Abnormal indices of autonomic function are no longer predictors of poor outcome in diabetic patients without neuropathy but with coexisting coronary artery disease who receive optimal pharmacological therapy

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Abstract

Background: Cardiovascular autonomic neuropathy (CAN) is a complication of diabetes mellitus (DM) and has been regarded as a parameter associated with a poor outcome.

Aim: We investigated whether indices of cardiovascular autonomic function have prognostic value in the current era of pharmacological therapy recommended for DM patients with coexisting coronary artery disease (CAD), which consists of drugs that affect autonomic balance, i.e. angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers, and statins.

Methods: We studied 127 consecutive patients with type 2 DM and angiographically documented stable CAD (age: 64 years, women: 28%, treatment: ACEI/ARBs: 100%, statins: 98%, beta-blockers: 88%, insulin therapy: 46%). The assessment of autonomic balance within the cardiovascular system included heart rate variability (HRV) (time and spectral-domain analyses) and non-invasive evaluation of baroreflex sensitivity (sequence and controlled breathing methods). Primary end-points were cardiovascular mortality and urgent hospital admissions due to cardiovascular symptoms.

Results: During the mean follow-up of 502 ± 161 days, 28 patients (22%) experienced a cardiovascular event: 7 died and 21 were admitted to hospital. We found the following predictors of an increased risk of the combined end point (cardiovascular death and hospitalisation): elevated level of N-terminal BNP (for log NT-proBNP – HR = 2.6, p = 0.004), severe CAD (3-vessel disease – HR = 2.4, p = 0.02), renal insufficiency (eGFR < 60 ml/min/1.73 m^2 – HR = 2.7, p = 0.008), and female gender (HR = 3.2, p = 0.002). None of the indices of autonomic balance had prognostic value (p > 0.2 for all).

Conclusion: In the population of diabetic patients with stable CAD who receive optimal pharmacological therapy, indices of impaired autonomic function are no longer predictors of poor outcome.

Key words: diabetes mellitus, coronary artery disease, autonomic balance, baroreceptor sensitivity, prognosis

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Introduction

Cardiovascular autonomic neuropathy (CAN) is one of the most common and clinically important complications of diabetes mellitus (DM) [1-3]. The CAN can cause exercise intolerance, silent myocardial ischaemia and orthostatic hypotension, which are all frequent in patients with DM. Moreover, CAN is a well established risk factor for cardiovascular events and death in this patient group [1-4]. Therefore it is essential to detect CAN early and examination of the autonomic system should be an integrated part of the complex clinical assessment in diabetics [1-4]. However, this approach has not yet become clinical routine in everyday practice, mostly because of

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a lack of simple and easily accessible measures of assessing autonomic dysfunction within the cardiovascular system. Analysis of heart rate variability (HRV) and non-invasive evaluation of blood pressure variability, which have recently been introduced to clinical practice, may provide measures to assess the sympathovagal balance [5, 6] and arterial baroreflex sensitivity [7, 8].

Diabetics with coronary artery disease (CAD) are a group of patients with high risk of cardiovascular events [9, 10]. It is essential to identify high-risk patients early so that an individual treatment reducing the risk of cardiovascular events can be applied. An assessment of the autonomic system seems to be fully justified as it is one of various prognostic factors which are significant in this patient group. It has been documented that impaired HRV and decreased arterial baroreflex sensitivity are associated with adverse long-term prognosis in patients with CAD [especially in patients with a history of myocardial infarction (MI) or heart failure (HF)] and with an increased risk of cardiovascular events, including sudden death and malignant ventricular arrhythmias [5, 11-13]. Surprisingly, not many studies have been carried out to confirm this hypothesis in patients with DM and coexisting CAD. Additionally, most of the data had been published before medications significantly affecting autonomic balance, such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and statins, started to be routinely used in everyday practice [14].

The aim of this study was to assess whether evaluation of autonomic indices maintain its prognostic value despite the current pharmacotherapy in patients with DM and coexisting CAD.

