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Cardiovascular autonomic neuropathy in patients with type 2 diabetes

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ABSTRACT

Aims/Introduction: Heart rate recovery (HRR) after exercise is considered to be a new index of autonomic dysfunction associated with cardiovascular disease and mortality. The present study aimed to investigate the risk factors of HRR and the effects of exercise on the abnormal HRR in type 2 diabetes.

Materials and Methods: A total of 123 type 2 diabetes patients were recruited, and the oral glucose tolerance test and exercise test were carried out to analyze the risk factors associated with abnormal HRR. Among these patients, 42 patients with abnormal HRR were further randomized to either the conventional therapy group (CT group; $n = 20$) or the intensive therapy group (IT group; $n = 22$). The CT group patients underwent metformin and diet control, whereas the IT group additionally underwent a combined moderate intensity aerobic and resistance training three times per week for 12 weeks. The results of blood sample analysis and HRR were recorded before and after the training.

Results: Abnormal HRR was related to fasting blood glucose, glycosylated hemoglobin, low-density lipoprotein cholesterol, and resting and maximum heart rates ($P < 0.05$ for both). After training, the IT group had significantly lower levels of fasting blood glucose, glycosylated hemoglobin and resting heart rate than the CT group (all $P < 0.01$ or $P < 0.005$). Significant improvement in HRR and metabolic equivalents was observed in the IT group compared with the CT group ($P < 0.05$).

Conclusions: These data suggested that combined aerobic and resistance training improved cardiac autonomic dysfunction as measured by HRR in type 2 diabetes patients. This might be due to better improvement of glycemic control, resting heart rate and physical fitness.

INTRODUCTION

Diabetes is often accompanied by cardiovascular autonomic neuropathy (CAN), which has been shown to be related to persistent tachycardia, severe orthostatic hypotension, exercise intolerance, silent myocardial infarction and even increased incidence of ischemic stroke[1]. The prevalence of CAN varies between 20–73% in patients with type 2 diabetes mellitus[2,3]. CAN presentation is not limited by age or the type of diabetes, and can occur before the diagnosis of diabetes mellitus[4]. This great diversity in CAN prevalence is attributed to the different diagnosis criteria of CAN and significant differences in the study groups, especially related to CAN risk factors (such as age, sex and diabetes mellitus duration, among others). However, with even such a high prevalence and serious impact for cardiovascular events, it is widely ignored by clinicians, and lacks specific treatment to prevent or slow the progression.

In recent years, heart rate recovery (HRR) after the treadmill exercise test has been widely used in CAN, which measures the 24-h heart rate variability (HRV)[5]. HRR is defined as the reduction in heart rate from the peak of strenuous exercise to 1 min after termination of exercise. It is a new index clinically significant in evaluating cardiac autonomic system, especially the parasympathetic nervous function after exercise[6]. Panzer *et al.*[7] reported that abnormal HRR was present among 42% of patients with impaired fasting glucose and 50% with diabetes. HRR is considered as a strong predictor of increased cardiovascular disease and overall mortality, independently of other cardiac risk factors[8,9]. Several studies have also shown that abnormal HRR is a predictor of poor prognosis in patients with

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heart failure[10,11]. In addition, abnormal HRR is associated with elevated resting heart rate and fasting glucose[12,13]. However, the risk factors and the strategies to improve CAN in patients with diabetes still remain unclear.

In studies to date, exercise training plays a critical role in the treatment and management of type 2 diabetes. Regular exercise can benefit glycolipid metabolism, blood pressure, weight control and insulin resistance, thereby decreasing diabetes-associated complications. Specifically, exercise training has been proven to enhance resting parasympathetic tone and lower sympathetic tone in both humans and animals[14,15]. Previous studies have also shown that exercise can improve cardiac autonomic neuropathy function in healthy individuals[16,17], post-myocardial infarction patients[18] and patients with chronic heart failure[19]. Therefore, we speculate that exercise training might also improve abnormal HRR in patients with type 2 diabetes. The aim of the present study was twofold: (i) to investigate the risk factors of impaired autonomic function in patients with type 2 diabetes; and (ii) to evaluate the effect of exercise intervention on autonomic dysfunction as measured by HRR and its risk factors in patients with type 2 diabetes.

