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Preventive role of exercise training in autonomic, hemodynamic, and metabolic parameters in rats under high risk of metabolic syndrome development

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Moraes-Silva IC, Mostarda C, Moreira ED, Silva KAS, dos Santos F, de Angelis K, Farah VMA V, Irigoyen MC. Preventive role of exercise training in autonomic, hemodynamic, and metabolic parameters in rats under high risk of metabolic syndrome development. *J Appl Physiol* 114: 786–791, 2013. First published January 17, 2013; doi:10.1152/jappphysiol.00586.2012.—High fructose consumption contributes to metabolic syndrome incidence, whereas exercise training promotes several beneficial adaptations. In this study, we demonstrated the preventive role of exercise training in the metabolic syndrome derangements in a rat model. Wistar rats receiving fructose overload in drinking water (100 g/l) were concomitantly trained on a treadmill (FT) or kept sedentary (F) for 10 wk. Control rats treated with normal water were also submitted to exercise training (CT) or sedentarism (C). Metabolic evaluations consisted of the Lee index and glycemia and insulin tolerance test (kITT). Blood pressure (BP) was directly measured, whereas heart rate (HR) and BP variabilities were evaluated in time and frequency domains. Renal sympathetic nerve activity was also recorded. F rats presented significant alterations compared with all the other groups in insulin resistance (in $\text{mg}\cdot\text{dl}^{-1}\cdot\text{min}^{-1}$: F: 3.4 ± 0.2 ; C: 4.7 ± 0.2 ; CT: 5.0 ± 0.5 FT: 4.6 ± 0.4), mean BP (in mmHG: F: 117 ± 2 ; C: 100 ± 2 ; CT: 98 ± 2 ; FT: 105 ± 2), and Lee index (in g/mm: F = 0.31 ± 0.001 ; C = 0.29 ± 0.001 ; CT = 0.27 ± 0.002 ; FT = 0.28 ± 0.002), confirming the metabolic syndrome diagnosis. Exercise training blunted all these derangements. Additionally, FS group presented autonomic dysfunction in relation to the others, as seen by an ~50% decrease in baroreflex sensitivity and 24% in HR variability, and increases in sympathovagal balance (140%) and in renal sympathetic nerve activity (45%). These impairments were not observed in FT group, as well as in C and CT. Correlation analysis showed that both Lee index and kITT were associated with vagal impairment caused by fructose. Therefore, exercise training plays a preventive role in both autonomic and hemodynamic alterations related to the excessive fructose consumption.

fructose; exercise training; autonomic nervous system

SEVERAL STUDIES HAVE SHOWN that poor eating habits and a large increase in fructose consumption in recent years has contributed to the epidemic of metabolic syndrome (2, 5). These unhealthy habits may result in physiological changes that contribute to a higher morbidity and mortality in humans (14). Among these changes, increase of blood pressure, plasma lipids, obesity, glucose intolerance, insulin resistance, and

hyperinsulinemia are the most evident. Additionally, studies have shown an association between these factors as hyperinsulinemia and hypertension, in both humans and animals (10, 21, 36), indicating that once these alterations are present, the higher is the incidence of cardiovascular diseases.

Autonomic nervous system dysfunction also accompanies these metabolic disturbances. Our research group has shown that 8 wk of a high-fructose diet promoted impairment of cardiac autonomic control and a reduction of vagal tone in female rats (6). In addition, this reduction in parasympathetic tone was associated with increased insulin resistance. In male mice, an increase in blood pressure variability after 8 wk of fructose overload was demonstrated (10). This result was accompanied by hypertension during the night (phase in which animals are most active) and increased sympathetic modulation (10). These studies suggest that the autonomic nervous system is a critical target during chronic excessive fructose consumption.

As a non-pharmacological treatment, aerobic exercise training of moderate intensity has been proven effective to mitigate fructose-induced hypertension in rats (28), and in humans it has been considered an important component in the treatment and prevention of cardiovascular disease (7).

