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Left Ventricular Function in Children and Adolescents With Type 1 Diabetes Mellitus

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ABSTRACT

Background and Objectives: Adult studies have reported that patients with diabetes mellitus (DM) show ultrastructural and functional myocardial deterioration. The aim of this study was to assess whether cardiac functional deterioration can be detected in pediatric patients with type I DM and whether or not a relatively short duration of DM and hyperglycemia influences cardiac function. **Subjects and Methods:** Forty-seven children and adolescents with DM and 38 healthy subjects (control group) were enrolled. Glycosylated hemoglobin (HbA1c), DM-induced complications, and left ventricular (LV) function as assessed using conventional and unconventional echocardiography [tissue Doppler imaging (TDI) and vector velocity imaging (VVI)] were evaluated. **Results:** The conventional echocardiographic parameters, with the exception of early peak mitral inflow velocity, the findings of pulsed wave TDI at the annular level, and regional ventricular function by VVI, were not significantly different between the two groups. Using the conventional and unconventional indices of systolic and diastolic function, no significant relationship was found between the duration of DM and the echocardiographic parameters. The deceleration time (DT) and E'/A' had an inverse correlation with HbA1c ($p=0.042$ and $p=0.016$, respectively). **Conclusion:** Patients with DM in childhood and early adolescence rarely have insight on the significance of DM, and their diet is difficult to control. An alteration of myocardial function induced by DM may begin earlier than generally thought, and these changes are accelerated when glycemic control is poor. We recommend the early institution of close observation of patients with diabetes for alterations in cardiac function, in addition to other diabetic complications. (*Korean Circ J* 2010;40:125-130)

KEY WORDS: Child; Diabetes mellitus; Hyperglycemia; Ventricular function.

Introduction

Studies in adults have reported that patients with diabetes mellitus (DM) show ultrastructural and functional deterioration of the myocardium.^{1,2)} These patients are susceptible to heart failure and have a higher prevalence of coronary heart disease, hypertension, and cardiomyopathy.³⁻⁶⁾

Deterioration of left ventricular (LV) function in patients with type 1 DM can exist in the absence of other combined cardiac problems.⁴⁾

Echocardiography can be used for the diagnosis of diabetic cardiomyopathy or diabetes-induced myocardial dysfunction. In adults with type 1 DM, numerous studies have reported controversial results. Several investigators have shown normal LV systolic function at rest and abnormal contractile responses during exercise.^{2,7)} With respect to LV diastolic function, several studies have reported an abnormal pattern,^{8,9)} whereas another study found no evidence of dysfunction at rest.¹⁰⁾ However, no studies have been conducted involving patients of a younger age with a shorter duration of DM and hyperglycemia.

The aim of this study was to assess whether or not cardiac functional deterioration can be detected in pediatric patients with type I DM and whether or not DM of a relatively short duration and hyperglycemia influence cardiac function.

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Subjects and Methods

Study population

We studied 38 children and adolescents who participated in the 2007 Diabetes Summer Education Camp in Daegu and 9 pediatric patients who were attending the Diabetes Clinic for Children of the Keimyung University Dongsan Medical Center. All patients were diagnosed with type I DM and received insulin therapy only. The patients consisted of 16 boys and 31 girls, with a mean age of 12.8 years (range, 7.1-16.8 years). The mean duration of disease was 3.4 years (range, 0.3-7.7 years). None of the patients had definite DM-induced complications, including renal impairment, retinopathy, neuropathy, and clinical symptoms of cardiac dysfunction or cardiomyopathy. The conventional laboratory chemistry results were normal, except for the glycosylated hemoglobin (HbA1c) level. The control group consisted of 38 children (18 boys and 20 girls), with a mean age of 11 years (range, 6.9-17.1 years). They were referred to us with a chief complaint of heart murmurs or chest pain, and did not show abnormal findings on laboratory testing, electrocardiograms, or echocardiography.

