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Состояние сердца и сосудов при кардиоваскулярной форме автономной нейропатии у больных сахарным диабетом 2 типа

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Цель. *Оценить состояние сердца и сосудов при кардиоваскулярной форме диабетической автономной нейропатии (ДАН) у больных сахарным диабетом 2 типа (СД2).*
Материалы и методы. *Обследовано 139 больных СД2 с артериальной гипертензией (АГ), средний возраст 53,1±4,9 лет, длительность АГ – 9,7±7,8 лет. На основании вегетативных ЭКГ-тестов и кардиоинтервалографии пациенты были разделены на две группы: без кардиоваскулярной формы ДАН (40 человек) и с кардиоваскулярной формой ДАН (99 человек). Группа сравнения была представлена 30 больными с АГ без нарушения углеводного обмена, средний возраст – 53,1±6,0 лет, длительность АГ – 10,9±8,5. Всем пациентам выполнено ультразвуковое исследование сердца и общей сонной артерии.*
Результаты. *Наличие кардиоваскулярной формы ДАН у больных СД2 сопровождалось достоверным снижением максимальной скорости трансмитрального кровотока в период раннего диастолического наполнения (0,61±0,12 м/с) в период позднего диастолического наполнения (0,65±0,11 м/с) по сравнению с пациентами без ДАН (0,66±0,09 м/с, 0,69±0,09 м/с соответственно, p<0,05) и группой сравнения (0,71±0,16 м/с, 0,69±0,14 м/с соответственно, p<0,05); увеличением массы миокарда левого желудочка и конечного диастолического объема (253,3±67,2 г, 120,6±25,2 мл, p<0,05) по сравнению с больными с АГ без нарушения углеводного обмена (204,6±72,7 г, 110,4±22,2 мл, p<0,05) и увеличением толщины комплекса интима–медиа (ТИМ) по сравнению с больными СД2 без ДАН (1,28±0,15 мм против 1,17±0,19 мм, p=0,004).*
Заключение. *Основными детерминантами кардиоваскулярной формы ДАН у больных СД2 являются: повышение массы миокарда левого желудочка и объемных параметров сердца, нарушение диастолической функции левого желудочка, увеличение диаметра общей сонной артерии за счет толщины комплекса интима-медиа.*
Ключевые слова: *сахарный диабет; сердце; кардиоваскулярная автономная нейропатия; детерминанты*

Morphological and functional parameters of the heart and vessels in patients with type 2 diabetes mellitus and cardiovascular autonomic neuropathy

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Objective. *To evaluate morphological and functional parameters of the heart and vessels in patients with type 2 diabetes mellitus (DM2) and diabetic cardiovascular autonomic neuropathy (CAN).*
Materials and methods. *A total of 139 patients with DM2 and hypertension (mean age: 53.1±4.9 years; mean duration of hypertension: 9.7±7.8 years) were included in this study. Based on cardiovascular autonomic function test results (electrocardiography, heart rate variability) patients were divided into 2 groups as follows: Group 1 included 40 patients without CAN and Group 2 included 99 patients with CAN. The control group comprised 30 patients with hypertension and normal carbohydrate metabolism (mean age: 53.1±6.0 years; mean duration of hypertension: 10.9±8.5 years). All patients underwent ultrasonography of the heart and common carotid artery.*
Results. *Group 2 patients showed a significant decrease in maximal transmitral flow velocity during early diastolic filling (0.61±0.12 m/s) and a decrease in maximal transmitral flow velocity during late diastolic filling (0.65±0.11 m/s) compared with Group 1 patients (0.66±0.09 m/s and 0.69±0.09 m/s, respectively, p <0.05) and control group patients (0.71±0.16 m/s and 0.69±0.14 m/s, respectively, p <0,05). Further, Group 2 patients showed a significant increase in left ventricular mass and ventricular end-diastolic volume (253.3±67.2 g and 120.6±25.2 ml, respectively) compared with control group patients (204.6±72.7 g and 110.4±22.2 ml, respectively, p <0.05) and a significant increase in intima-media complex thickness (IMT) (1.28±0.15 mm) compared with Group 1 patients (1.17±0.19 mm, p = 0.004).*
Conclusion. *Increased left ventricular mass and heart volume parameters (end-systolic volume and end-diastolic volume), left ventricular diastolic dysfunction and increased common carotid artery diameter caused by increased IMT are the main determinants of CAN in patients with diabetes.*