Methods

Study group

Patients admitted to our institution in 2005 were prospectively included in the study according to the following inclusion criteria: 1) at least 6-month history of type 2 DM diagnosed according to the guidelines of the American Diabetes Association [15]; 2) angiographically verified stable angina with clinical symptoms in the CCS class I to III; 3) optimal medical therapy of DM and CAD including ACEI or ARB and statin which has not been modified for at least 4 weeks before admission; 4) sinus rhythm in ECG.

Exclusion criteria consisted of: 1) history of acute coronary syndrome (ACS) or cardiac revascularisation during 3 months before admission; 2) heart rhythm other than sinus (supra-ventricular or ventricular arrhythmia, ventricular extrasystole > 1 per min) or paced rhythm; 3) HF with clinical symptoms in NYHA class III and IV or significant left ventricular systolic dysfunction (LVEF < 35%); 4) known symptomatic diabetic neuropathy; 5) other coexisting chronic conditions potentially affecting autonomic function (including chronic renal disease with creatinine level > 2.5 mg/dl, endocrinological diseases or poorly controlled hypertension).

The study was accepted by the local bioethics committee, and all patients gave informed consent to partcipate in the study.

Autonomic system examination protocol

All tests were carried out in a quiet room before noon. All patients participating in the study refrained from drinking coffee or strong tea and smoking for 24 h before examination. Subjects had a light meal at least one hour before the test and were asked to remain resting in a supine position for at least 20 min before the study. The study protocol consisted of a first phase of 30 min, during which patients were asked to breathe spontaneously and remain in a supine position, and a second phase of 5 min, during which they were asked to pace their breathing in time with a frequency of 6 breaths per minute. The following signals were continuously recorded during each session: ECG by means of a conventional bedside monitor (Hewlett Packard model 78354C, USA) and blood pressure by means of a photoplethysmographic finger transducer (Portapress, TPD Biomedical Instrumentation, Amsterdam, The Netherlands) placed on the middle finger of the non-dominant hand, which was comfortably rested at the level of the heart. The ECG signal was digitised at 10 000 Hz using a computer with an analogue-to-digital converter (National Instruments, USA). The computer software transformed the ECG signal into a sequence of RR intervals and transformed the linear blood pressure signal into a sequence of changes in systolic blood pressure (SBP) so that it produced a tachogram and systogram – diagrams of RR intervals and SBP variability in time, respectively [16].

From the ECG signal recorded during 30 min of the resting phase of the test, a 10-minute sequence of changes in RR interval was selected so that it provided the best available quality of recordings. On the basis of the selected 10-minute sequence, the HRV was assessed using time and frequency-domain analyses. The following time-domain parameters of HRV were determined within the analysed period: mean interval between two QRS complexes resulting from sinus node depolarisations (mRR), standard deviation of the RR intervals (SDRR), and percentage of the number of interval differences of successive RR intervals greater than 50 ms in the total number of RR intervals (pNN50). For the frequency-domain analysis, a previously described and validated method of autoregressive power spectral analysis was used [17]. Signal power (in ms^2) was calculated in the following bands: very low frequency (0.01-0.04 Hz, VLF), low frequency (0.04-0.15 Hz, LF) and high frequency (0.15-0.45 Hz, HF).

Simultaneous recordings of RR and SBP sequences served for two different previously described [16] methods of non-invasive assessment of arterial baroreflex sensitivity. They are also briefly described below.

Assessment of arterial baroreflex sensitivity – a sequence method

This method of baroreflex sensitivity analysis used 10-minute series of tachograms and systograms. Sequences of three heart beats in which RR and SBP concurrently increased or decreased were identified. The minimum change had to be 1 mm Hg for SBP and 4 ms for RR. Subsequently, the linear correlation between RR and SBP (RR as a function of SBP) was computed for each sequence. Arterial baroreflex sensitivity (BRS-Seq) was then expressed as an arithmetic mean of the regression coefficient of all selected sequences [18, 19].

