

## **BAROREFLEX SENSITIVITY IN PATIENTS WITH DIABETES MELLITUS AND ESSENTIAL HYPERTENSION: EFFECT OF COMBINED THERAPY**

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### **A b s t r a c t**

The study was aimed at evaluation of the effect of pharmacological and non-pharmacological therapy on baroreflex sensitivity of heart rate (BRS, ms/mm Hg) in patients with type 2 diabetes mellitus (DM) and essential hypertension (EH). BRS was significantly increased after 12 weeks of walking training program in diabetics without hypertension as well as in diabetics with hypertension controlled by monotherapy. The BRS value in normotensives corresponds to the BRS value in diabetics with hypertension after training as well as in patients with essential hypertension with combined pharmacotherapy.

### **Key words**

Diabetes mellitus type 2, Baroreflex sensitivity, Essential hypertension, Exercise therapy.

### **INTRODUCTION**

The coincidence of type 2 diabetes mellitus and hypertension is considered to be a malignant combination participating in additional increase of cardiovascular risk and mortality and they are clustered with other pathological condition (insulin resistance, abdominal obesity, dyslipidemia) in metabolic syndrome (1). Metabolic syndrome is accompanied with increased sympathetic activity that increases the cardiovascular risk (especially the risk of sudden death and life-threatening arrhythmias); therefore, the evaluation of cardiovascular autonomic functions is reasonable in these patients (1-6). Determination of baroreflex sensitivity using non-invasive method of measuring - spectral analysis of systolic blood pressure (SBP) and cardiac intervals (CI) fluctuation can contribute to evaluation of cardiovascular risk and the effect of therapy (both non-pharmacological and pharmacotherapy). Depressed value of BRS indicates an increased sympathetic nervous activity. Our study

was focused on the evaluation of potential favourable effect of walking training on the heart rate baroreflex sensitivity compared to the effect of pharmacotherapy of hypertension in patients with type 2 diabetes mellitus and hypertension.

## PATIENTS AND METHODS

In two groups of diabetics type 2 - with hypertension controlled by ACE inhibitors or Ca-channel-blockers (DMH, n = 7, age  $56 \pm 4$  years) and without hypertension (DMN, n = 6, age  $60 \pm 8$  years) BRS was evaluated before (1) and after (2) 12 weeks of walking training program that consisted of daily 30-60 min walking at least 3-4x a week. Furthermore, BRS was measured in patients with essential hypertension without treatment (EH, n = 11, age  $60 \pm 4$  years), in normotensives (N, n = 11, age  $58 \pm 6$  years), in patients with essential hypertension and monotherapy of ACE inhibitors or Ca-channel blockers (EHT1, n = 12, age  $59 \pm 6$  years) and in hypertensives with combined therapy of trandolapril and diltiazem (EHT2, n = 18, age  $48 \pm 5$  years). BRS was determined by a 5-minute continuous beat-to-beat recording of blood pressure according to the Peñáz method (7) (Finapres Ohmeda) at metronome-controlled breathing frequency of 0,33 Hz. The BRS value was calculated by spectral analysis of spontaneous fluctuations of systolic blood pressure (SBP) and cardiac intervals (CI). The value of cross-spectral power density of CI and SBP fluctuation was divided by the value of power spectral density of systolic blood pressure fluctuation at 0,1Hz. The value obtained, i.e. modulus, was considered to be the measure of BRS. The value of this function at frequency of 0,1Hz corresponds to BRS (ms/mm Hg).

The experimental protocol was approved by the local Ethics committee, prior the participation all subjects gave written informed consent.

Statistical analysis of data was performed using Wilcoxon paired test and ANOVA; the significant differences were considered at  $p < 0,05$ . The data are performed as mean  $\pm$  SD and were processed by Microsoft Excel 97.

## RESULTS

The results of BRS of all patients groups are given in *Table 1* and *Fig. 1*.

The walking training program increased significantly BRS in patients with type 2 diabetes mellitus (both with and without hypertension). The BRS value in non-diabetic groups was significantly increased in hypertensive patients with combined medication (EHT2) and in normotensives (N) compared to hypertensive group without therapy (EH) and hypertensives with monotherapy (EHT1). Systolic and diastolic blood pressure was significantly increased in hypertensive group without therapy (EH).

## DISCUSSION

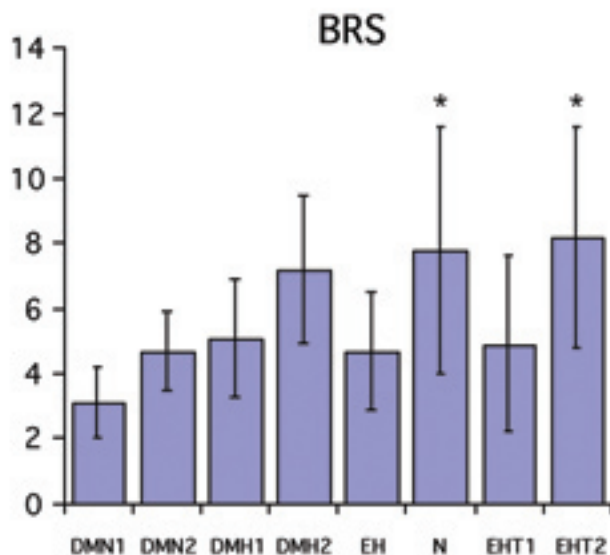
In patients with diabetes mellitus type 2 the average prevalence of hypertension is about 80%. In the majority of patients, diabetes type 2 is associated with insulin resistance (IR) that appears to be a key factor in the development of other pathological conditions (including hypertension), involved in the metabolic syndrome. Autonomic dysfunction with increased sympathetic activation expressed by low value of baroreflex sensitivity along with depressed heart rate variability (HRV) is the characteristic feature of metabolic syndrome. Several studies have demonstrated