Echocardiography

An echocardiography was performed using an Acuson Sequire 512 (Siemens Medical Solution, Mountain View, CA, USA) with a 4 or 8 MHz transducer. All of the tests which were performed were saved on a hard drive and magneto-optical (MO) disk of echocardiographic equipment. On the parasternal long axis view, with the use of M-mode and conventional echocardiography, several parameters, including fractional shortening (FS), ejection fraction (EF), LV dimension, and volume per surface area, were measured.

For diastolic functional analysis, the mitral inflow signal was acquired in an apical four-chamber view. The pulsed Doppler sample volume was 2 mm and it was placed at the mitral valve tip. The early peak flow velocity (E) and atrial filling velocity (A) were measured three times and averaged, and the E/A ratio was calculated. The time elapsed until the maximal E reached the baseline (the early filling deceleration time (DT)), and the time from aortic valve closure to mitral valve opening (the isovolumic relaxation time (IVRT)), were measured.

Tissue Doppler imaging (TDI) measurements were performed on the basal septum and mitral annulus. The maximal systolic myocardial velocity (S') and early and late diastolic myocardial velocity (E', A') were measured. In this study, the sample volume was set at 3 mm. The time between mitral valve closure and opening (a') and the systolic time (b') were measured. The value of (a'-b') was divided by b' and the modified myocardial performance index (modified Tei index) was obtained.

To analyze the vector velocity imaging (VVI), an ul-

trasound window of the images was controlled in such a manner that the number of frames should be >70 frames per single cardiac beat on an apical 4-chamber view and 2D images were acoustically captured. Secured images were saved on a MO disk for off-line analysis. The contour of the endocardium was manually traced before the analysis was performed on the saved images with the use of an offline analysis program (Syngo US Workplace 3.0 (Siemens Medical Solution, Mountain View, CA, USA)). The tracing was performed several times to achieve the most appropriate endocardial contour, which was confirmed by the visual display mode of the velocity images. In the septum and lateral wall of the LV, the basal and middle parts were subjected to the measurement of maximal velocity, strain, strain rate (SR), and displacement.

All of the echocardiographic parameters obtained for pulsed wave Doppler and TDI were measured by a single investigator from three cardiac cycles and averaged. The parameters which were obtained from the VVI were the average value of the measurement performed twice.

Statistical analysis

All of the results which were measured using echocardiography were expressed as the mean \pm SD. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 14.0 (SPSS Inc., Chicago, IL, USA). A comparison of echocardiographic measurements in the septum and lateral wall of the LV between the patient and control groups was made with the use of an independent t-test. The correlation between echocardiographic parameters and the duration of DM or the HbA1c level was assessed using correlation analysis. A $p < 0.05$ was considered statistically significant.

Results

Patients

The clinical data of the patients and controls are listed

Table 1. Clinical characteristics of patients with diabetes mellitus and controls in the study groups

	Patients with DM (n=47)	Controls (n=38)	p
Gender	M (16)/F (31)	M (18)/F (20)	
Age (year)	12.84 \pm 2.26	11.03 \pm 2.61	0.014
Height (cm)	150.1 \pm 12.4	144.50 \pm 17.7	NS
Weight (kg)	44.7 \pm 11.0	39.6 \pm 14.8	NS
BMI (kg/m ²)	19.5 \pm 3.1	18.4 \pm 3.1	NS
Glycosylated hemoglobin (%)	8.4 \pm 2.1	-	
Duration of DM (months)	42.37 \pm 27.20	-	

Continuous variables are expressed as the mean \pm standard deviation. DM: diabetes mellitus, M: male, F: female, BMI: body mass index, NS: non-specific

in Table 1. The age of patients was higher than the controls ($p=0.014$). The number of patients with a duration of disease <36 months was 19 and the number of patients with a duration of disease >48 months was 18.

