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ORIGINAL

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The effects of long-term and short-term glycemic control on cardiovascular autonomic function in subjects with type 1 diabetes mellitus

Abstract

Background. Hyperglycemia is the most important factor in the development of cardiovascular autonomic neuropathy (CAN). The aim of the study was to evaluate the association between short- and long-term glycemic control and cardiovascular autonomic function assessed by full Ewing's battery of tests in type 1 diabetic subjects.

Material and methods. The study group consisted of 39 patients with type 1 diabetes mellitus (mean age 30.5 ± 8.8 years; duration of diabetes 12.1 ± 6.9 years; BMI 23.7 ± 2.8 kg/m^2; recent HbA_{1c} 7.6 ± 1.9%; mean HbA_{1c} in the past few years 8.2 ± 1.6%). The control group consisted of 18 healthy adults (mean age 31.4 ± 9.3 years; BMI 22.0 ± 3.3 kg/m^2). All subjects underwent full Ewing's battery of tests using Portapres.

Results. In both groups, the mean results of all the classical cardiovascular function tests were within normal ranges except for the 30:15 ratio in the head-up tilt test, which was significantly lower in diabetic subjects (1.44 ± 0.3 *vs.* 1.61 ± 0.2; $P < 0.05$). Long-term glycemic control showed a positive correlation with resting heart rate ($r = 0.42$; $P < 0.05$) and minimum heart rate during the deep breathing test ($r = 0.45$; $P < 0.01$) and a negative correlation with the systolic blood pressure increase during the head-up tilt test ($r = –0.44$; $P < 0.001$), the heart rate increase during the deep breathing test ($r = –0.33$; $P < 0.05$) and in the handgrip test ($r = –0.39$; $P < 0.05$). Short-term glycemic control correlated significantly only with the minimum and maximum heart rate in the deep breathing test ($r = 0.33$, $P < 0.05$ and $r = 0.34$, $P < 0.05$, respectively).

Conclusions. Long-term versus short-term glycemic control was demonstrated to have a more pronounced effect on cardiac autonomic function in subjects with type 1 diabetes mellitus. Long-term glycemic control significantly correlated with heart rate increase in the deep breathing and the handgrip tests and with systolic blood pressure increase in the head-up tilt test.

key words: cardiovascular autonomic neuropathy, type 1 diabetes mellitus, glycemic control

Introduction

The autonomic nervous system is the most important system which regulates cardiovascular function. The main aim of the complex regulatory processes involves a reciprocal adjustment of heart rate, blood volume and the condition of blood vessels (vascular resistance, capacity of the vascular bed) in a manner that ensures an appropriate blood supply to tissues commensurate with the body's metabolic needs [1]. Cardiovascular autonomic neuropathy (CAN), a degenerative process of autonomic nerve fibres innervating the heart and blood vessels, along with the sensory fibres, leads to impaired adaptation of the cardiovascular system to the constantly changing internal and external conditions [2]. The heart rate and blood pressure reduction in response to simple tests has been used in the diagnostic assessment of CAN [3].

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Prospective studies have shown CAN to significantly increase mortality in patients with diabetes mellitus. In various periods of observation, the average mortality rate among patients with diabetes and CAN was 4–7 times higher than in patients with diabetes but without CAN [4–7].

Hyperglycemia is the most important factor in the development of autonomic neuropathy. The best-studied consequences of hyperglycemia, which trigger functional abnormalities in nerves and lead to structural changes, include: activation of the intracellular polyol (sorbitol) pathway, augmentation of oxidative stress and the process of non-enzymatic glycation [8]. Large clinical studies in type 1 diabetics, DCCT and EURODIAB IDDM Complications Study, have demonstrated an association between glycemic control and the development and severity of autonomic neuropathy [9–12].