Although aerobic exercise is an important non-pharmacological tool in the treatment of cardiovascular diseases (13, 16, 17, 19), little is known about the mechanisms by which exercise acts on the model of a high-fructose diet. Moreover, it is not known whether aerobic exercise of moderate intensity, performed concomitantly with a high-fructose diet, can minimize the cardiovascular, autonomic, and metabolic derangements promoted by a high-fructose diet in rats. Therefore, the aim of this study was to investigate whether moderate aerobic exercise performed during 10 wk of a high-fructose diet in Wistar rats can prevent cardiovascular, autonomic, and metabolic alterations.

METHODS

Ethical approval. This study was performed in accordance with both the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH publication no. 85-23, revised 1996) and by the University of São Paulo Ethical Committee.

Animals. Experiments were performed on male Wistar rats (2-mo-old, 251 ± 10 g) from the Animal Shelter from the University of Sao Paulo, Sao Paulo, Brazil; rats received standard laboratory chow and water ad libitum. The animals were housed in individual cages in a temperature-controlled room (22°C) with a 12-h dark-light cycle. The rats were randomly assigned into one of the four groups: control, sedentary, and receiving standard diet (C; $n = 7$), sedentary receiving high-fructose diet

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(F; $n = 7$), trained receiving standard diet (CT; $n = 7$), and trained receiving high-fructose diet (FT; $n = 7$).

High-fructose diet. The groups assigned to high-fructose diet received an overload of D-fructose (100 g/l) in drinking water for 10 wk. Control animals received only water during this period. Chow and fluid consumption were measured weekly. Caloric intake was calculated considering that 1 g of chow = 2.89 kcal and 1 g of fructose = 4.0 kcal (6).

Exercise training. Moderate-intensity exercise training (50–70% maximal running speed, 0.6–1.3 km/h, 0% inclination) was performed on a treadmill once a day in the early morning, 5 days/wk for 10 wk, as described in detail elsewhere (24).

All animals were adapted to the procedure (10 min/day; 0.3 km/h) for 1 wk before the beginning of the exercise training protocol. Sedentary and trained groups underwent a maximal treadmill test (25, 30). The tests were performed in *weeks 1, 5, and 10* of exercise training to determine aerobic capacity and adequate exercise training intensity.

Glycemia and insulin tolerance test. After 10 wk of fructose overload, blood glucose of all animals was measured after a 4-h fast with a specific device (ACCUCHEK Advantage, Roche, Brazil). Rats were also submitted to an intravenous insulin tolerance test (KITT) after a 2-h fast. Animals were anesthetized with thiopental (40 mg/kg body wt, ip), and a drop of blood from the tail was collected to measure blood glucose. This procedure was performed at baseline and 4, 8, 12, and 16 min after insulin administration (0.75 U/kg). The rate constant for blood glucose disappearance was calculated using the formula $0.693/t_{1/2}$, and where $t_{1/2}$ is the blood glucose half-time, which was calculated from the slope of the least squares regression of the blood glucose concentration during the linear phase of decline (6).

Obesity parameter in rats. Lee index for each animal was calculated to obtain obesity parameter at the end of the protocol. This index was calculated by the cube root of body weight (g) \times 10/naso-anal length (mm), for which a value ≤ 0.300 was classified as normal at the *month 3* of life. For values >0.300 , the rats were classified as obese (3).

Cardiovascular assessments. After the last training session, two catheters filled with 0.06 ml of saline were implanted into the femoral artery and vein (PE-10) while the animals were anesthetized (Ketamine 80 mg/kg + Xylazine 12 mg/kg) for direct measurements of arterial pressure (AP) and drug administration, respectively.

Rats were studied one day after catheter placement; the rats were conscious and allowed to move freely during the experiments. The arterial cannula was connected to a strain-gauge transducer (P23Db, Gould-Statham, Oxnard, CA), and AP signals were recorded over a 30-min period by a microcomputer equipped with an analog-to-digital converter board (Windaq, 2-kHz sampling frequency; Dataq Instruments, Akron, OH). The recorded data were analyzed on a beat-to-beat basis to quantify changes in mean AP and heart rate (HR). HR variability was determined by using the standard deviation of the basal HR recording period (25).