Analysis of the cardiac function using 2-dimensional and Doppler methods

The data derived from conventional echocardiographic analysis are listed in Table 2. The E velocity of the patients was significantly lower than that of controls ($p=0.028$). However, the other conventional echocardiographic parameters in the patient group, including mitral flow patterns, were not significantly different from

Table 2. Echocardiographic parameters derived from two-dimensional and Doppler imaging in the study groups

Parameter	Patients with DM (n=47)	Controls (n=38)	P
End-diastolic diameter (mm)	4.2±0.4	4.1±0.5	NS
End-systolic diameter (mm)	2.6±0.3	2.6±0.4	NS
Diastolic septal thickness (mm)	0.8±0.2	0.8±0.2	NS
Diastolic posterior wall thickness (mm)	0.8±0.1	0.8±0.1	NS
End-diastolic volume (cm ³)	79.6±19.5	76.8±22.2	NS
End-systolic volume (cm ³)	24.6±7.4	25.4±9.0	NS
Stroke volume (mL)	55.0±15.6	51.4±16.3	NS
Cardiac output (L/min)	4.5±1.6	4.5±1.5	NS
Fractional shortening (%)	38.6±5.4	36.9±5.4	NS
Ejection fraction (%)	69.0±6.8	66.8±7.2	NS
E (cm/s)	99.2±16.5	107.6±17.4	0.028
A (cm/s)	50.5±11.0	51.9±10.3	NS
E/A ratio	2.1±0.6	2.1±0.5	NS
Mitral deceleration time (ms)	144.6±21.9	134.1±27.2	NS
Isovolumic relaxation time (ms)	59.2±9.6	59.6±10.2	NS

All measures are expressed as the mean ± standard deviation. DM: diabetes mellitus, NS: non-specific

Table 3. Tissue Doppler imaging findings in the study groups

Parameter	Patients with DM (n=47)	Controls (n=38)	P
Septum			
S' (cm/s)	9.3±1.2	9.5±1.2	NS
E' (cm/s)	16.0±2.0	16.1±1.9	NS
A' (cm/s)	7.2±1.4	6.6±1.6	NS
E'/A'	2.3±0.5	2.6±1.7	NS
E/E'	6.3±1.3	6.7±1.2	NS
Tei index	0.5±0.1	0.4±0.2	NS
Lateral			
S' (cm/s)	12.2±2.5	11.3±2.5	NS
E' (cm/s)	21.5±2.9	20.8±2.6	NS
A' (cm/s)	6.9±1.4	6.6±1.5	NS
E'/A'	3.2±0.7	3.3±0.7	NS
E/E'	4.7±0.7	5.2±1.0	NS
Tei index	0.5±0.1	0.4±0.1	NS

All measures are expressed as the mean ± standard deviation. DM: diabetes mellitus, NS: non-specific

the controls. Although the findings of pulsed wave TDI at the annular level showed a lower S', E', and E'/A', and a higher Tei index in the patient group, these differences were not significant (Table 3).

An analysis of the cardiac function using vector velocity imaging

The regional myocardial velocity, strain, systolic and diastolic SR, and displacement findings evaluated at the basal and mid-septal, and basal and mid-lateral wall levels are listed in Table 4. These parameters also did not show significant differences between the patient and control groups.

Relationship between duration of diabetes mellitus and echocardiographic parameters

Characteristic and conventional echocardiographic data according to duration of DM are listed in Table 5. The group with a duration of DM >4 years had a higher HbA1c than the group with a duration of DM <3 years ($p=0.01$). The group with a duration of DM >4 years

