Exercise Training Improves Baroreflex Sensitivity in Type 2 Diabetes

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Type 2 diabetes is a strong risk factor for coronary heart disease and sudden cardiac death. It is associated with reduced baroreflex sensitivity (BRS) and heart rate variability (HRV), which are indicators of increased risk for mortality and morbidity in various patient populations. This study was designed to assess the effects of exercise training on BRS, HRV, and hemodynamics in patients with type 2 diabetes. Subjects (50 men, mean age 53.3 ± 5.1 years) with type 2 diabetes were randomized into either a control group, in which they received conventional treatment only, or an exercise group, in which they received conventional treatment together with heart rate–controlled endurance training twice a week and supervised muscle strength training twice a week for 12 months. Measurements taken at baseline and follow-up included Vo_{2max}, standard time and frequency domain measures of HRV during 24-h recording, and BRS by the phenylephrine method. Cardiac index, systemic vascular resistance index, stroke index, and pulse wave velocity were measured by whole-body impedance cardiography. Significant improvements in Vo_{2max} (exercise group: +2.3 ml · kg^{-1} · min^{-1}; $P < 0.005$ vs. control group), muscle strength, and glycemic control (exercise group: HbA_{1c} −0.9%; $P < 0.001$ vs. control group) were observed in the exercise group. BRS increased in the exercise group, from 6.8 to 8.6 ms/mmHg, and decreased in the control group, from 7.5 to 6.4 ms/mmHg (95% CI for the difference between 0.05 and 4.36 ms/mmHg; $P < 0.05$). No significant changes in the time or frequency domain measures of HRV or in systemic hemodynamics were observed. We concluded that exercise training improves BRS sensitivity in type 2 diabetes subjects in addition to increasing the exercise capacity and muscle strength and improving glucose control. These beneficial effects in reflectory autonomic regulation and glucose control caused by exercise may be associated with improved prognosis of type 2 diabetes patients. *Diabetes* 52: 1837–1842, 2003

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BRS, baroreflex sensitivity; ECG, electrocardiogram; ECW, extracellular water; HF, high frequency; HRV, heart rate variability; ICG, impedance cardiography; LF, low frequency; PWV, pulse wave velocity; SDNN, standard deviation of R-R intervals; SVRI, systemic vascular resistance index.

Nearly half of diabetic patients have diabetic autonomic neuropathy; when it is present, 5-year mortality is substantially increased (1). Both heart rate variability (HRV) and baroreflex sensitivity (BRS), describing tonic and reflectory cardiovascular neural regulation, respectively, are reduced in type 2 diabetes subjects compared with healthy counterparts with no evidence of glucose intolerance (2,3). Low HRV is associated with an increased risk of adverse cardiovascular events in the general population with no known cardiac disease (4), and both reduced HRV and BRS indicate an increased risk of mortality in patients with ischemic heart disease (5,6). In addition, acute ischemia decreases BRS in a number of patients, which may indicate a poorer outcome after myocardial infarction (7). It is well established that type 2 diabetes patients with poor glycemic control are at higher risk for cardiac death than patients with good control (8). Altered autonomic regulation has been proposed as one of the factors predisposing these patients to adverse cardiac events (9). To our knowledge, there have been no studies assessing the effects of any intervention on cardiovascular autonomic function in type 2 diabetes. Because exercise training has been suggested to improve cardiac autonomic regulation in other populations (10), this study was designed to assess whether combined endurance and muscle strength training improves BRS and HRV in asymptomatic patients with type 2 diabetes. Our aim was also to elucidate the potential mechanisms by which physical training might influence the cardiovascular autonomic regulation by assessing the effects of training on glycemic control, cardiovascular performance, and systemic vascular resistance.

RESEARCH DESIGN AND METHODS

Protocol. The study was a randomized, controlled trial with 50 men recruited through a newspaper advertisement. The subjects had been diagnosed with type 2 diabetes within three years of the trial. Of the 50 patients, 14 had diet-controlled diabetes and 36 were treated with oral hypoglycemic drugs; none was being treated with insulin. Hypertension was present in 26 patients, and none had clinical neuropathy or retinopathy. The number of smokers in the control and exercise groups was similar (11 and 12, respectively).

