Impact of combined exercise training on cardiovascular autonomic control and mortality in diabetic ovariectomized rats

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1Laboratory of Transactional Physiology, Universidade Nove de Julho (UNINOVE), São Paulo, Brazil; 2Hypertension Unit, Heart Institute (InCor), School of Medicine, University of São Paulo, São Paulo, Brazil; 3Human Movement Laboratory, São Judas Tadeu University, São Paulo, Brazil; and 4Faculty of Physical Education, University of Campinas, Campinas, Brazil

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Sanches IC, Conti FF, Bernardes N, Brito JD, Galdini EG, Cavaglioti CR, Irigoyen MC, De Angelis K. Impact of combined exercise training on cardiovascular autonomic control and mortality in diabetic ovariectomized rats. J Appl Physiol 119: 656–662, 2015. First published July 15, 2015; doi:10.1152/japplphysiol.00883.2014.—The purpose of this study was to compare the effects of aerobic, resistance, or combined exercise training on cardiovascular autonomic control and mortality in diabetic ovariectomized rats. Female Wistar rats were divided into one of five groups: euglycemic sedentary (ES), diabetic ovariectomized sedentary (DOS), diabetic ovariectomized aerobic-trained (DOTA), diabetic ovariectomized resistance-trained (DOTR), or diabetic ovariectomized aerobic+resistance-trained (DOTC). Arterial pressure (AP) was directly recorded and baroreflex sensitivity was evaluated by heart rate responses to AP changes. Cardiovascular autonomic modulation was evaluated by spectral analyses. No differences were observed in body weight and glycemia between diabetic rats. Animals in the DOTC and DOTA groups exhibited an increase in running time, whereas animals in the DOTC and DOTR groups showed greater strength. Trained groups exhibited improvement in total power and the high-frequency band of pulse interval and reduced mortality (vs. DOS). Animals in the DOTC (bradycardic and tachycardic responses) and DOTA (tachycardic responses) groups exhibited attenuation in baroreflex dysfunction that was observed in DOS and DOTR animals, and an improvement in AP variance. In conclusion, all training protocols led to reduced mortality, which may be due to an increase in physical capacity and to cardiovascular and autonomic benefits following training, regardless of any improvement in glycemic control. In this model, the aerobic and combined trainings seem to promote additional cardiovascular autonomic benefits when compared with resistance training alone.

aerobic exercise training; autonomic control; diabetes; mortality; resistance exercise training

CARDIOVASCULAR DISEASE is the leading cause of death among people with diabetes (12). Changes in cardiovascular autonomic control of circulation is a common complication of diabetes, because they reduce heart rate variability and impair baroreflex sensitivity (8, 26) and, as such, become the major contributors to high morbidity and mortality in this population (7, 38). Additionally, diabetes is associated with threefold to fivefold increase in cardiovascular risk in women and a twofold to fourfold increase in men (24). Moreover, diabetes and cardiovascular disease are more prevalent in postmenopausal women (34). Menopause has been reported to occur at a younger age in women with type 1 diabetes, which can have great clinical relevance (6). One explanation for early menopause in women with type 1 diabetes may lie in prolonged hyperglycemia and/or other long-term diabetes complications (41).

The American Heart Association has recently issued recommendations aimed at promoting regular physical activity as a powerful strategy to prevent and control adverse effects of diseases in both healthy women and women with known risk factors (23). In fact, a regular practice of physical exercise has been found to have beneficial effects on metabolic control and cardiovascular function while contributing to a reduction in risk factors for cardiovascular disease (27). However, most of the studies to date have focused on men and evaluated the effects of dynamic aerobic exercise training, whereas findings involving women or other types of exercise remain scarce and controversial (40).

Most clinical trials or experimental resistance training studies involving men and women with diabetes have focused on metabolic control in type 2 diabetes (31, 43). Thus the role of exercise training in the management of cardiovascular and autonomic dysfunction of women with diabetes after ovarian hormone deprivation remains unclear. We have previously demonstrated beneficial effects of dynamic aerobic exercise training on cardiovascular and autonomic control of euglycemic and diabetic ovariectomized rats (13, 33). However, it is critical that the scientific community fully understand the effects of different types of training on cardiovascular autonomic control of circulation in patients with diabetes. Thus this study aims to compare the effects of aerobic training, resistance training, or combined exercise training (i.e., aerobic plus resistance, on alternate days) on functional capacity, hemodynamic and autonomic control of circulation, and mortality in an experimental model associating ovarian hormone deprivation and diabetes. Moreover, because a recent systematic review has shown that combined (aerobic plus resistance) exercise protocols improved glycemic control in people with diabetes to a greater extent than isolated forms of exercise (25), we hypothesize that combined exercise training may yield additional cardiovascular benefits and reduced mortality compared with either aerobic or resistance training alone.