Table 4. Vector velocity imaging findings in the study groups

Parameter	Patients with DM (n=47)	Controls (n=38)	P
Septum basal			
Systolic velocity (cm/s)	5.5±1.28	5.7±1.3	NS
Diastolic velocity (cm/s)	9.7±1.8	9.8±2.3	NS
Strain (%)	24.0±7.1	24.3±5.5	NS
Systolic strain rate (s ⁻¹)	1.9±0.7	1.9±0.7	NS
Diastolic strain rate (s ⁻¹)	2.6±1.2	2.6±0.9	NS
Displacement (mm)	9.3±2.0	9.4±1.9	NS
Septum mid			
Systolic velocity (cm/s)	3.6±1.1	3.5±0.8	NS
Diastolic velocity (cm/s)	6.1±1.7	6.4±2.1	NS
Strain (%)	24.1±5.5	24.6±4.2	NS
Systolic strain rate (s ⁻¹)	1.9±0.5	1.8±0.4	NS
Diastolic strain rate (s ⁻¹)	3.0±0.9	2.8±0.7	NS
Displacement (mm)	5.4±1.6	5.4±1.6	NS
Lateral basal			
Systolic velocity (cm/s)	6.7±1.5	6.1±1.8	NS
Diastolic velocity (cm/s)	11.6±3.4	10.9±2.6	NS
Strain (%)	24.1±6.6	24.7±6.0	NS
Systolic strain rate (s ⁻¹)	2.4±0.8	2.2±0.5	NS
Diastolic strain rate (s ⁻¹)	2.7±1.1	2.7±1.1	NS
Displacement (mm)	10.7±2.6	10.0±2.9	NS
Lateral mid			
Systolic velocity (cm/s)	5.9±1.9	4.9±1.6	NS
Diastolic velocity (cm/s)	9.3±2.8	8.3±2.9	NS
Strain (%)	23.0±5.7	24.7±4.5	NS
Systolic strain rate (s ⁻¹)	2.0±0.7	1.9±0.5	NS
Diastolic strain rate (s ⁻¹)	3.0±1.1	3.1±1.0	NS
Displacement (mm)	8.2±2.6	6.9±2.2	NS

All measures are expressed as the mean ± standard deviation. DM: diabetes mellitus, NS: non-specific

had a lower EF, FS, E velocity, and prolonged IVRT compared to the group with a duration of DM <3 years; however, these results were not significantly different between the two groups. The findings of pulsed wave TDI at the annular level did not show significant differences. The regional myocardial systolic and diastolic velocities evaluated at the basal septum using VVI were lower in the group with a duration of DM >4 years than the group with a duration of DM <3 years and the control group

Table 5. Baseline characteristics and echocardiographic parameters according to duration of DM

Parameter	Duration of DM <3 years (n=19)	Duration of DM >4 years (n=18)	p
Gender	M (6)/F (13)	M (6)/ F (12)	
Duration of DM (months)	20 (3-29)	66(48-92)	
Glycosylated hemoglobin (%)	7.6±1.9	9.4±2.2	0.01
Conventional echocardiography			
Fractional shortening (%)	38.7±5.1	37.8±4.9	NS
Ejection fraction (%)	69.0±6.5	68.1±6.1	NS
E (cm/s)	99.7±16.4	98.4±18.7	NS
A (cm/s)	48.9±8.6	52.7±14.0	NS
Mitral deceleration time (ms)	148.5±20.3	143.6±26.0	NS
Isovolumic relaxation time (ms)	58.1±9.6	60.3±9.2	NS
Tissue Doppler imaging			
Septum			
S' (cm/s)	9.3±1.0	9.4±1.5	NS
E' (cm/s)	16.4±1.8	16.2±2.3	NS
A' (cm/s)	6.9±1.4	7.5±1.5	NS
E'/A'	6.2±1.4	6.1±1.2	NS
Tei index	0.5±0.1	0.5±0.1	NS
Lateral			
S' (cm/s)	12.5±2.6	11.9±2.4	NS
E' (cm/s)	22.5±2.4	21.2±3.4	NS
A' (cm/s)	6.7±0.9	7.1±1.5	NS
E'/A'	4.5±0.9	4.6±0.8	NS
Tei index	0.5±0.1	0.5±0.2	NS

All measures are expressed as the mean ± standard deviation. DM: diabetes mellitus, M: male, F: female, NS: non-specific

(Table 6). Also, the regional myocardial systolic and diastolic SRs evaluated at the basal and mid-septum were lower in the group with a duration of DM >4 years; however, none of the values were significantly different between the two groups.

