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Evaluation of Cardiac Functions with Tissue Doppler Imaging in Prediabetic Subjects

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Background and Objectives: The aim of the present study was to evaluate left ventricle systolic and diastolic function, using tissue Doppler echocardiography (TDE), in relation to blood glucose status in prediabetic patients who had no evidence of heart disease by conventional echocardiography (CE).
Subjects and Methods: We included 60 patients (30 female, 30 male) and 20 healthy controls (10 male, 10 female). All participants were randomised into four groups according to their oral glucose tolerance test. Group-I consisted of those patients who had only impaired fasting glucose (IFG). group-II consisted of patients who had only impaired glucose tolerance (IGT) and group-III consisted of patients who had both IFG and IGT, that is so-called combined glucose intolerance. Group-IV included the healthy controls. All subjects underwent both CE and TDE.
Results: No significant differences were found among the four groups in terms of CE. There was no significant difference between group-IV and group-I with respect to the early peak diastolic velocity (Ea) of medial mitral annulus (11.65 ± 0.66 vs. 9.72 ± 1.58, $p>0.05$), whereas a statistically significant difference was found between group-IV and group-II (11.65 ± 0.66 vs. 9.06 ± 1.07, $p<0.001$) and between group-IV and group-III (11.65 ± 0.66 vs. 9.74 ± 1.09, $p<0.05$).
Conclusion: Diastolic myocardial dysfunction in prediabetic patients may be identified by quantitative TDE before the appearance of CE indices of myocardial dysfunction. **(Korean Circ J 2013;43:82–86)**

KEY WORDS: Type 2 diabetes mellitus; Diabetic cardiomyopathies; Tissue Doppler imaging; Glucose intolerance.

Introduction

Diabetes mellitus (DM) has been increasing in both developed and developing communities as a result of epidemic obesity and increasingly sedentary lifestyles.[1] The relationship between DM and cardiovascular diseases[2] and the fact that cardiovascular diseases are the major reason for morbidity and mortality in diabetics have been known for a long period of time.[3] Heart failure is a common and serious complication of diabetes. The incidence of cardiomyopathy-induced congestive heart failure (CHF) has been found to be increased in diabetic patients even in the absence of coronary atherosclerosis.[4-6] Diabetic cardiomyopathy can be described as abnormalities in myocardial function or structure in the absence of hypertension (HT), alongside coronary artery disease (CAD) and serious valvular heart disease. The development of diabetic cardiomyopathy has been considered to be a multifactorial condition. Increased stiffness due to the accumulation of connective tissue and insoluble collagen on left ventricle (LV) wall,[7] autonomic dysfunction,[8] endothelial dysfunction, impairment in various ligand sensitivity[9] and anomalies in the proteins which arrange ion flow, particularly intracellular calcium, are some of the factors that play a role in development of disease.[10][11] In early stages of diabetic cardiomyopathy, the systolic and diastolic functions of LV were found to be preserved on conventional echocardiography (CE). Diastolic dysfunction can be sensitively detected

at the early stage by tissue Doppler echocardiography (TDE).[12][13] Diastolic dysfunction, systolic dysfunction and myocardial structural changes are three main clinicopathologic features of diabetic cardiomyopathy.

The basis of noninvasive evaluations of diastolic dysfunction is constituted by Doppler studies of transmitral flow, mitral flow velocities, deceleration times, isovolumic relaxation time (IVRT) and flow patterns. As the degree of diastolic dysfunction deteriorates, the "early diastolic LV filling (E wave)" decreases and a delayed relaxation pattern appears. However, by increasing left atrial pressure, the E wave can be normalized and turns into a mitral flow wave, in a so-called 'pseudonormal pattern' which cannot be distinguished from that of a normal wave. The advantages of this technique are that it achieves perfect temporal resolution and mono-directional correlation with progressive cardiac anomalies. In one study, the mitral early peak diastolic velocities (E) and late peak diastolic velocities (A) of 27 type 1 and 25 type 2 diabetic patients without HT and CAD were examined and the E/A ratio was found to be more markedly decreased in type 2 diabetics.[14] In another study, it was reported that ventricular filling, particularly early peak filling velocity, was more significantly impaired in type 2 diabetics compared to type 1 diabetics.[15] Several studies have demonstrated early impaired diastolic function, despite systolic function parameters remaining normal, in diabetics. This finding may be related to using more sensitive techniques in the detection of diastolic dysfunction and the absence of sufficiently adequate techniques to evaluate systolic dysfunction.