METHODS

Animals and groups. Experiments were performed using 44 female Wistar rats (10–12 wk) obtained from the Animal Shelter of the University of São Paulo, Brazil. The animals were housed in cages (four animals/cage) in a temperature-controlled room (22°C) with 12:12-h dark-light cycle. Animals were clinically evaluated twice a day (~10 A.M. and ~5 P.M.) and body weight was measured weekly.
Five experimental groups were used in this study: euglycemic and sedentary (ES, n = 8); diabetic, ovariec-tomized, and sedentary (DOS, n = 12); diabetic, ovariec-tomized, and subjected to aerobic exercise training (DOTA, n = 8); diabetic, ovariec-tomized, and subjected to resistance exercise training (DOTR, n = 8); or diabetic, ovariec-tomized, and subjected to aerobic and resistance (i.e., combined) exercise training (DOTC, n = 8). All surgical procedures and protocols were carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (Bethesda, MD) and were approved by the University of São Paulo Ethical Committee (protocol 0984/08).

Survival rate was investigated during the 10-wk protocol in all animals, and assessment began after streptozotocin (STZ) induction, avoiding the influence of anesthesia or surgical procedure stress. All other evaluations (metabolic, physical capacity, hemodynamic, and autonomic evaluations) were performed in all nondiabetic rats and in eight rats in each diabetic group.

Ovariec-tomy. At 10–12 wk of age, animals were anesthetized (80 mg/kg ketamine and 12 mg/kg xylazine ip), the oviduct was sectioned, and the ovary was removed as described in detail elsewhere (13, 33); all efforts were made to minimize suffering, including analgesia (tramadol 5 mg/kg sc). The ES group underwent sham surgery. In the present study, estrogen concentration at the end of the protocol, measured by immunoassay, was nondetectable in the rats that underwent ovariec-tomy.

Diabetes induction. Five days after ovariec-tomy, the animals were made diabetic via a single injection of STZ (50 mg/kg iv; Sigma) dissolved in citrate buffer (pH 4.5) after 6 h of fasting (11, 15, 33, 39). Blood samples (50 μl) were collected to measure blood glucose 72 h after STZ injection and at the end of the protocol with a Gluco test (Advantage; Roche Laboratories).

Exercise tests and exercise training protocols. One week after STZ injection, all animals were adapted to a motor treadmill (Inbramed TK-01; Brazil) (10 min/day, 0.3 km/h) for 1 wk before the maximal treadmill test and the beginning of the 8-wk exercise training protocol. Sedentary and trained rats underwent a maximum running test as described in detail in a previous study (29). Tests were performed at the beginning of the experiment and in weeks 4 and 8 of the training protocol. The sedentary groups were placed on a stationary treadmill at least three times a week to provide a similar environment. Aerobic training was performed on a treadmill at moderate intensity (40–60% of maximum running speed or approximately 50–75% of VO₂max) for 1 h per day, 5 days per week for 8 wk (13, 29, 33).

The resistance exercise training protocol was performed on a ladder that had been adapted for use by rats as previously described in detail (30). One week after STZ injection, the animals were adapted to the act of climbing for 5 consecutive days before the maximal load test and the beginning of the 8-wk exercise training protocol. Treadmill and climbing the ladder on the following day).

Hemodynamic assessment. At least 24 h after the last training session, two catheters filled with 0.06 ml of saline were implanted into the carotid artery and jugular vein of anesthetized rats (80 mg/kg ketamine and 12 mg/kg xylazine ip); all efforts were made to minimize suffering. To avoid detraining, hemodynamic measurements were made in conscious, freely moving rats in their home cage at least 48 h after the last training session. The arterial cannula was connected to a transducer (Blood Pressure XDCR; Kent Scientific), and arterial pressure (AP) signals were recorded for a 30-min period using a microcomputer equipped with an analog-to-digital converter (CODAS, 2 Kz; DATAQ Instruments). The recorded data were analyzed on a beat-to-beat basis to quantify changes in mean arterial pressure (MAP) and heart rate (HR) (13, 30, 33).

