2024, Retos, 55, 302-306

Association between exercise training and açai on calcium homeostasis and inflammation in the heart of rats submitted to a high-fat diet

Asociación entre el entrenamiento físico y el açai sobre la homeostasis del calcio y la inflamación en el corazón de ratas sometidas a una dieta rica en grasas

*Victor Neiva Lavorato, *Denise Coutinho de Miranda, **Luciano Bernardes Leite, ***Marcelo Eustáquio Silva, **Antônio José Natali

*Governador Ozanam Coelho University Center (Brazil), **Federal University of Viçosa (Brazil), *** Federal University of Ouro Preto (Brazil)

Abstract. The aim of the present study was to investigate the effects of the association of treatments with aerobic exercise training (AET) and açai supplementation on calcium homeostasis (Ca^{2+}) and inflammatory markers of the heart of rats submitted to a high-fat diet. Fisher rats were used, divided into five experimental groups: Control (C), High-fat Diet (H); High-fat Diet + Açai (HA); High-fat Diet + AET (HT); High-fat Diet + Açai + AET (HAT). The groups fed a high-fat diet received 21.8% lard and 1% cholesterol. The groups supplemented with lyophilized açai received 1% of açai in the diet. The animals in the trained groups were submitted to a progressive treadmill running program for 8 weeks. At the end, the hearts were dissected, and the left ventricles separated for real-time PCR analysis. The HT group had higher gene expression of ryanodine receptor type 2 (RyR2) compared to group H. Regarding the sodium/calcium exchanger (NCX), group H had lower gene expression compared to the other groups. Interleukin 10 (IL-10) was high in group HT when compared to group H. The treatments changed parameters of Ca^{2+} homeostasis and inflammation, but the association of interventions did not provide additional effects.
Keywords: Exercise training; Açai; Contractility; Inflammation; Heart.

Resumen. El objetivo del presente estudio fue investigar los efectos de la asociación de tratamientos con entrenamiento con ejercicios aeróbicos (AET) y suplementación con açai sobre la homeostasis del calcio (Ca^{2+}) y los marcadores inflamatorios del corazón de ratas sometidas a una dieta rica en grasas. Se utilizaron ratas Fisher, divididas en cinco grupos experimentales: Control (C), Dieta Alta en Grasas (H); Dieta alta en grasas + Açai (HA); Dieta alta en grasas + AET (HT); Dieta alta en grasas + Açai + AET (HAT). Los grupos alimentados con una dieta rica en grasas recibieron 21,8% de manteca de cerdo y 1% de colesterol. Los grupos suplementados con açai liofilizado recibieron un 1% de açai en la dieta. Los animales de los grupos entrenados fueron sometidos a un programa de carrera progresiva en cinta rodante durante 8 semanas. Al final, se diseccionaron los corazones y se separaron los ventrículos izquierdos para el análisis de PCR en tiempo real. El grupo HT tuvo una mayor expresión genética del receptor de rianodina tipo 2 (RyR2) en comparación con el grupo H. En cuanto al intercambiador de sodio/calcio (NCX), el grupo H tuvo una menor expresión genética en comparación con los otros grupos. La interleucina 10 (IL-10) fue alta en el grupo HT en comparación con el grupo H. Los tratamientos cambiaron los parámetros de la homeostasis del Ca^{2+} y la inflamación, pero la asociación de intervenciones no proporcionó efectos adicionales.
Palabras clave: Entrenamiento de ejercicio; açai; Contractilidad; Inflamación; Corazón.

Fecha recepción: 28-11-23. Fecha de aceptación: 10-03-24
Luciano Bernardes Leite
luciano.leite@ufv.br

Introduction

In Western countries, about 40% of the diet comprises lipids, exceeding nutritional recommendations by 5 to 10% (Gaillard, Passilly-Degrace, & Besnard, 2008). The consumption of high-fat diets leads to various cardiovascular alterations, including increased left ventricular (LV) mass and thickness, diastolic dysfunction, endothelial dysfunction, oxidative stress, elevated triacylglycerol content, and the release of cytokines and chemokines into the systemic circulation. Additionally, high-fat diets have deleterious effects on cardiac contractility and calcium homeostasis (Ca^{2+}) (Sánchez et al., 2018; VanWagner et al., 2015).