MATERIALS AND METHODS

Participants

Experimental data including the results of the oral glucose tolerance test and exercise test of all patients with type 2 diabetes were collected at the Department of Cardiovascular Rehabilitation, Xiangya Hospital of Central South University, Changsha, Hunan, China. From March 2012 to July 2014, 123 type 2 diabetes patients (age 21–73 years) with a duration of less than 2 years were enrolled for the purpose of investigating risk factors of abnormal HRR. A total of 42 type 2 diabetes patients with abnormal HRR selected from the 123 outpatients were randomized to two groups: (i) the conventional therapy group (CT group; $n = 20$); and (ii) the intensive therapy group (IT group; $n = 22$). Patients in the CT group underwent metformin and diet control, whereas patients in the IT group carried out 12-week aerobic and resistance exercises training besides the conventional therapy. Type 2 diabetes was diagnosed according to the World Health Organization/American Diabetes Association 2007 criteria. Blood kidney function analysis and urinalysis ruled out proteinuria, urine ketone and kidney damage. The results of chest X-ray and echocardiogram were normal. Finally, the patients were required to have a normal funduscopic examination carried out by a certified neurologist to rule out diabetic retinopathy before the test. These aforementioned variables were determined as control parameters to ensure the safety of exercise. Other exclusion criteria included a medical history with alpha- or beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors or other drugs with a direct influence on heart rate. Patients with sinus syndrome, atrial fibrillation, severe arrhythmias, severe hypertension and severe joint disease were also excluded from the study. Written informed consent was obtained from all the participants. Procedures were approved by the institutional review board at the Central South University of China, and conformed to the standards set by the Declaration of Helsinki.

Exercise test

Cardiopulmonary Exercise Testing (CPET) was completed by all participants before the intervention in a room with 50–55% humidity and a temperature of 24–25°C. Using an incremental and symptom-limited protocol, patients tried their best on a cycle ergometer test (SCHILLER CS-200, Baar, Switzerland). Both electrocardiogram and heart rate monitoring were used during the test. The maximum oxygen consumption (VO_{2max}) was defined as the highest value of oxygen consumption measured during the exercise period, and was recorded to determine cardiorespiratory capacity and exercise intensity for each of the participants. Resting heart rate, maximum heart rate, exercise time, HRR and maximum metabolic equivalents (Mets) were also recorded during the test. If any of the following symptoms occurred, such as chest pain, fatigue, dyspnea, leg pain, decrease in systolic blood pressure and electrocardiographic evidence of ischemia or serious arrhythmia, the test was terminated immediately. Participants were asked to self report the intensity of exercise by the Borg scale of rate of perceived exertion[20] at the end of the test. Abnormal HRR was defined as the reduction of heart rate ≤18 b.p.m. from the peak heart rate to 1 min after the termination of exercise[21]. A HRR value ≤18 b.p.m. at 1 min into the recovery phase was considered abnormal on the basis of previously published work.

Exercise protocol

The IT group received a combined program of supervised exercise training (at least 3 sessions) and home-based exercise. Supervised exercise training was applied at the beginning of the program at the Department of Cardiovascular Rehabilitation, Xiangya Hospital of Central South University in China. Each participant received in-person instructions on how to carry out an individualized moderate-intensity exercise program. The intervention was gradually shifted to home-based exercise, as the participants were familiar with the whole exercise procedure. The exercise therapy mainly consisted of aerobic exercise and resistance training. Aerobic exercise was carried out three times per week for a period of 12 weeks. Exercise intensity of each participant was set at 40–60% of his/her VO_{2max}. The exercise started at a low intensity of 40% VO_{2max}. As the weeks progressed, the exercise intensity was increased to 60% VO_{2max}. The aerobic exercise program generally consisted of a 10-min warm-up period, followed by 30 min of aerobic exercise, and ended with a 15-min cool-down period. The pulse palpation method was carried out to monitor heart rate[22]. The rate of perceived exertion (12–13 on the Borg scale) was also used to assist in estimating moderate exercise intensity[23]. These patients also carried out moderate-intensity (50–60% of the one repetition maximum) resistance training two to three times per week by using an elastic band (Thera-band; Hygenic Corporation,