After a detailed medical examination and BRS measurements, the subjects were randomized according to BRS index and smoking status to either a control group, in which they received conventional treatment of type 2 diabetes only, or an exercise group, in which they received conventional treatment, were required to jog or walk twice a week at a heart rate level corresponding to 65–75% of the maximal oxygen consumption (Vo_{2max}) measured at baseline, and underwent muscle strength training twice a week at a predefined intensity. Subjects with a BRS index ≤7 and >7, and smokers and nonsmokers were consecutively randomized into either study arm to avoid significant differences in the main outcome measure at baseline and a possible weaker response to exercise in BRS for smokers. The resistance

training program was progressive and performed at stations, with every session including eight exercises for large muscle groups from the trunk and upper and lower extremities. Resistance for each exercise station was assessed by repeated maximum tests, and three sets of 10–12 repetitions at 70–80% maximum voluntary contraction were performed. Exercises in the training program were changed every 2 months. One endurance session per week was supervised, and all sessions were heart rate and intensity controlled (Polar Smart Edge; Polar Electro Oy, Kempele, Finland) and recorded in a diary. The minimum duration of a session was 30 min at the target heart rate or intensity, and the intervention lasted for 12 months. The study was approved by the Ethics Committee of the Tampere University Hospital, and all subjects gave a written informed consent.

Measurements. Body height (cm) and weight (kg) were measured by standard methods. Resting heart rate was measured from a 12-lead electrocardiogram (ECG) after 10 min of supine rest in a quiet room. Fasting 12-h blood samples were taken from an antecubital vein 1 week before training began and 48 h after the last training session. Blood glucose was assessed by the glucose dehydrogenase method and HbA_{1c} was assessed by the immunoturbidimetric method (Roche, Basel, Switzerland). Cobas Mira Plus and Cobas Integra automatic analyzers were used for the analyses. Trunk muscle endurance was measured by maximum number of repetitions in a sit-up test. The maximum isometric strength of leg extensors was measured with a leg press dynamometer with a knee angle of 90° (Tamtron, Tampere, Finland).

Oxygen consumption. All subjects performed a maximal treadmill exercise test according to a standard protocol. Rest and stress ECGs were recorded by the modified Mason-Likar 12-lead system (Marquette Case 12; Marquette Electronics, Madison, WI) and $V_{O_{2max}}$ was measured using a respiratory gas analyzer (Sensormedics 2900Z; Sensormedics BV, Bilthoven, the Netherlands).

Baroreflex sensitivity and heart rate variability. BRS was assessed by the phenylephrine method, as previously described (11). BRS was determined from the R-R interval change in relation to change in systolic blood pressure [RRI(i + 1) versus SBP(i) ms/mmHg] and was calculated offline using commercial software (Medikro Cafts; Medikro Oy, Kuopio, Finland). BRS measurements are expressed as the mean of three recordings. The subjects underwent a 24-h QRS interval recording using a validated recorder with 1-ms timing accuracy (QRS Recorder; Polar Electro Oy) on a normal working day, and the recordings were transformed and analyzed using special software for HRV analysis, as previously described (Heart Signal Co., Kempele, Finland) (11). The standard deviation of all R-R intervals (SDNN) and the number of pairs of adjacent R-R intervals differing by >50 ms in the entire recording divided by the total number of all R-R intervals were used as time domain measures of HRV (12). An autoregressive model was used for the frequency domain variables of the HRV: high-frequency (HF) power (0.15–0.4 Hz), low-frequency (LF) power (0.04–0.15 Hz), and very-low-frequency power (0.005–0.04 Hz). Average 24-h values and SDs were calculated, and corresponding variables were determined during sleep.

