Evaluation of the left ventricular hemodynamic function and myocardial perfusion by gated single photon emission tomography, in patients with type 1 diabetes mellitus; prodromal signs of cardiovascular disease after four years

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Abstract

The aim of this study was to assess the changes in hemodynamic function and myocardial perfusion of the left ventricle occurring in patients with type 1 diabetes mellitus (DM1) 47-49 months after the first assessment. We have studied 20 asymptomatic patients, five females and 15 males, aged 22-46 y. The patients were under intensive insulin treatment and had normal electrocardiogram (ECG) at rest. In all patients gated single photon emission tomography (GSPET) was performed at rest and after exercise (examination I). After 47-49 months this test was repeated (examination II). GSPET was performed 60 min after the intravenous injection of 740 MBq of technetium-99m 2-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI), using a dual-headed gamma-camera. Left ventricular ejection fraction (LVEF), end diastolic volume (EDV) and end systolic volume (ESV) were calculated using quantitative GSPET (QGS). The intensity of perfusion defects was also evaluated based on a four degree QGS scale. Our results were as follows: a) In examination I, performed at rest: LVEF was 56.1%±7.5%, EDV 96.9±25.8 ml and ESV 42.6±16.3 ml. b) In examination I at stress: LVEF was 57.2%±7.5%, EDV 94.1±24.0 ml and ESV 40.5±15.5. c) In examination II performed at rest: LVEF was 58.1%±6.5%, EDV 112.1±26.1 ml and ESV 46.6±14.9 ml and d) In examination II at stress: LVEF 57.8%±5.6%, EDV 107.9±27.4 ml and ESV 44.9±14.4 ml. Significant differences were found between examinations I and II, regarding: a) EDV at rest ($P<0.001$) and at stress ($P<0.001$) and b) ESV at rest ($P<0.05$) and at stress ($P<0.005$). Correlation analysis revealed significant correlation between LVEF at rest and at stress both in examination I ($r=0.83$; $P<0.001$) and also in examination II ($r=-0.897$; $P<0.001$). Intensity of myocardial perfusion defects in examination I at rest and at stress was: 1.68±0.5 and 2.2±0.6 degrees respectively. Intensity of myocardial perfusion defects in examination II at rest and at stress was: 1.75±0.4 and 2.2±0.5 respectively. No significant differences in the intensity of these perfusion defects were found. EDV both at rest and at stress was significantly higher in examination II as compared with the examination I study. Similar, but less pronounced changes of ESV were found. This study confirms other authors' observations on LV, EDV and LV, ESV and also that the percentage of asymptomatic DM1 patients having silent myocardial ischemia is high as was in all our patients. Nevertheless, in the current literature, we were unable to find a study similar to the present one, comparing basal and after four years LV functional GSPET data, in asymptomatic DM1 patients. *In conclusion*, myocardial perfusion GSPET was useful as a screening test in DM1 patients in showing four years after the basal study, prodromal signs of cardiovascular disease, especially increase of left ventricular volumes and silent myocardial ischemia, in these patients. Our research on the above protocol is being continued.

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Introduction

The relation between diabetes mellitus (DM) and ischemic heart disease has been studied since the 1940s [1]. In the mid 1990s the question arose as to the purpose of screening tests in ischemic heart disease, even symptomless, in patients with type 1 diabetes mellitus (DM1) [2]. Coronary artery disease (CAD), cerebrovascular disease and peripheral vascular disease are the main causes of death in patients with DM, while DM increases two or even four times the risk of cardiovascular complications [3]. Cardiovascular

complications, including congestive cardiomyopathy, angina pectoris and sudden cardiac death, often concern patients with DM1. Advanced vascular sclerotic changes in patients with DM1 develop as early as in their third decade of life, irrespective of if the illness had begun in the first or the second decade of life [1]. The problem of early cardiac complications in young patients with DM1, especially relaxation abnormalities at rest, was studied before [4,5]. Gated myocardial perfusion SPET has been shown to be a reliable technique in the assessment of myocardial perfusion, left ventricle volumes and left ventricular ejection fraction (LVEF) [5]. In view of the rapid deterioration of the cardiovascular system in patients with DM1, it would be interesting to know how rapidly changes of the cardiovascular function in these patients, appear. We could not find in the accessible literature a reference similar to ours study, especially which included re-examination after a few year.

The aim of this article was the assessment by gated single photon emission tomography (GSPET) of hemodynamic changes of the left ventricle and of myocardial perfusion changes indicating the effect of DM1 on these cardiovascular parameters within a four years period of time.

