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Low intensity resistance training improves systolic function and cardiovascular autonomic control in diabetic rats

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ABSTRACT

Aims: We evaluated the effects of low intensity resistance training (RT) on left ventricular (LV) function, baroreflex sensitivity (BRS), and cardiovascular autonomic control of streptozotocin-induced diabetic rats.
Methods: Male Wistar rats were divided into (n = 8 each group): sedentary control (SC), trained control (TC), sedentary diabetic (SD), and trained diabetic (TD). Trained groups underwent low intensity RT (40%–50% 1 repetition maximum) for 10 weeks. Echocardiographic evaluation, arterial pressure (AP), heart rate (HR), BRS, and autonomic measurements were performed.
Results: Diabetes induced an increase in glycemia and a reduction in body weight in diabetics when compared with control animals. Diabetic rats displayed cardiac dysfunction, reduced systolic AP and HR, impaired BRS and autonomic derangement when compared to control rats. RT improved ejection fraction (SD: 68% ± 1.3% vs. TD: 75% ± 3.0%) and velocity of circumferential fiber shortening (SD: 0.32 ± 0.02 vs. TD: 0.40 ± 0.01 circ/seg.10^{-4}). Trained diabetic rats presented increased AP (+10.2%), HR (+10.4%), and BRS after RT protocol.
Conclusions: Low intensity RT induced an increase in systolic function in diabetic rats. This may be due to positive LV remodeling and BRS improvement, which may have played an important role in the attenuation of hemodynamic impairment and cardiac autonomic neuropathy in streptozotocin-diabetic rats.

1. Introduction

Diabetes mellitus (DM), an epidemic disease characterized by metabolic abnormalities and associated cardiovascular complications, affects an increasingly large proportion of the population across the world (Go et al., 2013; Zimmet, McCarty, & de Courten, 1997). Sedentary lifestyle and poor glycemic control have been found to contribute to increased morbidity and mortality in DM patients (Chudyk & Petrella, 2011; Zimmet et al., 1997).

Cardiac autonomic neuropathy in diabetic patients has been directly linked to baroreflex dysfunction, with consequent resting tachycardia, postural hypotension, exercise intolerance, increased incidence of asymptomatic ischemia, myocardial infarction and mortality. Cardiac autonomic neuropathy in diabetic patients has also been associated with cardiac arrhythmias and sudden death (De Angelis, Irigoyen, & Morris, 2009; Loimaala et al., 2003; Vinik, Erbas, & Casellini, 2013). Furthermore, cardiac autonomic neuropathy might be associated with left ventricle (LV) abnormalities in systolic and diastolic functions (the latter more often), even in the absence of cardiac disease in diabetic patients (Vinik et al., 2013).

To this effect, experimental studies have been conducted to investigate the mechanisms of autonomic and cardiac dysfunction in diabetes (Akula et al., 2003; De Angelis et al., 2009; Monckton & Pehowich, 1980; Schilling & Mann, 2012; Shao et al., 2009; Wichi et al., 2007). In the time course of streptozotocin-(STZ)-induced experimental diabetes, previous findings of our group have demonstrated that baroreflex, sympathetic/parasympathetic efferent responses (Dall'Ago, Fernandes, Machado, Belló, & Irigoyen, 1997; Harthmann et al., 2007; Mostarda et al., 2009; Schaan et al., 1997;

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Rodrigues et al., 2013; Souza et al., 2007), and ventricular function were impaired in these animals (De Angelis et al., 2000; Rodrigues et al., 2011; Wichi et al., 2007).

On the other hand, accumulating evidence in the past 2 decades has shown that exercise training (ET) seems to be a remarkable nonpharmacological strategy for the treatment of diabetes, as it significantly reduces the risk of cardiovascular disease development in diabetics (Chudyk & Petrella, 2011). We have previously shown the benefits of ET in diabetes-induced tonic and reflex cardiac autonomic dysfunction (Harthmann et al., 2007; Jorge et al., 2012; Mostarda et al., 2009; Souza et al., 2007), as well as in ventricular dysfunction of diabetic rats undergoing myocardial infarction (Rodrigues et al., 2012).

Although resistance training (RT) is currently recommended as a complementary part of an exercise program for diabetic patients (Colberg et al., 2010; Eves & Plotnikoff, 2006), its effects per se on the cardiovascular and autonomic complications remain poorly understood. This study was undertaken to test whether RT can improve cardiac function and autonomic control of circulation in STZ-diabetic rats. Therefore, the aim of this study was to evaluate the effects of low intensity RT on LV function, baroreflex sensitivity, and cardiovascular autonomic control of STZ-induced diabetic rats.

2. Methods

2.1. Animals

Experiments were performed in adult male Wistar rats (3 months old, 220–270 g) from the Animal House of the University of São Paulo, São Paulo, Brazil. Rats were fed standard laboratory chow and water *ad libitum*. The animals were housed in collective polycarbonate cages in a temperature-controlled room (22 °C) with a 12-h dark–light cycle (light 07:00–19:00).