Based on the conventional and unconventional in-

Table 6. Echocardiographic parameters derived from vector velocity imaging according to duration of DM

Parameter	Duration of DM <3 years (n=19)	Duration of DM >4 years (n=18)	p
Septum basal			
Systolic velocity (cm/s)	5.5±1.0	5.1±1.0	NS
Diastolic velocity (cm/s)	9.9±1.5	9.1±1.9	NS
Strain (%)	25.3±7.6	25.7±4.0	NS
Systolic strain rate (s ⁻¹)	2.0±0.8	1.6±0.5	NS
Diastolic strain rate (s ⁻¹)	2.7±1.3	2.3±0.8	NS
Displacement (mm)	9.7±1.9	8.5±1.7	NS
Septum mid			
Systolic velocity (cm/s)	3.6±1.0	3.5±1.2	NS
Diastolic velocity (cm/s)	6.2±1.9	6.1±1.8	NS
Strain (%)	25.5±5.4	25.0±2.8	NS
Systolic strain rate (s ⁻¹)	1.9±0.5	1.8±0.4	NS
Diastolic strain rate (s ⁻¹)	3.2±0.9	2.6±0.7	NS
Displacement (mm)	5.6±1.8	5.1±1.5	NS
Lateral basal			
Systolic velocity (cm/s)	6.7±1.5	6.7±1.7	NS
Diastolic velocity (cm/s)	10.7±2.9	11.9±3.5	NS
Strain (%)	25.1±5.9	25.6±3.2	NS
Systolic strain rate (s ⁻¹)	2.5±0.9	2.3±0.7	NS
Diastolic strain rate (s ⁻¹)	2.7±0.9	2.6±0.9	NS
Displacement (mm)	10.5±1.1	10.6±2.9	NS
Lateral mid			
Systolic velocity (cm/s)	6.1±2.2	5.6±1.8	NS
Diastolic velocity (cm/s)	9.2±2.8	9.4±3.1	NS
Strain (%)	24.2±4.4	25.2±4.0	NS
Systolic strain rate (s ⁻¹)	2.0±0.7	1.9±0.6	NS
Diastolic strain rate (s ⁻¹)	2.9±1.2	2.9±0.8	NS
Displacement (mm)	8.2±2.7	7.9±2.4	NS

All measures are expressed as the mean ± standard deviation. DM: diabetes mellitus, NS: non-specific

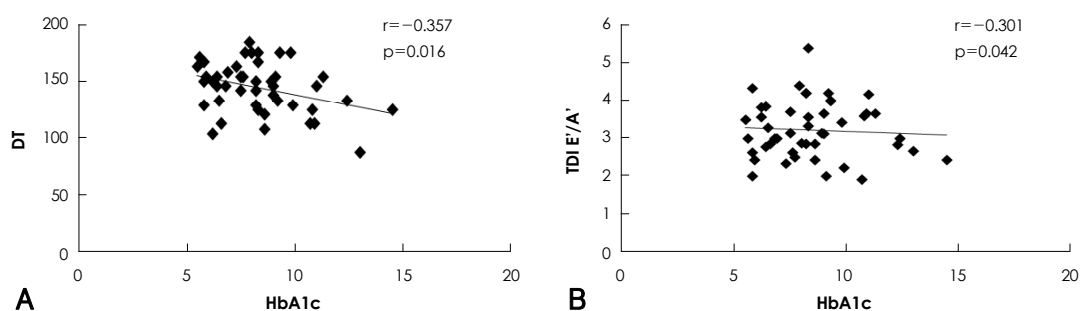


Fig. 1. Correlation between echocardiographic parameters and glycosylated hemoglobin (%). A: correlation between deceleration time (DT) and glycosylated hemoglobin (%). B: correlation between tissue Doppler imaging (TDI) E'/A' ratio and glycosylated hemoglobin (%).

dices of systolic and diastolic function, no significant relationship existed between the duration of DM and echocardiographic parameters. DT and E'/A' had significant inverse correlations with HbA1c (Fig. 1) ($p=0.042$ and $p=0.016$, respectively). No significant relationship existed between the duration of DM or HbA1c and several parameters obtained from the VVI.