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Key words: *diabetes mellitus; heart; cardiovascular autonomic neuropathy; determinants*

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Diabetes mellitus (DM) poses a challenge to health systems worldwide. According to official statistics, more than 2 million citizens of the Russian Federation suffer from DM, and as many as 200,000 new cases are registered annually. Type 2 DM (DM2) accounts for approximately 88% of all cases of diabetes in Russian Federation [1]. The clinical importance of diabetic autonomic neuropathy (DAN) has resulted in growing interest in investigating its pathogenesis in recent years. In particular, DAN can exacerbate cardiovascular symptoms and lead to poor prognosis of cardiovascular complications in patients with DM [2, 3]. Cardiovascular autonomic neuropathy (CAN) is the most clinically important form of DAN with the worst prognosis. It has been associated with an increased risk of sudden death even in the preclinical stage [4]. However, despite a strong negative influence on survival and quality of life, DAN is the least studied complication of DM [5], and there is controversy concerning its causes. Autonomic imbalance causes increased sympathetic and decreased parasympathetic activities, leading to unfavourable consequences. For example, morphological and functional changes occur in the heart and vessels when the cardiovascular system is subjected to continuous autonomic dysregulation [6].

STUDY AIMS

This study aimed to evaluate the morphological and functional parameters of the heart and vessels in patients with DM2 and CAN.

MATERIALS AND METHODS

The study included 139 patients (48 men, 91 women) with DM2 and was conducted at the Department of Endocrinology, Novosibirsk State Regional Clinical Hospital. The inclusion criteria were as follows: patients with DM2 aged 45–65 years. The exclusion criteria were as follows: patients aged <45 or >65 years; chronic kidney and liver failure, hypothyreosis, severe heart failure [Class III and Class IV congestive heart failure (CHF)], decompensation of concomitant chronic diseases, suppurative complications and alcohol abuse.

The mean age of the patients was 53.1 ± 4.9 years; the mean duration of diabetes, duration of hypertension and glycated haemoglobin (HbA_{1c}) levels were 7.7 ± 6.9 years, 9.7 ± 7.8 years and 9.4% ± 2.1%, respectively. Because all study participants were hypertensive, the control group comprised 30 patients (12 men and 18 women, mean age: 53.1 ± 6.0 years) with hypertension and normal carbohydrate metabolism. The mean duration of hypertension in the control group was comparable to that in the groups of patients with DM (see below). The groups were matched according to age and gender and did not differ in the type of hypertension. The Ethics Committee of the Department of Endocrinology, Novosibirsk State Regional Clinical Hospital, approved the study protocol (Protocol #24, 22.10.2007), and written informed consent was obtained from all patients.

Autonomic function was determined using electrocardiography (ECG), i.e. deep breathing, Valsalva manoeuver and orthostatic tests to diagnose CAN. Measurement of the R-R interval according to the protocol proposed by Baevsky et al. was used to confirm the diagnosis of CAN when ECG tests results were not definitive. This protocol assesses heart rate at rest and after standing upright. The severity of autonomic neuropathy was evaluated using the criteria proposed by Ewing as follows: Three negative test results suggested no autonomic dysfunction;

- 1 positive test and 2 borderline results indicated mild autonomic dysfunction;
- 2 positive tests results indicated moderate autonomic dysfunction
- 3 positive tests results indicated severe autonomic dysfunction.

