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CLINICAL STUDY

The detection of early myocardial changes in asymptomatic diabetic individuals by ^{99m}Tc – Myoview gated-SPET and heart rate variability measurement

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Abstract: *Aims:* Incidence of early myocardial changes in asymptomatic diabetic individuals is not clearly documented. In the present study, we examined diabetic patients without a history of cardiovascular disease with negative treadmill test and no signs of systolic dysfunction for presence of cardiac autonomic neuropathy established by measurement of heart rate variability (HRV) and ^{99m}Tc - Myoview gated-SPET.
Materials and methods: 47 type I and type II diabetic patients were subjected to prospective study including echocardiography and HRV measurement using the combination of Ewing´s testing and spectral analysis. Subsequently, patients underwent treadmill test and stress myocardial perfusion scintigraphy. Additionally, vascular and metabolic parameters were collected.
Results: Treadmill test was negative in all patients. Diastolic dysfunction was found in 10 % of T1DM and 11 % of T2DM patients by echocardiography, whereas none of the patients had systolic dysfunction. SPET confirmed hypoperfusion in 35 % T1DM (p=0.01) and in 60 % T2DM (p=0.001). Diagnosis of cardiac autonomic neuropathy based on Ewing´s testing and HRV examination was established in 60 % of T1DM patients (p=0.001) and 77 % of T2DM patients (p=0.001). In T1DM group, significant association was found between cardiac autonomic neuropathy (CAN) and frequency of hypoglycaemia (p=0.04). No such correlations were found in patients with T2DM.
Conclusion: The results of the present study show high incidence of myocardial hypoperfusion and cardiac autonomic neuropathy among asymptomatic diabetic patients, whereas the standard diagnostic approaches including treadmill test and echocardiography failed to show any changes. Therefore, we conclude that diabetic heart disease remains underdiagnosed by standard approaches, but could be detected in asymptomatic patients by more sensitive methods, such as HRV measurement and myocardial scintigraphy *(Tab. 2, Fig. 2, Ref. 26)*. Text in PDF *www.elis.sk*.
Key words: ^{99m}Tc - Myoview gated-SPET, HRV measurement, diabetic heart disease.

Abbreviations: HUS – Hypoglycaemia unawareness syndrome, HRV – heart rate variability, SPET – Single photon emission computed tomography, TAGs – Triglycerides, T1DM – Diabetes mellitus type 1, T2DM –Diabetes mellitus type 2.

Based on the results of experimental, pathological and epidemiological studies, it is well established that hypertension and coronary heart disease are not the exclusive underlying causes of diabetic cardiomyopathy (1). Under the conditions of long-term hyperglycaemia, microvascular damage occurs as a consequence of oxidative stress, activation of proteinkinase C and inflammation associated with endothelial dysfunction (2). Cardiac damage in diabetic patients is triggered by changes in both autonomic nervous system and cardiac muscle. Alteration in autonomic nervous system leads to cardiac autonomic neuropathy (CAN). Macrovascular changes affect the cardiac muscle due to narrowing of coronary arteries. The concept of endothelial dysfunction is widely accepted to play a principal role in the atherosclerotic process (3). Hyperglycaemia results in the release of local inflammatory mediators and activation of coagulation cascade leading to acceleration of atherosclerosis (4). Cardiovascular disease is a common complication of diabetes responsible for 80 % of the mortality in the diabetic population (1).

Literature data suggest increased risk of cardiovascular complications in diabetic patients. Therefore, there is a clear need to improve diagnostics of early cardiac changes to identify diabetic patients at risk of cardiovascular events. Therefore, we examined asymptomatic diabetic patients with negative standard examination methods (echocardiography, treadmill test) for presence of heart microvascular complications.

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Methods

Patients

47 individuals (20 individuals with diabetes mellitus type 1 and 27 individuals with diabetes mellitus type 2) were recruited in a pro-

Tab. 1. General characteristics of study groups.

