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Transient ischemic dilation ratio (TID) correlates with HbA_{1c} in patients with diabetes type 2 with proven myocardial ischemia according to exercise myocardial SPECT

Alena Adamikova,* Jiri Bakala,** Jaromir Bernatek,** Jaroslav Rybka* and Stepan Svacina***

*Diabetes Center, WHO Collaborating Center for the Study of Diabetes, **Department of Nuclear Medicine, Bata Regional Hospital, Zlín, Czech Republic
***First Faculty of Medicine, Charles University, Prague, Czech Republic

Objective: Abnormal values of the transient ischemic dilation ratio (TID) according to an exercise myocardial SPECT are linked to severe coronary artery disease. The authors investigated the relationship between TID and the levels of VCAM, ICAM, E-selectin, microalbuminuria, intima-media thickness and HbA_{1c} of diabetic subjects. ***Methods:*** We observed 38 subjects with diabetes type 2 (10 women, 28 men), of average age 56.08 ± 8.24 years, with no past history of cardiovascular disease. All subjects were examined using an exercise myocardial SPECT. Transient ischemic dilation, summed stress score (SSS), summed rest score (SRS) and stress total severity score (STSS) were determined to quantify myocardial ischemia. ***Results:*** The average IMT value was 1.05 ± 0.31 mm. The TID value was 1.02 ± 0.154, VCAM 795.24 ± 163.25 mg/*l*, ICAM 516.55 ± 164.07, E-selectin 63.82 ± 38.89, HbA_{1c} 7.09 ± 1.68%, microalbuminuria 68.01 ± 55.21 mg/*l*. When ascertaining the relation of TID to the other factors we used Pearson's correlation at the level of significance $p < 0.05$. We proved a statistically significant correlation between the value of TID and glycosylated hemoglobin HbA_{1c} ($p = 0.035$); the other factors did not show any significant correlation. ***Conclusion:*** Diabetes and its long term unsatisfactory compensation can be one of the factors which affect left ventricular transient ischemic dilation.

Key words: transient ischemic dilation, glycosylated hemoglobin, diabetes mellitus, coronary artery disease

INTRODUCTION

Diabetes mellitus is an important factor in the development of cardiovascular disease. It is stated that 80% of diabetic subjects die of CVD and 75% directly from atherosclerosis. Contrary to non-diabetic subjects their findings are more extensive. Further they have a lower left ventricular ejection fraction, more cardiac events and more frequent silent ischemia. Myocardial ischemia can be a consequence of small vessel disease in diabetic subjects. In addition to this it was proven that in diabetic subjects there were changes of coronary vasoreactivity and incidence of non-atherosclerotic vascular abnormalities. The exercise myocardial SPECT is a non-invasive examination sufficiently specific for the diagnosis of ischemic heart disease.[1,2] A finding of transient ischemic dilation of the left ventricle (TID > 1.22) during perfusion of the myocardium, diagnosed either by a pharmacological or exercise stress test is a marker of serious coronary atherosclerosis and of a bad prognosis.[3] However, some studies have proved more coronary events with transient ischemic dilation and negative perfusion myocardial SPECT than in the group without transient ischemic dilation. It is known that some diseases especially diabetes mellitus, can influence subendocardial perfusion. Our work was concerned with the relationship between inflammatory markers, atherosclerotic markers and glycosylated hemoglobin and the value of the transient ischemic dilation index in diabetic subjects with

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For reprint contact: Alena Adamikova, M.D., Diabetes Center, WHO Collaborating Center, Bata Hospital, Havlickovo nabr. 600, 762 75 Zlín, Czech Republic.
E-mail: adamikova@bnzlin.cz

proven myocardial ischemia according to the exercise myocardial SPECT.