Patients were divided into 2 groups on the basis of the presence or absence of CAN according to the ECG and R-R interval data. Group 1 included 40 patients without CAN (mean age: 52.4 ± 4.8 years; mean duration of diabetes and hypertension: 6.1 ± 5.2 and 9.1 ± 7.6 years, respectively). Group 2 included 99 patients with CAN (mean age: 53.4 ± 5.1 years; mean duration of diabetes and hypertension: 8.3 ± 7.4 and 10.1 ± 8.1 years, respectively). In Group 1, retinopathy was present in 37.5% patients, normoalbuminuria in 35.5% patients and polyneuropathy in 57.5% patients. In Group 2, retinopathy occurred in 51.1% patients, normoalbuminuria in 23.2% patients and polyneuropathy in 69.7% patients. The type of hypoglycaemic therapy did not differ significantly between Group1 and Group 2 patients. Insulin was administered to 47.5% and 35% patients in Group 2 and Group 1, respectively ($\chi^2 = 0.464$; $p > 0.05$).

There was no significant difference in the severity of hypertension, frequency of coronary heart disease, cardiac remodelling after acute myocardial infarction and NYHA classes of CHF between the groups (Table 1).

Morphological and functional changes in the heart were detected using a MEGAS ultrasound system (Esaote S.p.A., Italy) equipped with 3.5-MHz ultrasound probes. Standard one- and two-dimensional B- and M-mode echocardiography protocols of the American Heart Association (1987) were used to evaluate atrial and ventricular linear dimensions and systolic and diastolic volumes.

To test morphological and functional changes in vessels, patients underwent ultrasonography of the common carotid

Table 1

Clinical characteristics of patients.

Characteristic	Group 1 n = 40, (%)	Group 2 n = 99, (%)	p
Duration of DM, years	6,1±5,2*	9,1±7,6*	0,024
Polyneuropathy	23 (57,5)	69 (69,7)	0,631
Diabetic retinopathy non-proliferative pre-profilative proliferative	15 (37,5) 13 (86,7) 1 (6,7) 1 (6,7)	51 (51,5) 36(70,6) 10 (19,6) 5 (9,8)	0,456 0,802 0,528 0,864
Normoalbuminuria	14 (35,5)	23 (23,2)	0,389
Hypertension stage Stage 1 Stage 2 Stage 3	 3 (7,5) 21 (52,5) 16 (40)	 9 (9,1) 50 (50,5) 39 (39,4)	 0,956 0,968 0,895
Coronary heart disease Angina pectoris class 1 Angina pectoris class 2 Painless ischemia Cardiac remodelling	17 (42,5) 3 (17,6)* 14 (82,3) 0 8 (20)	49 (49,5) 0* 39 (79,6) 10 (20,4) 20 (20,2)	0,776 0,034 0,897 0,157 0,978
CHF Class 0 Class 1 Class 2	 6 (15) 16 (40) 18 (45)	 7 (7,1) 34 (34,3) 58 (58,6)	 0,323 0,805 0,520
Hypoglycaemic therapy Metformin Sulfonylurea Metformin + Sulfonylurea Insulin therapy	 5 (12,5) 18 (45) 3 (7,5) 14 (35)	 8 (8,1) 23 (23,2) 21 (21,2) 47 (47,5)	 0,679 0,103 0,156 0,496

*Significant difference, Student's t-test

artery (CCA). Thickening of CCA walls detected using ultrasonography reveals early signs of atherosclerosis. This parameter was used to identify target organ damage.

Patients underwent duplex ultrasound scanning of the brachiocephalic arteries using B-mode with pulsed wave Doppler and colour flow mapping using a Siemens ultrasound system equipped with 5–8 MHz ultrasound probes.

SPSS 13.0 software was used for statistical analysis. Descriptive statistics, analysis of variance and correlation analysis were used as well. The Kolmogorov–Smirnov test was performed to test the normality of data distribution. Because the data were normally distributed, parametric statistics were employed. All data are presented as the mean ± SD. Intergroup data comparisons were performed using Student's t-test (for 2 groups) or ANOVA (for 3 and more groups). Pearson's $\chi 2$ criterion was used to compare binary variables. Statistical significance was defined as 0.05.