Cardiovascular autonomic control. Baroreflex sensitivity was evaluated by increasing doses of phenylephrine (0.5 to 2.0 μg/ml) and sodium nitroprusside (5 to 20 μg/ml) that were given as sequential bolus injections (0.1 ml) to produce pressure responses ranging from 5 to 40 mmHg for both pressure and depressor responses. A 3- to 5-min interval between doses was needed for AP to return to baseline.

Peak increases or decreases in MAP after phenylephrine or sodium nitroprusside injection and the corresponding peak reflex changes in HR were recorded for each drug dose. Baroreflex sensitivity was evaluated by a mean index, calculated as the ratio between changes in HR to the changes in MAP, allowing a separate analysis of reflex bradycardia and reflex tachycardia (13, 33).

For frequency domain analysis of cardiovascular autonomic modulation, the time series (three time series of 5 min for each animal) of pulse interval (PI) and systolic arterial pressure (SAP) were cubic spline-interpolated (250 Hz) and cubic spline-decimated to be equally spaced in time by linear trend removal; power spectral density was obtained through the fast Fourier transformation. Spectral power for low-frequency (LF, 0.20–0.75 Hz) and high-frequency (HF, 0.75–4.0 Hz) bands was calculated by power spectrum density integration within each frequency bandwidth, using a customized routine (MATLAB 6.0; Mathworks, Natick, MA) (30).

Statistical analysis. Data are expressed as means ± SE. The Levene test was used to evaluate data homogeneity. One-way ANOVA (hemodynamic and autonomic evaluations) or one-way ANOVA for repeated measures (body weight, blood glucose, and exercise tests), followed by the Student-Newman-Keuls test was used to compare groups. The survival curve was estimated by using the Kaplan-Meier method and compared by using the log-rank test. Significance level was established at P < 0.05.

RESULTS

Metabolic evaluations. At the beginning of the protocol, body weight was similar between groups. The diabetic animals (i.e., those in the DOS, DOTA, DOTR, and DOTC groups) presented reduced body weight compared with that of the ES group at the end of the protocol. As expected, animals in the diabetic groups (DOS, DOTA, DOTR, and DOTC) had higher blood glucose levels than euglycemic animals (the ES group). Exercise training protocols did not result in a change in blood glucose levels (Table 1).

Physical capacity evaluations. At the beginning of the protocol (week 1) we found no differences between groups in their ability to perform the maximal treadmill exercise test. Animals in the DOS group showed reduced ability to run at the end of the protocol (week 8) in the maximal test carried out at the beginning of the protocol. Animals in the DOTA and DOTC groups showed an increase in running time at the maximal intermediate test (week 4) and final test (week 8), indicating the effectiveness of these exercise training protocols (Fig. 1A).

Animals in the DOTA group (0.11 ± 0.005 g) presented an increase in soleus muscle mass compared with those in the DOS group (0.09 ± 0.003 g). Animals in the DOTC group
(0.10 ± 0.005 g) showed similar values of soleus mass in relation to the DOS and DOTA groups.

There were no differences in maximum load normalized by body weight at the beginning of the protocol. At the end of the protocol, all animals showed greater strength, as evaluated by maximal load/body weight, compared with the initial values they attained. Animals in the DOS and DOTA groups exhibited decreased maximum load compared with those in the ES group at week 4 and week 8 of the protocol. However, animals that underwent resistance (DOTR) and combined (DOTC) exercise training showed greater strength gains than animals in the groups that did not undergo training on the ladder (ES, DOS, and DOTA groups), thus indicating the effectiveness of these exercise training protocols (Fig. 1B). Animals in the DOTR and DOTC groups presented increased plantar muscle mass (0.15 ± 0.009 g and 0.15 ± 0.005 g, respectively) compared with those in the DOS group (0.10 ± 0.005 g).

**Hemodynamic and autonomic evaluations.** As shown in Table 2, animals in the DOS group showed a reduction in SAP, MAP, and HR in relation to those in the ES group. Animals in all trained groups did not exhibit a reduction in MAP as was observed in the DOS group. Animals in groups that underwent exercise training presented attenuation in a reduction of basal HR regardless of the type of exercise training.

