (197-866)	346±114	333±190	0.74
Folic acid (ng/mL) (4.6-18.7)	6.47±3.21	6.29±2.31	0.8

The data are given as mean±SD. T3: Triiodotyyronine, T4: Tetraiodothyronine, TSH: Thyroid stimulating hormone

The results of conventional echocardiographic examination are displayed in Table 3. When LVEDD, LVESD, PWd, IVSd, and EF parameters were compared, no significant differences were determined between the two groups. Left atrium diameter ($P = 0.01$) and aorta diameter ($P = 0.003$) were higher in patients with CD than controls. The results of pulsed and continuous Doppler study of transmitral flow velocities are also listed in Table 3. The mitral late diastolic flow (A) velocity and E to E'm ratio were significantly higher ($P = 0.02$ and $P = 0.017$). E/A ratio was significantly lower ($P = 0.008$) and IVRT was significantly prolonged ($P = 0.014$) in patients with CD.

Septal and lateral wall TDE findings are given in Tables 4 and 5. Septal S'm, E'm, and E'm/A'm ratio were significantly lower (*P* values are 0.01, 0.001, and 0.001, respectively), and IVRT'm was longer ($P = 0.009$) in patients with CD than controls. Although MPI was higher in celiac patients, it did not reach a statistically significant value ($P = 0.08$).

When PW lateral wall TDE findings were compared between the two groups, S'm, E'm, and E'm/A'm ratio were significantly lower (*P* values are 0.001, 0.01, and 0.03, respectively) in patients with CD. PCT'm, PCT/ET ratio, and IVRT'm were longer and MPI was higher in celiac group, and these values were statistically significant ($P = 0.01$, 0.007, 0.003, 0.008, respectively).

DISCUSSION

The aim of the present study was to investigate whether TDE could contribute to better understanding of the natural history of cardiomyopathy in celiac disease, through its enhanced sensitivity to diastolic dysfunction, and identifying preliminary regional signs of systolic dysfunction, before the appearance of clinical symptoms of cardiac pathologies. In this study, we have demonstrated that systolic and diastolic functions were impaired in patients with CD. Also, the present study proved the hypothesis that TDE imaging is superior to conventional echocardiography to demonstrate cardiac involvement in patients with CD.

An increased incidence of dilated cardiomyopathy has been reported in CD patients. Also there are studies that investigated left ventricular systolic and diastolic functions at childhood age. Contradictory results were obtained from these studies. Methodological differences and limitations of conventional echocardiographic methods to diagnose left ventricular function may cause these discrepancies.[12,13] But, in our knowledge there is no such study to investigate left ventricular functions via TDE method in adult patients with celiac disease.

Table 3: The M-mode, 2-D, PW, and CW doppler echocardiographic measurements of the study groups

	Patient group	Control group	*P* value
M-mode, 2-D parameters			
LVEDD (mm)	4.5±0.36	4.51±0.36	0.94
LVESD (mm)	2.82±0.25	2.72±0.3	0.17
IVS (mm)	0.9±0.09	0.89±0.09	0.58
PW (mm)	0.88±0.08	0.87±0.1	0.68
Aorta diameter(mm)	2.34±0.3	2.17±0.17	0.01
Left atrium diameter (mm)	3.16±0.27	2.92±0.32	0.003
EF (%)	67±4.2	67.9±3.9	0.38
PW and CW doppler echocardiographic measurements			
Aortic velocity (m/s)	1.25±0.13	1.21±0.11	0.18
Pulmonary velocity (m/s)	0.86±0.08	0.85±0.1	0.78
E wave (m/s)	0.89±0.17	0.94±0.11	0.16
A wave (m/s)	0.67±0.13	0.6±0.1	0.02
E/A ratio	1.35±0.34	1.59±0.33	0.008
E/E' ratio	8.39±2.2	7.18±1.42	0.017
DT ms	192±41.8	185±40.2	0.67
IVRT (ms)	94.5±10	82.2±8.21	0.014

Data represented as mean± SD. DT: Deceleration time, EF: Ejection fraction, IVS: Interventricular septum, PW: Posterior wall, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, IVRT: Isovolumetric contraction time

Table 4: PW tissue Doppler echocardiography measurements of the septum in study groups

Variables	Patient group	Control group	*P* value
Sm (cm/sn)	7.9±0.8	8.6±1.1	0.01
Em (cm/sn)	11±2.6	0.13±2.3	0.001
Am (cm/sn)	7.9±2	7.1±1.5	0.1
Em/Am ratio	1.48±0.47	1.91±0.5	0.001
PCT	63.5±12.6	60±10.6	0.24
ETm (ms)	280±23.6	277±25.8	0.72
PCTm/ETm ratio	0.22±0.05	0.21±0.04	0.41
IVRTm (ms)	70.6±12.6	61.9±12	0.009
MPI	0.48±0.1	0.43±0.07	0.082

Sm: Systolic myocardial wave, Em: Early diastolic myocardial wave, Am: Late diastolic myocardial wave, PCTm: Myocardial precontraction time, ETm: Myocardial ejection time, IVRTm: Myocardial isovolumetric contraction time, MPI: Myocardial performance index

Table 5: PW tissue doppler echocardiography measurements of the lateral wall in study groups

Variables	Patient group	Control group	*P* value
Sm (cm/s)	9.8±1.8	11.1±1.9	0.001
Em (cm/s)	15±3.0	17.8±3.1	0.01
Am (cm/s)	9.6±3.3	8.8±2.5	0.3
Em/Am ratio	1.78±0.72	2.17±0.69	0.03
PCT	68.9±10.5	61±12.6	0.01
ETm (ms)	277±23.2	279±21.2	0.84
PCTm/ETm ratio	0.24±0.42	0.21±0.43	0.007
IVRTm (ms)	72.8±12.9	62.4±13.1	0.003
MPI	0.51±0.07	0.46±0.07	0.008