Assessment of baroreflex sensitivity – a controlled breathing test

During this test subjects were asked to pace their breathing in time with an electronic metronome set at a frequency of 0.1 Hz (6 breaths per minute). The physician conducting the test observed the subject's chest to ensure that the breathing pattern corresponded with the metronome. Throughout the study ECG and blood pressure were continuously recorded as previously described. Computer software detected the beat-to-beat intervals and systolic pressure changes to extract oscillation of RR and SBP at a frequency of 0.1 Hz. Arterial baroreflex sensitivity (BRS-CtrBr) was calculated as the mean amplitude of the RR oscillation divided by the mean amplitude of the SBP oscillation [19, 20].

Laboratory tests

In all subjects serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured using the enzyme-linked immunosorbent assay method (ELISA, System Elecsys 1010/2010 System, Roche Diagnostics GmbH, Mannheim, Germany), and C-reactive protein (hsCRP) serum levels were measured using the immunonephelometric high-sensitivity method (Dade Behring Marburg GmbH, Germany). Other tests including full blood count, serum levels of creatinine, glucose, glycosylated haemoglobin type A1c (HbA1c), sodium, potassium, total cholesterol, cholesterol fractions and triglycerides were carried out using standardised laboratory methods in our institution. Renal function was assessed by estimating glomerular filtration rate (GFR) with the MDRD (Modification in Diet in Renal Disease) calculator (estimated GFR, eGFR) [21].

Follow-up

As routine medical care of high-risk patients in our institution, follow-up was performed every 3 to 6 months in an outpatient cardiology department. Subjects or their family members were asked over the phone to answer questions related to cardiovascular symptoms, medications and hospital admissions.

Primary end-points were cardiovascular mortality and urgent hospitalisation due to cardiovascular symptoms.

Statistical analysis

Because most of the autonomic indices have a non-normal distribution (HRV parameters, pNN50, VLF, LF, HF and BRS-Seq, BRS-CtrBr), these data were normalised using log-transformation (natural logarithm). Also serum levels of hsCRP and NT-proBNP were normalised using log-transformation. The results are presented as medians and interquartile ranges (IQR). Other data are presented as means ± SD. Selected parameters are presented as absolute values or percentages in the study group.

Univariable and multivariable analyses of Cox proportional-hazards model were performed to assess the relationship between studied parameters and the end points. In the univariable model the following parameters were included: age, gender, body mass index, CCS class, history of HF, history of MI, history of revascularisation, severity of CAD, pharmacotherapy of DM, serum levels of glucose, HbA1c, uric acid, NT-pro-BNP and hsCRP, history of coexisting diseases (renal failure with eGFR < 60 ml/kg/1.73 m^2, anaemia with Hb < 12 g/dl) and indices of autonomic function (mRR, SDRR, pNN50, VLF, LF, HF, BRS-Seq, and BRS-CtrBr). Variables significantly associated with the combined end point were included in the step-wise multivariable model. Additionally, every variable in the multivariable model needed to have at least 10 end points. Time to the end point was included in the analysis.

Results

A group of 127 patients (91 men, average age 64 ± 9 years) with a history of DM (median time since diagnosis 4 years) and stable angina (CCS I/II/III – 32/42/26%) was included in the study. Detailed patient characteristics and laboratory test results are presented in Table I.

Table II shows the results of the autonomic function study. All autonomic indices were significantly decreased in the study group compared to the reference values in our lab established (in 25 healthy volunteers of corresponding age and gender).

The primary end point occurred in 28 (22%) subjects during a follow-up of 501 ± 161 days (over 6 months in all survivors, median 497 days): 7 patients died of cardiovascular causes (1-year mortality 4%) and 21 patients were urgently admitted to hospital due to cardiovascular symptoms. Direct reasons for admission were: MI (13), unstable angina requiring urgent revascularisation (2), compromised HF (5) and stroke (1).

In univariable analysis the following factors were significantly associated with a higher risk of the end point: increased serum levels of NT-proBNP, severe CAD (three-vessel disease), renal failure and female gender. Other parameters were not associated with an increased risk of adverse events during the follow-up period. Also, none of the studied autonomic indices had a significant impact on the prediction of death or hospital admission due to cardiovascular symptoms (details in Table III).

