

RELATION OF HEMOGLOBIN A_{1c} TO LEFT VENTRICULAR DIASTOLIC FUNCTION IN PATIENTS WITH TYPE 1 DIABETES MELLITUS AND WITHOUT OVERT HEART DISEASE

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SUMMARY

Left ventricular diastolic dysfunction is a main feature of diabetic heart disease. The aim of this prospective study was to evaluate the relation of hemoglobin A_{1c} and diastolic function in type 1 diabetes mellitus. We examined echocardiographic studies of 25 patients with type 1 diabetes without clinical evidence of heart disease and 25 healthy age- and sex-matched normal individuals. In patients with type 1 diabetes, there was a diastolic dysfunction with lower transmitral E/A (1.28 ± 0.3 vs. 1.6 ± 0.3 ; $p=0.01$), more prolonged isovolumic relaxation time (99 ± 11 vs. 71 ± 8 , $p=0.003$) in comparison with normal subjects. Furthermore, HbA_{1c} correlated with diastolic indices. These results demonstrate that asymptomatic diastolic dysfunction is common in patients with type 1 diabetes mellitus and that its severity correlates with glycemic control.

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INTRODUCTION

Diabetes mellitus (DM) is a risk factor for the development of symptomatic heart failure (1). Heart failure that occurs as the result of impaired myocardial relaxation and compliance has been termed diastolic heart failure (2). Diastolic heart failure develops despite normal left ventricular systolic contractile function and leads to significant morbidity, medical costs, and mortality (3).

There are few data on the appearance of markers of subclinical cardiovascular disease, which usually precede macrovascular disease in type 1 diabetes mellitus (4). Possible mechanisms for a specific diabetic cardiomyopathy include abnormalities of small intramural coronary vessels, deposition of collagen, and lipids and metabolic derangements that alter actomyosin and myosin adenosine triphosphatase activities (5).

Diastolic parameters are also highly influenced by changes in volume status, blood pressure, and heart rate, further complicating their interpretation in patients with diabetes. In addition, more exact analysis of left ventricular diastolic function requires direct left ventricular pressure measurements (6), which are not appropriate for clinical studies in healthy individuals. Noninvasive echocardiography with Doppler measure-

ments of transmitral blood flow, together with other measurements, have become the preferred means to evaluate diastolic function noninvasively (7). In this study, we sought to assess the occurrence of markers of subclinical cardiac (diastolic) dysfunction in asymptomatic patients with type 1 DM without any suggestion of macrovascular cardiac disease, and to evaluate the relation between diastolic dysfunction and glycemic control using echocardiographic techniques.

SUBJECTS AND METHODS

The study group included 25 type 1 (13 men aged 19 to 37 years) diabetic patients who were compared with 25 age- and sex-matched normal volunteers. Exclusion criteria were any history of hypertension, myocardial infarction, unstable angina pectoris, or congestive heart failure. Subjects were also excluded if they had any evidence of global or regional left ventricular (LV) dysfunction, valvular stenosis, or regurgitation, or abnormal end-diastolic or end-systolic dimensions on transthoracic echocardiography. All subjects had normal electrocardiograms. All study subjects provided an informed consent before the study.

Echocardiography

Echocardiographic studies were done in supine position by 2-dimensional transthoracic standard pulsed color Doppler echocardiography using a VING MED 750C echocardiographic machine. Recordings were acquired with a 1.7 to 3.5 harmonic Doppler transducer. Color-Doppler, M-mode and 2-dimensional echocardiographic images of the left ventricle were obtained for evaluation of ventricular septal and posterior wall thicknesses in diastole and systole, LV internal dimensions in diastole and systole, and left atrial areas. LV mass was calculated by the method proposed by Devereux *et al.* (8). From the apical 4-chamber view, the pulsed Doppler sample volume was placed at the tips of the mitral leaflets, and the mitral inflow velocity profiles were recorded with a horizontal speed of 100 mm/s and a minimized high-pass filter. A minimum of 6 beats were studied. From the mitral inflow recordings, peak early (E) and atrial (A) velocities of mitral flow and the E/A ratio were