MATERIALS AND METHODS

In the study we observed 38 diabetic subjects of Type 2, 10 women and 28 men of average age 56.08 ± 8.24 years, without a history of cardiovascular disease and with attendant hypertension and hyperlipoproteinemia. The patients were treated with ACE inhibitors and statins. Their therapy did not include vasodilators. From the aspect of diabetes therapy 28 patients used oral antidiabetic agents and 10 insulin. Microalbuminuria was investigated from samples of first morning urine obtained three days in succession. Three measurements were averaged to give the mean value. The average value of microalbuminuria was 68.01 ± 55.21 mg/*l*. For indication of the exercise test of subjects with diabetes we used the recommendation of the American Diabetes Association, 1998.[4] The subjects had 2 or more cardiovascular risk factors. An exercise myocardial SPECT (single-photon emission computed tomography) was performed followed by planar scintigraphy of both lower limbs on gamma camera AP (anteroposterior) and PA (posteroanterior) views. Resting scintigraphy followed by planar imaging at the same locality was performed in the next stage.

The test protocol was a two-day type. The first day the subjects underwent an exercise examination and the second day they were tested at rest. The exercise was performed as conventional bicycle ergometry with escalation of the exercise—radiofarmakon 750 MBq ^{99m}Tc was applied intravenously at the peak of the exercise, after exceeding 85% maximal aerobic capacity. Evaluation of SPECT images was performed in 20 segments using a summed stress score (SSS). A zero indicates a normal state. A value greater then 13 suggested serious ischemia. From further evaluations use was made of the summed rest score (SRS) and stress total severity score (STSS). STSS greater than 100 identified a subject at risk. Transient ischemic dilation ratio was determined with the help of appropriate software. On the basis of data published previously we considered the value of TID 1.22 (Emmett et al.)[5] as the upper limit of the standard. Further parameters evaluated were the left ventricle end diastolic volume (LVEDV) at rest and after exercise, left ventricle end systolic volume (LVESV) at rest and after exercise and left ventricle ejection fraction (LVEF). Of other investigations we measured carotid intima-media thickness using duplex sonography. All subjects underwent measurements of carotid artery intima-media thickness (IMT) by high-resolution real-time B mode ultrasonography with a 7.5 MHz linear transducer (Image Point HP, USA). Each subject was examined in the supine position. The left carotid arteries were investigated in the longitudinal projections. The examination included the segment of the common carotid artery 1 cm at left under the carotid bulb. Areas with calcified plaques were avoided. IMT was defined as the distance between the leading edge of the first echogenic line (lumen intima interface) and the second echogenic line (media-adventitia interface) of the far wall. Three measurements were averaged to give the mean IMT. The measurements were carried out by the same ultrasonographic physician.

Using laboratory methods we investigated the markers of cardiovascular diseases, adhesion molecules ICAM, VCAM and E-selectin, triglyceride levels and hs-CRP (C reactive protein). ICAM-1, VCAM-1 and E-selectin were analyzed using Instant ELISA from Bender Med Systems. Glycosylated hemoglobin HbA_{1c} was determined using HPLC-CE (combination of highly effective liquid chromatography and capillary electrophoresis) with reference values according to IFCC (International Federation of Clinical Chemistry and Laboratory Medicine). Reference limits of healthy adults lie between 2.8–4.0% (95% interval). Glycosylated hemoglobin HbA_{1c} is a parameter of long-term diabetes control, which is regularly utilized at intervals of 2–3 months for checking the disease status of a diabetic patient. According to IDF (International Diabetes Federation), levels of 4–6% are considered as satisfactory compensation, above 6% as unsatisfactory. The average value of HbA_{1c} in the retrospectively observed group from a year ago was 6.91 ± 1.70%. Thus these were diabetic patients whose long-term compensation was unsatisfactory.

Triglycerides were investigated on a Hitachi 911 analyzer by the routine spectrophotometric method and hs CRP by the highly sensitive turbidometric method on microparticles. Increase of turbidity was measured photometrically on a Hitachi biochemical analyzer. Data were expressed as means ± SD. The Pearson correlation analysis was used for evaluation of the statistical significance of correlation at the level $p < 0.05$ between the value of TID and HbA_{1c}, ICAM-1, VCAM-1, E-selectin, IMT, MAU, hs-CRP, triglycerides, LVEDV 1 values (rest), LVEDV 2 values (stress), LVSEV 1 (rest), LVSEV 2 (stress), LVEF 1 (rest), LVEF 2 (stress). As a subgroup we assessed patients with high and low values of HbA_{1c} and TID, i.e. far from the linear regression line. Software: StatSoft, Inc. (2001). STATISTICA. CZ.