Animals in the DOS and DOTR groups exhibited a reduction in bradycardic responses to rises in AP (vs. animals in the ES group). However, no changes in bradycardic responses were observed among animals in the DOTA or DOTC groups compared with those in the ES group. Animals in the DOTC group presented an increase in these responses compared with animals in the DOS group. Tachycardic responses to reductions in AP were reduced in animals in the DOS and DOTR groups compared with those in the ES group. Tachycardic responses were similar among animals in the ES, DOTA, and DOTC groups.

In evaluating autonomic modulation, total power of PI variability (VAR-PI) was lower in the DOS group compared with the other groups (Fig. 2A). The LF band of PI (LF-PI) (i.e., sympathetic modulation to the heart) was lower in the DOS group compared with the ES group (Fig. 2B). Animals in all groups that underwent exercise training exhibited an increase in LF-PI in relation to the sedentary groups (ES and DOS). The HF band of PI (HF-PI) (i.e., parasympathetic modulation to the heart) was reduced in animals in the DOS group compared with those in the ES group, which was not observed in the groups that had been trained (Fig. 2C).

In SAP autonomic modulation, the total power of SAP variability (VAR-SAP) and the LF band of SAP (LF-SAP) were lower in animals in all diabetic groups (DOS, DOTA, DOTR, and DOTC groups) compared with those in the ES group. However, animals in the DOTA and DOTC groups showed an increase in these parameters compared with those in the DOS and DOTR groups (Fig. 2, D and E). Moreover, analysis involving all diabetic ovariectomized groups demonstrated correlations between VAR-SAP ($r = 0.69, P < 0.05$) and LF-SAP ($r = 0.68, P < 0.05$) in running time at the maximal final exercise test, showing that ovariectomized diabetic rats with improved SAP variability presented higher...
performance on the exercise test. No correlations were found between VAR-SAP or LF-SAP and the maximal load test.

Mortality evaluation. Mortality was assessed from the period covering the induction of diabetes until the end of week 8 of the exercise training period. All deaths occurred between 5:00 P.M. and 10:00 A.M. (the active period of rats). Additionally, no humane endpoint was used in our experiments because animals did not fill the criteria for this procedure. No euglycemic (the ES group) or diabetic animals that underwent exercise training (animals in the DOTA, DOTR, and DOTC groups) died during the time course of the experiments, whereas animals in the DOS group showed 14% mortality (Fig. 3).

DISCUSSION

Because postmenopausal women have an increased risk for diabetes, this study was performed to investigate and compare the effects of aerobic, resistance, or combined (aerobic plus resistance) exercise training on functional capacity, hemodynamic, and autonomic parameters in diabetic ovariectomized rats. Our findings corroborate data from previous studies that have pointed to the beneficial cardiovascular effects of aerobic exercise training on this model (33). Furthermore, our study may contribute toward gaining new insights on nonadverse cardiovascular effects observed after moderate-intensity dynamic resistance training. More importantly, we were able to demonstrate additional benefits on cardiovascular autonomic control of circulation, as shown by improved baroreflex sensitivity, VAR-SAP, and LF-SAP, in diabetic ovariectomized rats undergoing the aerobic and combined dynamic training protocols compared with resistance training alone.

Because no rat models of menopause are considered ideal, most investigators have used relatively young (6–12 wk) female rats ovariectomized for short periods (3–5 wk) (see Ref. 22). Although this model may not be appropriate for determining long-term changes in cardiovascular regulation during menopause, the ovariectomy procedure is an effective way to simulate menopause status because it suppresses ovarian hormone levels. In the present study, female rats were ovariectomized at 10 wk of age, and physiological measurements were performed 9 wk later. Additionally, 1 week after ovariectomy, diabetes was induced by STZ. Rats treated with STZ display many of the features observed in human subjects with uncontrolled diabetes mellitus, including hyperglycemia, hypoin-su-