obtained. From the apical 4-chamber view, the color Doppler sector map of the mitral inflow was displayed. Fine adjustments were made to acquire the longest column of color flow from the mitral annulus to the apex. An M-mode cursor was positioned through the center of the flow and the spectra were displaced on the video screen at 100 mm/s. Color Doppler measurements were obtained as previously described (9). Because the objective was to detect subclinical cardiac dysfunction, the patients included in the study had no obvious signs of macrovascular disease and had LV ejection fractions of >55% as assessed by the modified biplane Simpson's method. LV hypertrophy was defined as an interventricular septum thickness of ≥ 1.3 cm. Diastolic function was determined from the mitral inflow (early rapid filling wave, late filling wave, deceleration time, isovolumic relaxation time).

Each variable was measured and the results of 3 beats were averaged for each subject. Chart reviews of 25 type 1 diabetic patients were performed. Mean hemoglobin (Hb) A_{1c} was obtained from all available values before echocardiographic study. The severity of nephropathy was defined in terms of albuminuria as normal (urine protein <30 mg/24 h), microalbuminuria (urine protein 30 to 300 mg/24 h), and macroalbuminuria (urine protein >300 mg/24 h). Neuropathy was defined as the presence of any of the following: sensory loss, loss of ankle reflexes, abnormal position sense, presence of gastroparesis, or tachycardia at rest.

Control subjects

Twenty-five healthy age- and sex-matched subjects were recruited after an informed consent. A complete medical history was obtained and physical examination was performed, after which echocardiographic measurements were performed. They all were lifelong nonsmokers and had no family history of premature vascular disease. None had arterial hypertension, diabetes mellitus (DM), or hyperlipidemia, none took regular medications, and DM was excluded by a normal fasting glucose level, according to the American Diabetes Association guidelines.

Statistical analysis

The Wilcoxon rank-sum test was used to analyze differences between the groups. Pearson's correlation analysis was used to measure the strength of association between pairs of variables. Simple and multiple linear regression was used to assess the relation between diastolic indices and predictor variables (age, sex, HbA_{1c}, duration of diabetes, nephropathy, and systolic blood pressure).

RESULTS

Baseline characteristics of the control group and diabetic patients are listed in Table 1 and Table 2. There were no significant differences in age, body mass index, or systolic and diastolic blood pressures. Six diabetic patients had microalbuminuria, and one had proteinuria. Baseline two-dimensional and M-mode echocardiographic measurements are listed in Table 3. Both groups had similar LV ejection fractions. However, diabetic patients had a trend toward higher LV mass and left atrial area.

There were no significant differences in the mean peak pulse Doppler E velocity between the normal and diabetic groups (Table 4). However, the mean peak pulse Doppler A velocity was higher in diabetic group,

Table 1. **Clinical characteristics of diabetic subjects and normal controls**

Characteristic	Normal controls (n=25)	Diabetic subjects (n=25)
Age (yrs)	28 ± 10	28 ± 9
Men	12 (48%)	13 (52%)
Body mass index (kg/m ²)	22 ± 6	24 ± 5
Systolic blood pressure (mm Hg)	110 ± 9	110 ± 11
Diastolic blood pressure (mm Hg)	75 ± 3	72 ± 3
Heart rate (beats/min)	71 ± 5	78 ± 9

Continuous variables are presented as mean ± SD; categorical variables are presented as number (%) of patients

Table 2. **Other clinical characteristics of diabetic subjects**

Characteristic	Type 1 diabetic subjects (n=25)
Duration of diabetes (yrs)	15 ± 9
Mean hemoglobin A _{1c} (%)	7 ± 1.5
Total serum cholesterol (mg/dL)	171 ± 32
High-density lipoprotein cholesterol (mg/dL)	53 ± 18
Low-density lipoprotein cholesterol (mg/dL)	101 ± 19
Triglycerides (mg/dL)	100 ± 37
Normal albuminuria	18 (78%)
Microalbuminuria	6 (24%)
Proteinuria	1 (4%)

Continuous variables are presented as mean ± SD; categorical variables are presented as number (%) of patients

Table 3. **Baseline echocardiographic characteristics of diabetic subjects and normal controls**