Coronary angiography was carried out in 10 patients (26.3%) with an SSS score above 13; one patient underwent percutaneous coronary intervention (PCI) by introduction of a Cypher stent due to a finding of 80% stenosis in proximal ACD (arteria coronaria dextra); one patient needed a quadruple aortocoronary bypass while the others had small vessel disease (21.1%).

RESULTS

In the study group of diabetic subjects, asymptomatic from the aspect of cardiovascular disease, we proved via an exercise myocardial SPECT variously abnormal

Fig. 1

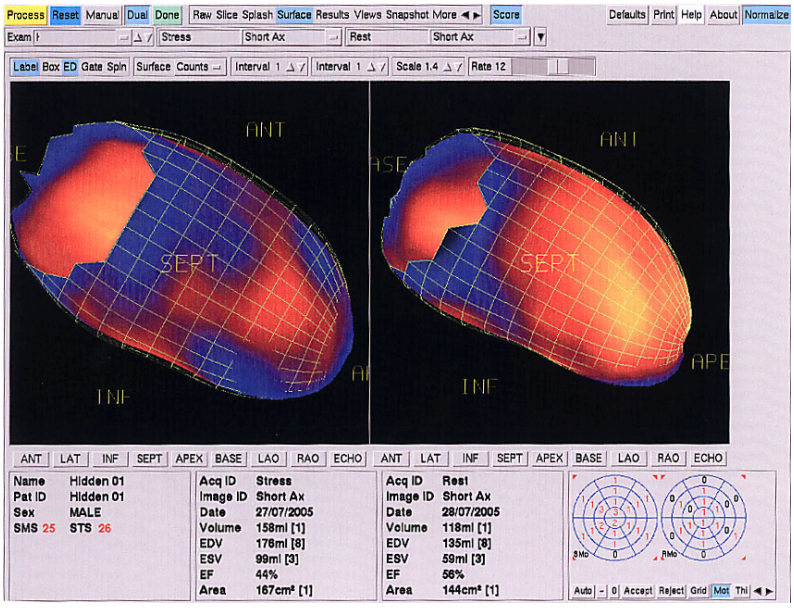

Fig. 2

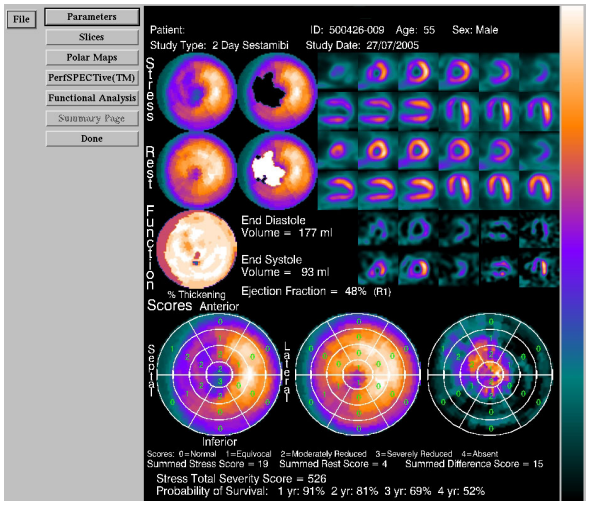

Fig. 1 End diastolic volume on exercising (stress) and at rest using exercise myocardial SPECT.

Fig. 2 Combined conventional SPECT and gated SPECT and calculation of SSS/SRS scores following exercise (stress) and at rest.

Fig. 3 Assessing TID using exercise myocardial SPECT.