Table 2. Hemodynamic evaluations and baroreflex sensitivity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ES</th>
<th>DOS</th>
<th>DOTA</th>
<th>DOTR</th>
<th>DOTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP, mmHg</td>
<td>129 ± 2.5</td>
<td>114 ± 1.6*</td>
<td>124 ± 4.4</td>
<td>121 ± 3.5</td>
<td>122 ± 2.9</td>
</tr>
<tr>
<td>DAP, mmHg</td>
<td>97 ± 2.2</td>
<td>90 ± 2.1</td>
<td>98 ± 3.6</td>
<td>98 ± 3.6</td>
<td>96 ± 3.0</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>113 ± 1.4</td>
<td>103 ± 1.6*</td>
<td>112 ± 2.1†</td>
<td>110 ± 2.3†</td>
<td>110 ± 2.7†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>351 ± 8.3</td>
<td>251 ± 5.7*</td>
<td>275 ± 5.9†</td>
<td>276 ± 6.2†</td>
<td>277 ± 5.6†</td>
</tr>
<tr>
<td>Bradycardic response, bpm/mmHg</td>
<td>−1.71 ± 0.20</td>
<td>−1.11 ± 0.09*</td>
<td>−1.45 ± 0.10</td>
<td>−1.28 ± 0.10*</td>
<td>−1.53 ± 0.11†</td>
</tr>
<tr>
<td>Tachycardic response, bpm/mmHg</td>
<td>3.93 ± 0.29</td>
<td>2.98 ± 0.14*</td>
<td>3.32 ± 0.20</td>
<td>2.78 ± 0.23*</td>
<td>3.35 ± 0.22</td>
</tr>
</tbody>
</table>

SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure. Data are means ± SE, n = 8 animals/group. *P < 0.05 vs. ES; †P < 0.05 vs. DOS.

Fig. 2. A: total power of pulse interval (PI) variability (VAR); B: low-frequency (LF) band of PI; C: high-frequency (HF) band of PI; D: total power of systolic arterial pressure (SAP) variability; E: LF band of SAP; n = 8 animals/group. *P < 0.05 vs. ES; †P < 0.05 vs. DOS; ‡P < 0.05 vs. DOTA; §P < 0.05 vs. DOTR.
linemia, and increased urinary glucose levels resulting in polyuria, together with reduced body weight (11, 15, 33, 39). In fact, animals in the DOS group in our study presented hyperglycemia and reduced body weight compared with animals in the ES group. Moreover, the experimental diabetes induced by STZ has been used extensively to study the relationship between diabetes and cardiovascular autonomic dysfunction (see Ref. 2). This experimental model of diabetes bears a much closer resemblance to human type 1 diabetes. However, accumulated data from clinical studies have suggested that autonomic dysfunction is a common feature of both type 1 and type 2 diabetes. Study of this neural disorder is of prime importance in the understanding in how of a variety of cardiovascular pathologies develop, from atherosclerosis to myocardial infarction (7, 38). In this sense, it is important to remind that the risk of mortality from cardiovascular disease is sharply increased after menopause (23, 34) and in women with diabetes (24). Moreover, the significance of diabetic neuropathy in disease evaluation and therapy have long been emphasized in publications for healthcare professionals (7, 38).

The ovariectomized diabetic rats that underwent aerobic (DOTA) or combined (DOTC) exercise training in our study exhibited an increase in running time on the maximal treadmill test compared with animals in the other groups (ES, DOS, and DOTR). Moreover, animals in the DOTA group presented an increase in oxidative soleus muscle mass (vs. those in the DOS group). In addition, sedentary animals (DOS) showed reduced running time in this test at the end of protocol compared with their initial values, indicating loss of exercise capacity after the induction of diabetes caused by STZ. We stress that although the animals that underwent resistance exercise training did not increase their running time on the treadmill at the end of protocol, no reduction in this parameter was detected; this was also true for animals in the DOS group. This demonstrates that resistance exercise training was effective, at least in promoting the maintenance of functional aerobic capacity in these animals. All animals showed strength gains during the ladder exercise protocol, probably related to growth over that week and, consequently, favorable changes in muscle properties, resulting in an increased ability to generate force (9). This gain was attenuated in animals in the DOS and DOTA groups, which may be due to STZ-induced skeletal muscle mass loss (30). Note that animals that underwent either resistance (DOTR) or combined (DOTC) exercise training were able to climb with higher loads than animals in the other groups (ES, DOS and DOTA), and exhibited an increase in glycolytic plantar muscle mass, indicating the effectiveness of the protocol based on the maximum load test. Interestingly, because postmenopausal women usually present reduced force and aerobic capacity (23, 34), animals that underwent the combined (DOTC) exercise training (performed on alternate days on the treadmill and on the ladder) showed increased ability to run and to attain the maximum load of climbing. Thus this type of training could provide an additional gain in quality of life for diabetic postmenopausal women, should it be confirmed by future clinical studies.