Akron, OH, USA). One repetition maximum was roughly estimated by several Load-Repetition tests[24]. This resistance training had to avoid the Valsalva maneuver. In addition to exercise, these patients were provided with routine diet guidance and psychological counseling.

Blood sampling

A 75-g oral glucose tolerance test was carried out according to the World Health Organization/American Diabetes Association 2007 criteria. The blood samples were drawn from the antecubital vein. Plasma glucose and insulin concentrations were analyzed using the glucose-hexokinase method and a radioimmunoassay kit (Beijing North Institute, Beijing, China), respectively. Serum glycosylated hemoglobin (HbAlc%) was measured by affinity chromatography. Serum total cholesterol, low-density lipoprotein (LDL-c), high-density lipoprotein and triglyceride concentrations were determined by using a Cobas Fara robot (Roche, Basel, Switzerland). All the assays were carried out at the Department of Cardiovascular Rehabilitation, Xiangya Hospital of Central South University in China.

Statistical analysis

Analyses of the data were carried out using SPSS 19.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and were compared with independent samples *t*-test to determine the clinical characteristics of the participants. The relationship between abnormal HRR and cardiovascular risk profile levels was determined using Pearson's correlation coefficients. Binary logistic regression analysis was used to determine the possible risk factors, which are independently associated with abnormal HRR. Statistical differences for exercise testing characteristics and blood sampling after exercise training between the CT group and the IT group were also analyzed using independent samples *t*-test. $P < 0.05$ was considered to be statistically significant.

RESULTS

General characteristics of both the abnormal and normal HRR groups of 123 patients are summarized in Table 1. A total of 70 patients (35 men and 35 women, mean age 53.60 ± 10.46 years) with abnormal HRR time were reported (56.9%). In the control group, the number of patients with normal HRR time was 53 (43.1%; 28 men and 25 women, mean age 51.92 ± 8.38 years). The difference in age and sex between the patients was not statistically significant ($P > 0.05$). No significant correlation ($P > 0.05$) was observed between triglyceride, total cholesterol and LDL levels. In univariate analysis, the abnormal HRR time was significantly associated with fasting glucose (8.01 ± 2.39 vs 7.04 ± 1.69, $P < 0.01$) and HbA1c (7.01 ± 1.62 vs 6.50 ± 0.86, $P < 0.01$), whereas 2-h postpran-

Table 1 | Clinical characteristics of participants according to heart rate recovery

	Heart rate recovery		*P*-value
	Abnormal (n = 70)	Normal (n = 53)	
Age (years)	53.60 ± 10.46	51.92 ± 8.38	0.341
Male/female (n)	35/35 (total 70)	28/25 (total 53)	
Ever smoker	19	18	
Ever alcohol user	15	16	
DD (month)	14.6 ± 2.3	12.8 ± 1.9	0.611
SBP (mmHg)	135 ± 18.2	133.7 ± 17.1	0.714
DBP (mmHg)	82.5 ± 12.4	84.6 ± 11.5	0.605
TG (mmol/L)	2.60 ± 2.31	2.23 ± 1.33	0.293
TC (mmol/L)	5.32 ± 1.47	5.09 ± 1.21	0.355
LDL-c (mmol/L)	3.13 ± 1.10	2.97 ± 0.92	0.426
Fasting glucose (mmol/L)	8.01 ± 2.39	7.04 ± 1.69	0.009
2-h postprandial glucose (mmol/L)	12.80 ± 4.42	11.43 ± 3.90	0.078
Fasting insulin (μU/mL)	10.27 ± 6.60	10.15 ± 6.91	0.926
2-h postprandial insulin (μU/mL)	70.58 ± 77.03	65.07 ± 60.70	0.669
Glycosylated hemoglobin (%)	7.01 ± 1.62	6.50 ± 0.86	0.042
Lactate (mmol/L)	2.17 ± 0.65	2.13 ± 0.56	0.731
Resting heart rate (b.p.m.)	86.13 ± 9.85	79.58 ± 9.87	0.000
Max heart rate (b.p.m.)	137.44 ± 15.94	141.85 ± 15.14	0.124
Max Mets (mets)	7.41 ± 2.26	9.14 ± 12.34	0.252
Exercise time (min)	6.99 ± 1.62	7.36 ± 1.60	0.213
HRR (b.p.m.)	11.29 ± 4.52	26.87 ± 7.53	0.000