Fig. 3

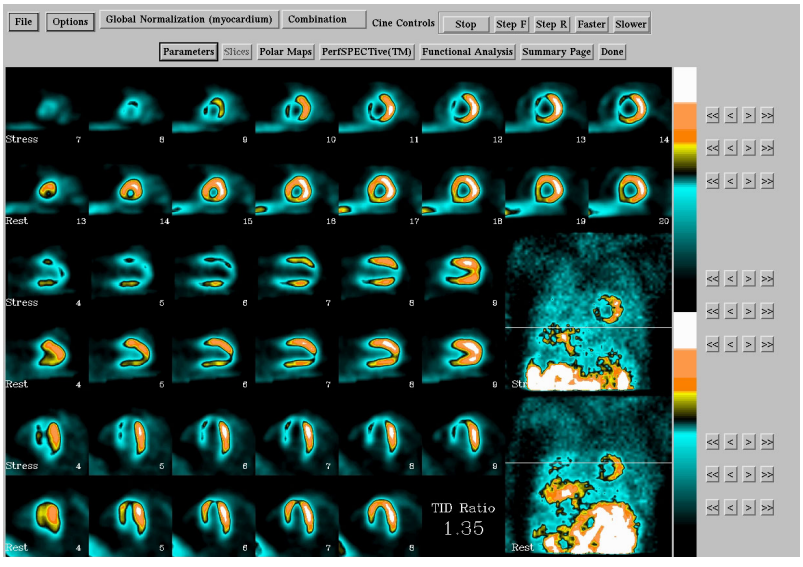

Table 1 Group characteristics, observed parameters and correlation TID with observed parameters

Observed parameters	N	Mean	± SD	Correlation TID ($p < 0.05$)	Correlation TID ($p < 0.05$)		
				p	p 1	p 2	p 3
M 28 F 10	38				n-12	n-14	n-12
Age years	38	56.079	8.348	0.884	0.492	0.628	0.001*
MAU mg/*l*	38	68.008	55.21	0.403	0.146	0.023	0.649
IMT mm	38	1.052	0.309	0.333	0.269	0.866	0.777
TID	38	1.018	0.154	—	—	—	—
VCAM-1 mg/*l*	38	795.237	163.246	0.494	0.750	0.787	0.917
ICAM-1 mg/*l*	38	516.553	164.065	0.908	0.509	0.323	0.992
E-selectin mg/*l*	38	63.816	38.890	0.471	0.458	0.781	0.652
HbA_{1c} %	38	7.097	1.682	0.035*	0.0001*	0.0001*	0.126
SRS	38	7.763	4.377	0.754	0.557	0.950	0.124
SSS	38	10.553	6.525	0.766	0.012*	0.068	0.300
STSS	38	124.132	115.855	0.389	0.025*	0.104	0.365
LVEDV 1 rest (m*l*)	38	113.816	23.954	0.525	0.627	0.788	0.661
LVEDV 2 stress	38	114.342	19.191	0.115	0.355	0.142	0.620
LVESV 1 rest (m*l*)	38	56.553	14.930	0.175	0.590	0.259	0.412
LVESV 2 stress	38	57.868	14.644	0.158	0.081	0.371	0.861
LVEF 1 rest (m*l*)	38	51.132	5.153	0.111	0.937	0.526	0.234
LVEF 2 stress	38	51.711	5.973	0.643	0.237	0.103	0.596
TG mmol/*l*	38	2.865	1.090	0.245	0.255	0.068	0.092
CRP mg/*l*	38	3.771	3.024	0.182	0.023*	0.957	0.003*

M: male, F: female, MAU: microalbuminuria, IMT: intima-media thickness, TID: transient ischemic dilation, VCAM-1: vascular adhesion molecules, ICAM-1: intercellular adhesion molecules, HbA_{1c}: glycosylated hemoglobin, SRS: summed rest score, SSS: summed stress score, STSS: stress total severity score, LVEDV: left ventricle end diastolic volume, LVESV: left ventricle end systolic volume, LVEF: left ventricle ejection fraction, TG: triglycerides, CRP: C-reactive protein, p 1: division above regression line, p 2: within regression line, p 3: under regression line. * statistical significance of correlation at the level $p < 0.05$ (Pearson).