Sequential bolus injections of increasing doses of phenylephrine (0.25–32 μ g/kg) and sodium nitroprusside (0.05–1.6 μ g/kg) were given to induce responses at four doses (for each drug) ranging from 5 to 40 mmHg. A 3- to 5-min interval between doses was necessary for AP to return to baseline. Peak increases or decreases in mean AP after phenylephrine or sodium nitroprusside injection and the corresponding peak reflex changes in HR were recorded for each dose of the drug. Baroreflex sensitivity (BRS) was evaluated by a mean index, calculated by the ratio between changes in HR to the changes in mean AP, allowing a separate analysis of bradycardic and tachycardic responses. The mean index was expressed as $\text{beats}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$, as described elsewhere (34).

Blood pressure and pulse interval variability. Time-domain analysis consisted of calculating the mean pulse interval (PI) and systolic blood pressure (SBP), as well as their variability as the standard deviation from their respective time series. In the frequency-domain analysis, fast Fourier transforming method (FFT) was used to evaluate

systolic blood pressure, pulse interval, and RR interval variability (SBPV and PIV, respectively). The spectral bands for rats [very low frequency (VLF): 0.0–0.2 Hz; low frequency (LF): 0.2–0.75 Hz; high frequency (HF): 0.8–2.8 Hz] were defined as in previous studies (26, 33). Spectral power for LF and HF bands was calculated by means of power spectrum density integration within each frequency bandwidth. The power density of each spectral component was calculated both in absolute values and in normalized units. Power in LF and in HF for pulse intervals was normalized by calculating the variance minus the power in VLF and were expressed in normalized units (nu). The sympathovagal balance was defined by the LFnu-to-HFnu ratio. The LF components of the PIV and LF components of the SBPV were considered markers of efferent sympathetic cardiac and vascular modulation, respectively, whereas the HF component of the PIV reflected respiratory-driven vagal modulation to the sinoatrial node. For frequency-domain analysis, the entire 10-min time series of blood pressure and pulse, or RR intervals, were evaluated under basal conditions using non-parametric methods (FFT), described in detail above. Beat-to-beat values of SBP and PI intervals were used to estimate the BRS by spectral analysis, using the alpha index for the LF band (0.20–0.75 Hz). The alpha index analysis evaluates short-term changes in the systolic blood pressure and in the RR interval. This method has been proposed to quantify cause-and-effect events linked with the baroreflex. Indeed, several studies showed a good correlation between the alpha index and the consequences of systemic phenylephrine infusions. The coherence between the PI and the SBP signal variability was assessed by means of a cross-spectral analysis. The alpha index in the LF band was calculated only when the magnitude of the squared coherence between the PI and SBP signals exceeded 0.5 (range, 0–1). After coherence calculation, the alpha index was obtained from the square root of the ratio between PI and SBP variability in the two major LF bands (29, 36).

Renal sympathetic nerve activity. On the day of the experiment, a thin bipolar platinum electrode was placed around a branch of the left renal nerve and insulated with silicone rubber (Wacker Sil-Gel 604) while the rat was under pentobarbital anesthesia. Measurements were performed 4–6 h after complete rat recovery. The signal from the nerve electrode was recorded after being amplified (Tektronix 5A22N differential amplifier), filtered (band-pass filter, 100 Hz to 2 kHz), and processed according to a previous study by our group (22). To compare different groups of rats, renal sympathetic nerve activity (RSNA) values were expressed as a percentage of the maximal (100%) and minimal (0%) nerve activity during 1,000 cardiac cycles, as described previously (22). Normalization was necessary to account for the varying intensity of the recorded signal, consistent with its multifiber nature. Briefly, values of maximal and minimal nerve activity (100 and 0%) were determined from the 3% of the recorded cardiac cycles that showed the highest and lowest activity levels.

Statistical analysis. Data were analyzed post-intervention and are reported as means \pm SE. ANOVA (two-way) was used to compare groups, followed by the Student-Newman-Keuls post hoc test. Pearson correlation was used to study the association between variables. Significance was considered when $P < 0.05$.

RESULTS

Metabolic evaluations. Caloric intake (in kcal/wk: C = 387.5 ± 8.5 , CT = 390.0 ± 9.2 , F = 376.8 ± 10.7 , and FT = 379.2 ± 8.9) and naso-anal length (in cm: C = 25.94 ± 0.2 , CT = 25.51 ± 0.3 , F = 26.53 ± 0.13 , and FT = 26.06 ± 0.25) were similar among the groups. Body weight was higher in F group than in the other groups (Fig. 1A). Consequently, Lee index was increased in F group compared with the other groups (Fig. 1B). Lee index was similar between C and FT groups.