Patients and methods

We have studied 20 nonconsecutive patients (5 women and 15 men) aged 22-46 y (mean age 30±10 y), who had been suffering from DM1 for 4 to 37 y (mean 13±9.71 y). The patients did not complain about any procardial pain, and had no ischemic changes in the ECG at rest. All patients were under intensive insulin treatment and taking acetylsalicylic acid as an anticoagulant. Eight patients were also taking statins as antilipidic treatment. Table 1 contains the clinical characteristics of the patients. Based on medical history of the patients, there were only three light smokers, who smoked only for a short period of time (10-18 months) and gave up smoking three-five years before the examination I, so there were no active smokers at the time of our study.

Myocardial perfusion scintigraphy was performed using a two days protocol and the gated single photon emission tomography (GSPET) technique. Both rest and stress GSPET were performed in all patients one hour after the intravenous (iv) injection of 740 MBq of technetium-99m-2-methoxy-isobutylisonitrile (^{99m}Tc-MIBI) (examination I). The same tests were repeated after 47-49 months (examination II).

Exercise test was performed with a bicycle ergometer using 3-min steps (25 watt increments) to reach an adequate exercise level, as defined by heart rate ≥85% of the maximum heart rate as predicted for age (= 220 - age). In examination I during stress tests, patients received a work load of 75 to 200 watts (mean 148.7±40.9 watts). In examination II during stress test, a work load of 100 to 200 watts was applied (mean 141.7±29.9 watts). The radionuclide tracer was iv injected at peak exercise, which was maintained for at last 1 min. Standard 12-lead ECG and blood pressure were recorded every 2-3 min during stress tests and during recovery. The exercise ECG was considered positive for ischemia in the presence of a ST segment depression of ≥2 mm, horizontal or downsloping.

The GSPET was performed using a dual-headed gamma camera (Varicam, Elscint, Haifa, Israel), equipped with low-energy, high-resolution parallel-hole collimators. Standard energy settings were used (20% energy window centered at 140 keV). The heads were set in the so-called "L-mode". GSPET was performed using 90 degrees rotation for each head, with the "step and shoot" method (step of three degrees). The data was collected from 60 projections (50s/projection) on 64x64 matrix and zoom 1.28. The heart cycle was divided into eight sequences. To reconstruct the pictures, Butterworth filter 2.5 was used with cut-off frequency of 0.4 cycles/pixel. The series of slices obtained in the plane, transverse, coronal and sagittal planes of the left ventricle, was estimated visually and using the "bull's eye" method [6]. For the estimation of LVEF, end diastolic volume (EDV) and end systolic volume (ESV), a commercially accessible method which had been worked out by the Germano-Quantitative Gated SPET - QGS was used [7]. Intensity of perfusion defects was described based on the Orientation Polar Maps included in GSPET-QGS in a four degrees scale, similar to the one used by others [8], as follows: 1: normal perfusion, 2: slightly impaired, 3: impaired, 4: severely impaired perfusion. A dedicated computer system XpertPro (Elscint, Haifa, Israel) was used. The results obtained were subject to statistical analysis as follows: For numerical data, mean values ±SD were calculated. Differences in the mean values were assessed by Student's paired t-test. In all statistical comparisons, probability values <0.05 were considered significant.

All studies were after routine tests ordered by patients' cardiologists.

Table 1. *The clinical characteristics of the patients*

Variable	Examination I (mean±SD)	Examination II (mean±SD)
n	20	20
Age	31.6±10.35	36.2±9.99
Active smokers (n)	0	0
Women (n)	5	5
BMI (kg/m^2)*	24.5±2.50	24.6±2.53
HbA1c (%)**	7.63±1.64	7.43±1.04
Mean blood glucose level (mg %)	147.4±46.23	136.8±23.04
Total cholesterol (mg/dl)	201.2±45.58	192.1±46.45
HDL cholesterol (mg/dl)	54.3±10.99	55.58±14.66
LDL cholesterol (mg/dl)	124.13±36.7	122.8±46.43
Triglycerides (mg/dl)	114.1±52.48	100.0±50.26
Systolic blood pressure (mmHg)	127.25±14.46	124.5±18.70
Diastolic blood pressure (mmHg)	83.2±9.77	80.7±9.77

*BMI – *Body mass index (kg/m^2)*

**HbA1c – *Glycosylated haemoglobin*

Results

In examination I during stress tests, the heart rate varied from 151 to 203 beats/min (mean 173.1±14.7 beats/min), and maximum pulse value, varied from 85% to 100% of the mean: 92.1% ± 6.45%. ST segment depression was observed in 20% of stress ECG tests.

In examination II during stress test, the heart rate ranged from 151 to 184 beats / min (mean 165.1 ± 10.8 beats/min) with maximum pulse value was 85% to 100% of the mean: 89.61% ± 3.5%. ST segment depression was observed in 20% of stress ECG tests. In both examinations (I and II) there were no serious cardiovascular side effects during stress tests and no statistically significant differences of stress tests parameters.