RESULTS AND DISCUSSION

CAN was observed in 71.3% patients as follows: mild in 17.8% patients; moderate in 27.4% patients and severe in 26.1% patients. There was no detectable autonomic involvement in 28.7% patients. Left ventricular (LV) diastolic dysfunction is an early sign of morphological and functional changes in the heart in patients with diabetes. LV diastolic dysfunction occurs at frequencies ranging from 50% to 75% in patients with DM2 without hypertension or coronary and other heart diseases [7, 8] and increases to 85% in patients with combined DM2 and hypertension [9, 10].

LV diastolic dysfunction examined using echocardiography was detected in 87% patients with diabetes and hypertension and in 66.7% patients with hypertension and normal carbohydrate metabolism ($\chi 2 = 7.417$, $p < 0.05$). There was no significant difference between the characteristics of LV diastolic dysfunction between Group 1 and control group patients. In contrast, there was a significant decrease in maximal transmitral flow velocity during early diastolic filling (E-peak) and a decrease in maximal transmitral flow velocity during late diastolic filling (A-peak), changed E/A ratio and increased LV isovolumic relaxation time (LVIVRT) in Group 2 patients. These data indicate that the signs of LV diastolic dysfunction were more likely to appear in patients with CAN, and severe CAN was associated with increased LV diastolic dysfunction (Table 2).

Our results are consistent with those of a study conducted by Kaderli et al. who found that DAN was associated with more severe LV and right ventricular diastolic dysfunction. Evidence indicates that hyperglycaemia [11, 12], hyperinsulinemia and insulin resistance [13, 14] cause severe alterations of LV diastolic relaxation. Moreover, changes in respiratory quotient and increased heart rate lengthened the isovolumic relaxation time and decreased maximal transmitral flow velocity during late diastolic filling (A-peak) in patients with diabetes ($R2 = 0.244$, $p = 0.017$). A multivariate regression model was used to analyse these data.

Increased sympathetic activity in patients with diabetes is associated with increased cardiac output, total peripheral

Table 2

Characteristics of diastolic dysfunction in patients with diabetes and different stages of CAN

Characteristic	Control group, n = 30	Group 1, n = 40	Mild CAN, n = 25	Moderate CAN, n = 36	Severe CAN, n = 38
E, m/s	0,71±0,16	0,66±0,09	0,64±0,11	0,64±0,12*	0,58±0,11*,**,***,****
A, m/s	0,69±0,14	0,69±0,09	0,66±0,12	0,65±0,12	0,63±0,08*,**
E/A	1,07±0,35	0,95±0,14	0,96±0,30	0,98±0,18	0,92±0,22*
LVIVRT, ms	109,1±17,4	113,7±25,3	115,8±27,4	123,9±27,0*	125,0±28,5*

*Significant difference compared with the control group ($p < 0.05$); **Significant difference compared with Group 1 ($p < 0.05$); ***Significant difference compared with the 'Mild CAN' group ($p < 0.05$); ****Significant difference compared with the 'Moderate CAN' group ($p < 0.05$).

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Table 3

Characteristics of cardiac structural parameters in patients with diabetes with or without CAN

Characteristic	Control group, n = 30	Group 1, n = 40	Group 2, n = 99
EDD, cm	4,83±0,42	4,87±0,49	5,01±0,44*
ESD, cm	3,13±0,61	3,14±0,45	3,28±0,47
EDV, ml	110,4±22,2	112,9±27,9	120,6±25,2*
ESV, ml	41,2±21,4	40,4±14,9	44,8±15,8
LVPWd, cm	0,95±0,22	1,07±0,16*	1,08±0,15*
IVSd, cm	1,02±0,21	1,12±0,18*	1,14±0,18*
RWT, cm	0,41±0,06	0,45±0,08*	0,45±0,07*
LVMM, g	204,6±72,7	236,9±62,1*	253,3±67,2*
LVMI, g/m^2	107,7±35,1	122,3±27,9	128,5±28,8*