Table I. Patient characteristics and laboratory data

Variables	Patients (n = 127)
Age [years]	64 ± 9
Gender, men, n (%)	91 (72)
BMI [kg/m^2]	29.5 ± 4.8
WHR	0.97 ± 0.09
CCS class, I/II/III, n (%)	39/54/34 (31/43/26)
Three-vessel disease, n (%)	48 (38)
History of MI, n (%)	60 (47)
History of revascularisation (PCI/CABG), n (%)	56 (44)
Hypertension, n (%)	104 (82)
History of HF symptoms, n (%)	23 (18)
LVEF [%]	55 ± 10
Laboratory results	
Glucose [mg/dl]	152 ± 62
HbA_{1c} [%]	7.1 ± 1.7
Total cholesterol [mg/dl]	189 ± 49
Cholesterol LDL [mg/dl]	99 ± 33
NT-proBNP [pg/ml]	214.3 (443.1)
hsCRP [mg/l]	2.49 (4.11)
Uric acid [mg/dl]	5.7 ± 1.5
Haemoglobin [g/dl]	13.6 ± 1.5
Creatinine [mg/dl]	1.1 ± 0.3
eGFR [ml/min/1.73 m^2]	74.7 ± 22.8
Patients with eGFR < 60 ml/min/1.73 m^2, n (%)	39 (31)
Treatment	
Sulfonylurea, n (%)	68 (54)
Metformin, n (%)	27 (23)
Insulin, n (%)	56 (44)
ACEI/ARB, n (%)	127 (100)
Beta-blockers, n (%)	113 (88)
Statins, n (%)	127 (100)
Antiplatelet treatment, n (%)	124 (98)

Abbreviations: DM – diabetes mellitus, BMI – body mass index, WHR – waist-to-hip ratio, CCS – Canadian Cardiovascular Society, MI – myocardial infarction, HF – heart failure, LVEF – left ventricular ejection fraction, HbA_{1c} – glycosylated haemoglobin type A_{1c}, NT-proBNP – N-terminal pro-brain natriuretic peptide, hsCRP – high-sensitive C-reactive protein, eGFR – glomerular filtration rate according to MDRD calculator, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker

Because of the number of end points (total number 28), only two variables, which were significant in univariable analysis, could be included in the multivariable model. Results of bivariable analyses are shown in Table IV. Among four variables all were independent risk factors of death or hospital admission for cardiovascular reasons in the group of patients with DM and stable CAD.

Discussion

Two conclusions drawn from our study are of significant clinical importance. First, in patients with type 2 DM and CAD, indices of impaired autonomic function have no prognostic value in cardiovascular event risk stratification. Secondly, a poor prognosis is associated with elevated serum levels of NT-proBNP, renal insufficiency, severe multivessel CAD and female gender.

Cardiovascular autonomic neuropathy is an important and considerably frequent complication of DM resulting from damage to the autonomic nerve fibres that innervate the heart and blood vessels [1-3]. It can lead to abnormalities of the heart rate and blood pressure control which can give many clinical symptoms. Moreover, according to the traditional approach, CAN is an independent risk factor for cardiovascular events, including death, in patients with DM [1-3]. Therefore assessment of autonomic function should be an integral part of the clinical examination in diabetics (especially in those with a long history of DM) in order to provide risk stratification and to establish the treatment strategy [1, 2]. However, it is not clear what measures for assessing autonomic system in diabetics should be used. The gold standard validated in multiple studies was proposed by Ewing et al. and consists of five cardiovascular reflex tests (Valsalva manoeuvre, heart rate response to deep breathing, heart rate and blood pressure response to standing and blood pressure response to isometric exercise such as handgrip test) [3, 22]. Although these tests give an insight into both sympathetic and parasympathetic activities [1, 22], they are far too time consuming, not routinely used in everyday practice and reveal abnormalities at advance stages of CAN [1]. Many authors believe that analysis of HRV and blood pressure variability enables earlier detection of abnormal autonomic balance and therefore these methods should be more frequently used in patients with DM [1, 23].