Recently, a diabetes-specific cardiomyopathy has been demonstrated in diabetic patients; however the pathophysiology and diagnostic criteria of this condition have not yet been elucidated. This condition has been described in diabetics without CAD, HT or valvular heart disease, and in the early stage of the disease systolic functions are preserved and diastolic dysfunction develops. Although diabetic cardiomyopathy develops in patients with overt DM, the stage of this condition has not yet been clarified in the prediabetic period. The aim of the present study was to evaluate whether tissue Doppler imaging can detect a pre-clinical impairment of diastolic function in prediabetic patients with preserved systolic functions in CE, so as to detect possible early cardiac dysfunction.

Subjects and Methods

Study population

The patients enrolled in our study were selected between May 2007 and May 2009. Taking excluding criteria into consideration, all participants were divided into four groups according to oral glucose tolerance test (OGTT). The healthy controls consisted of 20 patients (mean age: 46.40±4.64), who formed the fourth group (group 4). Ex-

clusion criteria were: HT or antihypertensive use, cardiac arrhythmia, presence or history of CAD, presence of findings consistent with CAD in electrocardiography, wall movement defect in CE, serious valvular heart disease or existing artificial valve, smoking, acute disease or psychiatric disease, and poor image quality in echocardiography. Written informed consent was obtained from all the patients and the study was approved by the Abant Izzet Baysal University Ethics Committee.

Method of oral glucose tolerance test and laboratory analysis

Oral glucose tolerance test was performed using 75 g of glucose. Before the start of OGTT, a polyethylene catheter was placed into an antecubital vein and blood samples were collected at 0, 30, 60, 90 and 120 minutes for the measurement of plasma glucose.

Samples for serum chemistry were analyzed by a central medical research laboratory. Glucose levels were measured using colorimetric enzymatic methods on the Abbott Architect C8200 analyzer (Integrated System for ABBOT Diagnostic, Montreal, Canada) and reagents from the same manufacturer. All blood samples were collected at 08:00 a.m. after a 10 hours fasting period.

Conventional echocardiography

Transthoracic echocardiographic assessment was performed on patients in the left lateral decubitis position during normal respiration after five minute resting with a commercially available ultrasound transducer and equipment (2.5 MHz transducer of Vingmed Vivid System III, Vingmed, General Electric, Horten, Norway). Images were obtained in the standard views of the LV (parasternal long and short axis, apical four- and two-chamber and apical long-axis). Doppler echocardiography was performed in accordance with the recommendations of the American Society of Echocardiography.[16] Measurements were performed at the end of expirium in order to avoid possible artificial effects of respiration. Operators were blinded to patients and groups. Transmitral peak early diastolic velocity (E), peak late diastolic (A) velocity, E/A ratio, IVRT and E-wave Edec were measured. The ejection fraction (EF) was calculated as the percentage change of left ventricular chamber volumes between diastole and systole from apical four- and two-chamber views using modified biplane Simpson's rule based on three measurements. An EF >55% indicated a normal systolic function. An E-wave DT >140 and <220 ms, an E/A ratio >1 and <2, and IVRT <100 ms indicated normal diastolic function.[17]

Tissue Doppler echocardiography

Pulsed-wave tissue Doppler measurements were conducted on all patients following CE technique. A total of six measurements were performed from medial and lateral sites of the annular area. Medial

mitral annular systolic velocity (Smed-a), medial mitral annular early (Emed-a) and late (Amed-a) diastolic velocities were measured. Emed-a/Amed-a ratios were detected. Lateral mitral annular systolic velocity (Slat-a), lateral mitral annular early (Elat-a) and late (Alat-a) diastolic velocities were measured.