*Table 1*  
Results of BRS in examined patients groups

Patients groups	BRS (ms/mmHg) (mean ± SD)	SBP (mm Hg) (mean ± SD)	DBP (mm Hg) (mean ± SD)	CI (ms) (mean ± SD)
DMN1	3,1 ± 1,1	119 ± 17	71 ± 10	775 ± 114
DMN2	4,7 ± 1,2*	122 ± 13	71 ± 13	788 ± 69
DMH1	5,1 ± 1,8	140 ± 26	70 ± 14	946 ± 146
DMH2	7,2 ± 2,3*	135 ± 18	68 ± 11	947 ± 170
EH	4,7 ± 1,8	156 ± 12†	98 ± 7 †	759 ± 159
N	7,8 ± 3,8†	121 ± 10	75 ± 8	789 ± 115
EHT1	4,9 ± 2,7	129 ± 9	85 ± 7	750 ± 93
EHT2	8,2 ± 3,4†	128 ± 8	82 ± 9	789 ± 60

DMN1, DMN2, normotensive diabetics before(1) and after(2) walking training; DMH1, DMH2, diabetics with hypertension before(1) and after(2) walking training; EH, hypertensives without therapy; N, normotensive patients; EHT1, hypertensive patients with monotherapy; EHT2, hypertensive patients with combined therapy.

\* statistically significant at  $p < 0,05$  against to DMN1 a DMH1; † statistically significant at  $p < 0,05$  against to EH, EHT1; ‡ statistically significant at  $p < 0,05$  against to all groups



*Fig. 1*

Baroreflex sensitivity in patients with diabetes mellitus type 2 (DM) with hypertension (DMH) and without hypertension (DMN), essential hypertension (EH) and normotensive subjects (N).

that depressed BRS and HRV are strong independent risk factors for sudden cardiac death in patients after myocardial infarction (8,9) and the authors have later demonstrated a favourable impact of exercise on BRS and improvement of patients' prognosis (10). Moreover, in diabetic patients decreased BRS and HRV can be considered to be an early sign of cardiovascular autonomic neuropathy (CAN) accounting for an approximately five fold increase in mortality and some studies have suggested that exercise can improve diabetic cardiovascular autonomic dysfunction (11-14). One of the main therapeutic objectives in patients with diabetes type 2 is to decrease both IR and increased sympathetic tone represented by low value of baroreflex sensitivity. Physical activity is one of the non-pharmacological therapeutic means that increase insulin sensitivity (15) and BRS. In some studies the authors found out that ACE inhibitors are able to influence not even blood pressure, but insulin sensitivity and BRS (16, 17).

We conclude that the walking training program increased significantly BRS in patients with type 2 diabetes mellitus both with and without hypertension. Comparing this non-pharmacological treatment to pharmacotherapy of hypertension, we found out that the value of BRS in normotensives (N) corresponds with BRS value in the diabetics with hypertension after training (DMH<sub>2</sub>) and hypertensives with combined medication (EHT<sub>2</sub>).

The results show the beneficial role of regular physical activity on impairment of autonomic nervous system in patients with diabetes mellitus type 2.

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## BAROREFLEXNÍ SENZITIVITA U PACIENTŮ S DIABETEM 2. TYPU A ESENCIÁLNÍ HYPERTENZÍ: VLIV KOMBINOVANÉ LÉČBY

### Souhrn

Diabetes mellitus 2. typu je v 80% doprovázen esenciální hypertenzí. Tato kombinace je spolu s dalšími abnormalitami sdruženými v metabolickém syndromu doprovázena inzulinovou rezistencí a zvýšenou aktivitou sympatického nervového systému, což vše představuje zvýšené kardiovaskulární riziko. Snížení baroreflexní senzitivity je indikátorem zvýšené sympatické aktivity. Cílem studie bylo hodnocení vlivu farmakologické a nefarmakologické léčby na baroreflexní senzitivitu srdeční frekvence u pacientů s diabetem 2. typu a esenciální hypertenzí. Vyšetřili jsme celkem 13 pacientů s diabetem 2. typu (podskupiny s hypertenzí a bez hypertenze), 41 pacientů s esenciální hypertenzí (podskupiny bez léčby, s léčbou monoterapií a s léčbou kombinací Ca-blokátorů a ACE inhibitorů) a kontrolní skupinu 11 zdravých osob. U pacientů s diabetem 2. typu (jak u skupiny s hypertenzí, ak bez hypertenze) došlo k signifikantnímu zvýšení BRS po 12 týdnech tréninku chůzí. Hodnoty BRS u hypertoniků byly signifikantně vyšší u skupiny léčené kombinací ACE inhibitoru a Ca-blokátoru, stejně jako hodnota BRS u jedinců kontrolního souboru. Hodnoty BRS skupiny hypertoniků s kombinací terapií, normotoniků a diabetiků s hypertenzí po 12-týdenním tréninku chůzí byly přitom srovnatelné. Výsledky tak vedou k závěru, že jak nefarmakologický přístup (fyzická aktivita), tak kombinace antihypertenziv u pacientů s hypertenzí a diabetem může příznivě ovlivnit BRS u těchto rizikových pacientů.

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