Glycemia was also increased in F group after 10 wk of fructose overload compared with control rats, but there was no difference

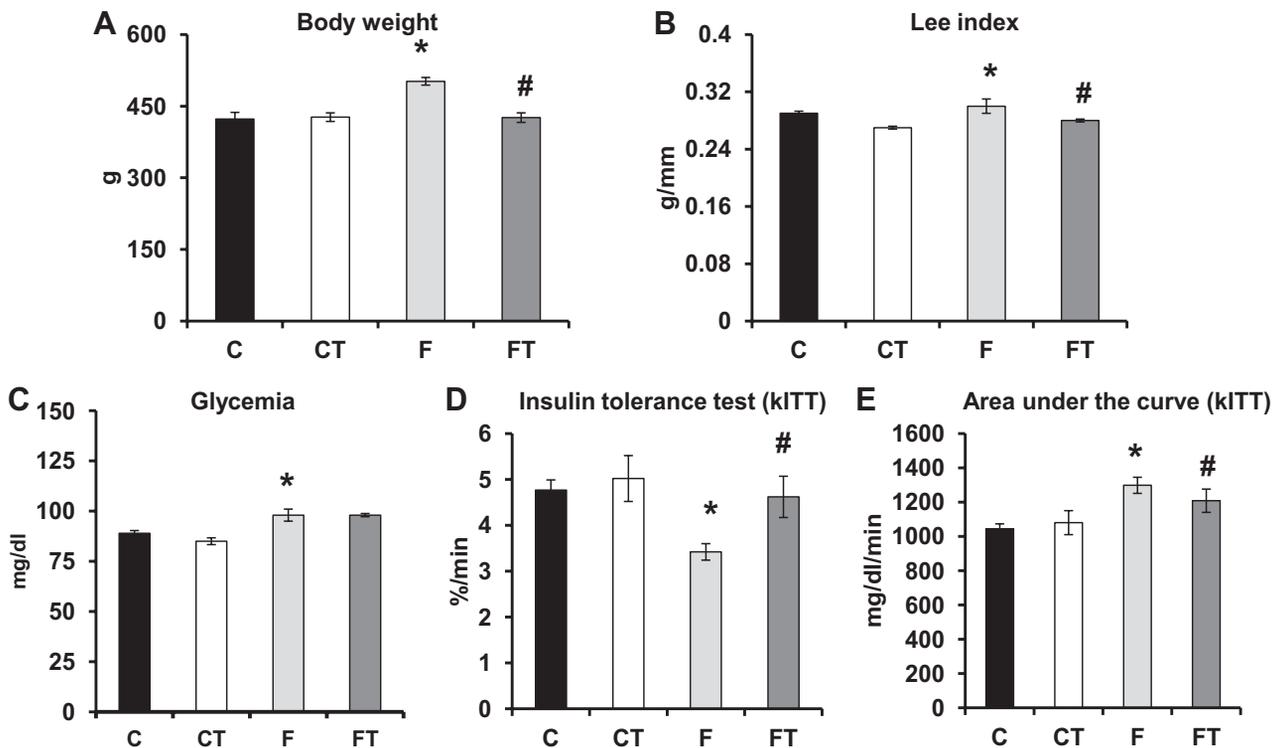


Fig. 1. Metabolic parameters. C, control rats; CT, control rats trained on a treadmill; F, fructose-fed rats; FT, fructose-fed rats trained on a treadmill. *Significant difference vs. C and CT (two-way ANOVA; $P < 0.05$). #Significant difference vs. F (two-way ANOVA; $P < 0.05$).

in relation to F and FT groups for glycemia (Fig. 1C). The rate constant for blood glucose disappearance (kITT) was reduced in F rats compared with C, CT, and FT rats; thus the area under the curve was increased in F group (Fig. 1, C and D, respectively). Exercise training prevented this alteration.