Whole-body impedance cardiography. Impedance cardiography (ICG) measurements were performed at rest before BRS measurement. We used a commercially available circulation-monitoring device for impedance-derived measurements (CircMon B 202; JR Medical), which has been described in detail elsewhere (13). The cardiac index (milliliters per meter squared), stroke index (milliliters per meter squared), pulse wave velocity (PWV; meters per second), systemic vascular resistance index (SVRI; $dyn*s \cdot cm^{-5} \cdot m^{-2}$), and extracellular water (ECW) were determined. The arterial PWV was measured between the aortic arch and the popliteal artery using the time delay between the beginnings of the sharp upstroke of simultaneously recorded whole-body impedance cardiogram and calf impedance plethysmogram. The distance between the aortic arch and the knee joint was estimated from the patient's height by using the ratio of height divided by 1.61. Recordings were made with voltage-sensing channels of the CircMon monitor and automatically analyzed by the same device.

Statistical methods. Baseline characteristics of the study groups are presented as means ± SD. To detect a clinically significant effect of exercise training on BRS (an increase of at least 4 ms/mmHg and SE of the estimate of 4 ms/mmHg), with 80% power and at the 5% significance level, 13 patients in both study arms should complete the study. Changes in study variables were assessed by ANCOVA with age and baseline values as covariates. Because the HRV indexes were skewed, a natural log transformation was used in all analyses, but the results are presented as crude.

RESULTS

In all, 49 study subjects completed the 52-week intervention successfully; their baseline characteristics are presented in Table 1. One subject from the exercise group withdrew from the study because of lack of time for training. Significant changes in medication were not observed between the study groups. The exercise group met the requirements for a minimum duration and intensity of training sessions. Table 2 summarizes the exercise data and the ergospirometry results in the study groups. The $V_{O_{2max}}$ improved significantly in the exercise compared to the control group (+9.0 vs. −1.6%), and all muscle strength parameters were substantially improved in the exercise group (Table 2). HbA_{1c} decreased significantly in the exercise group and increased in the control group, and systolic blood pressure decreased in the exercise group. The changes in stroke index and SVRI were not significant (Table 2).

TABLE 1
Baseline characteristics of the study groups

	Control	Exercise
n	25	24
Age (years)	54.0 ± 5.0	53.6 ± 6.2
Height (cm)	180 ± 6	179 ± 6
Weight (kg)	94.1 ± 12.8	90.2 ± 9.5
BMI (kg/m^2)	29.8 ± 3.6	29.3 ± 3.7

Data are n or means ± SD.

BRS and HRV data for the 24-h period are summarized in Table 3. Resting HR decreased significantly in the exercise group. The BRS increased on average by 2 ms/mmHg in the exercise group, and decreased by 1 ms/mmHg in the control group during the intervention ($P = 0.045$). Although a trend toward higher values in SDNN, HF, and LF powers were observed in the exercise group for the sleep values compared with those of the control group, these changes did not reach statistical significance. Likewise, the 24-h time and frequency domain measures of HRV did not change in the study groups (Table 3).

The change in BRS during the intervention had a significant inverse correlation with the change in HbA_{1c} ($r = -0.29$; $P < 0.05$). However, changes in resting systolic blood pressure ($r = -0.116$, $P = 0.44$), resting heart rate ($r = -0.006$, $P = 0.97$), and cardiac index ($r = 0.056$, $P = 0.70$) did not correlate significantly with improved BRS. The change in performance in the sit-up test showed a borderline significant correlation with BRS change ($r = 0.292$, $P = 0.075$). In addition, the improved HbA_{1c} correlated significantly with the change in muscle power (sit-up, $r = -0.464$, $P = 0.002$) and $V_{O_{2max}}$ ($r = -0.311$, $P = 0.030$) during the intervention.

DISCUSSION

The main finding of this study was that exercise training improves the cardiovascular autonomic regulation, in addition to having other beneficial effects on cardiovascular risk variables in type 2 diabetes. BRS improved in the type 2 diabetes subjects randomized to exercise training, whereas it had a tendency to decrease in the control group, even during a relatively short follow-up period. These observations give new insight into the mechanisms by which physical training can reduce the risk for cardiac events in diabetes.

Physical exercise and autonomic function. Several cross-sectional studies have shown that measures of autonomic function, such as HRV and BRS, are better in trained subjects than in their sedentary counterparts.