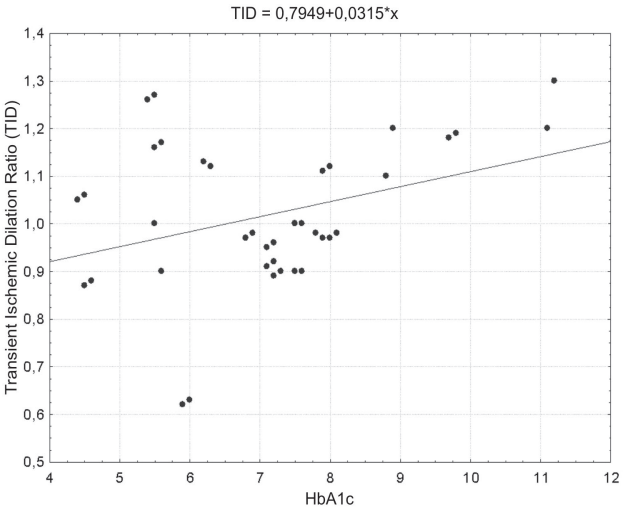

Fig. 4 Correlation of HbA_{1c} with increased values of the transient ischemic dilation index (TID).

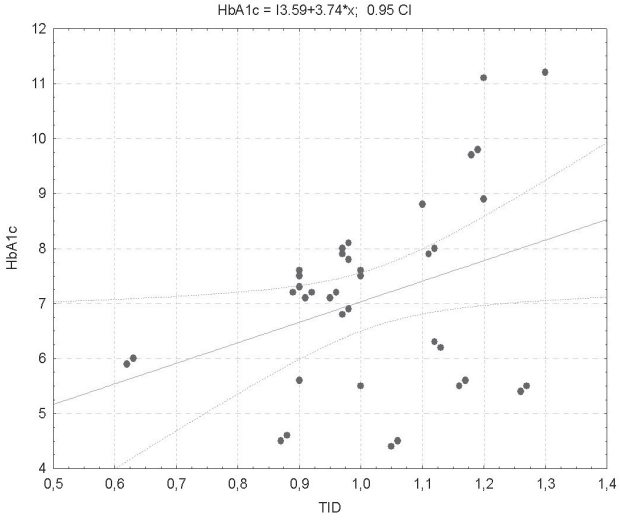

Fig. 5 Correlation TID and HbA_{1c} i.e. on division under the regression line (n-12) (Confidence Interval, 95%), within (n-14) and above (n-12) of the regression line.

perfusion of the myocardium. The mean value of summed stress score SSS 10.55 ± 6.52, summed rest score SRS 7.76 ± 4.37 and stress total severity score was 124.13 ± 115.85 (Figs. 1, 2). The subjects' TID value was 1.02 (0.62–1.30) ± 0.154. Only 2 subjects (5.3%) had a value above 1.22 (Fig. 3). The mean value of the SSS score in these subjects was 3. A total of 20 subjects (53%) had an STSS value greater than 100. LVEDV 1 (rest) was 113.82 ± 23.95 m*l*, LVEDV 2 (stress) 114.34 ± 19.19 m*l*, LVESV 1 (rest) 56.55 ± 14.93 m*l*, LVESV 2 (stress) 57.87 ± 14.64

Table 2 Correlation between LV volume parameters and observed blood parameters (Pearson, $p < 0.05$)

Observed parameters	Correlation * $p < 0.05$					
	VCAM-1	ICAM-1	E-selectin	Hs-CRP	TG	HbA_{1c}
LVEDV 1	0.153	0.014*	0.021*	0.630	0.218	0.773
LVEDV 2	0.789	0.013*	0.090	0.614	0.058	0.419
LVESV 1	0.066	0.012*	0.126	0.610	0.230	0.970
LVESV 2	0.194	0.217	0.741	0.082	0.0001*	0.051
LVEF 1	0.073	0.228	0.434	0.496	0.216	0.644
LVEF 2	0.019*	0.471	0.002*	0.781	0.001*	0.911

VCAM-1: vascular adhesion molecules (mg/*l*); ICAM-1: intercellular adhesion molecules (mg/*l*); HbA_{1c}: glycosylated hemoglobin (%); LVESV: left ventricle end systolic volume 1 rest, 2 stress (m*l*); LVEDV: left ventricle end diastolic volume 1 rest, 2 stress (m*l*); LVEF: left ventricle ejection fraction 1 rest, 2 stress (%); TG: triglycerides (mmol/*l*); hs-CRP: C-reactive protein (mg/*l*).