Characteristics	T1DM			T2DM		
	All	Men	Women	All	Men	Women
N	20	13	7	27	13	14
BMI (kg/m2)	25.03	25.98	23.17	30.05	34.71	28.31
Age (years)	37±12.7	37±13.8	36.5±11.3	59.5±7.5	60±8.2	59±6.9
Diabetes duration (yrs)	10.8±3.2	9.5±2.8	12±3.4	9.5±2.8	10±3.0	9±2.6
Hypertension	0	0	0	9	5	4
Smoking	7	5	2	12	5	7

spective study (2006–2010). Basic characteristics of the cohort are shown in Table 1. None of the patients presented clinical evidence, or had a history of myocardial infarction or heart failure at the time of the study. Diabetic retinopathy and nephropathy were assessed by chart records. Diabetic retinopathy was present in 35 % type 1 diabetes and 33 % type 2 diabetes individuals. Renal disease characterized by microalbuminuria or diabetic nephropathy was found in 30 % of type 1 diabetes patients and 15 % of type 2 diabetes cohort.

Inclusion criteria were as follows: age over 18 years, diagnosis of diabetes mellitus defined by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (5) and well-compensated diabetes as confirmed by glycaemia levels. Written informed consent was obtained from all patients prior to the study.

Exclusion criteria were gestation, age below 18 years, metabolic decompensation, hypoglycaemia on the day of the study, history of alcohol or drug abuse and a history of heart failure.

Medical history, hypoglycaemia questionnaire

Medical history was assessed by a standardized questionnaire addressing cardiovascular and other accompanied disorders, medication use, diabetes duration and smoking. Criteria for hypoglycaemia were glycaemia below 3.5 mmol/l (measured by patient glucometer) followed by typical clinical symptoms. Hypoglycaemia questionnaire involved the detailed information about insulin or oral drugs therapy, frequency and symptoms of hypoglycaemia. Hypoglycaemia unawareness syndrome (HUS) was diagnosed by questionnaire when individual stated plasma glucose level bellow 3 mmol/l in the absence of hypoglycaemic symptoms.

Laboratory testing

Venous blood samples for basic parameters of metabolic compensation (glucose plasma level, HBA_{1c} according to DCCT, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides – TAGs) were measured by standard laboratory biochemical kits.

Echocardiography

Systolic and diastolic function was evaluated in all recruited individuals by Siemens Acuson CV 70. Diastolic function was measured using the transmitral valve inflow, pulmonary vein flow and tissue Doppler imaging.

^{99m}Tc-Myoview myocardial gated single photon emission computed tomography (SPET)

All individuals underwent stress myocardial SPET. The treadmill test by standard Bruce protocol was performed. Criteria for the interruption of the test were clinical or ECG signs of coronary insufficiency, reaching of submaximal heart rate or extracardial reasons (fatigue, claudicatory pain). Following the stress test, 370 MBq (10 mCi) of radiopharmacum ^{99m}Tc-Myoview was administered by intravenous injection in the peripheral vein. A GE Medical Systems dual head Gamma Camera Millenium VG with Hawkeye was used for signal detection.

Heart rate variability

In stable conditions the heart rate variability was assessed using the VariaCardio TF4 (Sima Media Olomouc). We used the combination of Ewing´s testing and spectral analysis of heart rate variability (HRV). The battery of Ewing testing included continual ECG and blood pressure monitoring during hyperventilation, orthostatic, finger grip and Valsalva testing. Heart rate is measured by telemetrical signal. Spectral analysis of 900 R-R intervals using the Fourier transformation provides the information about the heart rate variability. Splitting of measured signal by frequency domains we obtained 3 components representing the parasympathetic, sympathetic and combined sympathetic-parasympathetic activity. Results of HRV were compared to the standard values of HRV parameters in a control group of individuals without history of diabetic or cardiovascular disorder. Mild CAN was diagnosed when two parameters of spectral analysis were borderline or one of them was pathological. Moderate CAN was identified when two parameters of spectral analysis were pathological and severe CAN was defined by borderline or pathological result in two tests during Ewing´s testing.

Statistical analyses

Collected data were analyzed using the nonparametric statistical methods. In an intergroup comparison of quantitative parameters Kruskal-Wallis and Mann-Whitney U test were used. For determination of relationship between two qualitative parameters Pearson chi quadrate test was used.

Results

Parameters of metabolic control

HBA_{1c} (p=0.001) and TAGs (p=0.008) levels were significantly different between the type 1 diabetes and type 2 diabetes patients. Dyslipoproteinaemia was found in 35 % of type 1 diabetes and in 65 % of type 2 diabetes group (Tab. 2).

Hypoglycaemia occurred on average 6 plus minus SEM times per month in type 1 diabetes (males 5 times per month, females 9

Tab. 2. Laboratory parameters.

