Impact of Moderate intensity Aerobic Exercise versus High Eccentric Strength Training on Heart Rate Variability in Diabetic Patients with Cardiac Autonomic Neuropathy

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Abstract

Objective: Cardiac autonomic neuropathy (CAN) as a result of diabetic autonomic neuropathy is positively related to a poor prognosis in diabetic patients. The aim of this study was to determine the effectiveness of moderate intensity aerobic exercise versus high eccentric strength training on heart rate variability in diabetic patients with CAN. **Methods**: 38 male Participants with type 2 diabetes with CAN were randomly divided into two equal groups: the first group undergo aerobic exercise (AE) while the second group who undergo high intensity strength training (RE) for three months. Diastolic blood pressure (DBP), systolic blood pressure (SBP), resting heart rate (RHR) and fasting glucose (F G) were measured in both groups. Heart rate variability (HRV) and The Six-Minute Walk Test (6MWT) were determined. **Results:** within group comparisons, it showed significant difference between pre and post result of both groups ($p< 0.05$). However aerobic exercise group showed better improvement. **Conclusion:** The data suggested that three months of moderate intensity aerobic exercise and high eccentric strength training improve the cardiac autonomic nervous system function in type 2 diabetic patients. However, more favorable effects were obtained with moderate intensity aerobic exercise.

Key words: Cardiac autonomic neuropathy, Heart rate variability, Aerobic exercise, Eccentric strength training

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INTRODUCON

Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes. Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, its major clinical manifestations include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes," and hypoglycemic autonomic failure. It causes damage of the autonomic nerves and damage disrupts signals between the brain and portions of the autonomic nervous system, such as the heart, blood vessels and sweat glands[1-3]. A significant negative impact on survival and quality of life in people with diabetes associated with these complications. Because of its association with a variety of adverse outcomes including cardiovascular deaths, cardiovascular autonomic neuropathy (CAN) is the most clinically important[4-5], CAN is one of the most overlooked of all serious complications of diabetes; Which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics[6-8].

A common form of diabetic autonomic neuropathy and causes abnormalities in heart rate control as well as central and peripheral vascular dynamics; its symptoms are the blood pressure changes when rise from laying down, dizziness when stand up, hypertension, arrhythmia and slow heart rate [9]. It represents a significant cause of morbidity and mortality in diabetic patients and is associated with a high risk of cardiac arrhythmias and sudden death, possibly related to silent myocardial ischemia; therefore, it has important clinical and prognostic relevance[10-13]. It is ultimately the result of complex interactions among degree of glycemic control, disease duration, age-related neuronal attrition, and systolic and diastolic blood pressure. Hyperglycemia plays the key role in the activation of various biochemical pathways related to the metabolic and/or redox state of the cell, which, in concert with impaired nerve perfusion, contribute to the development and progression of diabetic neuropathies[14-15].

Long term aerobic exercise seems to improve symptoms of cardiac neuropathy and could be considered as non pharmacological therapy. In fact, aerobic exercise plays an important role in the maintenance of physical working capacity[16]. Regarding the effect of aerobic exercise with CAN in diabetes, a comparative study proved that the effect of low-grade endurance training was more pronounced in the group with early CAN than in subjects with no CAN.

It demonstrates the already known phenomenon that pathologic values (including blood lipids, blood pressure values; incipient CAN, low initial fitness levels) are more strongly influenced towards normal by endurance training than normal values[17]. Among the existing types of contraction , the eccentric one has been recommended for strength training (ST) programs because it leads to hypertrophy without over loading on the cardiovascular system [18]. Few studies have evaluated the effect of ST on autonomic control (HRV) [19-20].

Heart rate variability (HRV) is a noninvasive, practical and reproducible measure of autonomic nervous system function. A heart rate that is variable and responsive to demands is believed to bestow a survival advantage, whereas reduced HRV may be associated with poorer cardiovascular health and outcomes[21-24]. It is mainly caused by efferent autonomic modulation of the sinus node. For many years, this variable has been expressed only as mean values and standard deviations, i.e., a measure in the time domain representation[25].The current study concerned studying the effect of moderate intensity aerobic exercise versus high eccentric strength training on heart rate variability in diabetic patients with cardiac autonomic neuropathy.