However, despite the positive changes in physical capacity observed in the present study, there were no differences in body weight or blood glucose between studied groups. It should be emphasized that STZ-induced diabetes is a model that closely reflects type I diabetes in humans, for which it is generally agreed that exercise training does not alter glycemic control (28, 42). Furthermore, previous studies carried out by our group have demonstrated that aerobic exercise training on a treadmill does not change blood glucose in STZ-diabetic male rats (3) or STZ-diabetic ovariectomized females rats (33).

Despite the different physiological stimuli brought about by different types of exercise training, the behavior of the hemodynamic variables was similar between the trained groups. All types of exercise training—aerobic (DOTA), resistance (DOTR), or combined (DOTC)—resulted in normalized AP, thereby reversing STZ-induced hypotension and HR (vs. DOS) (3, 33). In fact, diabetic male rats presented reduced systolic and diastolic cardiac function and cardiac output (3, 5, 39), which may be associated with AP reduction observed in male and female rats in this model (3, 33, 39). Moreover, our data corroborate previous studies showing that exercise training normalizes AP in diabetic rats (3, 11, 33), which suggests that this improvement is mediated by an increase in cardiac output associated with improved cardiac function (3) or even improved cardiac autonomic control (11, 33). We have previously observed that aerobic training resulted in improved cardiac function associated with the normalization of peripheral vascular resistance and an increase in ejection fraction and cardiac output, which account for the normalization of AP in infarcted rats (14). In addition, all trained animals (DOTA, DOTR, and DOTC groups) exhibited a higher LF-PI band, which represents the sympathetic modulation to the heart, suggesting a normalization of sympathetic activity for the cardiac pump. Thus increased cardiac sympathetic modulation to the heart may have contributed to increased cardiac output and chronotropism and, consequently, to reverse hypotension and attenuate the resting bradycardia observed in this experimental model.

With regard to autonomic control/modulation of circulation, the mechanisms underlying hemodynamic alterations also seem to be associated with the type of training: although the VAR-PI and LF-PI bands were higher in all trained groups, the VAR-SAP and LF-SAP bands were normalized only in the groups that underwent dynamic aerobic exercise (DOTA and DOTC). These parameters of SAP variability may be associated with sympathetic vascular modulation. In a recent study, Kwon et al. (18) demonstrated that in women with type 2 diabetes, to improve endothelial cell function, aerobic exercises must be tailored by changing the stimulus duration to promote improvements in cardiovascular fitness. In line with these findings for patients with type 2 diabetes, animals with
type 1 diabetes undergoing resistance exercise training on a
tower showed no improvement in running time on the tread-
mill, and as such, we might postulate that impairment in SAP
variability may be associated with lower cardiopulmonary
fitness. In fact, in the present study, we observed correlations
between the improvement in VAR-SAP (r = 0.69) and LF-
SAP (r = 0.68) with increased performance on the maximal
treadmill exercise test in diabetic ovariectomized rats.

It is now common knowledge that HR variability has been
used as a marker of parasympathetic integrity (37). Previous
studies have observed reduced HR variability in rats and
women after ovarian hormone deprivation (10) both in humans
and rats with diabetes (7, 8, 38), as well as experimentally
in the association of these conditions (33). Although VAR-PI was
higher in the trained animals (vs. DOS), which would indicate
a greater parasympathetic modulation, a widely accepted hy-
thesis to account for the normalization of HR in diabetic
animals after exercise training lies in the improvement of
cardiac pacemaker (sinoatrial node), which increases intrinsic
HR (3, 33).

For long it was believed that the parasympathetic autonomic
nervous system was most affected by diabetes (21) not only in
experimental models (2, 3, 8, 33), but also in patients (1). However, currently, there is clear and consistent evidence that
the sympathetic component is also greatly affected in diabetic
autonomic neuropathy (3, 17). In this respect, both the HF-PI
band (representing parasympathetic modulation) and the LF-PI
band (cardiac sympathetic modulation) were higher in trained
groups compared with sedentary rats (DOS). Furthermore, a
recent study with euglycemic ovariectomized rats that under-
went resistance training at low or high intensity (8 wk, 3 days
per week) has shown a reduction in the LF-PI band in both
training intensities, but an increase in the HF-PI band only in
the group trained at high intensity (32).