TABLE 2
Exercise, clinical, blood glucose, and hemodynamic data on the study groups

	Control	Exercise	*P*
n	25	24	—
Vo_{2max} (ml · kg^{-1} · min^{-1})			
Before	32.6 ± 6.4	31.9 ± 5.1	—
After	31.8 ± 6.6	33.8 ± 5.5	—
Net difference	—	2.9	—
95% CI	—	1.0–4.8	0.003
BMI (kg/m^2)			
Before	29.8 ± 3.7	29.3 ± 3.8	—
After	29.8 ± 3.7	28.9 ± 3.8	—
Net difference	—	−0.4	—
95% CI	—	−0.9 to 0.1	0.098
Sit-up			
Before	14.6 ± 9.6	12.7 ± 7.3	—
After	13.1 ± 9.2	20.8 ± 6.8	—
Net difference	—	7.7	—
95% CI	—	4.9–10.5	0.000
Leg ext.			
Before	217 ± 46	202 ± 38	—
After	255 ± 54	293 ± 73	—
Net difference	—	53	—
95% CI	—	23–82	0.001
HbA_{1c} (%)			
Before	8.0 ± 1.3	8.2 ± 2.1	—
After	8.3 ± 1.4	7.6 ± 1.4	—
Net difference	—	−1.0	—
95% CI	—	−1.6 to −0.3	0.006
Systolic blood pressure (mmHg)			
Before	145 ± 14	142 ± 17	—
After	144 ± 14	138 ± 16	—
Net difference	—	−5.7	—
95% CI	—	−11.1 to 0.2	0.041
Stroke index (ml/m^2)			
Before	44.2 ± 7.8	40.8 ± 7.9	—
After	43.0 ± 7.2	42.7 ± 7.5	—
Net difference	—	−3.2	—
95% CI	—	−3.5 to 2.8	0.84
Cardiac index (ml · min^{-1} · m^{-2})			
Before	2.9 ± 0.6	2.8 ± 0.5	—
After	3.0 ± 0.4	2.7 ± 0.5	—
Net difference	—	−0.2	—
95% CI	—	−0.5 to 0.1	0.083
SVRI (dyn*s · cm^{-5} · m^{-2})			
Before	2,598 ± 516	2,638 ± 517	—
After	2,541 ± 691	2,807 ± 673	—
Net difference	—	247	—
95% CI	—	−136 to 630	0.201
PWV (m/s)			
Before	13.8 ± 2.7	14.2 ± 2.6	—
After	15.0 ± 3.7	14.8 ± 2.3	—
Net difference	—	−0.5	—
95% CI	—	−2.0 to 0.9	0.448
ECW			
Before	0.97 ± 0.08	0.95 ± 0.06	—
After	1.01 ± 0.06	1.04 ± 0.08	—
Net difference	—	0.04	—
95% CI	—	0.02–0.07	0.001

Data are *n* or means ± SD. Before/After, before and after intervention; net difference, difference of change compared with the control group (ANCOVA); 95% CI = 95% CI for the net difference of change between study groups; sit-up, sit-up test, number of repetitions; leg ext., maximum power produced by leg extensors.

TABLE 3
Baroreflex sensitivity, resting heart rate, and heart rate variability before and after 12-month intervention