m*l*, LVEF 1 (rest) 51.13 ± 5.15% LVEF 2 (stress) 51.71 ± 5.97%. The mean value of intima-media thickness of the common carotid reached 1.05 (0.61–2.05) ± 0.31 mm. Laboratory values of inflammatory markers of cardiovascular disease in the case of vascular adhesion molecules were measured within the range 472.0–1170.0, with an average value of 795.24 ± 163.25 mg/*l*, the value of intercellular adhesion molecules was 516.55 (269.0–1000.0) ± 164.07 mg/*l*, levels of E-selectin reached 63.82 (9.0–146.0) ± 38.89 mg/*l*. The value of glycosylated hemoglobin HbA_{1c} was 7.09 (4.4–11.2) ± 1.68%. The triglyceride level was 2.86 ± 1.09 mmol/*l*, hs-CRP 3.77 ± 3.02 mg/*l* (Table 1). During statistical evaluation of the dependence of TID on atherosclerosis markers and on diabetes control we were able to demonstrate a statistically significant correlation at the level of $p < 0.05$ only for glycosylated hemoglobin HbA_{1c} $p = 0.035$ (Table 1).

The increase in HbA_{1c} values correlated with increased values of the transient ischemic dilation index (Fig. 4). For other markers including triglycerides and hs-CRP, this correlation at $p < 0.05$ level was not significant. On more detailed analysis of the subgroup at correlation TID and HbA_{1c} i.e. on division under the regression line (n-12, p 1) (Confidence Interval, 95%), within (n-14, p 2) and above (n-12, p 3) of the regression line, using non-parametric statistical methods (Pearson correlation, level of significance $p < 0.05$) we demonstrated a significant correlation between TID and HbA_{1c} in the subgroup above and within the confidence interval, while in the group under the regression line this correlation was not statistically significant. In the subgroup under the regression line we demonstrated a positive correlation between TID and the SSS score, as well as between SSS score and CRP. In the other subgroups these findings were not confirmed, although this concerns relatively small groups (Table 1, Fig. 5).

The Pearson correlation analysis was used for evaluation of the statistical significance of the correlation at the level $p < 0.05$ between LV volume parameters and blood parameters. During statistical evaluation of the dependence of LV volume parameters (LVEDV rest, LVEDV stress, LVESV rest, LVESV stress, LVEF rest, LVEF stress) on blood parameters (VCAM-1, ICAM-1, E-selectin, triglycerides, hs-CRP, HbA_{1c}) we were able to demonstrate a statistically significant correlation at the level of $p < 0.05$ only for LVEDV rest and ICAM 1 ($p = 0.014$), LVEDV stress and ICAM-1 ($p = 0.013$), LVESV rest and ICAM-1 ($p = 0.012$), LVEF stress and VCAM-1 ($p = 0.019$), LVESV stress and triglycerides ($p = 0.0001$), LVEF stress and triglycerides ($p = 0.001$) (Table 2).

DISCUSSION

Transient ischemic dilation is characterized by an expansion of the left ventricle cavity on a post-exercise myocardial SPECT in comparison with rest images.[6–14] In the study of Abidov et al.[15] subjects were investigated for adenosine stress myocardial perfusion SPECT and then also angiographically. Abnormal values of TID correlated with a serious angiographic finding of ≥ 90% stenosis in the proximal left anterior descending artery or in 2 or more coronary arteries. In a published work the same authors Abidov et al.[16] proved in a group with transient ischemic dilation and normal perfusion myocardial SPECT 2.4% of cardiac events, while in a group without transient ischemic dilation the incidence was only 1% per year. Emmett et al.[5] concerned themselves with etiologic transient ischemic dilation. Nineteen (18%) of 103 subjects had transient ischemic dilation, 19 (18%) had left ventricular hypertrophy, and 23 (22%) had diabetes. A high percentage had severe coronary artery disease (45%), whereas 55% had less severe coronary artery disease (29%) or non-significant coronary artery disease (25%). Severe coronary artery disease, diabetes, left ventricular hypertrophy and the ischemia scores were independent predictors of transient ischemic dilation by multivariate logistic regression. In subjects with severe coronary artery disease, the effect of left ventricular hypertrophy on the incidence of transient ischemic dilation was additive and also in diabetic subjects the incidence of transient ischemic dilation increased to 54%, while in non-diabetic subjects the incidence was 21%. The authors conclude

that the incidence of transient ischemic dilation is associated with the presence of severe coronary artery disease. However the association is modified by the presence of left ventricular hypertrophy and by diabetes.