Data are presented as mean ± standard deviation. DD, diabetic duration; DBP, diastolic blood pressure; HRR, heart rate recovery; LDL-c, low-density lipoprotein cholesterol; Max Mets, maximal metabolic equivalents; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 2 | Relationships of heart rate recovery and cardiovascular risk profiles measured by Pearson's correlation coefficients in patients with type 2 diabetes

	Age	FPG	PPG	FPI	PPI	Hba1c	Lac	TG	TC	LDL-c	RHR	Max HR	Max Mets	ET
R	−0.156	−0.274	−0.249	−0.005	−0.050	−0.191	−0.118	−0.183	−0.158	−0.147	−0.275	0.277	0.021	0.186
P	0.85	0.002	0.006	0.952	0.586	0.034	0.195	0.043	0.081	0.105	0.002	0.002	0.821	0.040

n = 123. ET, exercise time; FPG, fasting glucose; FPI, fasting insulin; Hba1c, glycosylated hemoglobin; HRR, heart rate recovery; Lac, lactate; LDL-c, low-density lipoprotein cholesterol; Max HR, maximum heart rate; Max Mets, maximal metabolic equivalents; PPG, postprandial glucose (2-h); PPI, postprandial insulin (2-h); RHR, resting heart rate; TC, total cholesterol; TG, triglycerides.

Table 3 | Logistic regression model with odds ratios for the relationship between key risk factors and abnormal heart rate recovery

	OR	95% CI	*P*-value
Fasting glucose (mmol/L)	1.900	1.112–3.247	0.019
Glycosylated hemoglobin (%)	1.740	1.062–2.851	0.028
Resting heart rate (b.p.m.)	2.430	1.374–4.296	0.002
LDL-c (mmol/L)	2.325	1.157–4.672	0.018
Maximum heart rate (b.p.m.)	0.595	0.400–0.883	0.010

Continuous variables had transformed to categorical variables, and cut-off values are shown: age 6, >70 years; 5, 60–70 years; 4, 50–60 years; 3, 40–50 years; 2, 30–40 years; 1 <30 years; fasting glucose 4, >7; 3 6.5–7; 2, 6.5–6.1; 1, <6.1; postprandial glucose 4, >15; 3, 11.1–15; 2, 7.8–11.1; 1, <7.8; fasting insulin 4, >30; 3, 20–30; 2, 10–20; 1, <10; postprandial insulin 3, >100; 2, 50–100; 1, <50; glycosylated hemoglobin 4, >7; 3, 6.5–7; 2, 6.5–6.0; 1, <6; triglycerides 3, >2.2; 2, 1.5–2.2; 1, <1.5; total cholesterol 3, >6; 2, 4.5–6; 1, <4.5; low-density lipoprotein cholesterol (LDL-c) 3, >3.3; 2, 2.6–3.3; 1, <2.6; resting heart rate 1, <60; 2, 60–70; 3, 70–80; 4, 80–90; 5, 90–100; 6, >100; maximum heart rate 1, <100; 2, 100–110; 3, 110–120; 4, 120–130; 5, 130–140; 6, 140–150; 7, >150; lactate 2, >2.2; 1, <2.2; maximal metablic equivalents 3, >7; 2, 5–7; 1, <5; exercise time 5, >8; 4, 8–7; 3, 6–7; 2, 5–6; 1, <5. CI, confidence interval; OR, odds ratio.

dial glucose, fasting insulin, 2-h postprandial insulin and lactate levels did not show any significant correlation. Abnormal HRR time was also significantly associated with resting heart rate (86.13 ± 9.85 vs 79.58 ± 9.87, $P < 0.01$).