Characteristic	Normal controls (n=25)	Diabetic subjects (n=25)	p value
Left atrial area (cm ²)	15.1 ± 2.6	19 ± 5.1	0.07
LV mass index (gm/m ²)	91 ± 36	106 ± 40	0.06
LV ejection fraction (%)	65 ± 4	66 ± 5	0.2
Posterior LV thickness (cm)	0.7 ± 0.1	0.91 ± 0.3	0.001
Interventricular septal wall thickness (cm)	0.97 ± 0.2	1 ± 0.2	0.33
LV end diastolic diameter (cm)	4 ± 0.3	4 ± 0.4	0.61
LV end systolic diameter (cm)	2.3 ± 0.4	2.4 ± 0.6	0.73

Continuous variables are presented as mean ± SD

Table 4. **Doppler indices in normal and diabetic subjects**

Variable	Normal controls (n=25)	Diabetic subjects (n=25)	p value
LV peak early transmitral flow velocity E (cm/s)	75 ± 1.1	77 ± 0.9	0.3
Peak atrial contraction A (cm/s)	48 ± 15	70 ± 14	0.003
E/A ratio	1.6 ± 0.3	1.28 ± 0.31	0.01
Deceleration time (ms)	185 ± 36	209 ± 34	0.02
Isovolumic relaxation time (ms)	71 ± 8	99 ± 11	0.003

Continuous variables are presented as mean ± SD

and consequently the mean E/A ratio was significantly decreased in this group. The mean deceleration time of early diastolic transmitral flow and mean isovolumic relaxation time were longer in diabetic group. In DM group, HbA_{1c} showed positive correlation with E/A ratio ($r=0.34$; $p=0.01$) and isovolumic relaxation time ($r=0.79$; $p=0.0003$).

DISCUSSION

In this study, we found a higher prevalence of asymptomatic diastolic dysfunction in type 1 diabetes mellitus, even in the absence of hypertension and cardiac disease. These results support the concept of a specific subclinical diabetic cardiomyopathy, which may be related to glycemic control.

We showed that children and adolescents with type 1 diabetes had altered cardiac function compared with age-matched individuals without diabetes. Subjects included in the study had no cardiac signs or symptoms or diabetes complications, and were not taking medications known to modify cardiac structure or function. The most striking findings were recorded in patients with type 1 diabetes, who had a reduced diastolic function compared with control subjects.

Prolonged isovolumic relaxation time reflects the rate of active left ventricular diastolic relaxation between aortic valve closure and opening of the mitral valve. Relaxation of the myocardium is an energy-dependent process requiring calcium sequestration from the cytosol into the sarcoplasmic reticulum, and it is altered in diabetes. Interestingly, recent magnetic resonance studies have correlated changes in myocardial high-energy phosphates and parameters of diastolic function in patients with type 2 diabetes. Experimental studies have also shown abnormalities in the calcium pump activity in diabetic animals (10).

In this study, we found low transmitral E/A ratio as an evidence of reduced diastolic function, left ventricular chamber compliance, and changes in the left atrial pressure. In the presence of mild diastolic dysfunction, early filling is often blunted, leading to an exaggerated atrial contribution to left ventricular filling and a low E/A ratio. In more advanced heart failure, this pattern is often lost due to high left atrial and left ventricular pressure and the E/A ratio pseudo-normalizes or increases, complicating interpretation (5).

Prior studies have shown a correlation between HbA_{1c} and diastolic function in older individuals with type 1 diabetes, suggesting that glycemic control may be an important determinant of diastolic function (11).

Hyperglycemia influences heart metabolism, the production of advanced glycosylation end products, oxidative stress, and protein kinase C activation (12,13). The relation between glycemic control and diastolic indexes in our study supports the hypothesis that hyperglycemia by itself can lead to subclinical cardiomyopathy. Our results indicate that diabetic patients with worse glycemic control are at an increased risk of early diastolic dysfunction.

Therefore, in our study, patients with type 1 diabetes had increased isovolumic relaxation time, and a decreased E/A ratio compared with normal volunteers. These results are consistent with prior studies in asymptomatic normotensive type 1 and 2 diabetic patients (14-18). Also, diastolic dysfunction was closely related to an increased urinary albumin excretion (19).

Further study is needed to determine whether intensification of glycemic control improves diastolic parameters.

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