MATERIAL AND METHODS

Participants for this study were 38 male subjects with type 2 diabetes, they were selected randomly from the Cairo University Hospitals, (age: 51±6.7 years, weight: 84.3 ± 23.8 kg, height: 170.5±8.5cm) who completed the three months interventions. All of them were under oral hypoglycemic medication and healthy diet for diabetic patients. All patients were NIDDM patients of at least 3 years, diagnosed clinically by plasma glucose levels fasting and clinical presentation. Written approvals were obtained from their physician to participate in the exercise portion of the study. Participants with no more than 2 risk factors (in addition to diabetes) on the Physical Activity Readiness Questionnaire(PARQ), at least moderate glycemic control, and having been diagnosed with diabetes for at least 3 years were included in the study. All subjects had a diagnosis of T2DM, confirmed by either an oral glucose tolerance test of >200 mg/dL or fasting blood glucose of >126 mg/dL on 2 separate occasions within the previous year. They were sedentary (not participating in regular aerobic or strengthening exercise over the 6 months prior to entering the study) and who were willing to commit to a 12-week, supervised exercise program.

After informed consent was obtained, a medical history (including resting heart rate, blood pressure, date of T2DM diagnosis, medications, and comorbidities) was collected.

Subjects were medically cleared for exercise by their primary care physician in the form a written prescription. While uncontrolled hypertension (systolic blood pressure >165/95 mm Hg); orthopedic problems that limited their ability to use exercise equipment without pain; central or peripheral nervous system disorders; diabetic retinopathy; myopathy; inability to concentrate, follow directions, or work independently; neurologic insult that resulted in mobility impairment; rheumatological disease that affected mobility; impaired knee flexion of <90 degrees; or extreme claustrophobia were excluded from the study. Participants have been divided into two groups, the first group enrolled into aerobic exercise training program and the second group enrolled into eccentric strength training program. The study was conducted in the Out Patient Clinic of Faculty of Physical Therapy.

All participants finished the Physical Activity Readiness Questionnaire (PARQ) and a survey to report exercise history and social behaviors, such as smoking. Nominated participants were prepared for an baseline assessment, which included, measurements for body weight, body height, FG, SBP, DBP, HRV and RHR. The measurements were taken at the beginning and at the end of the study. Body height (cm) and body weight (kg) were measured by standard methods. After a 5-min rest, participants had their sitting blood pressure and RHR measured.

Anthropometric and metabolic measurements: Participants were invited for an outpatient research visit after an 8-h overnight fast. Diabetic patients were asked to withhold their diabetic medications, on the morning of the visit until after the blood draw was complete. All participants were asked to refrain from any strenuous exercise, smoking, or caffeinated drinks 12 h prior to the visit. Height was measured in centimeters using a stadiometer and weight in kilograms using a standardized weighing machine. BMI was calculated as weight in kilograms divided by the square of height in meters. Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times, using aneroid sphygmomanometer, while the subjects were seated for at least 5 min, and the average of the three measurements was taken[26-28].

Assessment of HRV: All measurements of HRV were conducted in the morning between 7 and 11 A.M. in a room with a stable room temperature while the participant was lying in the resting supine position for 10 min and breathing at a normal pace, using the Sphygmocor device (AtCor Medical). The device takes into account the normal heart beats, ignoring the ectopic beats, to derive the statistical parameters of the normal R-R intervals (NN intervals) of the ECG and computes several time and frequency domain HRV indices [29-30] .

The time domain indices of HRV used in these analyses(Table 1.) were the SD of the NN intervals (SDNN), the root mean square differences of successive NN intervals (RMSSD) an number of successive N-N intervals differing by >50 ms divided by the total number of successive N-N intervals (pNN50**)** [31-33] **.**

Table 1. Time domain measures of heart rate variability (HRV)

Parameter	Description
SDNN(ms)	SD of all normal R wave to R wave (N-N) intervals
rMSSD(ms)	Square root of the mean of the sum of squares of successive N-N interval differences. Reflects vagal modulation
pNN50(ms)	Number of successive N-N intervals differing by >50 ms divided by the total number of successive N-N intervals. Reflects vagal function

FBG: Fasting Blood Glucose has been measured by using (Glucose Analyzer). It is considered as the most accurate method in medical labs .The researcher asked his patients to have dinner at 8 o'clock and sleep early before FG test. Hence, patients performed the test in the next day at 8 o'clock. By this way, they fasted around 12 hours and it could be considered as adequate period. Both groups performed the test before and at the end of the training program[34-35]**.**

Physical performance: The Six-Minute Walk Test (6MWT), a measure of the distance a person walks in 6 minutes, it was used to assess overall physical performance. Subjects were asked to cover as much distance as possible within 6 minutes without running. The 6MWT has been shown to be reliable and valid in detecting differences in mobility performance and has high test- retest reliability[36].