Sm: Systolic myocardial wave, Em: Early diastolic myocardial wave; Am: Late diastolic myocardial wave; PCT: Myocardial precontraction time; ETm: Myocardial ejection time; IVRTm: Myocardial isovolumetric contraction time; MPI: Myocardial performance index

Several mechanisms have been proposed for the development of cardiomyopathy in CD. Nutritional deficiencies secondary to chronic malabsorption may lead to cardiomyopathy.[14] CD causes increased systemic absorption of various luminal antigens and infectious agents, which may cause myocardial damage secondary to immune-mediated mechanisms.[15] Myocardial injury may be secondary to an immune response directed against an antigen present in both the myocardium and the small intestine.[4,7,16] In older age, ischemic heart disease (IHD) becomes one of the most important cardiomyopathy reasons in celiac disease. Recently, a Swedish population-based cohort study examined the risk of IHD in patients with CD. They found a positive association between CD and IHD. The authors found a 19% increased risk of IHD in CD, which translated into an absolute risk of 375 events per 100,000. Because cardiovascular disease is the most common cause of death in this group of patients, the authors emphasized that increased awareness of IHD risk factors in CD is warranted.[17]

Despite a preserved global function measured by conventional echocardiography, TDE may represent an early stage of myocardial abnormality.[9-11] We used many conventional and TDE techniques to investigate diastolic functions in celiac patients. They are as follows: Left atrium size, Peak E and A wave velocities, DT, E/A ratio, IVRT, septal and lateral Em velocity by pulsed TDE, septal and lateral Am velocity by pulsed TDE, IVRTm, and Em/Am ratio.

In the early phase of diastolic dysfunction, E wave decreases and A wave increases in amplitude, E–A reversal occurs, DT and IVRT prolongs. With progression of diastolic dysfunction,

LV filling and LA pressure rises and left atrium size increases. In this study, we found a significant decrease of A wave, significant prolongation of IVRT, and decrease in E/A ratio in patients with celiac disease. Although left atrium diameter was within normal limits in both groups, it was significantly greater in the CD group ($P = 0.003$). This relative left atrial dilatation can also be an important clue of diastolic dysfunction in the CD group. It is well documented that the increased left ventricular filling pressure and the resultant elevated left atrial pressure lead to left atrial dilatation in patients with diastolic dysfunction, Higher mitral A wave, lower E/A ratio, and prolonged IVRT in the CD group together with increased left atrium diameter indicate the beginning of impairment in left ventricle diastolic functions.

Septal and lateral Em velocity, IVRTm, and Em/Am ratio measured with TDE and E/E'm ratio is more reliable index of ventricle relaxation than conventional echocardiography, which can be affected by preload, afterload, heart rate, inspiration, and expiration[18-21] The ratio is correlated with left ventricle filling pressure measured with invasively.[22] In this study, we found that E/E'm ratio was higher, septal and lateral wall E'm and E'm/A'm ratio were significantly lower, septal and lateral wall IVRT'm was longer and lateral wall PCT'm, PCT/ET ratio were longer in patients with CD than in controls. These parameters were all helpful to the diagnosis of diastolic dysfunction in patients with CD. In the present study, other potential causes of diastolic dysfunction such as hypertension, obesity, and coronary artery disease were excluded.

The parameters of systolic function assessed by conventional echocardiography did not differ between the two groups. Left ventricular ejection fraction and cavity diameters were not different among the groups. When we assessed systolic functions by TDE methods, Sm measured from septal and lateral wall were found to be lower and PCT/ET ratio measured from lateral wall was higher in the CD group than in the control group. We showed that TDE might facilitate the diagnosis of systolic dysfunctions in patients with CD despite a normal echocardiography result with conventional echocardiography.

Myocardial performance index (MPI), is a parameter that displays both systolic and diastolic (global) performance of the ventricle. The mean MPI measured from septal wall by TDE was 0.48 ± 0.1 in the patient group and 0.43 ± 0.07 in the control group ($P = 0.082$). The mean MPI measured from lateral wall by TDE was 0.51 ± 0.07 in the CD group and 0.46 ± 0.07 in the control group ($P = 0.008$). Lower MPI values reflect better overall (systolic and diastolic) ventricular function. Significantly increased MPI in the CD group suggests that overall ventricular function impaired in these patients, when compared to healthy controls.

Some limitations of our study should be noted. First of all, we used the conventional echocardiographic methods and tissue Doppler echocardiographic methods to evaluate the cardiac functions. TDE technique has some limitations such as tissue effects, tethering, and the rotation motion of the heart. Second, our study population is very small. This study power is inadequate to making a judgement. Future studies are needed to examine this issue which has a large study population. Lastly, in CD, the presence of antibodies has a positive interaction between the disease severity and its prognosis. Polat *et al*. showed that antiendomysium antibody-positive patients' systolic velocity is higher than seronegative patients. At this point, another limitation of our study, we did not group the patients according to the presence of antibodies.

CONCLUSION

Our study showed that TDE and conventional echocardiography demonstrate the impairment of myocardial diastolic function in patients with CD. Furthermore, we also found deterioration of systolic dysfunction with TDE but not with traditional echocardiography. These results demonstrated that TDE is better to identify early stage of cardiac changes in patients with CD. We recommend to use TDE parameters to identify subclinical cardiac deterioration in patients with CD.

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