Authors of studies investigating CAN uniformly agree that hyperglycemia adversely affects cardiovascular autonomic function in type 1 diabetics. Due to the various diagnostic methods used to evaluate CAN, such as the incomplete Ewing's battery of tests, and the reliance on a one-off determination of glycated haemoglobin (HbA_{1c}), divergent opinions exist as to the effect of glycaemic control on the results of specific tests.

We therefore aimed to evaluate in this study the short-term glycaemic control (current HbA_{1c}) versus long-term glycaemic control (mean HbA_{1c} in the past years) on cardiovascular autonomic function as assessed using the full Ewing's battery of tests in type 1 diabetic subjects.

Material and methods

The study investigated 39 patients with type 1 diabetes mellitus, including 27 women (69.2%) and 12 men (30.8%), managed at the Outpatient Diabetology Clinic or hospitalised at the Clinic of Endocrinology and Diabetology (Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń). The control group consisted of 18 healthy volunteers, including 12 women (66.7%) and 6 men (33.3%) without diabetes and with normal fasting venous plasma glucose (below 100 mg/dl).

Exclusion criteria include hypertension (≥ 140/90 mm Hg), ischaemic heart disease, a history of myocardial infarction, heart failure, renal failure, alcohol abuse and ECG changes (atrial flutter or fibrillation, signs of left ventricular hypertrophy or strain).

All the participants had been informed of the aims and course of the study and given a written consent to participate. The study had been approved by the Bioethics Committee of the Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń.

Short-term glycemic control (about 3 months prior to the study) was evaluated in patients with diabetes based on a determination of glycated haemoglobin (HbA_{1c}). Long-term glycemic control was evaluated on the basis of HbA_{1c} levels in the previous years. These included determinations performed at least twice a year over the previous 1–14 years, with an average of 7.3 ± ± 3.37 years. HbA_{1c} was determined turbidimetrically (Tina-quant, Roche/Hitachi) at the Laboratory Diagnostics Department, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń.

The characteristics of the study and control groups is presented in Table 1.

Cardiovascular autonomic function was examined in the morning, in a quiet, isolated, air-conditioned room, at the temperature of thermic comfort for the investigated subject (24–26°C in practice). The subjects reported following a night's sleep, about 1.5 hours after breakfast and the morning dose of insulin (if diabetic). Subjects refrained from drinking caffeine-containing beverages for 12 hours prior to the examination and from strenuous physical exercise for 24 hours. On the day before the examination, the diabetic subjects measured their blood glucose (using personal blood glucose meters) fasting, 2 hours after main meals and at 3 am. Absence of hypoglycaemia in the 24 hours prior to the study was a condition of participation. Twenty-four to 72 hours prior to the examination (depending on the half-life), drugs affecting the autonomic nervous system were discontinued (this was the case in 2 subjects and the

Table 1. Characteristics of the study group and the control group

Parameter	Study group				Control group				P value
	Mean	SD	Min	Max	Mean	SD	Min	Max	
Age (years)	30.5	8.8	19.0	52.0	31.4	9.3	20.0	55.0	NS
BMI [kg/m^2]	23.7	2.8	17.8	29.4	22.0	3.3	17.4	31.1	< 0.05
Duration of diabetes (years)	12.1	6.9	1.0	27.0	–	–	–	–	–
Current HbA_{1c} (%)	7.6	1.9	5.1	13.3	–	–	–	–	–
Mean HbA_{1c} in the past years (%)	8.2	1.6	6.0	12.8	–	–	–	–	–

discontinued drugs were angiotensin-converting enzyme inhibitors).

We used non-invasive continuous blood pressure measurement (Portapres, TNO–TPD Biomedical Instrumentation, Amsterdam, The Netherlands) with concurrent recording of respiratory movements of the thorax (using an electrode placed in the left costal arch). Blood pressure measurement using Portapres relies on a non-invasive, photoelectric, isovolumetric method of continuous recording of the pulse curve in a human finger artery [13]. The cuff was placed on the middle finger of the non-dominant hand. Thanks to the fact that the device was additionally fitted with a mechanism which eliminates the hydrostatic effect and artefacts caused by changes of hand position, the arm did not need to be immobilised. Blood pressure tracing (systolic, diastolic and mean blood pressure curves), duration of heart cycles, the ECG curve and the respiratory movement curve were visible all the time on the monitor display. The signals generated by the device, upon digitalisation, were archived in real time and processed by a personal computer. After a 20 minutes' rest and adaptation to the cuff, individual Ewing's tests were recorded. In addition to the five classical parameters (Table 2), additional values were evaluated (in the deep breathing test and in the handgrip test).