Non-pharmacological treatments for the effects of a high-fat diet often involve the consumption of açai (Euterpe oleracea Martius). This fruit is particularly rich in polyphenols, which exhibit broad antioxidant activity by neutralizing reactive oxygen species (Schauss et al., 2006). Açai has demonstrated its anti-inflammatory properties by reducing lipid peroxidation, subsequently lowering the activation of nuclear factor kappa B (NF-κB), or inhibiting the activity of cyclooxygenases (COX-1 and COX-2) (Browning & Horton, 2004; Schauss et al., 2006). Additionally, by offering cardioprotection, açai can contribute to more efficient Ca^{2+} homeostasis and enhance heart contractile mechanics.

Aerobic exercise training (AET) represents another effective strategy against the cardiac damage induced by a high-fat diet. A significant portion of the benefits attributed to AET is linked to its anti-inflammatory capacity. Studies have shown a reduction in the inflammatory infiltrate in the hearts of animal models subjected to both a high-fat diet and AET (Chen et al., 2019). Moreover, AET is known to modulate proteins responsible for the contraction and relaxation of cardiomyocytes, leading to improvements in intracellular Ca^{2+} transient and cardiomyocyte mechanics (Natali, Turner, Harrison, & White, 2001). These favorable effects of AET on contractility have been observed in obese animals subjected to a high-fat diet (Paulino et al., 2010; Silveira et al., 2017). However, the effects of combining açai supplementation with AET on

the hearts of animals subjected to a high-fat diet are not well-understood. Recently, (Lavorato et al., 2021) identified positive effects of treatments involving açai and AET on the contractile mechanics of cardiomyocytes and oxidative stress in the hearts of rats fed a high-fat diet. Therefore, we hypothesize that treatments through physical training and açai supplementation can reduce the damage caused by a high-fat diet on calcium homeostasis and inflammatory markers in cardiac tissue. The objective of the current study is to investigate the impact of combining AET with açai supplementation on Ca^{2+} homeostasis and inflammatory markers in the hearts of rats exposed to a high-fat diet.

Materials and Methods

The study involved Fischer rats aged 60 days, divided into five experimental groups (n = 6 each): Control (C), High-fat Diet (H), High-fat Diet + Açai (HA), High-fat Diet + Aerobic Exercise Training (HT), and High-fat Diet + Açai + Aerobic Exercise Training (HAT). The rats were housed in boxes with a 12/12-hour light-dark cycle at a controlled temperature of 22°C (Lavorato et al., 2016). Weekly measurements were taken to monitor body weight gain. The research protocols and procedures were approved by the Ethics Committee for the Use of Animals at the Federal University of Ouro Preto (Ethics Committee approval number: 22/2016).

The groups were introduced to their respective diets two weeks before the initiation of the Aerobic Exercise Training (AET) period, allowing the animals to acclimate to the diets. Group C was provided with the standard AIN-93M diet (Reeves, Nielsen, & Fahey Jr, 1993). Groups H and HT were given a modified high-fat diet (21.8% lard and 1% cholesterol). Groups HA and HAT were supplied with a modified diet consisting of freeze-dried açai (Liotécnica, Brazil) (21.8% lard, 1% cholesterol, and 1% freeze-dried açai) (Table 1).

The nutritional composition of freeze-dried açai pulp per 100 g included 541 kcal, 5 g of total carbohydrates, 9.8 g of protein, 54 g of total fat, and 27 g of dietary fiber, as per the supplier's information (Liotécnica, Brazil). Freeze-dried açai pulp demonstrated an antioxidant capacity (ORACFL) of 70,000 μmol (Eq. Trolox/100 g), total polyphenols of 3300 mg (eq. gallic acid/100 g), and anthocyanins of 385 mg/100g, according to the manufacturer (Liotécnica, Brazil). These values surpass those reported for filtered açai pulp, which typically has total polyphenols ranging from 118.13 to 458.60 mg (eq. gallic acid/100 g) and anthocyanins from 6.45 to 31.0 mg/100 g (Bonomo et al., 2014; Pereira et al., 2016).