Characteristics	Men		Women		Together		$p^{Together}$ (n) (T1DM v.s. T2DM)
	T1DM	T2DM	T1DM	T2DM	T1DM	T2DM	
Glycaemia (mmol/l)	6.2±1.1	7.1±1.16	6.6±1.5	6.7±0.9	6.3±1.24	6.9±1.05	0.94
Creatinin (μmol/l)	85.2±10.5	86±14.08	65.9±12.8	78±12.1	78.5±14.5	82±13.6	0.65
HbA1c DCCT %	7.8±1.61	6.7±1.09	8.4±0.64	6.9±1.1	8.2±1.36	6.8±1.07	0.001
Cholesterol (mmol/l)	4.8±0.47	4.6±0.6	4.9±0.86	5.2±1.1	4.8±0.61	4.9±0.9	0.58
HDL (mmol/l)	1.4±0.32	1.1±0.2	1.4±0.27	1.3±0.4	1.4±0.29	1.2±0.36	0.24
LDL (mmol/l)	2.7±0.43	2.6±0.69	2.7±1.29	2.8±0.8	2.7±0.8	2.7±0.73	0.83
TAGs (mmol/l)	1.7±1.39	1.7±0.66	0.85±0.32	1.9±1.0	1.4±1.21	1.8±0.86	0.008

times per month) and once a month in type 2 diabetes (p<0.001). We found negative correlation between frequency of hypoglycaemia and HDL cholesterol levels (p=0.004). Hypoglycaemia unawareness syndrome (HUS) was present consistently in 30% of type 1 diabetes (57 % females, 17 % males) and in 30 % of insulin treated type 2 diabetes group (33 % females, 25 % males). There was no association among frequency of hypoglycaemia or presence of HUS and any of the measured parameters.

Echocardiography, treadmill test

Treadmill test was negative in all examined diabetic subjects. Ultrasound findings were without systolic dysfunction or alteration in wall movement in any of the patients. We found first type of diastolic dysfunction in 10 % of type 1 diabetes patients and 11 % of type 2 patients.

^{99m}Tc-Myoview myocardial SPET

Myocardial hypoperfusion was detected in 35 % of type 1 diabetes subjects and in 60 % of type 2 diabetes. Localization of perfusion disturbances is documented in Figure 1. Hypokinesis assessed by gated myocardial SPET was detected in 5 % of type 1 diabetes and 11 % of type 2 diabetes group.

Heart rate variability

Diagnosis of cardiac autonomic neuropathy (CAN) based on Ewing´s testing and examination of HRV was established in 60 % T1DM patients (p=0.001) and 77 % T2DM patients (p=0.001) as shown in Figure 2. Mild CAN was present in 20 % T1DM group and 18.5 % T2DM group, moderate CAN in 30 % T1DM and 48.1 % T2DM. We did not measure severe CAN in T1DM subjects, in T2DM it was present in 7.4 %. We did not find any statistically significant difference between T1DM and T2DM subjects. Occurrence of CAN tended to correlate with duration of diabetes in T1DM group (p=0.069). Myocardial hypoperfusion was related to frequency of hypoglycaemia in type 1 diabetes individuals (p=0.04). Most of the patients with positive CAN diagnosis were also diagnosed with myocardial hypoperfusion. We did not find any relation with classical cardiovascular risk factors (smoking, hypertension and dyslipoproteinaemia). There was no association of CAN nor SPET results with retinopathy nor nephropathy.

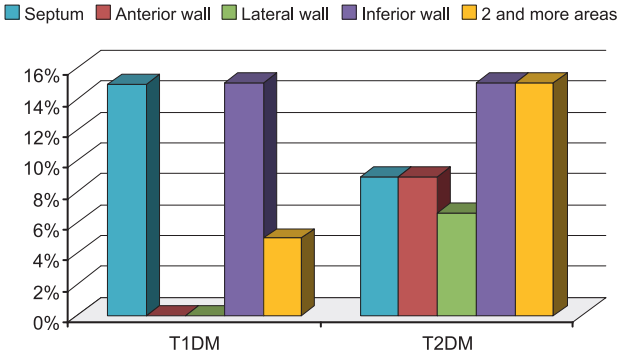

Fig. 1. Localization of perfusion disturbances.

