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Improved metabolic control does not reverse left ventricular filling abnormalities in newly diagnosed non-insulin-dependent diabetes patients

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Abstract. In this study left ventricular diastolic function at rest was evaluated in ten newly diagnosed, non-insulin-dependent diabetic patients by Doppler echocardiography, performed at the onset of disease and after 6 and 12 months of adequate glycaemic control. Glycosylated haemoglobin A_{1C}, total cholesterol and triglyceride levels were assessed at the same time. The control group consisted of ten healthy subjects of matching age and body mass index. The following parameters of left ventricular function were evaluated: ejection fraction (EF), peak velocity of the early (E) and late atrial (A) mitral flow, A/E ratio, duration of the early (Ei) and of the atrial (Ai) filling phase, and heart rate. The diabetic patients had significantly higher total cholesterol and triglyceride levels compared with healthy subjects. These remained elevated throughout the follow-up period, in spite of improved glycaemic control. A significantly shorter duration of Ei (0.15 ± 0.008 vs 0.18 ± 0.004, $P < 0.01$) and a higher value of A (0.51 ± 0.02 vs 0.39 ± 0.01, $P < 0.001$) and A/E (1.06 ± 0.05 vs 0.73 ± 0.02, $P < 0.001$) were found in the diabetic patients before treatment. The parameters did not significantly change after 1 year of adequate glycaemic control. These results indicate a left ventricular filling abnormality which is present in newly diagnosed non-insulin-dependent diabetic patients and does not reverse with improved glycaemic control.

Key words: Non-insulin-dependent diabetes – Diastolic dysfunction – Doppler echocardiography

Introduction

Diabetes mellitus induces specific changes in the myocardium, independently of coronary heart disease and arterial hypertension [1]. Non-enzymatic glycosylation [2], energetic deficit [3] and cardiac autonomic neuropathy [4] are implicated in the development of subclinical left ventricular dysfunction, preceding diabetic cardiomyopathy [5]. Left ventricular filling abnormalities are the first to be detected by Doppler echocardiography, their occurrence being unrelated to the type and duration of the diabetes [6]. Haemodynamic studies of newly diagnosed diabetic patients have revealed a higher blood pressure and lower stroke volume during exercise, which improve with adequate insulin therapy [7].

The aim of this study was to evaluate left ventricular function by Doppler echocardiography in newly diagnosed non-insulin-dependent diabetic (NIDDM) patients at the time of diagnosis of the disease and during 1 year of adequate glycaemic control.

Subjects and methods

Subjects

Ten newly diagnosed NIDDM patients (7 women and 3 men), who had no evidence of cardiac disease on physical examination and who were normotensive, were studied. All were recruited from the outpatient clinic as "newly" diagnosed, since an elevated blood glucose level was discovered on routine blood testing for the first time in their life. They were without symptoms of diabetes and unaware of the exact duration of the illness. None had ketoacidosis at the beginning of the study. All were free of microvascular complications, as proved by fundoscopic examination and clinical neurologic testing. They had preserved stretch reflexes and an intact vibratory sense. Cardiovascular autonomic function tests were performed for the assessment of autonomic neuropathy: heart rate response to standing up (30:15 ratio, normal being >1.04, abnormal < 1.00), heart rate response to deep breathing (maximum minus minimum heart rate, normal being >15 beats/min, abnormal < 10 beats/min) and blood pressure response to standing up (normal fall in systolic blood pressure being < 10 mmHg, abnormal >30 mmHg). All had normal responses to cardiovascular tests and no symptoms of autonomic neuropathy of other systems. The diabetic patients had a normal renal function, with a serum creatinine concentration of less than 124 μmol/l, normal creatinine clearance and no microalbuminuria. Microalbuminuria was defined as 30–300 mg protein in the collected 24-h urine

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Table 1. Clinical and laboratory data of diabetic patients at the start of the study

No.	Age (years)	Sex	BMI (kg/m^2)	Th (%)	HbA_{1c} (mmol/l)	Glycaemia	C-peptide (nmol/l)	
							Basal	Stimulated
1.	30	F	21.7	Ch	9.2	10.1	0.78	1.50
2.	41	F	24.3	Gl	10.2	12.1	1.23	2.05
3.	49	M	26.3	Dt	8.8	8.5	0.57	1.63
4.	44	F	23.3	Ch	11.1	14.9	0.58	1.43
5.	49	M	24.9	Dt	9.2	9.5	1.30	2.65
6.	42	M	25.8	Gl	11.7	15.4	1.50	3.10
7.	49	F	25.6	Ch	10.0	12.4	0.75	1.32
8.	39	F	33.1	Gl	10.8	13.5	1.30	3.50
9.	43	F	22.8	Ch	9.4	10.5	0.79	1.29
10.	31	F	34.8	Gl	11.4	14.9	1.60	3.34

BMI, Body mass index; Th, therapy; HbA_{1c}, glycosylated haemoglobin; Ch, chlorpropamide; Gl, glibenclamide; Dt, diet

sample and was considered absent if not detected on three evaluations during the first 6 months of follow-up. The patients gave informed consent for participation in the study. The hospital's Ethical Committee approved the study.