AET was conducted using a treadmill (AVS Projetos, Brazil) for 5 sessions per week, each lasting 60 minutes, at an intensity of 60-70% of the maximum running speed (MRS), over a period of 8 weeks (Carneiro-Júnior et al., 2013). Prior to commencing AET, the animals underwent an adaptation phase on the treadmill (10 min/day, 5 m/min). After a 48-hour rest period, the exercise tolerance test on the treadmill was conducted to determine the MRS and the total time until fatigue (TTF). This test was repeated after 4 weeks of training for load readjustment and again after 8 weeks of training to assess the final running capacity.

Table 1.
Composition of the diets (g/Kg of diet).

Nutrients	C	H/HT	HA/HAT
Casein	198,3	198,3	198,3
Corn starch	563,3	335,3	325,3
Soybean oil	40,0	40,0	40,0
Lard	-	218,0	218,0
Cholesterol	-	10,0	10,0
Choline	2,5	2,5	2,5
Mineral mixture	35,0	35,0	35,0
Vitamins mixture	10,0	10,0	10,0
Cellulose	50,0	50,0	50,0
Saccharose	100,0	100,0	100,0
L- methionine	0,9	0,9	0,9
Lyophilized açai	-	-	10,0
Total	1000,0	1000,0	1000,0

C, Control. H, High-fat diet. HA, High-fat diet + Açai. HT, High-fat diet + AET. HAT, High-fat diet Açai + AET.

Left ventricle samples (50 mg) underwent homogenization for RNA isolation using trizol (Invitrogen, São Paulo, SP, Brazil) (Drummond et al., 2023). Quantification of messenger RNA (mRNA) levels of beta-actin (β-actin), ryanodine receptor type 2 (RyR2), sarcoplasmic reticulum calcium ATPase (SERCA2a), phospholamban (PLB), sodium/calcium exchanger (NCX), interleukin 6 (IL-6), and interleukin 10 (IL-10) was performed using the real-time polymerase chain reaction (qRT-PCR) technique. For reverse transcription (cDNA), 2μg of total RNA was combined with oligo dT (0.5 μg), RiboLockTM RNAse inhibitor (20U), 1mM dNTP Mix, and RevertAidTM Reverse Transcriptase (200U) to form a solution with a final volume of 20 μL (Fermentas, Glen Burnie, MD, USA). This mixture was incubated for 60 minutes at 42°C, followed by 10 minutes at 70°C, completing the reverse transcription process.

Gene expression analysis was conducted via qRT-PCR, utilizing primers (Thermo Fisher Scientific, USA) and Power SYBR Green PCR (Thermo Fisher Scientific, USA). Fluorescence quantification and band amplification analysis were carried out using the ABI Prism 7500 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). The results were expressed using the comparative cycle threshold (Ct) method, and delta Ct (ΔCt) values were calculated for each sample and gene of interest, with β-actin as the normalizer. The relative changes in the expression level of the gene of interest (ΔΔCt) were calculated by subtracting the mean of the ΔCt of the control group from the corresponding ΔCt of each sample in the other groups, followed by 2(-ΔΔCt).

The values for the control group were arbitrarily set to 1 for representative purposes. The sequence of primers used is provided in Table 2.

Table 2.
Real-time PCR primer sequence.