After assessment had been finished, the participants in the first group were enrolled in 3 session/week of three months in program of aerobic exercise. Aerobic exercise (also known as cardio) is physical exercise of relatively low intensity that depends primarily on the aerobic energy-generating process. In order to produce the desired metabolic effects, each exercise session lasted 50 min; 10 min of warm-up, 30 min of activity (brisk walking, light running, on treadmill) and 10 min of cool-down.

Considering the linear relationship between heart rate and % VO2 reserve, exercise intensity was set between 60 and 85 % of the maximum heart rate, which was calculated by the following formula: ([220 – age – resting heart rate] * % of maximum heart rate + resting heart rate) [37].

92 ± 3 % Participants performed the planned exercise sessions. One incidence of hypoglycemia that occurred immediately post exercise was resolved with administration of glucose dissolved in lukewarm water. Two participants had an exercise session terminated due to abrupt elevation of blood pressure.

The participants in the second group were enrolled in 3 session/week of three months in program of eccentric strength training. Prior to training, the stepper seat setting was individually adjusted to each subject's leg length, and safety guidelines were reviewed. The recumbent eccentric stepper was powered by a 3-hp motor that drives the foot pedals in a "backward" direction (ie, toward the individual). Eccentric muscle contractions occurred when the subject attempted to resist this motion by pushing on the pedals (with verbal instruction to "try to slow down the pedals") as the pedals moved toward the subject. Because the magnitude of the force produced by the stepper exceeded that of the subjects, the pedals continued to move toward the participant at a constant velocity, resulting in eccentric contractions of the knee and hip extensors, including the quadriceps femoris muscles (Fig.1).

The subjects began with a 5-minute session on the stepper and progressed to a maximum of 20 minutes over the next 3 to 4 weeks. The progression of the eccentric exercise work rate was determined as a function of the rating of perceived exertion (RPE) using a "target" workload on a computer monitor and is summarized in (Table 2.). Once the subjects achieved an RPE of "somewhat hard," they were instructed to maintain that RPE for the duration of the exercise program. A visual analog scale (VAS) was used to monitor muscle pain prior to each session, and heart rate and RPE values were collected at the halfway point of each session.

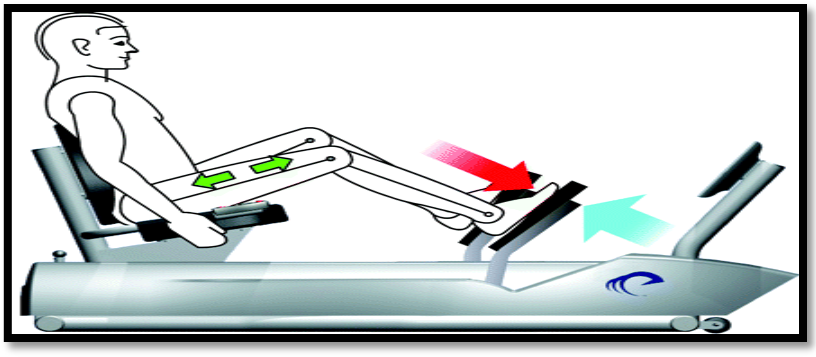

Fig. (1) Eccentric stepper. High muscle forces were generated on an eccentric stepper powered by a 3-hp motor that drives the pedals. As the pedals move toward the subject (blue arrow), the subject resists by applying force to the pedals (red arrow). Because the magnitude of force generated by the motor exceeds that produced by the subject, the leg extensors (green arrows) work eccentrically (lengthening), creating negative work.

Table 2. Description of Eccentric exercise for group II

Week	No/week	Duration	RPE*
1-3	3	5-10 min	7-11(very to fairly light)
4-6	3	15-20 min	11-13 (fairly light to somewhat hard)
6-12	3	20 min	13 (somewhat hard)

RPE*Rating of perceived exertion for the lower extremities.

The data was collected on pre-designed proforma and all such maneuvers were under medical ethics. All statistics were calculated by using the statistically package of social sciences (SPSS) version 16.descriptive statistics (mean and standard deviation) were computed for all outcomes measures. Paired t-test was applied to compare changes between pre and post test for HRV and 6MWT for both groups.