Hemodynamic evaluations. The direct BP evaluation performed during the protocol showed that the fructose-fed group presented an increase in systolic, diastolic, and mean arterial pressure compared with the other groups. Resting HR values were similar among C, F, and FT groups. Resting bradycardia was observed in CT rats compared with sedentary controls (Table 1). The F group showed a marked reduction in bradycardic (BR) and tachycardia (TR) responses in relation to the other groups. Exercise training prevented this baroreflex sensitivity impairment, as FT and C groups presented similar results for BR and TR responses.

HRV and SBPV in time and frequency domains. The results of HRV, RMSSD (the square root of the mean squared difference of successive R-R intervals), and SBPV are presented in Table 1. The HRV and RMSSD were lower in the F group compared with the C, CT, and FT groups, which were similar among them. SBPV increased in the F group compared with the C group. FT showed similar SBPV compared with the C group. The absolute LF and absolute HF power components of HRV were similar among groups (absolute LF = 4.07 ± 0.38 ms² in F, 2.79 ± 0.27 ms² in C, 4.07 ± 0.38 ms² in CT, and 3.17 ± 0.68 ms² in FT; absolute HF = 7.42 ± 1.29 ms² in F, 12.07 ± 0.84 ms² in C, 13.55 ± 1.3 ms² in CT, and 10.27 ± 1.9 ms² in FT). However, normalized LF component of HRV was increased in the F group compared with the C, CT, and FT groups (Fig. 2A). Furthermore, normalized HF component of HRV was lower in the F group compared with the other

Table 1. Hemodynamic and autonomic variables in time domain

Variable	C	CT	F	FT
SAP, mmHg	121 ± 3	117 ± 3	141 ± 4*	125 ± 3#
MAP, mmHg	100 ± 2	98 ± 2	117 ± 2*	105 ± 2#
DAP, mmHg	82 ± 3	85 ± 4	100 ± 2*	89 ± 3#
HR, beats/min	330 ± 7	307 ± 7*	337 ± 10	323 ± 9
TR, beats · min ⁻¹ · mmHg ⁻¹	3.50 ± 0.36	3.61 ± 0.23	1.61 ± 0.87*	2.96 ± 0.45#
BR, beats · min ⁻¹ · mmHg ⁻¹	2.45 ± 0.24	2.67 ± 0.41	1.36 ± 0.22*	2.39 ± 0.33#
HRV, ms ²	83 ± 4	82 ± 7	63 ± 6*	85 ± 5#
SAPV, mmHg ²	26 ± 3	24 ± 4	37 ± 2*	29 ± 3#
RMSSD, ms	6.97 ± 0.11	6.5 ± 0.50	4.96 ± 0.45*	6.76 ± 0.58#

Values are mean ± SE. Results of systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP), heart rate (HR), heart rate variability (HRV), systolic arterial pressure variability (SAPV), the root mean square successive difference (RMSSD), tachycardic (TR), and bradycardic (BR) responses to arterial pressure changes. C, control rats; CT, control rats trained on a treadmill; F, fructose-fed rats; FT, fructose-fed rats trained on a treadmill. *Significant difference vs. C and CT (two-way ANOVA; $P < 0.05$). #Significant difference vs. F (two-way ANOVA; $P < 0.05$).

groups. Consequently, sympathovagal balance was significantly increased in F rats (Fig. 2C). Although there was no statistical difference, CT rats presented a tendency to increase the HF component of HRV (Fig. 2B). Additionally, the LF component of SBPV was increased in the F group compared with the C and FT groups (Fig. 2D). Baroreflex sensitivity (alpha index) was reduced in the F group compared with the other groups (Fig. 2E). Exercise training prevented autonomic dysfunction promoted by fructose overload, as the FT and C groups presented similar results for all variables in HRV and SBPV in time and frequency domains.

RSNA. The results of direct RSNA are presented in Fig. 3. Fructose overload group (F) increased the activity of the renal nerves compared with the other groups, which showed similar results among them.

Correlation analysis. Correlation analyses were carried out by associating autonomic and metabolic parameters. The rate constant calculated from the kITT test was associated with both vagal indexes, RMSSD and HF ($r = 0.6$, $P = 0.002$ and $r = 0.7$, $P = 0.0008$, respectively). Furthermore, LF component of BPV, sympathovagal balance, and SBPV showed negative correlations with kITT ($r = -0.6$, $P = 0.01$; $r = -0.6$, $P = 0.03$; and $r = -0.6$, $P = 0.009$, respectively). Additionally, negative correlations were observed between autonomic parameters (RMSSD, HF%, and HRV) and Lee index ($r = -0.6$,

$P = -0.004$; $r = -0.6$, $P = 0.005$; and $r = -0.7$, $P = 0.003$, respectively). kITT and Lee index were also negatively correlated ($r = -0.7$, $P = 0.002$).