Deep breathing test

The subject was in the lying position, was breathing evenly and deeply, with a frequency of 6 breaths per minute (the inspirations and expirations were 5 seconds each) for 1 minute. The test was repeated 3 times at 10 minutes' intervals. The maximum heart rate (HR_{max} on inspiration) and the minimum heart rate (HR_{min} on expiration) as well as the difference between the two were calculated in 3 subsequent respiratory cycles, in each of the tests, and the result was averaged. The greatest difference ($HR_{max} - HR_{min}$) was included in the analysis. A heart rate increase of ≥ 15 bpm was considered normal [14, 15].

Valsalva manoeuvre

After 10 minutes in the sitting position, the subject took a forced expiration for 15 seconds against a closed glottis into a mouthpiece connected to a mercury manometer set to 40 mm Hg. The test was repeated twice, at 10 minutes' interval. The quotient of the longest R-R interval after the manoeuvre and the shortest interval during the manoeuvre was calculated (the so-called Valsalva ratio, $V_{max/min}$). The greatest quotient was included in the analysis. A Valsalva ratio of ≥ 1.21 was considered normal [14, 15].

Handgrip test (long isometric contraction of the hand and forearm muscles)

The test was performed using a handgrip dynamometer in the sitting position. The subject maintained 30% of the maximum handgrip for 3 minutes. The difference between pre-test diastolic blood pressure (mean value obtained during about 30 seconds of measurement 2–3 minutes before the test) and post-test diastolic blood pressure (mean value obtained during about 15–30 seconds of measurement directly after the test), ΔDBP. A diastolic blood pressure increase of ≥ 16 mm Hg was considered normal [14, 15].

In addition, pre-test and post-test heart rates were measured (HR_s and HR_h) (from the same time intervals

Table 2. Mean values of the results in Ewing's tests in the study group and in the control group

Test	Study group		Control group		P value
	Mean	SD	Mean	SD	
Deep breathing test ($HR_{max} - HR_{min}$) [beats per minute]	26.5	10.0	26.5	6.3	NS
Valsalva manoeuvre ($V_{max/min}$)	1.65	0.26	1.54	0.32	NS
Head-up tilt test (30:15 ratio)	1.44	0.3	1.61	0.2	< 0.05
Head-up tilt test (ΔSBP) [mm Hg]	15.9	9.7	16.4	11.8	NS
Steady handgrip (DDBP) [mm Hg]	19.6	10.9	24.8	15.7	NS

$HR_{max} - HR_{min}$ — heart rate increase during the deep breathing test; $V_{max/min}$ — the ratio of the longest to shortest RR interval after Valsalva manoeuvre during the procedure; 30:15 — the ratio of the longest RR interval around the 30th heart beat and the shortest RR interval around the 15th heart beat after standing; ΔSBP — the difference between systolic blood pressure 1–2 minutes after standing up and the mean systolic blood pressure in the lying position; ΔDBP — the increase of diastolic blood pressure during handgrip

as in the case of diastolic blood pressure) and a difference was calculated ($HR_h - HR_s$).