RESULS

Thirty eight subjects with T2DM completed the 3-months of supervised exercise-training program. Ten subjects were required by their referring physicians to undergo a pre-exercise stress test, and the remaining subjects were cleared by their physicians to exercise without a stress test. No subjects were screened out because of unacceptable performance on the pre-exercise stress test. There was non-significant difference between both groups concerning body mass index (BMI), Age, Diabetic period, Fasting blood glucose (FBG), resting heart rate (RHR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and 6MWT performance before training ($p > 0.05$), this refer to homogeneity of the samples (Table 3).This study was conducted on 38 type 2 diabetic patients (male) with cardiac autonomic neuropathy. They were divided into two groups (equal in number), the first group were enrolled into aerobic exercise training program, while the second group were enrolled into high eccentric strength training program for three months. Pre training and post training measurements of SDNN, rMSSD and pNN50 were taken within the week before beginning or following the cessation of the respective exercise programs (Table 4). Aerobically-trained show a higher significant changes at means of SDNN, r M S S D and pNN50 compared with eccentrically- trained ($p< 0.05$). Regarding 6MWT, there was no significant difference between both groups with respect to change in mean 6MWT distance(Table 5).

Table 3. Characteristics of the study participants (mean ±SD)

Characteristics	AE group(*n*=20)	RE group(*n*=18)	P- value
Age, yr	50.5±8.6	51.3±6.1	P>0.05
Weight, kg	62.2±4.3	71.8±3.6	P>0.05
BMI, kg/m^2	24.5±2.6	27.7±2.1	P>0.05
Diabetic period, yr	5±3.7	4±2.7	P>0.05
FBG(mg/dl)	160.60 ±47.32	159.8±50.3	P>0.05
RHR(bpm)	78±1.9	78±2.01	P>0.05
SBP (mmHg)	129±18.13	130.2±16.43	P>0.05
DBP (mmHg)	78.03±7.53	77.23±6.73	P>0.05
6MWT distance, m	554.5±59.3	520.3±33.0	P>0.05

BMI=Body Mass Index, FBG=Fasting Blood Glucose, RHR=Resting Heart Rate, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure and 6MWT=6. Minute Walking Test.

Table 4. Mean ± SD of heart rate variability parameters in both groups.

X ± SD / Group	SDNN (ms)		P-value	rMSSD (ms)		P-value	pNN50 (%)		P-value
	Pre	Post		Pre	Post		Pre	Post	
AE group (n=20)	113.7 ±6.2	121.5 ± 11.9	< 0.05	23.43± 21.52	29.5 ± 9.7	< 0.05	3.9± 1.4	5.1± 1.6	< 0.05
RE group (n=18)	114.17± 10.51	119.5 ± 14.9	< 0.05	22.83± 21.20	26.1± 8.2	< 0.05	4.1± 3.5	4.9± 1.03	< 0.05
P- value	>0.05	< 0.05		>0.05	< 0.05		>0.05	< 0.05	

SDNN = standard deviation of the NN interval; **rMSSD** = square root of the mean squared successive differences between adjacent RR intervals; **pNN50** = percentage of successive interval differences larger than 50ms.

Table 5. ***Outcomes for physical performance in both groups***

X ± SD	6MWT distance (m)		P-value
Group	Pre	Post	
AE Group (n=20)	554.5 ±59.3	600.0 ±51.9	< 0.05
RE Group (n=18)	520.3±33.0	550.2 ±55.9	< 0.05
P- value	>0.05	>0.05	

DISSCUSSION

Impaired autonomic nervous function among patients with diabetes as assessed by HRV has been observed in otherwise healthy adults [38]. In the current study, we sought to compare aerobic exercise with high-force eccentric resistance training in diabetic patient with cardiac neuropathy [39-41]. As our trial was designed to investigate the training-induced reversibility of diabetic cardiovascular autonomic neuropathy, data were gathered on the HRV related impact of aerobic versus eccentric strength training in diabetic subjects.

According to our results, heart rate variability parameters assessed by measurement of SDNN, rMSSD and pNN50 showed significant improvements occurred in both the AE and RE groups- more improvement was observed in AE group after participating in a three month training program, this refer to physical exercise modulates cardiac autonomic control by lessening sympathetic influence and enhancing vagal tone. This shift toward greater vagal modulation may positively affect the prognosis of individuals with a variety of morbidities[42]. Enhanced cardiac vagal tone may offer a survival advantage; Greater vagal influence decreases the amount of work and oxygen consumed by the heart via a reduction in resting heart rate and myocardial contractility. It appears that stimulation of the vagus nerve directly acts on the sinus node and the myocardium, and hinders sympathetic influences, Cardiac vagal tone may also reduce the risk of frequently lethal ventricular dysrhythmias including ventricular fibrillation[43-45].