DISCUSSION

The main finding of the present study was that aerobic exercise of moderate intensity during 10 wk performed concomitantly with a high-fructose diet prevented the deleterious effects induced by fructose overload in rats in hemodynamics, autonomic, and metabolic parameters.

Metabolic, hemodynamics, and autonomic changes induced by fructose overload. Although high fructose consumption promoted an increase in glycemia compared with control rats, these values were still in the normality range. Other studies, even with longer periods of high-fructose diet, did not find sharp alterations in glycemia (1, 6). In fact, this model characterizes an increase in insulin resistance and not hyperglycemia (1, 6).

Likewise, studies in humans have demonstrated that consumption of fructose can induce weight gain, reduced insulin sensitivity, dyslipidemia, and high blood pressure (9). Although caloric intake was similar among groups, it is noticeable that chronic fructose consumption results in altered production and secretion of appetite regulating hormones and

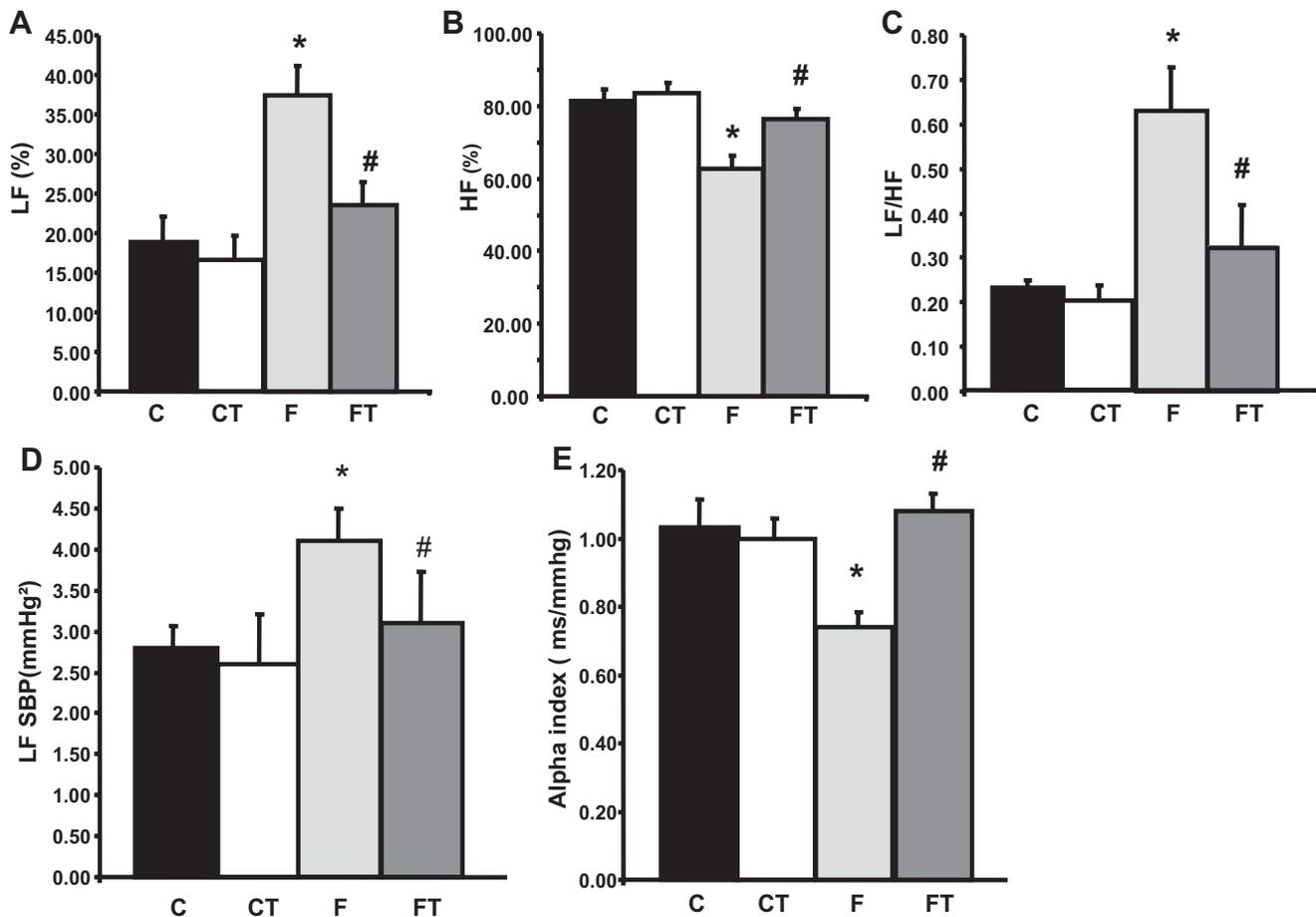