EDD: End-diastolic dimension
ESD: End-systolic dimension
EDV: End-diastolic volume
ESV: End-systolic volume
LVPWd: Left ventricular end-diastolic posterior wall dimension
IVSd: Interventricular septal end-diastolic dimension
RWT: Relative wall thickness
LVMM: Left ventricular myocardial mass
LVMI: Left ventricular mass index
*Significant difference compared with the control group ($p < 0.05$), **Significant difference compared with Group 1 ($p < 0.05$)

resistance, sodium and water reabsorption [15], circulating volume and blood pressure. Decreased parasympathetic activity increases heart rate and is associated with decreased vascular wall elasticity. Together, these symptoms lead to morphological and functional changes in the heart with increased LV mass and ventricular end-diastolic volume, cardiac dilation, diastolic dysfunction, decreased LV systolic function [16] and early development and rapid progression of CHF. The posterior wall and interventricular septum of the left ventricle were significantly thicker and the relative wall thickness of the left ventricle and LV mass were significantly higher in Group 1 patients than in control group patients. CAN was associated with LV hypertrophy (increased posterior wall and interventricular septum thickness, LV relative wall thickness and LV mass) and increased heart volume parameters (end-systolic volume and end-diastolic volume) (Table 3).

Analysis of morphological changes in the heart conducted according to the severity of CAN revealed that increased heart volume parameters (end-systolic volume and end-diastolic volume) occurred in the group of patients with severe CAN (Group 2) but not in Group 1 or control group patients ($p < 0.05$) (Table 4). Increased heart volume parameters (end-systolic volume and end-diastolic volume) were associated with changed Valsalva coefficient ($R2 = 0.202$, $p = 0.017$), suggesting increased sympathetic activity, whereas LV mass and LV mass index were associated with increased heart rate ($R2 = 0.272$, $p = 0.001$) in patients with diabetes. The analysis was performed using a multivariate regression model.

LV systolic function [ejection fraction (EF) > 50%] was normal in all study participants.

Group 2 patients showed a significant decrease in LV systolic function [EF and fractional shortening (FS)] to 63.4% ± 7.6% and 34.8% ± 6.0%, respectively, compared with control group patients (37.0% ± 3.1% and 66.9% ± 4.4%, respectively, $p < 0.05$). Group 2 patients had lower EF and FS compared with Group 1 patients (65.1% ± 8.2% and 35.6% ± 5.8%, respectively, $p < 0.05$).

Morphological changes in patients with DM may represent symptoms of atherosclerosis. Intima-media complex thickness (IMT) of the ACC allows assessment of arterial remodelling in atherosclerosis even in early stages [17]. Using IMT as a marker of atherosclerosis provides higher specificity and sensitivity compared with other lipid profile components [17].

According to numerous large prospective studies [Atherosclerosis Risk in Communities (ARIC), Second Manifestations of ARTerial disease (SMART), Longevity and Aging in Hokkaido County (LILAC) and the Hoorn Screening Study], IMT serves as an independent risk factor for transient ischemic attack, stroke and heart attack. DM, smoking, hypertension and dyslipidaemia are the main factors that increase IMT [18]. Moreover, hyperglycaemia,

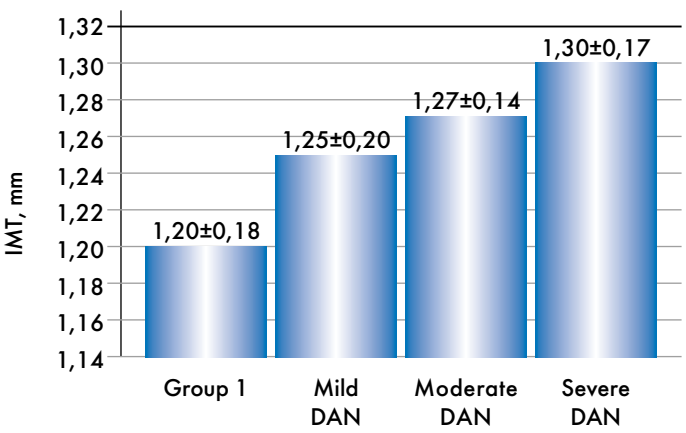

Figure 1. IMT (mm) of CCA in patients with diabetes and different stages of CAN.