Exercise training may enhance vagal tone and thereby decrease susceptibility to lethal

arrhythmias[43]. While the underlying mechanisms by which exercise training improves vagal modulation are speculative at present, angiotensin II and nitric oxide (NO) are potential mediators. A potential mechanism underlying the exercise training-cardiac vagal tone association is

angiotensin II; Angiotensin II is known to inhibit cardiac vagal activity[46]. One theory is that exercise training suppresses angiotensin II expression[43]; this finding is important given that athletes with lower plasma renin activity would presumably have lower angiotensin II and higher associated levels of cardiac vagal activity. Therefore, it is possible that the suppression of angiotensin II via exercise may, to some extent, mediate enhancement of cardiac vagal tone[42]. NO may also play a role in increasing cardiac vagal control and, in doing so, may indirectly inhibit sympathetic influences[47]. Exercise training has been found to improve endothelial function[48] and NO bioavailability among individuals with coronary risk or coronary atherosclerosis. Therefore, it is possible that the relationship between exercise and cardiac vagal activity is mediated, at least in part, by NO[49]. Boutcher and Stein[50] found no change in HRV in a group of 19 middle-aged men compared with an age-matched control group (n = 15); HRV was assessed after 24 exercise sessions of moderate intensity exercise training (during 8 weeks). In the exercise group, VO2max increased after the training period, but without altering HRV. These results showed that short duration (2 months) and moderate intensity aerobic training in a middle-aged population, is insufficient to alter HRV parameters in that age group. Also Perini et al. [51] reported that no changes in HRV parameters in an elderly population after an intense 8- week aerobic training programme. However, Schuit et al.[52] found a general increase in HRV after a training programme of 6 months of supervised aerobic training sessions in an elderly populations. Loimaala et al. [53] found no changes in HRV parameters in both time and frequency domains and concluded: “exercise training was not able to modify the cardiac parasympathetic activity in sedentary, middle-aged persons”. Many factors affect the physiological significance of these studies. One of the most important is the age factor, which contributes to the discrepant findings in the literature. It is well known that HRV parameters are decreasing with age[54].

Al Ani et al. [55] concluded that , exercise training in young adults generally report increases in measures of HRV whereas Davy et al. [56] studied the effect of exercise in middle-aged and older adults[57] and showed no changes in cardiac autonomic function, as determined from

HRV. It was found that no significant changes in HRV associated with an increase in aerobic capacity induced by aerobic training. They concluded that resting bradycardia induced by short-term aerobic training in both young and middle-aged men is more related to intrinsic alterations in the sinus node than to changes in efferent parasympathetic-sympathetic modulation[58]. In summary, it can be stated that there are conflicting reports in the literature concerning the effects of aerobic training in a general population on HRV parameters under resting conditions; While some studies have reported an increase in the magnitude of HRV in the time domain[59]. Therefore studies of aerobic training effects on HRV on a previously not-trained (young and/or elderly) population still remain necessary, preferably under well-controlled conditions[60]. The improvement of physical performance is related to an improvement of glucose control following exposure to aerobic exercise and strength training[61].

Biochemical adaptations include an up regulation of mitochondrial proteins involved in respiration (citrate synthase) [62], increased glycogen synthase activity, [63] and increases in GLUT4 protein content[64]. Several potential mechanisms associated with improved glucose control after exercise have been proposed. They include biochemical and structural adaptations of skeletal muscle and systemic influences on physical activity. Endurance exercise resulted in increased mitochondrial proteins and improvements in the capillary to muscle fiber ratio, thereby increasing the distribution of substrates. Structural adaptations from resistance training include increases in contractile protein content (hypertrophy), resulting in a higher basal metabolic rate[65] and, therefore, potentially greater absolute glucose uptake[66]. The high-force–producing characteristic of eccentric exercise has previously been reported to result in an amplified muscle hypertrophic response in other patient populations[67-68].

CONCLUON

The findings of the present review suggested that exercise therapy may improve HRV by increasing vagal tone and decreasing sympathetic activity. One hypothesis is that a shift toward greater vagal modulation may positively affect prognosis of individuals with a variety of morbidities[42]. Furthermore, speculation could be made that there is a potential reduction in mortality and morbidity related to HRV change in patients who exercise.

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