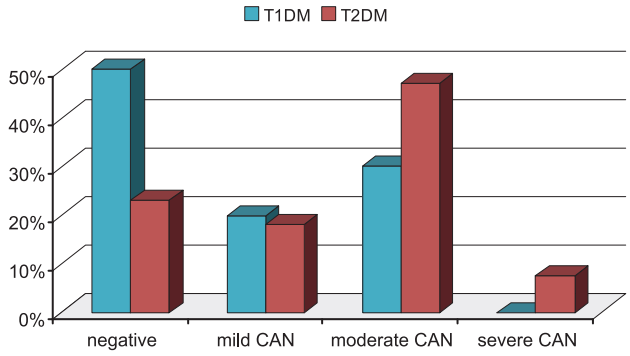

Fig. 2. Diagnosis of cardiac autonomic neuropathy (CAN) based on Ewing´s testing and examination of HRV in 60 % T1DM patients (p=0.001) and 77 % T2DM patients (p=0.001).

Discussion

Heart rate variability, cardiac autonomic neuropathy

In our study, we examined a group of diabetic individuals without history of ischemic heart disease or heart failure. High incidence of myocardial hypoperfusion and cardiac autonomic neuropathy among asymptomatic diabetic patients was found, whereas the standard diagnostic approaches including treadmill test and echocardiography failed to show any changes. Novel finding is association between frequency of hypoglycaemia and myocardial hypoperfusion in T1DM subjects.

Although the literature reports detrimental effect of smoking and hypertension on the development of diabetic cardiomyopathy we did not find any association with the presence of CAN.

Treadmill test was negative in all individuals. Literature data refer 47 % sensitivity and 81 % specificity of treadmill test in dia-

betic subjects. Positive predictive value is 85 %, negative 41 % (6). In our cohort we did not find even sings of silent ischemia which is typically observed in diabetic patients. Cosson reports the occurrence of silent ischemia in 20–50 % diabetic patients (7). Recent papers use the term true silent ischaemia or clandestine ischaemia characterized by normal treadmill test finding accompanied by myocardial perfusion defects in SPECT (8). Although there is a strong connection between positive SPECT finding and narrowing of coronary arteries, changes in the detected signal during SPECT are not always due to perfusion defects and therefore we consider this term vague.

In our study diastolic dysfunction type I was diagnosed in 10 % T1DM and 11 % T2DM. Diastolic dysfunction is caused by collagen accumulation and cardiomyocyte dysfunction and is manifested more frequently in elderly population and subjects with T2DM (1). The presence of systolic and diastolic dysfunction seems to by dependent on the level of metabolic control and type of the treatment. Hyperinsulinaemia and insulin resistance aggravates dyslipoproteinaemia leading to increase in Randle cycle (4). We did not assess insulin resistance but we did not find any relation with type of the antidiabetic treatment or parameters of metabolic control.

Long-term alterations in several metabolic pathways in conditions of hyperglycaemia evoke changes in autonomic nervous system. There are two possible mechanisms leading to CAN – metabolic and vascular. The first theory presumes direct toxicity of hyperglycaemia to axonal fibers (9). Vascular theory is based on the endothelial dysfunction of vasa nervorum (10). It is however feasible, that both mechanisms contribute to the development of CAN.

Decrease in HRV closely reflects alterations in autonomic nervous system. Sympathetic and parasympathetic tone are not equally affected. Decrease in parasympathetic tone was demonstrated in the early stages of diabetes, subsequently followed by mild alteration in sympathetic component (11). The most prominent changes of autonomic neurous system were found in the area of inferior wall (12). In contrast, the most common localization of hypoperfusion in our study was the area of posterior wall, what seems to endorse the vascular etiology of CAN. Literature data suggest an association between decrease in HRV and occurrence of diastolic dysfunction (1) confirmed in our study.

Prevalence of CAN in diabetic population is 26–34 % when measured by HRV (1) and 58 % when measured by ^{123}I-MIBG scintigraphy (12) and it is a strong predictor of sudden cardiac death caused by malignant arrhythmia (13). In our study CAN was diagnosed in 50 % of T1DM and in 77 % of T2DM by measurement of HRV. In both groups moderate CAN was the most frequent subtype. We did not find any association between the severity of CAN and gender or type of antidiabetic treatment. Literature data suggest more common occurrence of CAN in T2DM subjects (14), what is probably related to age of the patients and hyperinsulinaemia. Hyperinsulinaemia and insulin resistance stimulate sympathetic tone (4, 15). Furthermore, in T2DM subjects with hyperinsulinaemia a significant decrease in parameters of spectral analysis has been reported when compared to normoinsulinaemic T2DM subjects (16).