The present study also examined the correlation of CAN and cardiovascular risk profiles in all the participants. Pearson's correlation coefficients for abnormal HRR and cardiovascular risk profiles of patients with type 2 diabetes are shown in Table 2. The main finding of the present study was that HRR was significantly correlated with fasting glucose, 2-h postprandial glucose, resting heart rate, Hba1c, triglyceride and maximum heart rate ($P < 0.01$, $P < 0.05$; Table 2). In logistic regression analysis, fasting blood glucose (odds ratio [OR] 1.900, 95% confidence interval [CI] 1.112–3.247; $P = 0.019$), HbA1c (OR 1.740, 95% CI 1.062–2.851; $P = 0.028$), LDL (OR 2.325, 95% CI 1.157–4.672; $P = 0.018$), maximum heart rate (OR 0.595, 95% CI 0.400–0.883; $P = 0.010$) and resting heart rate (OR 2.430, 95% CI 1.374–4.296; $P = 0.002$) were significantly associated with abnormal HRR after adjustment for other risk factors (Tables 2 and 3).

A total of 42 patients who were assigned to the CT group and the IT group received treatment from March 2012 to July 2014. No participants missed any session during the study. There were no adverse events, such as the deterioration or serious complications of diseases, reported by the participants during the treatment process. There were no significant differences of the demographic and baseline clinical characteristics of the participants between the two groups (Table 4).

The alterations in the levels of blood glucose, insulin, HbA1c, lactate, blood lipid and exercise testing characteristics after exercise training in the participants is shown in Table 5. Fasting glucose, 2-h postprandial plasma glucose, HbA1c level and resting heart rate were all significantly reduced after treatment in both the CT group and the IT group, whereas HRR increased significantly ($P < 0.05$, $P < 0.01$, Table 5). After intensive exercise interventions, fasting glucose (5.88 ± 0.66 vs 6.35 ± 0.75, $P < 0.01$) and HbA1c level (5.64 ± 0.47 vs 6.16 ± 0.48, $P < 0.05$) were significantly lower in the IT group than that in the CT group. Compared with the CT group, Maximum Mets increased significantly after exercise in the IT group (8.88 ± 1.68 vs 6.96 ± 1.40, $P < 0.05$). Resting heart rate (77.95 ± 5.32 vs 82.20 ± 6.16, $P < 0.05$) and HRR (19.77 ± 5.08 vs 15.75 ± 6.30, $P < 0.05$) in the IT group improved significantly after exercise training.

DISCUSSION

The present study was designed to evaluate the risk factors associated with HRR and the effects of exercise training on abnormal HRR in patients with type 2 diabetes. Cardiac autonomic neuropathy could be regarded as a result of dysfunction of sympathetic activity, parasympathetic activity or a combination of both[25]. Exercise training leads to quick retreat of parasympathetic tone and subsequent sympathetic activation, whereas HRR after exercise is related to parasympathetic activation followed by sympathetic pullout. Therefore, HRR reflects a dynamic balance between the sympathetic and parasympathetic nervous system regulation of cardiovascular function. HRR can thus be used as an indicator to evaluate the autonomic dysfunction, especially under the condition of exercise load, compared with the conventional tests, such as tests of cardiovascular reflex function, heart rate variability and baroreflex sensitivity. However, little is known about the underlying mechanism of abnormal HRR induced by type 2 diabetes. The main

Table 4 | Participants' characteristics at baseline in the conventional therapy group and the intensive therapy group

Characteristic	CT group (n = 20)	IT group (n = 22)	P-value
Age (years)	53.5 ± 10.7	52.6 ± 8.1	0.658
Male/female (n)	11/9 (total 20)	12/10 (total 22)	
Ever smoker	8	7	
Ever alcohol user	7	7	
Systolic blood pressure (mmHg)	134 ± 22.2	132.7 ± 20.1	0.764
Diastolic blood pressure (mmHg)	84.9 ± 13.5	83.7 ± 10.9	0.645

Values represent means ± standard deviation. CT, conventional therapy group; IT, intensive therapy group.