The aim of this study was to prospectively verify the hypothesis that HRV and blood pressure variability have prognostic value in diabetics with CAD. These patients are a high-risk group from the clinical point of view [9, 10]. Diabetes with coexisting CAD usually leads to more severe atherosclerosis of coronary arteries and more frequently is associated with multi-vessel CAD, silent ischaemia, painless MI and a higher risk of ACS [9, 10, 24]. Diabetes is also a significant risk factor for poor short-term and long-term prognosis after ACS [25]. Among multiple explanations of poor prognosis in coexisting DM and CAD, impaired autonomic balance is often mentioned [1, 26].

In this paper we have studied not only standardised methods of spectral and time HRV analysis, but also assessment of arterial baroreflex sensitivity on the basis of HR and blood pressure recordings [6, 7]. It has been shown that both abnormal HRV parameters and decreased arterial baroreflex sensitivity are risk factors of cardiovascular events in patients with CAD and a history

Table II. Values of autonomic activity indices

	Values in study patients (n = 127)	Reference values*	p
Parameters of HRV			
mRR [ms]	906 ± 129	923 ± 113	0.54
SDRR [ms]	26.8 ± 11.1	36.4 ± 11.2	< 0.01
pNN50 [%]	0.3 (2.1)	4.9 (6.6)	< 0.001
VLF [ms^2]	151.1 (212.5)	259.1 (318.3)	< 0.05
LF [ms^2]	77.9 (145.3)	155.8 (257.6)	< 0.05
HF [ms^2]	51.8 (83.7)	56.4 (113.3)	0.81
Arterial baroreflex sensitivity			
BRS-Seq [ms/mmHg]	5.4 (3.9)	8.2 (3.4)	< 0.01
BRS-CtrBr [ms/mmHg]	5.9 (5.2)	8.4 (2.7)	< 0.05

Abbreviations: DM – diabetes mellitus, HRV – heart rate variability, mRR – mean interval between two QRS complexes resulting from sinus node depolarisations, SDRR – standard deviation of the RR intervals, pNN50 – percentage of the number of interval differences of successive RR intervals greater than 50 ms in the total number of RR intervals, VLF, LF, HF – very low frequency (0.01-0.04 Hz, VLF), low frequency (0.04-0.15 Hz, LF) and high frequency (0.15–0.45 Hz, HF), respectively, BRS-Seq, BRS-CtrBr – arterial baroreflex sensitivity assessed by sequence method (16) and controlled breathing test (16), respectively

** reference values for our lab (25 healthy subjects selected to match the study group according to age and gender)*

Table III. Prognostic factors of mortality and urgent hospital admissions for cardiovascular reasons – Cox proportional-hazards univariable model results

Prognostic factors	HR	95% CI	p
ln NT-proBNP [pg/ml]	1.51	1.13-2.00	0.004
NT-proBNP (first quartile vs. other quartiles)	0.10	0.01-0.79	0.03
Three-vessel CAD vs. others	2.44	1.15-5.15	0.02
eGFR [in 1 ml/kg/1.73 m^2]	0.98	0.96-1.00	0.05
eGFR < 60 ml/min/1.73 m^2 vs. others	2.74	1.30-5.76	0.008
Women vs. men	3.17	1.51-6.66	0.002
mRR [ms]	0.99	0.99-1.00	0.29
SDRR [ms]	1.02	0.99-1.05	0.20
ln pNN50 [%]	1.08	0.63-1.86	0.78
ln VLF [ms^2]	0.97	0.65-1.46	0.88
ln LF [ms^2]	0.89	0.65-1.22	0.48
ln HF [ms^2]	1.06	0.76-1.47	0.75
ln BRS-Seq [ms/mmHg]	1.17	0.55-2.51	0.67
ln BRS-CtrBr [ms/mmHg]	0.83	0.44-1.55	0.55

Abbreviations: CAD – coronary artery disease, HR – hazard ratio, CI – confidence interval, other – see Table II

of MI [11] or HF [12]. The group of patients with DM has not been studied yet.