The patients were 41.7 ± 2.17 years of age, with a mean body mass index of 26.26 ± 1.36 kg/m^2. Basal C-peptide and its response 6 min after intravenous 1 mg glucagon stimulation were assessed in all probands. Two were treated by diet alone, four by chlorpropamide and four by glibenclamide (Table 1). Measurements of glycosylated haemoglobin, total cholesterol and triglycerides were performed before treatment and after 6 and 12 months of therapy. The patients maintained normal blood pressure at rest and throughout the follow-up period. None had values above 140/90 mmHg, which was considered the upper limit of normal. The control group consisted of ten healthy subjects (5 men and 5 women) of the same age (40.7 ± 7.17 years) and body mass index (24.15 ± 2.76 kg/m^2).

Methods

Plasma glucose (mmol/l) was analysed by an enzymatic method, using glucose dehydrogenase. The glycosylated haemoglobin (HbA_{1c}) level was measured by column chromatography (Microcolumn Boehringer), the normal range being 5%–8%. Total cholesterol and triclycerides were assayed by an enzymatic colorimetric peroxidase-antiperoxidase (PAP) method using commercial Gilford Systems (Ohio, USA) kits. The normal range for cholesterol is 3.4–5.2 mmol/l and for triglyceride 0.5–1.9 mmol/l. C-peptide was determined by double antibody radioimmunoassay using commercial Serono kits, the normal basal level being 0.3–0.9 nmol/l.

A complete two-dimensional echocardiographic examination was performed using a Diasonics DRF 400 ultrasonoscope with a 3.5-MHz transducer. Each patient underwent a pulsed Doppler examination of the left ventricular inflow tract. From an apical four-chamber view, the Doppler cursor line was placed in the mitral valve inlet at an angle as nearly parallel to the flow as possible, the sample volume being positioned near the tips of the mitral leaflets. All examinations were recorded at a paper speed of 25 mm/s, with simultaneous recording of the electrocardiogram. The measurements were performed at the end of an expiration and recorded on film.

Doppler echocardiography was performed at the onset of disease and after 6 and 12 months of therapy, by an ultrasonographer unaware of the patient's treatment. Room temperature and lighting were constant during the study, and examinations were performed at the same time of the day. The following parameters were recorded: ejection fraction (EF), peak velocity of the early (E) and late atrial (A) mitral flow, A/E ratio, duration of the early (Ei) and of the atrial (Ai) filling phase, and heart rate (HR). Five beats were measured and averaged for each of the parameters.

Table 2. Lipid and haemodynamic data (mean ± SE)

	Diabetic	Controls	*P* value
n (men/women)	10 (3/7)	10 (5/5)	
Total cholesterol (mmol/l)	7.61 ± 0.8	5.4 ± 0.1	< 0.05
Triglycerides (mmol/l)	4.13 ± 0.8	1.6 ± 0.2	< 0.01
Blood pressure (mmHg)			
Systolic	129 ± 3.8	129 ± 1.9	NS
Diastolic	78 ± 1.8	77 ± 0.9	NS
Heart rate (/min)	81.8 ± 3.1	69.4 ± 2.0	< 0.01
Ejection fraction (%)	60.6 ± 2.8	61.0 ± 0.8	NS

Statistical analysis

All results are expressed as mean ± SEM. Intergroup variables were compared by Student's unpaired *t*-test. Standard regression techniques were used to evaluate the relation between diastolic filling and metabolic control of diabetes. The level of significance was set at $P < 0.05$.

Results

The diabetic patients had significantly higher total cholesterol and triglyceride levels compared with healthy subjects (Table 2). No difference was found in the systolic and diastolic blood pressures and ejection fraction of the left ventricle in the two groups. The heart rate was significantly higher in the diabetic patients.

A significantly shorter Ei was found in the diabetic patients at the time of discovery of the disease. No differences were found in Ai and E. However, the diabetic patients had a higher A and a higher A/E ratio (Table 3).

Glycosylated haemoglobin decreased significantly after 6 months, with a further decrease after 12 months of treatment. Total cholesterol and triglycerides levels showed a slight, but not significant, decreasing trend during the 12-month period. It is evident that even though better HbA_{1c} levels were achieved, there was a slight, but not significant, improvement in the parameters of diastolic filling over the 12-month period (Table 4). There was a slight prolongation of Ai and a slight reduction in A and A/E ratio. Heart rate, Ei and E remained unchanged.