	Control	Exercise	*P*
n	25	24	—
Resting heart rate (bpm)			
Before	66.3 ± 9	68.8 ± 10	—
After	68.1 ± 9	65.7 ± 8	—
Net difference	—	4	—
95% CI	—	−7.8 to 0.3	0.033
BRS (ms/mmHg)			
Before	7.5 ± 3.8	6.8 ± 2.9	—
After	6.4 ± 3.5	8.6 ± 4.6	—
Net difference	—	2.2	—
95% CI	—	0.05–4.4	0.045
SDNN (ms)			
Before	84 ± 23	74 ± 20	—
After	84 ± 25	79 ± 17	—
Net difference	—	2.2	—
95% CI	—	−8 to 12	0.66
pNN50 (%)			
Before	8.9 ± 9.5	5.7 ± 6.1	—
After	9.6 ± 10.4	7.6 ± 6.5	—
Net difference	—	1.2	—
95% CI	—	−1.6 to 4.0	0.39
HF (ms^2)			
Before	266 ± 268	207 ± 264	—
After	307 ± 296	271 ± 313	—
Net difference	—	28	—
95% CI	—	−69 to 125	0.56
LF (ms^2)			
Before	731 ± 488	578 ± 337	—
After	785 ± 563	666 ± 373	—
Net difference	—	64	—
95% CI	—	−100 to 229	0.43
VLF (ms^2)			
Before	2,071 ± 1,280	1,607 ± 674	—
After	2,171 ± 1,300	1,896 ± 933	—
Net difference	—	155	—
95% CI	—	−297 to 608	0.49
HF/LF			
Before	0.33 ± 0.22	0.32 ± 0.16	—
After	0.37 ± 0.29	0.39 ± 0.24	—
Net difference	—	.003	—
95% CI	—	−0.12 to 0.059	0.51

Data are *n* or means ± SD. pNN50, number of pairs of adjacent R-R intervals differing by >50 ms in the entire recording divided by the total number of all R-R intervals; HF, high-frequency power, 24-h mean value; LF, low-frequency power, 24-h mean value; VLF, very-low-frequency power, 24-h mean value; HF/LF, high frequency/low frequency ratio; net difference, difference of change compared with the control group (ANCOVA); 95% CI = 95% CI for the net difference of change between study groups.

There are relatively few controlled longitudinal studies aiming to assess the exercise training on cardiovascular autonomic function (14,15). Most of these studies have used measurements of various components of HRV as a method of assessing the autonomic regulation (16,17), but only a few studies have focused on the effects of physical exercise on cardiovascular baroreflex regulation (10,18). In patients with a recent uncomplicated myocardial infarction, significant improvement in BRS has been observed (14). This improvement occurred within the study groups combined, but not between the study groups, suggesting that the slight improvement in BRS was a spontaneous

phenomenon after myocardial infarction. In a recent study, BRS was improved even after only 2 weeks of exercise training among patients with uncomplicated coronary artery disease when measured by an ambulatory ECG method from time windows of three consecutive beats (18). In agreement with that study, we observed that physical exercise improved the BRS in type 2 diabetes subjects without clinical evidence of ischemic heart disease.

The change in BRS correlated significantly with the change in HbA_{1c} during the intervention; a borderline significance for the change in muscle power was also observed. Change in muscle power also correlated significantly with the improvement of glycemic control, indicating that increased muscle mass and performance improve the glucose balance. Changes in $V_{O_{2max}}$, systolic blood pressure, heart rate, and cardiac function did not correlate with the improvement in BRS, suggesting that improved autonomic function caused by exercise is related more closely to improved glucose control than to changes in central hemodynamics.

Our original hypothesis was that exercise training might improve the autonomic function by decreasing the systemic vascular stiffness and resistance. Arteries of type 2 diabetes patients are characterized by increased amounts of connective tissue (e.g., collagen), glycoproteins, and calcium in the medial layer of the arterial wall (19), which results in reduction of elasticity and is reflected in higher PWV. However, these organic changes do not seem to be reversed by exercise, because we observed an increase in PWV in both the exercise and control group, indicating stiffening of the large arteries during the study. Type 2 diabetes is also characterized by impaired nitric oxide–mediated vasodilation (20–22), and HbA_{1c} is inversely correlated with forearm blood flow and impaired endothelium-dependent vasodilation in type 2 diabetes (21). Exercise training has been shown to improve endothelial function, for example, in the main coronary arteries (22). We observed that increased muscle and cardiovascular performance was associated with better glucose balance, which in turn was the only factor associated with improved BRS. Therefore, it seems plausible that the mechanisms by which exercise training increases the BRS might include improved endothelial function and enhanced endoneurial blood flow (23,24). Endothelial function was not measured directly in the present population, which is a limitation of the study design. Therefore, more experimental work is needed to confirm this hypothesis. Our results suggest, however, that exercise training is not powerful enough to alter the unfavorable structural changes in large arteries.