In T1DM individuals we observed a trend towards association between the occurrence of CAN and duration of diabetes. The ARIC study found a time-dependent decrease in parameters of spectral analysis in diabetic subjects. Diabetic patients showed at each control a significant decrease in parameters of spectral analysis compared to non-diabetic group, but the absolute difference between initial and end-point values was not significant. Therefore, the impairment of autonomic nervous system is assumed already in the early stages of diabetic heart disease (16).

Although we did not measure relation between CAN and metabolic parameters, the ARIC study showed relation between plasma glucose level and parameters of HRV (16) and Chen et al. reported an association between glycated hemoglobin levels and duration of diabetes (17).

^{99m}Tc-Myoview myocardial gated SPET

Cardiovascular risk is 2-4 times higher in diabetic patients when compared to standard population. In addition to the development of CAN and diabetic cardiomyopathy, atherosclerotic process of coronary arteries is accelerated in diabetic patients and risk of myocardial infarction is comparable to risk of reinfarction in non-diabetic population (18). Number of young diabetic patients hospitalized for acute coronary syndrome is increasing and during invasive procedures multifocal narrowing of coronary arteries is often found. Several other authors however, did not support the hypothesis that diabetes is a "coronary heart disease equivalent" and recommend appropriate cardiovascular risk estimation (19). Nevertheless, a sensitive and specific diagnostic method is needed in order to enable early diagnosis of increased cardiovascular risk and atherosclerotic plaque. Myocardial SPET seems to be suitable for such purpose (20). Significant association between occurrence of multivessel coronary disease and positive SPET finding has been demonstrated (21).

In our study myocardial hypoperfusion was detected in 35 % of T1DM and 60 % of T2DM group. Wackers documents perfusion defects in 22 % asymptomatic T2DM individuals, significantly more common in men (20), the finding confirmed also by others (8). In our study, hypoperfusion was detected only in men in T1DM cohort, whereas there was no gender-related difference in T2DM group. This is probably due to age difference between T1DM and T2DM patients and possibly higher proportion of younger women among T1DM patients with intrinsically lower cardiovascular risk.

In T1DM patients we document an association between hypoglycaemia and myocardial hypoperfusion. Recent papers suggest aggravation of atherosclerosis after repeated episodes of hypoglycaemia (22). Hypoglycaemia provokes sympatho-adrenal activation and counter-regulatory hormone secretion, which exert pronounced cardiovascular effects, eventually even a fatal cardiovascular event (23).

Myocardial-gated SPET is an appropriate diagnostic method for determination of cardiovascular risk in symptomatic individuals. The DIAD study suggests positive SPET finding as an independent risk factor (20). The J-ACCESS study reported the occurrence of perfusion defect being the strongest predictor of sudden cardiac death, non-fatal myocardial infarction and severe heart failure. (24). American Diabetes Association recommends myocardial SPET in diabetic patients with positive ECG finding

of ischemia or myocardial infarction. In asymptomatic individuals without the ECG signs of ischemia, currently no recommendation for myocardial SPET is given (25). In contrast, American Heart Association in cooperation with American Society of Nuclear Medicine recommends the myocardial SPET in asymptomatic individuals. These differences are probably related to higher costs of inteventional procedure. Perfusion defects can be diagnosed in about 33 % of asymptomatic diabetic individuals, 72 % of whom are likely to suffer from hemodynamically severe coronary stenosis. Nevertheless, the decrease in mortality was shown only in of patients undergoing cardiac surgery (26).

According to the current guidelines of European Society of Cardiology, a positive SPET finding without clinical or ECG signs of subendocardial ischemia is not an indication for selective coronary angiography. There is no evidence for prognosis improvement in asymptomatic subjects after coronary angioplasty because of possible periprocedural complications and risk of instent restenosis (26).

Myocardial SPET provides information about functional state of cardiac metabolism and blood supply. It is important for evaluation of myocardial viability prior to myocardial intervention or cardiac surgery or in conditions when intravascular ultrasound is not accessible.

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