Table 5 | Comparison of metabolic and exercise testing characteristics in patients before and after the exercise

Items	CT group (n = 20)		IT group (n = 22)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
FBG (mmol/L)	7.00 ± 0.50	6.35 ± 0.75*	6.91 ± 1.04	5.88 ± 0.66**‡
PBG (mmol/L)	13.03 ± 1.37	9.37 ± 0.91**	12.82 ± 3.74	8.69 ± 2.50**
FIN (μU/mL)	11.77 ± 5.63	11.34 ± 3.94	12.81 ± 10.16	8.30 ± 4.41*
PIN (μU/mL)	91.11 ± 40.33	62.01 ± 36.9**	103.39 ± 87.20	78.46 ± 62.57**
HbA1c (%)	6.91 ± 0.62	6.16 ± 0.48**	6.50 ± 0.96	5.64 ± 0.47**
TG (mmol/L)	2.65 ± 1.18	2.56 ± 0.92	2.40 ± 1.47	1.79 ± 0.98
TC (mmol/L)	4.47 ± 1.04	4.31 ± 1.05	5.50 ± 1.20	4.88 ± 1.17*
LDL-c (mmol/L)	3.22 ± 1.18	3.03 ± 0.67	3.60 ± 1.06	2.86 ± 1.08**
ET (min)	6.93 ± 1.38	6.90 ± 1.87	6.70 ± 1.43	7.20 ± 1.55
Max HR (b.p.m.)	132.7 ± 12.84	136.0 ± 20.61	142.45 ± 13.98	135.00 ± 11.17*
Max Mets (mets)	6.73 ± 1.53	6.96 ± 1.40	7.07 ± 1.86	8.88 ± 1.68**†
HRR (b.p.m.)	12.90 ± 5.71	15.75 ± 6.30*	14.00 ± 3.47	19.77 ± 5.08**†
RHR (b.p.m.)	87.90 ± 7.29	82.20 ± 6.16*	86.59 ± 11.81	77.95 ± 5.32**†

Values represent means ± standard deviation. Compared with the pre-treatment group *P < 0.05, **P < 0.01; compared with the conventional-therapy group, †P < 0.05, ‡P < 0.01. ET, exercise time; FPG, fasting glucose; FPI, fasting insulin; PPG, postprandial glucose (2-h); Hba1c, glycosylated hemoglobin; HRR, heart rate recovery; LDL-c, low-density lipoprotein cholesterol; Max HR, maximum heart rate; Max Mets, maximal metabolic equivalents; PPI, postprandial insulin (2-h); RHR, resting heart rate; TC, total cholesterol; TG, triglycerides.

findings of the current study preliminarily showed the probable risk factors of HRR and the predictable improvement in cardiac autonomic activity as measured by HRR in type 2 diabetic patients.