Results of comparing LVEF, EDV and ESV examinations I and II at rest and after stress are presented in Tables 2 and 3, respectively. Significant differences were observed by comparing in examinations I and II: a) EDV at rest (P<0.001), b) EDV at stress (P<0.001), c) ESV at rest (P<0.05) and d) ESV at stress P<0.005 (Tables 2 and 3). In examinations I and II there was a statistically significant correlation between LVEF at rest and at stress (r=0.830, P<0.001 and r=-0.897, P<0.001 respectively). Visual estimation of myocardial perfusion defects for both examinations I and II is shown in Table 4.

Intensity of perfusion defects evaluated by GSPET-QGS in a 4-degree scale in both examinations I and II at rest and stress and their significance is shown in Table 5.

Significant impairment of the left ventricle function and myocardial perfusion tests were not found in five women in this study.

Table 2. *Comparison between hemodynamic parameters of the left ventricle at rest obtained in examination I and examination II*

Examination I	n	LVEF (%) ±SD	EDV (ml) ±SD	EDV (ml) ±SD
	20	56.1	96.9	42.6
		7.5	25.8	16.3
Examination II	**N**	**LVEF (%) ±SD**	**EDV (ml) ±SD**	**EDV (ml) ±SD**
	20	58.1	112.1	46.6
		6.5	26.1	14.9
P		ns	P<0.001	P<0.05

Table 3. *Comparison between hemodynamic parameters of the left ventricle after stress study obtained in examination I and examination II*

Examination I	n	LVEF (%) ±SD	EDV (ml) ±SD	EDV (ml) ±SD
	20	57.2	94.1	40.5
		7.5	24.0	15.5
Examination II	**N**	**LVEF (%) ±SD**	**EDV (ml) ±SD**	**EDV (ml) ±SD**
	20	57.8	107.9	44.9
		5.6	27.4	14.4
P		ns	P<0.001	P<0.05

Table 4. *Visual assessment of myocardial perfusion defects*

Examination	Normal perfusion	Fixed defects	Reversible defects
Examination I	55%	25%	20%
Examination II	55%	25%	20%

Table 5. *Intensity of perfusion defects at rest and after stress*

Examination I	N	Rest x±SD	Stress x±SD
	20	1.68 ±0.5	2.2 ±0.6
Examination II	**N**	**Rest**	**Stress**
	20	1.75±0.4	2.2 ±0.5
P		NS	NS

Discussion

Because of the small number of women in our study, it was not possible to compare our findings among both sexes. The fact that intensive insulin treatment as applied in our patients helped achieve near normoglycemia and reduce the risk of cardiovascular disease events by 42%, indicates that our patients were at a rather steady state of treatment as also mentioned by others [9]. Our group of patients was comparable regarding: age, sex, type and duration of diabetes, insulin treatment, blood pressure, body mass index (BMI) and glycosylated haemoglobin (HbA1c) with similar groups studied by others [5, 10-13].

Values of LVEF at rest and stress in our patients were within normal range in both examinations I and II as also found by others who studied similar groups of diabetic patients – but without re-examination [10,11]. Our findings for LVEF and myocardial perfusion showed no statistical difference, indicating that after four years there were no prodromal signs of cardiovascular disease related to the above parameters.

The values of EDV and ESV, especially in examination II, were in our patents higher than showed by other authors [11] in patients with diabetes mellitus and higher, compared with patients without DM and with normal results of myocardial perfusion scintigraphy. Our patients, who were subject to intensive insulin therapy, showed after four years an increase in EDV at rest, and at stress, and a modest increase in ESV. These changes in ventricular volume, increase the risk of "diabetic cardiovascular disease", may reflect the moderate enlargement of the left ventricle [12] and could lead to "diabetic cardiomyopathy".

There are numerous papers showing silent myocardial ischemia (SMI) in asymptomatic persons with diabetes mellitus type 1 [13-16], but as far as we know, in current accessible bibliography, there is no study similar to ours, comparing LV

functional GSPET data after a few years of clinical follow-up in the same asymptomatic group of patients. For that reason we have compared our results to those of others, related to our study.

In our young patients with DM1, with no history of chest pain, the prevalence of reversible defects was in both examinations I and II, 20%. Very similar results were obtained in other study [17], in asymptomatic patients with type 1 DM, where 22% of patients had SMI, but the authors did not re-examined their patients.

Priori et al. (2005) in a single, without a follow-up study, have found silent, stress induced ischemia in 31% of patients without chest pain whereas in patients with stenocardia, the prevalence of reversible perfusion defects was 29% [18]. Other authors in the same conditions underline a worse outcome for diabetes patients with SMI than for those without ischemia. Higher evidence of CAD – 39% in asymptomatic diabetic patients and 51% in patients with symptoms of angina, were stated by other authors [15].

In conclusion, myocardial perfusion GSPET was useful as a screening test in DM1 patients in showing four years after the basal study, prodromal signs of cardiovascular disease, especially increase of left ventricular volumes and silent myocardial ischemia, in these patients. Our research on the above protocol is being continued.

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