Head-up tilt test

After 15 minutes in the lying position, the subject got up (within 3–4 seconds) and remained in the standing position for 15 minutes). The ratio of the longest R-R interval (about 30 cardiac cycles after the start of assuming the vertical position; in practice, about 21–45 cycles) to the shortest R-R interval (about 15 cardiac cycles after the start of assuming the vertical position; in practice, about 5–25 cycles), the so-called 30:15 ratio, was evaluated as well as the difference between systolic blood pressure measured 1–2 minutes after assuming the standing position (mean value obtained during about 30 seconds of measurement) and blood pressure in the lying position (mean value obtained during about 30 seconds of measurement performed about 5 minutes prior to assuming the vertical position), ΔSBP. A 30:15 ratio of ≥ 1.04 and a systolic blood pressure reduction of ≤ 10 mm Hg were considered normal [14, 15].

The results were statistically analysed. The calculations were performed using the computer programme Statistica. The results were expressed as means and standard deviations. The Shapiro-Wilk test was used to check that the obtained distribution of variables was normal. The means were compared using the Student test for independent variables. The relationship between two traits was assessed using the Pearson's linear correlation coefficient. P values of < 0.05 were considered statistically significant.

Results

The mean values of all the classical cardiovascular tests were normal in both the study group and the control group. Both groups differed with respect to the value of the 30:15 ratio, which was significantly lower in diabetic subjects (Table 2).

The only parameters which correlated significantly with short-term glycaemic control were the minimum and the maximum heart rates in the deep breathing test (positive correlation). Long-term glycaemic control showed a significant negative correlation with the systolic blood pressure increase in the head-up tilt test, the heart rate increase in the deep breathing test and the handgrip test, and a positive correlation with resting heart rate and the minimum heart rate in the deep breathing test. These correlations are summarised in Table 3.

Discussion

The mean values of the classical cardiovascular tests were normal in the study group of type 1 diabetic patients. In the diabetic group, there was a significantly lower value of the 30:15 ratio verus control. Burak et al. conducted a study in a group of slightly younger patients (mean age 26 years) with a slightly shorter duration of type 1 diabetes (mean 7.3 years) but who demonstrated a poorer glycaemic control (HbA_{1c} 9.1%), and obtained normal results in all of the Ewing's battery of tests. Compared to the control group, these patients were characterised by significantly lower Valsalva ratios, lower heart rate increases in the deep breathing test and lower diastolic blood pressure increases in the handgrip test [16].

Table 3. Correlations between the investigated parameters and: the current HbA_{1c} and the mean HbA_{1c} in the past years in the study group

Test	Parameter	Curent HbA_{1c}		Mean HbA_{1c} during the past years	
		r	P	r	P
Deep breathing test	HR_{max}	0.34	< 0.05	0.13	NS
	HR_{min}	0.33	< 0.05	0.45	< 0.01
	$HR_{max} - HR_{min}$	–0.05	NS	–0.33	< 0.05
Valsalva manoeuvre	$V_{max/min}$	0.004	NS	–0.22	NS
Handgrip test	ΔDBP	–0.21	NS	–0.18	NS
	HR_s	0.29	NS	0.42	< 0.05
	$HR_h - HR_s$	–0.26	NS	–0.39	< 0.05
Head-up tilt test	30:15	–0.1	NS	–0.07	NS
	ΔSBP	–0.28	NS	–0.44	< 0.01

r — correlation coefficient; HR_{max}, HR_{min} — maximum and minimum heart rate during the deep breathing test; $HR_{max} - HR_{min}$ — the heart rate increase during the deep breathing test; $V_{max/min}$ — the ratio of the longest to shortest RR interval after Valsalva manoeuvre during the procedure; ΔDBP — the increase of diastolic blood pressure during the handgrip test; HR_s — resting heart rate before the handgrip test; $HR_h - HR_s$ — the heart rate increase during the handgrip test; 30:15 — the ratio of the longest RR interval around the 30th heart beat and the shortest RR interval around the 15th heart beat after standing; ΔSBP — the difference between systolic blood pressure 1–2 minutes after standing up and the mean systolic blood pressure in the lying position

We found no association between the results of the five classical cardiovascular tests and glycemic control over about 3 months preceding the study. The mean value of the last HbA_{1c} determination in the study group was 7.6%. We only showed a significant positive correlation of the minimum and maximum heart rates in the deep breathing test with HbA_{1c} levels.