In the present work all subjects had diabetes mellitus type 2. They were asymptomatic of cardiovascular disease. However they had markers of cardiovascular disease—microalbuminuria, hyperlipoproteinemia and hypertension—present. During exercise gated myocardial SPECT the mean value of SSS moved within 10.55 ± 6.52. In 53% of the subjects we demonstrated the value of stress total severity score above 100. Only 2 subjects had TID values above the norm, i.e. 1.22. During statistical evaluation using Pearson's correlation at the level of significance $p < 0.05$ we proved a statistically significant correlation between the value of TID and HbA_{1c} ($p = 0.035$). The increase in HbA_{1c} values correlated with increased values of the transient ischemic dilation index. Other values of inflammatory markers i.e. VCAM, ICAM, E-selectin and CRP did not have this significant correlation. It has been stated already in the work of Emmett et al.[5] that the TID mechanism remains controversial and that quite a few factors may be involved. In the work of Takeishi et al.,[13] Sugihara et al.[17] and others transient ischemic dilatation was concluded to be related to subendocardial hypoperfusion. Diabetes is a disease in which inadequate compensation leads primarily to microvascular damage.

Levels of CRP above 3 mg/*l* bore witness to the high risk of developing cardiovascular disease, despite the fact that they correlated with levels of TID only in the subgroup above the regression line. The absence of a correlation between TID and adhesion molecule levels may be caused by the participation of advanced glycation end products (AGE) in the etiology of microangiopathy as a consequence of inadequate compensation of diabetes, more than low active inflammation which leads to the development of atherosclerotic lesions. Correlation of certain left ventricle parameters with atherosclerosis inflammation markers (ICAM-1, VCAM-1, E-selectin) and also with triglyceride levels documents the presence of an active atherosclerotic process, which is considered to be a low-grade inflammation. TID represents pseudo-dilation of the left ventricle due to diffuse subendocardial ischemia.

Diabetic cardiomyopathy and diabetic autonomous neuropathy are present in diabetic patients as opposed to non-diabetic patients. Diabetic cardiomyopathy expresses a complex of changes evoked in the myocardium by the metabolic pathways.[18] Hyperglycemia leads to glycation of myocardial proteins. Studies confirm cardiomyocyte hypertrophy, interstitial fibrosis and apoptosis. Dysfunction of myocardial contractility develops from the aspect of hemodynamics. Cardiac autonomic neuropathy leads to impairment of parasympathetic innervation, domination of sympathetic innervation, development of coronary vasoconstriction and ischemia.

Results of the UKPDS study show that better compensation of diabetes type 2 leads to a distinct reduction of the risk of microangiopathy, yet the risk of coronary events is reduced only by 16%, which is at the borderline of significance. This study confirms the fact that the total risk of macrovascular complications is less affected by diabetes control than the risk of microvascular changes. Our results from coronary angiography testing also confirmed a propensity towards small vessel disease, which also influences transient ischemic disease of the left ventricle. A number of observations have already shown that patients with poor diabetes control have a higher mortality rate. Myocardial disease in diabetes is complex in nature and for this reason improved diabetes control is in any case, a desirable target.

According to the results, despite the small study group for the time being, it is possible to consider the cumulative effect of long term inadequate diabetes control on the post-exercise dilation of the left ventricle, as determined by the transient ischemic dilation index.

In conclusion, the increased values of TID correlated with increased HbA_{1c} values in type 2 diabetic subjects with proven myocardial ischemia. Diabetes and its long term inadequate control can be one of the factors which affect the transient ischemic dilation index.

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