Fig. 2. Heart rate variability expressed by normalized components of low- (A) and high-frequency (B) components, sympathovagal balance (C), and estimated baroreflex in frequency domain by the alpha index (E). Systolic blood pressure variability in the frequency domain was expressed by the absolute low-frequency (D) components. *Significant difference vs. C and CT (two-way ANOVA; $P < 0.05$). #Significant difference vs. F (two-way ANOVA; $P < 0.05$).

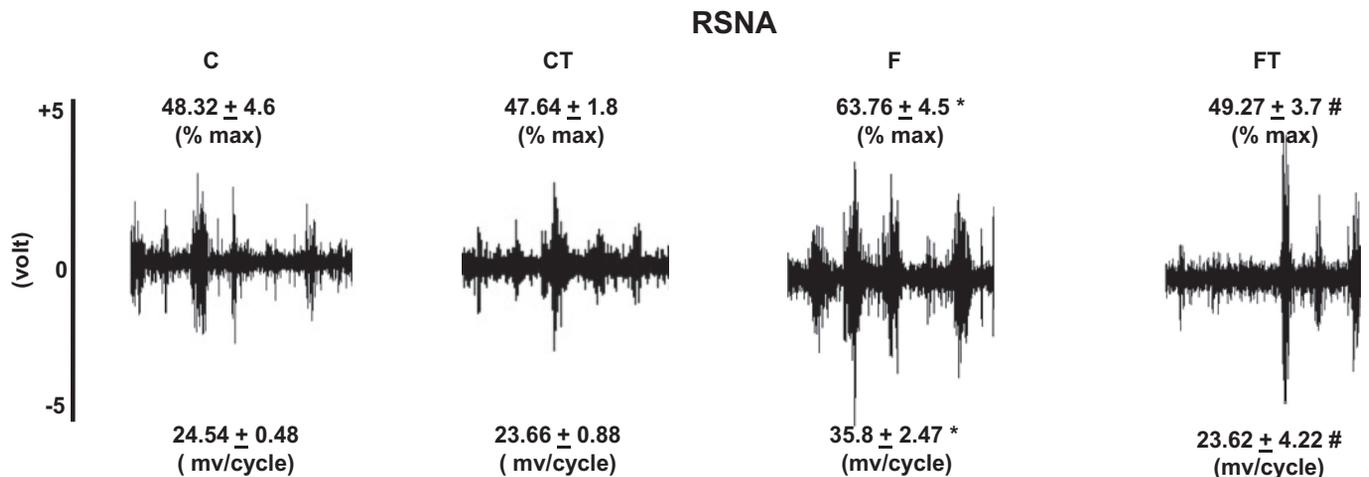


Fig. 3. Direct record of renal sympathetic nerve activity (RSNA). RSNA expressed by mv/cycle measured in C, F, and FT rats. *Significant difference vs. C and CT (two-way ANOVA; $P < 0.05$). #Significant difference vs. F (two-way ANOVA; $P < 0.05$).

peptides, for instance, ghrelin, leptin, and PYY, thus contributing to fat and weight gain (20). Furthermore, several studies identified in obese subjects an increase in plasma catecholamine levels (35, 37), cardiovascular autonomic abnormalities, and activation in renin-angiotensin system (18). Moreover, the sympathetic nervous system seems to play a primary role in metabolic and cardiovascular alterations present in metabolic syndrome (18, 23, 29).