As abnormal HRR has an important clinical application in evaluating autonomic nerve function, the study of its risk factors is very important for both treatment and prognosis of type 2 diabetes. In the present study, we found that fasting blood glucose, HbA1c, LDL-c resting heart rate and maximum heart rate were the independent risk factors for decreased HRR. This finding is in accordance with previous studies, showing that decreased HRR was associated with fasting plasma glucose and HbA1c[26], whereas either an acute or a chronic poor glycemic control might progress into CAN[27]. The relationships among high fasting blood glucose, HbA1c and autonomic dysfunction might be explained by the negative effect of poor glycemic control. The mechanisms include microcirculation disturbance, hemorheological abnormalities and decreased synthesis of neurotrophic factors. Another risk factor of cardiovascular disease is elevated LDL. As suggested by one of the studies, autonomic nervous system injury was associated with the level of LDL-c[28]. This finding was consistent with our previous results. High resting and maximum heart rate are relative to a reduction of vagal tone and an increase of sympathetic tone. A higher resting heart rate is associated with an increased risk of cardiovascular complications and death. Several studies have confirmed that reduced HRR was associated with resting heart rate[12,13]. To our knowledge, the present study is the first documented evidence to suggest that maximum heart rate was associated with the occurrence of abnormal HRR in patients with type 2 diabetes. However, no relationship was observed between abnormal HRR and level of insulin in blood, whereas previously studies showed that elevated levels of fasting insulin might reduce vagal cardiac control through the sympatho-excitatory effects of insulin[29]. Another study has shown that reduction in the levels of serum insulin might improve cardiac autonomic function in patients without diabetes. These disparate results were probably observed because of the different study populations with diverse blood glucose levels and the duration of diabetes.

It is well known that exercise plays a key role in the management of type 2 diabetes mellitus. Studies have shown that exercise including a home-based exercise program improved blood glucose, lipid, quality of life and physical fitness in type 2 diabetes patients[30,31]. We further investigated the effects of exercise on abnormal HRR and its risk factors in type 2 diabetes mellitus. In the present study, we found that abnormal HRR was significantly improved in the intensive exercise group rather than in the conventional group. The results showed that regular exercise training had beneficial effects on the activity of cardiac autonomic nervous system measured by HRR. Previous studies also showed that exercise is beneficial for cardiac autonomic neuropathy function in healthy children[32], obese children[33] and children with type 1 diabetes[34]. This is consistent with the present results. In recent years, more and more studies declared that exercise rehabilitation can improve the long-term prognosis and alleviate the symptoms of cardiovascular diseases. The mechanism of exercise therapy, however, still remains unclear. We speculated that it is probably related to mainly two aspects on the basis of the present study results: on the one hand, exercise training benefits the glycemic control of diabetic patients in the present study, thereby improves HRR. As shown in the present study, fasting blood glucose and HbA1c were two major independent risk factors of HRR, and could be reduced significantly by exercise training. Intensive glycemic control slowed the progression and modified symptoms of CAN. It is in agreement with the previous study, showing that mild abnormalities of the cardiac autonomic nerves were improved with the decrease in HbA1c values from 9.5 to 8.4%[32]. On the other hand, exercise itself can regulate autonomic nervous function and improve the ability of HRR. The present study also showed that exercise training could reduce the resting heart rate and improve maximum Mets or exercise capacity, suggesting that exercise training might increase the vagus nerve activity and reduce the sympathetic nerve tension. A recent review has concluded that exercise can improve cardiac autonomic function significantly in both type 1 diabetes and type 2 diabetes, in favor of parasympathetic dominance, independent of body mass index, glycemic or blood pressure control and duration of diabetes[35]. Other possible mechanisms include exercise improving cardiac microcirculation and hormones metabolism, and so on. All in all, HRR and autonomic nervous function of the participants in the study were improved by exercise training.

Unfortunately, limitations of the present study include relatively small sample size and lack of further research on the autonomic nervous precise underlying pathophysiological mechanisms in patients with type 2 diabetes. Nevertheless, this is the first study, to the best of our knowledge, which has investigated the correlation among HRR, its risk factors and exercise training in patients with type 2 diabetes. A major finding of the study was the positive effect of exercise training on the management of cardiac autonomic nerve damage in patients with type 2 diabetes. From this aspect, the present study might provide valuable information in clinical practice.

In conclusion, the results of the present study showed a strong association between elevated glucose, LDL levels, resting heart rate, maximum heart rate and abnormal HRR in patients with type 2 diabetes. Exercise training could play an important role in the treatment of type 2 diabetes through improving cardiac autonomic neuropathy, and stabilizing blood glucose and lipid metabolism. Regular exercise therapy should, therefore, be more widely recommended to patients with type 2 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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