Discussion

This study yielded the following results: 1) no change of LV systolic function when evaluated by new sensitive echocardiographic techniques, such as VVI, in the presence of normal systolic function during conventional and unconventional echocardiographic examinations; 2) the change in LV diastolic function when evaluated by conventional echocardiographic (transmitral) examination in the presence of normal diastolic function during unconventional echocardiographic examination; 3) significant inverse correlations between conventional/unconventional echocardiographic parameters and HbA1c level; and 4) mild progression of LV systolic and diastolic functions from normal to dysfunction according to the duration of DM in spite of no significant differences between the groups.

In the current study, LV systolic function was evaluated during the resting state and did not show a significant difference between the two groups. The results of the current study, which documented normal contraction at rest, were the same as previous studies.^{2,7)}

LV diastolic dysfunction in patients with DM may be caused by increased LV diastolic stiffness, deposition of advanced glycation end products, and cardiac fibrosis, all as a consequence of DM.^{11,12)} Previous studies have reported a change in early diastolic ventricular function in young adults with type I DM with normal LV EF.^{8,9)} The study to determine the relationship between LV diastolic dysfunction and the duration of DM demonstrated that a duration of DM >4 years was correlated with significant LV diastolic dysfunction.¹³⁾ In comparison to the previous study, although LV diastolic function using mitral inflow Doppler analysis showed a significant change in the DM group, LV diastolic function evaluated by TDI and VVI analysis, which were more sensitive for the detection of LV functional alteration, did not show a significant difference between the groups. The present data showed that there was no alteration in LV diastolic function in pediatric patients with type I DM. Indeed, the subjects in the current study were younger (mean age, 12 years and 5 months) and of shorter disease duration (mean duration, 3 years and 5 months). However, the striking finding involved the demonstration that LV functional alteration was based on the duration of DM. Although there were no significant differences between the duration of DM in the

>3 and >4 years groups, several echocardiographic parameters were lower in the group with a duration of DM >4 years. We therefore suggest that LV systolic and diastolic function may progress from normal to subtle changes or dysfunction according to the duration of DM.

In the current study, a higher HbA1c was associated with a lower DT and E'/A'. When LV compliance decreases and relaxation is abnormal, the DT becomes shorter and the E'/A' ratio becomes <1.^{14,15)} The present data suggest that hyperglycemia induces changes in LV diastolic function, especially decreased compliance and relaxation. However, of the subjects in the present study, decreased DT and E'/A' according to hyperglycemia, were not significantly different in comparison with the control group and do not necessarily indicate definite LV diastolic dysfunction. The influence of hyperglycemia on LV function suggest that hyperglycemia may decrease the expression of sarco(endo)plasmic reticulum Ca²⁺-ATPase (SERCA2a) and the SERCA2a-to-phospholamban ratio.^{16,17)} These reports imply that active control of hyperglycemia and lowering blood glucose levels may attenuate these processes. Although it is difficult to clinically identify whether hyperglycemia is associated with myocardial dysfunction in patients with DM, recent echocardiographic studies have shown that correlations exist between the state of glycemic control and ventricular function. Recent studies involving adult patients with type 2 DM showed that hyperglycemia influences on LV systolic function, especially with respect to ventricular long axis function.^{18,19)} A study using magnetic resonance imaging indicates that there is a correlation between hyperglycemia and LV function in type 1 DM as well.²⁰⁾ The other study demonstrated that appropriate control of hyperglycemia improves LV function and reduced LV mass in type 1 DM patients,²¹⁾ and that there is a significant correlation between hyperglycemic control and changes in LV function. In the current study, LV diastolic function showed a significant and inverse correlation with HbA1c. Of importance, this finding was demonstrated in a very early stage of type I DM. We suggest that to maintain normal ventricular function in patients with DM apart from the duration of DM, more aggressive control of blood glucose levels are needed and must be started as early as possible.

The limitations of the present study were that the number of enrolled patients was relatively small and that it was a cross-sectional study in which a comparison was made without baseline data.

Children and young adolescents rarely have insight on regarding their disease, and their diet is accordingly difficult to control. Therefore, alteration of myocardial function induced by DM may begin earlier than is generally thought and these changes may be accelerated when glycemic control is poor. We recommend that close observation should begin early and should include de-

tection of diabetic cardiac alterations, as well as other diabetic complications.

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