Our study confirmed that DM is associated with a significant decrease of autonomic indices related to sympathovagal balance (HRV parameters) and with a decrease in arterial baroreflex sensitivity measured non-invasively. Surprisingly, we failed to demonstate that autonomic dysfunction in the cardiovascular system has prognostic value in predicting cardiovascular events. Although this study does not give an explanation for that, attention should be drawn to a number of facts. First of all, nowadays algorithms for treating CAD and DM consist of medical therapy including beta-blockers [27, 28], ACEI [29], ARB [30] and statins, which modifies autonomic balance in the cardiovascular system [31]. In the studied population all patients were on ACEI or ARB and statins and most of the patients (88%) received beta-blockers. This could influence the prognostic value of autonomic indices. Furthermore, there were 7 deaths and 17 ACS among cardiovascular events during the follow-up period. Thus, it cannot be excluded that abnormal autonomic indices would have had significance in the prognosis of cardiovascular death rather than ACS (taking into account different pathophysiology in theory). Finally, as mentioned before, in our study group most of the patients suffered from mild to moderate impaired autonomic balance

Table IV. Prognostic factors of mortality and urgent hospital admissions for cardiovascular reasons – Cox proportional-hazards bivariable model results

Prognostic factors	HR	95% CI	χ^2 in model	p
ln NT-proBNP	1.43	1.07-1.94		0.02
Three-vessel CAD vs. others	1.96	0.88-4.37		0.10
			10.66	0.005
ln NT-proBNP	1.37	1.01-1.84		0.04
eGFR < 60 ml/min/1.73 m^2 vs. others	2.41	1.06-5.44		0.04
			12.48	0.003
ln NT-proBNP	1.45	1.07-1.98		0.02
Female gender	2.57	1.18-5.60		0.02
			13.50	0.001
Three-vessel CAD vs. others	2.22	1.05-4.76		0.04
eGFR < 60 ml/min/1.73 m^2 vs. others	2.53	1.20-5.35		0.01
			11.36	0.003
Three-vessel CAD vs. others	2.32	1.09-4.90		0.03
Female gender	3.03	1.44-6.36		0.004
			13.81	0.001
eGFR < 60 ml/min/1.73 m^2 vs. others	2.08	0.95-4.54		0.07
Female gender	2.54	1.16-5.56		0.02
			12.34	0.002

Abbreviations: see Tables II and III

(patients with known diabetic neuropathy were excluded from the study, mean time from diagnosis of DM – 4 years). It is possible that the studied indices would turn out to be significant prognostic factors in a population with more severe CAN. Maser et al. [3] in their meta-analysis found that an association between CAN and increased mortality is observed mainly in patients with a higher number of abnormal autonomic test results, indicating more severe autonomic dysfunction.

However, it should be noted that our study showed that elevated serum level of NT-proBNP was one of the significant prognostic factors. This confirms the results of previous studies on the use of natriuretic peptide levels in risk stratification in diabetics [32, 33]. It should be emphasised that only a small percentage of patients suffered from coexisting CAD in these studies. Renal disease is a well established risk factor for cardiovascular events in patients with DM. It is especially important if we take into consideration that the studied population included patients with preserved or mildly impaired renal function (mean eGFR 75 ml/min/1.73 m^2). We also confirmed that female gender is related to adverse prognosis in diabetics with CAD, as previously reported [34].

Study limitations

This study was carried out on a selected group of patients with type 2 DM and stable CAD, who were admitted to a tertiary cardiology centre, and therefore the results may not necessarily extrapolate to an outpatient population. The considerably small number of cardiovascular events (n = 28) allowed only bivariable prognostic model analysis, and is another study limitation.