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Table 4

Characteristics of cardiac structural parameters in patients with DM2 and different stages of DAN.

Characteristic	Control group, n = 30	Group 1, n = 40	Mild CAN, n = 25	Moderate CAN, n = 36	Severe CAN, n = 38
EDD, cm	4,83±0,42	4,87±0,49	4,93±0,51	5,01±0,40	5,06±0,47*
ESD, cm	3,13±0,61	3,14±0,45	3,21±0,47	3,23±0,36	3,37±0,56**
EDV, ml	110,4±22,2	112,9±27,9	116,2±27,5	120,0±22,2	123,2±26,5*
ESV, ml	41,2±21,4	40,4±14,9	42,6±14,3	42,7±11,5	48,4±19,6**
LVPWd, cm	0,95±0,22	1,07±0,16*	1,07±0,14*	1,07±0,15*	1,09±0,15*
IVSd, cm	1,02±0,21	1,12±0,18*	1,15±0,15*	1,16±0,20*	1,12±0,18*
RWT, cm	0,41±0,06	0,45±0,08*	0,46±0,07*	0,45±0,07*	0,45±0,07*
LVMM, g	204,6±72,7	236,9±62,1*	245,5±64,9*	254,7±66,6*	257,2±70,4*
LVMI, g/m^2	107,7±35,1	122,3±27,9	124,2±27,9	128,1±27,4*	131,7±31,1*

EDD: End-diastolic dimension
ESD: End-systolic dimension
EDV: End-diastolic volume
ESV: End-systolic volume
LVPWd: Left ventricular end-diastolic posterior wall dimension
IVSd: Interventricular septal end-diastolic dimension
RWT: Relative wall thickness
LVMM: Left ventricular myocardial mass
LVMI: Left ventricular mass index
*Significant difference compared with the control group ($p < 0.05$); **Significant difference compared with Group 1 ($p < 0.05$)

hyperinsulinemia and insulin resistance serve as markers for increased IMT in patients with DM [19].

Further, increased IMT causes microvascular complications of diabetes, such as nephropathy [Epidemiology of Diabetes Interventions and Complications Study (EDIC)] and retinopathy [20]. However, no data are available regarding the effects of DAN on IMT.

Here we show a significant increase in IMT in Groups 1 and 2 patients (1.26 ± 0.17 mm) compared with control group patients (1.10 ± 0.14 mm, $p < 0.05$), which indicates more severe atherosclerosis.

CAN was associated with a significant increase in IMT in Group 1 patients compared with Group 2 patients (Figure 1).

Increased IMT was influenced by the duration of diabetes ($r = 0.203$, $p < 0.05$), systolic blood pressure ($r = 0.234$, $p < 0.05$), fasting hyperglycaemia ($r = 0.215$, $p < 0.05$), low high-density lipoprotein cholesterol levels ($r = –0.288$, $p < 0.05$), and differences in autonomic ECG test results (respiratory quotient) ($r = –0.239$, $p < 0.05$).

Increased CCA diameter was associated with increased heart rate ($R2 = 0.214$, $p = 0.026$) in Groups 1 and 2. Changed respiratory quotient, indicating decreased parasympathetic activity, was a determinant of IMT ($R2 = 0.245$, $p = 0.019$) according to the results of multivariate regression analysis.

In our present study, CAN was associated with increased LV mass and volume parameters of the heart, LV diastolic dysfunction and increased ACC diameter caused by IMT in patients with diabetes. These observations stress the importance of diagnosing LV diastolic dysfunction and IMT changes in patients with diabetes and CAN to diagnose early stages of atherosclerosis and CHF.

CONCLUSION

1. CAN is associated with LV diastolic dysfunction, increased heart volume parameters and increased LV mass in patients with diabetes.
2. Morphological changes in CCA are characterized by increased overall diameter due to increased IMT in patients with diabetes and CAN.
3. IMT must be assessed in all patients with diabetes and CAN to diagnose and treat atherosclerosis at early stages.

DISCLOSURE INFORMARION

The authors declare that they have no conflicts of interest.

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