High levels of fructose consumption promoted impairment in metabolic parameters and cardiac autonomic control by reduction of vagal tone and an increase in sympathetic modulation with additional insulin resistance after 8 wk of fructose overload in female rats (6). In mice, fructose overload promoted activation in renin-angiotensin system (11).

Furthermore, sympathetic hyperactivity contributes to insulin resistance, resulting in alpha 1-adrenoceptor activation. This sympathetic activation can cause a reduction in blood flow and therefore a reduction in glucose delivery to the skeletal muscle (27).

As mentioned above, our study showed increased renal sympathetic activity in F rats. Increase in renal sympathetic activity can modulate renal glucose reuptake by GLUT1 and GLUT2 expression. Furthermore, a previous study has demonstrated that hyperglycemia in diabetes associated with a hypertension condition increased sympathetic activity and GLUT2 expression (115% elevation), contributing to nephropathy. Interestingly, renal sympathetic denervation in these animals contributed to lower GLUT2 expression. These data demonstrate the neural regulation effect in GLUT2 expression (31, 32). Since exercise training decreased renal sympathetic activity, we may postulate that the FT rats are prevented from renal damage in relation to the sedentary ones.

Preventive effect of physical exercise during fructose overload. Except from glycemia, all the hemodynamic, autonomic, and metabolic derangements observed in F group were prevented by exercise training. However, it is noticeable that F rats presented only a slight increase in glycemia, with levels kept within the normal range (up to 99 mg/dl). Therefore, exercise training did not alter it.

Possibly, exercise training during fructose overload enhanced the energetic demand and lipolysis, preventing weight gain and

triglycerides augment, which contributed to the improved insulin sensitivity, thus attenuating the autonomic changes and maintaining blood pressure in the normal ranges. In fact, the reduction of weight, intra-abdominal adiposity, and insulin resistance by exercise may interfere with other mechanisms of action in the treatment of hypertension, since hypertension has been associated with all these variables (15).

Several studies have shown the importance of physical training as non-pharmacological treatment of cardiovascular diseases (15, 17, 25, 34). The regular practice of physical exercise can promote chronic metabolic and cardiovascular adaptations. It is known that regular exercise improves glycemia, lipid profile (8), and insulin sensitivity, promotes weight reduction, and improves muscle glucose uptake. In diabetic and hypertensive rats, physical training has been important in the treatment of metabolic and autonomic disorder by contributing to the improvement in HRV, baroreflex sensitivity, vagal modulation, and blood pressure (4, 25, 28). Additionally, exercise training can influence metabolic, hemodynamic, and autonomic control even in healthy individuals (12, 19).

A recent study evaluated the time course of metabolic syndrome establishment in fructose-fed mice and reported that the autonomic dysfunction preceded the metabolic alterations (1). Interestingly, in the present study, we showed that the cardiovascular autonomic parameters in FT rats were kept similar to control ones. It indicates that the main target of the preventive role of the exercise training may be the autonomic nervous system. Once the autonomic function is preserved, metabolic alterations were prevented by the exercise training in this metabolic syndrome model.

Although some limitations of the present study have to be addressed (for instance, the lack of data on the functional analysis of the cardiovascular system, as well as further investigations on the mechanisms underlying exercise training preventive role), our observations on the hemodynamic, autonomic, and metabolic profiles led us to conclude that exercise proved to be an effective option to prevent the derangements promoted by a high-fructose diet in rats.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: I.C.M.-S., C.T.M., E.D.M., and K.A.d.S.S. performed experiments; I.C.M.-S., C.T.M., and F.d.S. analyzed data; I.C.M.-S., C.T.M., K.D.A., and V.d.M.A.F. interpreted results of experiments; I.C.M.-S. and C.T.M. prepared figures; I.C.M.-S. and C.T.M. drafted manuscript; I.C.M.-S., C.T.M., K.D.A., V.d.M.A.F., and M.C.I. edited and revised manuscript; I.C.M.-S., C.T.M., and M.C.I. approved final version of manuscript; M.C.I. conception and design of research.

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