References

1. Andrew JM, Boulton AJM, Vinik AI, et al. Diabetic Neuropathies: A statement by the American Diabetes Association. *Diabetes Care* 2005; 28: 956-62.
2. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007; 115: 387-97.
3. Maser RE, Mitchell BD, Vinik AI, et al. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care* 2003; 6: 1895-901.
4. American Diabetes Association and American Academy of Neurology: proceedings of a consensus development conference on standardized measures in diabetic neuropathy. *Diabetes Care* 1992; 15: 1080-107.
5. Task Force of the European Society of Cardiology and the North American Society of pacing. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996; 93: 1043-65.
6. Lombardi F, Malliani A, Pagani M, et al. Heart rate variability and its sympatho-vagal modulation. *Cardiovasc Res* 1996; 32: 208-16.
7. Lanfranchi PA, Somers VK. Arterial baroreflex function and cardiovascular variability: interactions and implications. *Am J Physiol Regul Integr Comp Physiol* 2002; 283: R815-26.
8. James MA, Panerai RB, Potter JF. Applicability of new techniques in the assessment of arterial baroreflex sensitivity in the elderly: a comparison with established pharmacological methods. *Clin Sci* (*Lond*) 1998; 94: 245-53.
9. Eberly LE, Cohen JD, Prineas R, et al. Impact of incident diabetes and incident nonfatal cardiovascular disease on 18-year mortality: the multiple risk factor intervention trial experience. *Diabetes Care* 2003; 26: 848-54.
10. Schramm TK, Gislason GH, Køber L, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation* 2008; 117: 1945-54.

11. Bigger JT Jr, Fleiss JT, Steinman RC, et al. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992; 85: 164-71.
12. Ponikowski P, Anker SD, Chua TP, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; 79: 1645-50.
13. La Rovere MT, Bigger Jr JT, Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998; 351: 478-84.
14. Rydén L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007; 28: 88-136.
15. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003; 26: S5-20.
16. Witkowski T, Jankowska EA, Ponikowska B, et al. Zastosowanie nieinwazyjnych metod oceny odruchu z baroreceptorów tętniczych u pacjentów z chorobami układu krążenia. *Pol Przegląd Kardiologiczny* 2004; 6: 159-65.
17. Colhoun HM, Francis DP, Rubens MB, et al. The association of heart-rate variability with cardiovascular risk factors and coronary artery calcification: a study in type 1 diabetic patients and the general population. *Diabetes Care* 2001; 24: 1108-14.
18. Pitzalis MV, Mastropasqua F, Passantino A, et al. Comparison between noninvasive indices of baroreceptor sensitivity and the phenylephrine method in post-myocardial infarction patients. *Circulation* 1998; 97: 1362-7.
19. Davies LC, Francis DP, Scott AC, et al. Effect of altering conditions of the sequence method on baroreflex sensitivity. *J Hypertens* 2001; 19: 1279-87.
20. Davies L C, Colhoun H, Coats AJ, et al. A noninvasive measure of baroreflex sensitivity without blood pressure measurement. *Am Heart J* 2002; 143: 441-7.
21. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461-70.
22. Ewing DJ, Martyn CN, Young RJ, et al. The value of cardiovascular autonomic tests: 10 years' experience in diabetes. *Diabetes Care* 1985; 8: 491-8.
23. Mésangeau D, Laude D, Elghozi JL. Early detection of cardiovascular autonomic neuropathy in diabetic pigs using blood pressure and heart rate variability. *Cardiovasc Res* 2000; 45: 889-99.
24. Goraya TY, Leibson CL, Palumbo PJ, et al. Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. *J Am Coll Cardiol* 2002; 40: 946-53.
25. Donahoe SM, Stewart GC, McCabe CH, et al. Diabetes and mortality following acute coronary syndromes. *JAMA* 2007; 298: 765-75.
26. Stirban AO, Tschoepe D. Cardiovascular complications in diabetes: targets and interventions. *Diabetes Care* 2008; 31 (Suppl. 2): S215-21.
27. Mortara A, La Rovere MT, Pinna GD, et al. Nonselective beta-adrenergic blocking agent, carvedilol, improves arterial baroflex gain and heart rate variability in patients with stable chronic heart failure. *J Am Coll Cardiol* 2000; 36: 1612-8.
28. Ebbehoj E, Poulsen PL, Hansen KW, et al: Effects on heart rate variability of metoprolol supplementary to on going ACE-inhibitor treatment in type I diabetic patients with abnormal albuminuria. *Diabetologia* 2002; 45: 965-75.
29. Kontopoulos AG, Athyros VG, Didangelos TP, et al. Effect of chronic quinapril administration on heart rate variability in patients with diabetic autonomic neuropathy. *Diabetes Care* 1997; 20: 355-61.
30. Maser RE, Lenhard MJ. Effect of treatment with losartan on cardiovascular autonomic and large sensory nerve fiber function in individuals with diabetes mellitus: a 1-year randomized, controlled trial. *J Diabetes Complications* 2003; 17: 286-91.
31. Szramka M, Harriss L, Ninnio D, et al. The effect of rapid lipid lowering with atorvastatin on autonomic parameters in patients with coronary artery disease. *Int J Cardiol* 2007; 117: 287-91.
32. Huelsmann M, Neuhold S, Strunk G, et al. NT-proBNP has a high negative predictive value to rule-out short-term cardiovascular events in patients with diabetes mellitus. *Eur Heart J* 2008; 29: 2259-64.
33. Tarnow L, Gall MA, Hansen BV, et al. Plasma N-terminal pro-B-type natriuretic peptide and mortality in type 2 diabetes. *Diabetologia* 2006; 49: 2256-62.
34. Natarajan S, Liao Y, Cao G, et al. Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. *Arch Intern Med* 2003; 163: 1735-40.