The majority of studies using cardiovascular tests for the diagnosis of CAN based on a one-off, current determination of HbA_{1c}.

In a study performed by Spallone, HbA_{1c} significantly correlated with abnormalities in each of the tests from the Ewing's battery and pooled score from all the tests. The study included patients with type 1 diabetes mellitus of the mean age of 40.8 years, duration of diabetes of 18.3 years and unsatisfactory glycemic control (HbA_{1c} 8.6%) [17].

A study by Valensi also cocerns patients with poor glycemic control (mean HbA_{1c} 9.29%), of similar age (mean 44.3 years) but a shorter duration of diabetes (7.9 years). The author found a significantly poorer glycemic control in patients with CAN, but the multivariate analysis showed HbA_{1c} to significantly correlate only with heart rate variability in the head-up tilt test. The interpretation of the study results is confounded by the fact that the study included both type 1 and type 2 diabetics, and by the fact that the author failed to provide a separate characteristics of both patient groups [18].

It seems that the poorer correlation of the last determination of HbA_{1c} with cardiovascular test results in our study compared to studies by Spallone and Valensi may be explained by the poorer short-term glycemic control in patients participating in the two studies [17, 18].

Wolnik, on the other hand, did not demonstrate differences in the results of classical test between type 1 diabetics with good glycemic control (HbA_{1c} 6.25%) and patients with poor glycemic control (HbA_{1c} 9.05%). Patients with poorer glycemic control were characterised by faster heart rate and reduced parameters of the spectral analysis of sinus heart rate variability (HRV). The absence of differences in the classical tests between these two groups may be explained by the short duration of diabetes (mean 3.5 years). The results of this study also allow to conclude that autonomic dysfunction in poorly controlled diabetes of short duration can, however, be detected using a more sensitive method, such as HRV spectral analysis [19].

Given our results, which suggest no correlation between current HbA_{1c} levels and the results of the 5 classical Ewing's tests, it seems that short-term glycemic control does not significantly affect cardiovascular autonomic function. Long-term glycaemic control seems to play a greater role. In our study, the mean HbA_{1c} level in the past years (8.2%) showed a positive correlation with resting heart rate and minimum heart rate in the deep breathing test and a negative correlation with the systolic blood pressure increase in the head-up tilt test, heart rate increase in the deep breathing test and in the handgrip test. Of note is the fact that the evaluation of heart rate variability performed on the basis of the deep breathing test and systolic blood pressure in the head-up tilt test are, in addition to Valsalva test, tests considered to be the most reproducible, the best-standardised and recommended for long-term monitoring of cardiovascular neuropathy [20].

A prospective study by Larsen resulted in similar findings. He showed a negative correlation between the mean HbA_{1c} value, calculated from annual determinations over a period of 18 years, and the results of the deep breathing test, the Valsalva test and the head-up tilt test in a group of patients with type 1 diabetes. In his study, patients with type 1 diabetes and mean HbA_{1c} below 8.4% did not experience deterioration of autonomic function over the 18 years of follow-up, in contrast to patients with HbA_{1c} values exceeding 8.4%, in whom the results of classical tests were progressively worse [21].

Conclusions

Long-term versus short-term glycemic control was demonstrated to have a more pronounced effect on cardiac autonomic function in subjects with type 1 diabetes mellitus. Long-term glycemic control significantly correlated with heart rate increase in the deep breathing and the handgrip tests and with systolic blood pressure increase in the head-up tilt test.