Improvement of BRS by means of exercise may also be related to repeated activation of the baroreflex and cardiovascular end-organ responses. During physical exercise, rapid changes in systemic vascular resistance and blood pressure will always activate the whole regulatory system. By doing this, systemic physical training will also "train" the baroreflex to respond more appropriately and effectively to blood pressure changes. The importance of this training effect in baroreflex regulation of the circulatory system is also supported by the results of two different studies. Reybrouck et al. (25) recently showed that abnormal autonomic reflex activity of neurocardiogenic syncope can be treated by a program of continued tilt training without administration of drugs; that is, by training the baroreflex. Decrease and slow restoration of BRS has also been observed in association with prolonged spaceflight (26). Absence of orthostatic stress during spaceflight probably leads to desensitization of the baroreceptor and weakening of the vascular responses. After the flight, the orthostatic load reactivates the regulatory system, resulting in gradual improvement of the reflex. Together these data support the view that prolonged low-level activity decreases the baroreflex and vice versa, and that endothelial function may be an underlying factor mediating the training effect on the baroreflex arch (22).

Previous studies have shown that endurance-trained subjects have significantly higher HRV than sedentary subjects (16,17). In those studies, HRV was compared between young athletes and their sedentary age-matched controls. However, it is not known whether HRV can be improved by exercise in type 2 diabetes. Only a few prospective studies have assessed the effects of exercise training on HRV (15–17), and in agreement with the present study, those studies have found that HRV remained unchanged. These studies were limited by small sample size, short duration of intervention, or lack of randomization, and thus the results cannot be generalized to diabetic patients. The present results confirm our previous finding: even 12 months of exercise training is not long enough to improve HRV in type 2 diabetic patients (11). However, the decrease in heart rate suggests that vagal tone was probably increased after training. Furthermore, a nonsignificant trend toward increasing values of HRV was observed in the exercise group, suggesting that a longer training period could improve HRV in type 2 diabetes.

Effects of physical exercise on other risk variables in type 2 diabetes. Endurance training together with resistance training is effective in lowering blood glucose, as was observed in this study (27). The decline of HbA_{1c} was slightly lower than that achieved in the U.K. Prospective Diabetes Study by intensive medical treatment, but the risk for micro- and macrovascular complications is reduced and the patient prognosis improved by the nonpharmacological approach (28,29). Glucose balance in the intervention group was almost brought to a good level in type 2 diabetic patients (i.e., one at which the risk of complications is low), whereas conventional treatment resulted in worsening control of diabetes. The BMI decreased slightly, but not significantly, in the exercise group. However, muscle strength and ECW were substantially improved, suggesting that the muscle mass was increased and body fat mass reduced. This change together with improved insulin sensitivity was most likely responsible for the favorable changes in blood glucose in the present study (30).

Implications. Low BRS has been shown to be a risk marker of mortality in various populations (6). In particular, impaired BRS is related to an increased risk for sudden arrhythmic death both in experimental models (10) and in clinical studies (31–33). One experimental study has suggested that exercise training has antifibrillatory effects by impacting the cardiovascular autonomic function (10). All

these studies support the concept that the baroreflex regulation of the cardiovascular function plays an important role in protecting individuals from sudden arrhythmic death caused by an acute ischemic event.

Type 2 diabetes patients without previous myocardial infarction have a mortality risk from coronary artery disease comparable to that of myocardial infarction patients without diabetes (34). Epidemiological data suggest that diabetic patients are at a particularly high risk of experiencing sudden death as an initial manifestation of their heart disease (35). The present data show that regular physical training significantly improves the baroreflex modulation of cardiovascular function. This beneficial effect on autonomic regulation may have clinical importance in preventing sudden cardiac death in type 2 diabetes subjects. The adherence to the exercise program of the relatively inactive and obese men was good in the present population, suggesting that guided exercise protocols may have clinical importance in the prophylactic treatment of type 2 diabetes subjects. More epidemiological data in a large sample of type 2 diabetes patients are needed to confirm that these beneficial effects observed in the metabolic and autonomic variables after the training period have favorable effects on the clinical outcome of the patients.

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