Upośledzone wskaźniki aktywności układu autonomicznego nie mają znaczenia prognostycznego u osób z cukrzycą bez cech neuropatii i z chorobą niedokrwienną serca optymalnie leczonych farmakologicznie

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Streszczenie

Wstęp: Neuropatia obejmująca włókna autonomiczne układu krążenia jest częstym powikłaniem cukrzycy (DM), tradycyjnie uznawanym za czynnik złego rokowania.

Cel: W pracy oceniano, czy w dobie współczesnej farmakoterapii zalecanej u pacjentów z DM i chorobą niedokrwienną serca (CHNS), obejmującej leki wpływające na układ autonomiczny [beta-blokery, inhibitory enzymu konwertującego angiotensynę (ACEI), blokery receptora angiotensyny (ARB), statyny], ocena wskaźników autonomicznych ma znaczenie prognostyczne.

Metody: Do badania włączono kolejnych 127 pacjentów z DM typu 2 i angiograficznie potwierdzoną, stabilną CHNS (wiek 64 lata, 28% kobiet, leczenie: ACEI lub ARB – 100%, statyny – 98%, beta-blokery – 88%, insulina – 46%). Ocena równowagi autonomicznej obejmowała zmienność rytmu serca (analiza czasowa i spektralna) i nieinwazyjne metody oceny funkcji baroreceptorów (metoda sekwencyjna oraz kontrolowanego oddychania). Punktem końcowym był zgon oraz pilna hospitalizacja z przyczyn sercowo-naczyniowych.

Wyniki: W trakcie obserwacji trwającej średnio 502 ± 161 dni punkt końcowy wystąpił u 28 (22%) chorych: 7 osób zmarło, 21 było hospitalizowanych. W analizie prognostycznej znaleziono następujące czynniki ryzyka wystąpienia punktu końcowego: podwyższony poziom NT-proBNP (dla *log* NT-proBNP – HR = 2,6, p = 0,004), zaawansowanie zmian w naczyniach wieńcowych (choroba 3-naczyniowa – HR = 2,4, p = 0,02), niewydolność nerek (eGFR < 60 ml/min/1,73 m^2; HR = 2,7, p = 0,008), płeć żeńska (HR = 3,2, p = 0,002). Żaden z ocenianych wskaźników układu autonomicznego nie miał znaczenia w prognozowaniu ryzyka zgonu lub hospitalizacji z przyczyn sercowo-naczyniowych (p > 0,2 dla wszystkich).

Wniosek: W populacji optymalnie leczonych farmakologicznie pacjentów z DM i stabilną CHNS upośledzone wskaźniki równowagi autonomicznej nie mają istotnego znaczenia w prognozowaniu ryzyka epizodu sercowo-naczyniowego.

Słowa kluczowe: cukrzyca, choroba niedokrwienna serca, równowaga autonomiczna, wrażliwość baroreceptorów, rokowanie

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