It is now well known that baroreflex sensitivity is reduced in
experimental models of diabetes and diabetic humans (11, 20,
33), and after ovarian hormone deprivation in humans and rats
(10). In this sense, baroreflex sensitivity was reduced in ani-
mals in the DOS group in relation to the ES group, both for
tachycardic and bradycardic responses. However, the barore-
flex sensitivity was similar in animals undergoing aerobic
exercise training on a treadmill (DOTA and DOTC groups)
compared with animals in the ES group. In 1998, the ATRAMI
study (19) provided clinical evidence of the prognostic value of
baroreflex sensitivity and HR variability in postmyocardial
infarction mortality, suggesting that strategies to promote
improvement in baroreflex sensitivity or in HR variability carry
important health implications for the population at cardiovas-
cular risk. In this context, several clinical and experimental
studies have demonstrated the positive role of exercise training
on the baroreflex sensitivity in patients with diabetes (20),
postmenopausal women (16), or ovariectomized diabetic fe-
male rats (33), as observed after aerobic or combined exercise
training in the present study.

Our data provide experimental evidence that effects of exercise training on hemodynamic, cardiovascular autonomic
modulation, and baroreflex sensitivity are independent of any
improvement in glycemic control in ovariectomized diabetic
animals. Moreover, the data from our study suggest that the
improvement in autonomic control of circulation observed
after exercise training may have positively influenced in-
flammation and oxidative stress by promoting hemodynamic
and physical capacity improvements and reducing mortality
in this experimental model of diabetes and menopause. In
fact, there is compelling evidence that the autonomic ner-
vous system is involved in the genesis of cardiometabolic
disorders, causing alterations in inflammatory status and
oxidative stress (4, 35, 36).

Recently, the Diabetes Aerobic and Resistance Exercise
(DARE) trial investigators (31) provided evidence of the ad-
ditional effects of combined exercise training on glycemic
control and aerobic capacity compared with aerobic or resis-
tance training alone in patients with type 2 diabetes. In this
sense, future studies may provide further evidence that both
the critical management of glycemic control and the prevention/
attenuation of cardiovascular autonomic neuropathy, which is
a common dysfunction observed in type 1 or type 2 diabetes,
plays a fundamental role in the prognosis of postmenopausal
women with diabetes.

In conclusion, the results of this study show that aerobic
training, resistance training, or combined exercise training all
lead to reduced mortality, probably due to an increase in
physical capacity and cardiovascular and autonomic benefits
observed after ovarian hormone deprivation in diabetic rats,
regardless of any improvement in glycemic control. However,
in this model, the aerobic and combined exercise training
protocols seem to promote additional cardiovascular auto-
monic benefits compared with resistance training alone.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

C.R.C., M.C.I., and K.D.A. conception and design of research; I.C.S.,
F.F.C., N.B., and J.d.O.B. performed experiments; I.C.S., F.F.C.,
C.R.C., M.C.I., and K.D.A. interpreted results of experiments; I.C.S., F.F.C., and K.D.A. prepared figures; I.C.S.,
F.F.C., and K.D.A. drafted manuscript; I.C.S., E.G., C.R.C., M.C.I., and
K.D.A. edited and revised manuscript; I.C.S., E.G., C.R.C., M.C.I., and
K.D.A. approved final version of manuscript.

REFERENCES

1. Chang KS, Lund DD. Alterations in the baroreceptor reflex control
of heart rate in streptozotocin diabetic rats. J Mol Cell Cardiol 18: 617–624,
1986.

2. De Angelis K, Irigoyen MC, Morris M. Diabetes and cardiovascular
autonomic dysfunction: application of animal models. Auton Neurosci

3. De Angelis KL, Oliveira AR, Dall’Ago P, Peixoto LR, Gadonski G,
Lacchini S, Fernandes TG, Irigoyen MC. Effects of exercise training on
autonomic and myocardial dysfunction in streptozotocin-diabetic rats.

4. De Angelis K, Senador DD, Mostarda C, Irigoyen MC, Morris M.
Sympathetic overactivity precedes metabolic dysfunction in a fructose


44. Downloaded from http://jsp.ampath.org by 10.220.0.33 on September 9, 2017