References

1. Bieniaszewski L. Zastosowanie analizy widmowej w badaniu zmienności częstości akcji serca. Probl Ter Monitor 1994; suppl 1: 21–30.
2. Tatoń J. Neuropatia autonomicznego układu nerwowego (neuropatia autonomiczna) spowodowana przez cukrzycę. In: Tatoń J, Czech A. ed. Diabetologia. T. II. Wydawnictwo Lekarskie PZWL, Warszawa 2001: 281–287.
3. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic tests: 10 years experience in diabetes. Diabetes Care 1985; 8: 491–498.
4. O'Brien IA, McFadden JP, Corral RJM. The influence of autonomic neuropathy on mortality in insulin-dependent diabetes. Q J Med 1991; 79: 495–502.
5. Rathmann W, Ziegler D, Jahnke M, Haastert B, Gries FA. Mortality in diabetic patients with cardiovascular autonomic neuropathy. Diabet Med 1993; 10: 820–824.
6. Orchard TJ, Lloyd CE, Maser RE, Kuller LH. Why does diabetic autonomic neuropathy predict IDDM mortality? An analysis from the Pittsburg Epidemiology of Diabetes Complications Study. Diab Res Clin Pract 1996; suppl: S165–S171.
7. Maser ER, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy in individu-

als with diabetes. A meta-analysis. Diabetes Care 2003; 26: 1895–1901.
8. Tomlinson DR. Pathogenesis of diabetic neuropathies. In: Pickup JC, Williams G. ed. Textbook of diabetes 2. Blackwell Publishing 2003: 50.1–50.12.
9. The DCCT Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). Diabetologia 1998; 41: 416–423.
10. The DCCT Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002; 287: 2563–2569.
11. Kempler P, Tesfaye S, Chaturvedi N. et al and the EURODIAB IDDM Complications Study Group. Blood pressure response to standing in the diagnosis neuropathy: The EURODIAB IDDM Complications Study. Archives of Physiology and Biochemistry 2001; 109: 215–222.
12. Witte DR, Tesfaye S, Chaturvedi N, Eaton SE, Kepler P, Fuller JH and EURODIAB Prospective Complications Study Group. Risk factors for cardiac autonomic neuropaty in type 1 diabetes mellitus. Diabetologia 2005; 48: 164–171.
13. Trzebski A. Fizjologia krążenia krwi. In: Traczyk W, Trzebski A. ed. Fizjologia człowieka z elementami fizjologii stosowanej i klinicznej. Wyd. III. Wydawnictwo Lekarskie PZWL, Warszawa 2001: 560–588.
14. Consensus statement. Report and recommendations of the San Antonio conference in diabetic neuropathy. Diabetes 1988; 37: 1000–1004.
15. Ewing DJ. Autonomic neuropathy. In: Pickup JD, Williams G. ed. Textbook of diabetes. Blackwell Scientific Publications, Oxford 1991: 635–647.
16. Burak W, Grzeszczak W, Bujak-Rosenbeiger E. Diagnostyka cukrzycowej neuropatii autonomicznej u młodych chorych na cukrzycę typu 1. Pol Arch Med Wew 2000; 5–6: 235–239.
17. Spallone V, Maiello MR, Cicconetti E, Menzinger G. Autonomic neuropathy and cardiovascular risk factors in insulin-dependent and non insulin-dependent diabetes. Diabetes Res Clin Pract 1997; 34: 169–179.
18. Valensi P, Huard JP, Giroux C, Attali JR. Factors involved in cardiac autonomic neuropathy in diabetic patients. J Diabetes Compl 1997; 11: 180–187.
19. Wolnik B. Ocena funkcji autonomicznego i obwodowego układu nerwowego w zależności od stopnia wyrównania metabolicznego u chorych z krótkotrwałą cukrzycą typu 1. Rozprawa doktorska, promotor Stefania Horoszek-Maziarz. Gdańsk 2000.
20. Boulton AJM, Vinik AI, Arezzo JC. et al Diabetic neuropathies. A statement by the American Diabetes Association. Diabetes Care 2005; 28: 956–962.
21. Larsen JR, Sjøholm H, Berg TJ. et al Eighteen years of fair glycaemic control preserves cardiac autonomic function in type 1 diabetes. Diabetes Care 2004; 27: 963–966.