Elat-a/Alat-a ratios were detected. A total of three measurements were performed from the lateral myocardium. LV Lateral myocardial systolic velocity (Slat-m), lateral myocardial early (Elat-m) and late (Alat-m) diastolic velocities were measured. Elat-m/Alat-m ratios were detected. Velocity at any measurement of annulus was evaluated pathologically as <8 cm/sec.

Statistical analysis

Results are given as mean±SD. Kolmogorov-Smirnov test was used. Non-normally distributed data were analyzed by Kruskal-Wallis tests and normally distributed data were assessed by analysis of variance. A p<0.05. was considered statistically significant. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) for Windows version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

The main features of the subjects studied are summarized in Table

Table 1. Demographic and clinical characteristics of groups

	IFG	IGT	CGT	Control	p
Age (years)	45.15±7.32	48.80±3.42	48.55±4.85	46.40±4.64	NS
Female (%)	10 (50)	10 (50)	10 (50)	10 (50)	NS
Male (%)	10 (50)	10 (50)	10 (50)	10 (50)	NS
Systolic BP (mm Hg)	125±6.46	127.5±2.57	123.75±3.79	123±6.46	NS
Diastolic BP (mm Hg)	75.25±3.52	74.65±2.35	74.50±2.93	79.50±3.63	NS
BMI (kg/m²)	25.70±3.04	25.05±1.06	25.59±0.92	25.25±1.95	NS

BP: blood pressure, BMI: Body Mass Index, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, CGT: IFG+IGT, NS: not significant

Table 2. CE parameters of groups

CE	IFG	IGT	CGT	Control	p
LVEDD (mm)	51.35±2.08	50.16±1.96	49.60±2.25	52.20±1.73	NS
LVESD (mm)	31.75±1.67	31.23±1.90	30.75±1.77	32.40±1.73	NS
LAD (mm)	35.15±2.30	33.87±1.56	34.45±1.84	36.70±1.55	NS
IVS (mm)	9.14±0.67	9.53±0.49	9.40±0.54	9.45±0.52	NS
PW (mm)	9.12±0.82	8.87±0.65	9.35±0.51	9.50±0.56	NS
LVEF (%)	68.15±2.61	66.89±2.73	67.30±3.05	67.45±2.68	NS
IVRT (msn)	77.75±3.33	82.30±3.55	79.85±4.49	76.70±4.33	NS
Evel (m/sn)	0.77±0.08	0.76±0.15	0.70±0.09	0.87±0.08	NS
Avel (m/sn)	0.64±0.09	0.70±0.09	0.63±0.08	0.68±0.05	NS
E/A ratio	1.18±0.24	1.07±0.13	1.14±0.22	1.29±0.11	NS
Edec (msn)	169.95±21.52	200.05±25.64	179.65±38.06	186.70±14.01	NS

CE: conventionel echocardiographic, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, CGT: IFG+IGT, NS: not significant, LVEDD: left ventricle end-diastolic diameter, LVESD: left ventricle end-systolic diameter, LAD: left atrial diameter, IVS: interventricular septum thickness, PW: posterior wall thickness, LVEF: left ventricular ejection fraction, IVRT: isovolumic relaxation time, Evel: transmitral early peak diastolic flow velocity, Avel: transmitral late peak diastolic flow velocity, Edec: deceleration time

Table 3. TDE parameters of groups

TDE	IFG	IGT	CGT	Control	p
Sa	7.77±0.91	8.39±0.60	7.67±0.89	7.90±0.57	NS
Ea	9.72±1.58	9.06±1.07*	9.74±1.09*	11.65±0.66*	<0.05
Aa	10.34±0.99	10.19±0.95	10.16±1.07	9.06±0.66	NS
Ea/Aa	0.99±0.22	0.93±0.19*	1.02±0.24	1.35±0.11*	<0.05

*p<0.05 when compared control group. TDE: tissue Doppler echocardiographic, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, CGT: IFG+IGT, NS: not significant, Sa: mitral medial annulus peak systolic velocity, Ea: mitral medial annulus early peak diastolic velocity, Aa: mitral medial annulus late peak diastolic velocity