The experimental protocol was approved by the institutional animal care and use committee of the Medical School of the University of São Paulo (protocol no. 1063/04), and this investigation was conducted in accordance with the Principles of Laboratory Animal Care as formulated by the National Institutes of Health (National Institutes of Health Publication No., 96-23, Revised 1996). Rats were randomly assigned to 4 groups (n = 8, each group): sedentary control (SC), sedentary diabetic (SD), trained control (TC) and trained diabetic (TD).

2.2. Diabetes induction

Experimental diabetes was induced by an intravenous injection of 50 mg/kg streptozotocin (STZ, Sigma Chemical Co., St. Louis, MO) dissolved in citrate buffer (pH 4.2). The rats were fasted overnight before STZ injection. The SC and TC groups were injected with buffer only (10 mM citrate buffer, pH 4.5). Forty-eight hours after the STZ injection, diabetes was confirmed in fasted animals (6 h) by measuring blood glucose levels >200 mg/dL (Rodrigues et al., 2012, 2013, 2011).

2.3. Resistance training protocol

After one week of diabetes induction, trained groups (TC and TD) underwent low intensity RT for 10 weeks. Animals were exercised following a model described by Tamaki, Uchiyama, and Nakano (1992), and as previously performed by our group (Barauna, Rosa, Irigoyen, & de Oliveira, 2007). Briefly, animals fitted with a canvas jacket were able to regulate the twisting and flexing of their torsos and were suspended in a standard position on their hind limbs. An electrical stimulation (20 V, 0.3 s duration at 3 s intervals) was applied to the rat tail through a surface electrode. As a result, the rats flexed their legs repeatedly, which lifted the weight-arm of the training apparatus.

In order to determine the intensity of training and to adjust the training load, measurements of the maximum weight lifted (1 repetition maximum) with the squat-training apparatus were performed biweekly. The maximum power generated for jumping (1-maximum repetition) was defined as the maximum load [that the] rats were able to jump following electrical stimulation. The low intensity training protocol was established with a load set at 40% of 1-maximum repetition. From the first to fifth week of training protocol, trained groups (CT and DT) were exercised with 4 sets of 20 repetitions each, with a 90 s rest period between each set. From the sixth to tenth week, trained groups were exercised with 4 sets of 30 repetitions each, with a 90 s rest period between each set.

2.4. Echocardiography

Echocardiographic evaluation was performed by a blind observer, under the guidelines of the American Society of Echocardiography, after 10 weeks of RT protocol or following. Rats were anesthetized (80 mg/kg ketamine and 12 mg/kg xylazine, i.p.), and images were obtained with a 10 to 14 MHz linear transducer in a SEQUOIA 512 (ACUSON Corporation, Mountain View, CA) for measurements of: morphometric parameters — LV mass, relative wall thickness (RWT) and left ventricular diameter during diastole (LVDD); systolic function — ejection fraction (EF) and velocity of circumferential fiber shortening (VCF); diastolic function — left ventricular isovolumetric relaxation time (IVRT), and the ratio of maximal early diastolic peak velocity (E) and late peak velocity (A) of mitral flow (E/A ratio). The global index was quantified by the myocardial performance index (MPI). Echocardiographic parameters were measured as previously described (Rodrigues et al., 2012, 2011).

2.5. Hemodynamic evaluations

Twenty-four hours after the echocardiographic evaluation, two catheters filled with 0.06 mL of saline were implanted into the femoral artery and femoral vein of the anesthetized rats (80 mg/kg ketamine and 12 mg/kg xylazine, i.p.). On the following day, an arterial cannula was connected to a transducer (Blood Pressure XDCR; Kent Scientific, Torrington, CT), and arterial pressure (AP) signals and pulse intervals (PI) were recorded over a 30-min period in conscious animals by a microcomputer equipped with an analog-to-digital converter board (WinDaq, 2-kHz, DATAQ, Springfield, OH) (Mostarda et al., 2009; Rodrigues et al., 2012, 2013).

2.6. Autonomic function measurements

Baroreflex sensitivity — After AP baseline measurements, sequential bolus injections (0.1 mL) of increasing doses of phenylephrine (0.25–32 mg/kg) and sodium nitroprusside (0.05–1.6 mg/kg) were given to induce increases or decreases in MAP responses (for each drug), ranging from 5 to 40 mm Hg. Baroreflex sensitivity was expressed as bradycardic response (BR) and tachycardic response (TR) in beats per minute per millimeter of mercury, as described elsewhere (Rodrigues et al., 2011; Souza et al., 2007).

Sympathetic and Vagal Tonus — After baroreflex sensitivity assessment, AP and PI were continuously recorded at a basal state and after intravenous injection of methylatropine (4 mg/kg, Sigma; 0.2 mL). Because HR response to these drugs reaches its peak within 3 to 5 min, this time interval was allowed to elapse before heart rate measurement. Intravenous injection of atenolol (4 mg/kg, Sigma; 0.2 mL) was injected 10 min after methylatropine, and again the response was evaluated after simultaneous blockade with atenolol and methylatropine. On the following day, the sequence of injections was inverted (first atenolol and then methylatropine). Intrinsic heart