Table 3. Left ventricular diastolic parameters at the start of the study (mean ± SE)

	Ei (s)	Ai (s)	E (m/s)	A (m/s)	A/E
Diabetic patients	0.15 ± 0.008	0.10 ± 0.007	0.50 ± 0.03	0.51 ± 0.02	1.06 ± 0.05
Controls	0.18 ± 0.004	0.11 ± 0.003	0.54 ± 0.01	0.39 ± 0.01	0.73 ± 0.02
P value	< 0.01	NS	NS	< 0.001	< 0.001

Ei, Early diastolic filling time; Ai, atrial filling time; E, peak velocity of early diastolic filling; A, peak velocity of atrial filling

Table 4. Metabolic control and diastolic filling in ten newly diagnosed non-insulin-dependent diabetic patients during the 12 months of therapy (mean ± SE)

	Start of disease	6-month follow-up	12-month follow-up
Glycosylated haemoglobin (%)	10.18 ± 0.32	7.91 ± 0.31*	7.08 ± 0.62**
Total cholesterol (mmol/l)	7.61 ± 0.88	7.28 ± 0.52	7.09 ± 0.67
Triglycerides (mmol/l)	4.14 ± 0.86	3.36 ± 0.68	3.34 ± 0.57
Ei (s)	0.15 ± 0.008	0.16 ± 0.01	0.16 ± 0.01
Ai (s)	0.10 ± 0.007	0.104 ± 0.004	0.112 ± 0.006
E (m/s)	0.504 ± 0.03	0.502 ± 0.02	0.505 ± 0.03
A (m/s)	0.508 ± 0.02	0.487 ± 0.02	0.471 ± 0.01
A/E	1.06 ± 0.05	0.965 ± 0.05	0.961 ± 0.06
Heart rate (/min)	82.8 ± 2.96	81.1 ± 1.96	80.3 ± 2.01

* $P < 0.01$ vs start; ** $P < 0.05$ vs 6 months

Discussion

The most important finding of this study is that impairment of diastolic filling present at the time of discovery of NIDDM is not reversed during the first year of treatment and achievement of glycaemic control.

Studies performed on animals have revealed impaired myocardial contraction and relaxation in acute diabetes [8]. These were caused by biochemical changes: decreased myosin ATPase activity with a predominance of the V3 isoform of myosin [9] and diminished calcium transport by sarcoplasmic reticulum [3]. Such changes were completely reversed after adequate insulin therapy, and the degree of reversibility depended on the dose of insulin [10].

Haemodynamic studies on newly diagnosed juvenile diabetic patients have revealed the presence of higher blood pressure, increased heart rate and decreased stroke volume during exercise [11]. With adequate insulin therapy, the stroke volume increases and the heart rate decreases, but the response of arterial blood pressure to exercise remains unchanged [7]. No difference in arterial blood pressure and stroke volume at rest exists between new diabetic patients and healthy subjects.

Our study has shown an increased heart rate and impairment of diastolic filling in newly diagnosed type 2 diabetic patients. Similar findings have been reported in long-term type 1 diabetes [12] and in adolescents with diabetes [13]. They reflect an abnormal ventricular relaxation which occurs in acute diabetes and a diminished left ventricular compliance due to specific structural changes in the heart. Non-enzymatic glucosylation, which forms the biochemical basis of diabetic microangiopathy, causes alterations in myocardial small vessels and interstitium. Hyalin changes of the arterioles, perivascular and interstitial fibrosis, degeneration and fragmentation of myocytes appear to form the pathologic basis of a distinct cardiomyopathic process in diabetes [14]. However, its pathogenesis has not been completely elucidated, which explains why the relationship of type, duration and severity of the diabetes to the myocardial abnormalities still remains uncertain. Also, diastolic dysfunction may or may not be related to the extent of other microvascular complications [15]. Autonomic neuropathy may contribute to left ventricular systolic and dystolic dysfunction due to diminished sympathetic stimulation [16]. None of our patients had autonomic neuropathy or other microvascular disease.

Reversibility of left ventricular diastolic filling abnormalities has been questioned. Studies on patients with NIDDM have shown considerable improvement of the left ventricular function upon correction of the hyperglycaemia with diet or oral hypoglycaemic drugs [17]. Our patients had some, but not significant, improvement in the parameters of diastolic function after adequate glycaemic control. Glycaemic control was assessed through the level of glycosylated HbA_{1c}, which has not been shown to correlate with cardiac function [18]. The rates of acquisition and turnover of glycosylated myocardial proteins are not known. Hence, a more sensitive method is needed to evaluate the effect of glycaemic control on cardiac function.

The levels of cholesterol and triglycerides in new NIDDM patients remained elevated throughout the study. It is therefore possible that a coexistent disorder of lipid metabolism contributes to the left ventricular diastolic dysfunction. Indeed, the accumulation of lipids in the myocardium has been implicated in the development of left ventricular diastolic dysfunction, also known to be present in the cardiomyopathy of obesity [19]. This could explain the persistence of left ventricular diastolic dysfunction, in spite of a significant improvement of glycaemic control. Further studies are needed to clarify this point.

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