1. Baseline demographic and clinical characteristic were comparable across the four groups. The CE and TDE parameters of all groups are demonstrated in Table 2 and 3, respectively. The four groups were similar in terms of CE parameters. In TDE evaluation. The early peak diastolic velocity of medial mitral annulus (Ea) of impaired fasting glucose (IFG) patients were similar to controls (11.65±0.66 vs. 9.72± 1.58, p=0.084). However, statistically significant difference between controls and impaired glucose tolerance (IGT) patients (11.65±0.66 vs. 9.06±1.07, p≤0.001) and between controls and CGT patients (11.65±0.66 vs. 9.74±1.09, p=0.008) were found. However, there was no difference between groups in terms of measurements from the lateral mitral annulus (SlatA, ElatA, AlatA) and the lateral myocardium (SlatM, ElatM, AlatM).

Discussion

The present study has two significant findings. Firstly, it was shown that the process of cardiomyopathy initiates in IGT and CGT conditions before overt diabetes develops. In measurements by TDE, we detected that the systolic functions of prediabetics were preserved whereas diastolic functions were impaired. This condition was found to be prominent in IGT and CGT patients. In a study performed with TDE, García-Fernández et al.[18] demonstrated that LV diastolic dysfunction might be regional.[18] Although in line with this view we did detect diastolic dysfunction findings in the medial of mitral annulus, diastolic functions were within normal ranges in the lateral annulus and lateral myocardium in the present study. Secondly, we can propose that insulin resistance plays a pivotal role in the effects of diabetes on the myocardium. There is evidence that the cardiac muscle in type 2 diabetics is resistant to insulin, although underlying CAD was not excluded.[19] In an animal study by Mizushige et al.[20] it was found that diastolic function in prediabetic rats might be associated with insulin resistance.

The prevalence of CHF and diastolic dysfunction has been increasing in diabetic patients.[21] LV diastolic dysfunction may present as the first stage of CHF and is associated with high mortality/morbidity.[22] In various studies it has been demonstrated that diabetic cardiomyopathy contributed to the incidence of increased heart failure in diabetics. Almost all these studies were conducted on overt diabetics with normal systolic/diastolic function. However, this condition has not been investigated in prediabetics such as those with IFG and IGT. Importantly, CE and normal cardiac functions have not been examined by TDE. Recently, noninvasive techniques that evaluate diastolic function have improved. However, we do not have enough data about early stage of diabetic cardiomyopathy and the pathophysiology of this disease remains unclear.

If physiologic adaptation to metabolic changes and degenerative changes, which comprise two main aspects of diabetic cardiomyopathy, are treated in the early stages of diabetes, clinicians may be able to intervene in the progress of the disease. Studies on antihyperglysemic treatment advocate the view that myocardial function and structural differences are correlated with glysemic control. Pogátsa et al.[23] investigated the effects of antihyperglysemic treatment on diabetic dogs with serious hyperglicemia and it was found that LV passive elastic module (the marker of stiffness) and LV end-diastolic pressure were higher and cardiac output was lower in nontreated dogs. Similarly, in another study it was indicated that diabetic cardiomyopathy-induced changes in diabetic rats may be reversible with insulin treatment.[24] Contrary to these findings, in a study conducted on diabetic dogs Regan et al.[25] suggested that diabetic cardiomyopathy was not reversible with antihyperglycemic treatment.

The current study has some potential limitations that should be noted. First, the study sample size was small. Second, we did not measure the insulin sensitivity of subjects since insulin resistance and hyperinsulinemia are already present in patients with IGT, IFG and CGI. Third, one of the important supplementary methods for assessment of diastolic function is pulmonary venous flow velocity evaluation, which was not reported in this study. Although this study has several limitations, the results nevertheless provide important information about cardiac functions in prediabetic patients.

In conclusion, there as yet exists no effective treatment for diabetic cardiomyopathy, which is one of the leading causes of morbidity and mortality in patients with overt diabetes. Therefore it is important to prevent the occurrence or progression of the disease. Studies have clearly demonstrated that prediabetes is a reversible condition. In the present study, we obtained data indicating that the effect of prediabetes may be reversible. This finding needs be supported by standardized methods and studies conducted on a wide number of patient populations.

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