	Forward	Reverse
β-actin	AGCCATGTACGTAGCCAT	CTCTCAGCTGTGGTGGTGAA
RyR2	TGGCAAAGAGTTGTCAC-GATG	CTTTTCCTTGCTGCGTTGGG
SERCA2a	TGTTCGCGTGGACCTCAAAT	CCCAGTATGCCCGCTATCTC
NCX	GTGGCCCTCACCATTATTCG	ACACCAGTAAATTCAGCGCC
PLB	AGGCATTCTACAACACAGCA	CGAATCAGCATGCCTTCAGC
IL-6	TCTACCCCAACTTCCAATGC TC	TTGGATGGTCTGGTCCTTAG CC
IL-10	TTGAACCACCCGGCATCTAC	CCAAGGAGTTGCTCCCGTTA
β-actin	AGCCATGTACGTAGCCAT	CTCTCAGCTGTGGTGGTGAA
RyR2	TGGCAAAGAGTTGTCAC-GATG	CTTTTCCTTGCTGCGTTGGG

The data are presented as mean ± standard error of the mean. The normality of the data was assessed using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) with Tukey post-hoc or Kruskal-Wallis with Dunn's post hoc analysis were employed for statistical comparisons. To compare the initial and final TTF in the same group, the paired T test was performed. A significance level of $p < 0.05$ was adopted for all analyses. The data were analyzed using GraphPad Prism 6.0® software.

Results

In Figure 1, the data illustrate the weight gain and TTF for the experimental groups. The group treated with açai (HA) (168.30 ± 29.20g) exhibited a significantly greater weight gain compared to the C (127.70 ± 22.90g), HT (131.60 ± 14.23g) and HAT (15.30 ± 18.77g) groups (ANOVA one-way - $p = 0.0003$). Both the HT (19.95 ± 5.15min *vs* 31.26 ± 5.03min) and HAT (20.44 ± 4.37min *vs* 33.13 ± 4.40min) groups demonstrated a significant increase in TTF at the end of the experiment compared to the beginning ($p < 0.0001$ and $p = 0.0001$, respectively) and exhibited higher TTF compared to the other groups (HT = 31.26 ± 5.03min and HAT = 33.13 ± 4.40min *vs* C = 17.43 ± 4.48, H = 17,63 ± 4.53, and HA = 16.84 ± 3.64) at the end of the intervention period (ANOVA one-way - $p < 0.0001$).

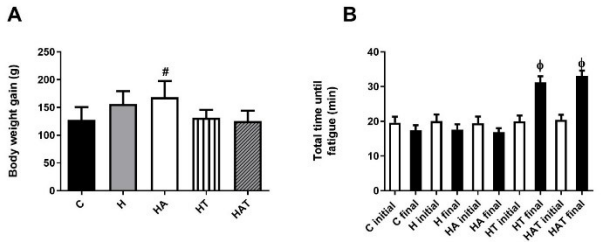

Figure 1. Body weight gain and total time to fatigue in the experimental groups. C, Control. H, High-fat Diet. HA, High-fat Diet + Açai. HT, High-fat Diet + AET. HAT, High-fat Diet + Açai + AET. Data are presented as mean and mean standard error. ANOVA one way with Tukey post-hoc analysis or Kruskal-Wallis with Dunn's post hoc and paired T test were performed. #, difference for groups C, HA, and HAT. Φ, difference for their initial pairs and for the other groups at the end of the experiment.

Figure 2 presents the mRNA expression levels of proteins involved in Ca^{2+} homeostasis in left ventricular cardiomyocytes. Specifically, for RyR2, the HT group (2.47 ± 0.80) exhibited significantly higher expression compared to the H group (0.80 ± 0.32) (ANOVA one-way - $p = 0.0233$) (Figure 2A). However, the expressions of SERCA2a and PLB did not exhibit significant changes between the groups (ANOVA one-way - $p > 0.05$) (Figure 2B and 2C, respectively). Notably, the expression of NCX was significantly lower in the H group (0.24 ± 0.10) compared to the othe0r groups (C = 1.00 ± 0.00, HA = 2.33 ± 1.31, HT = 3.41 ± 0.95, and HAT = 2.13 ± 1.42) (ANOVA one-way - $p = 0.0002$) (Figure 2D).

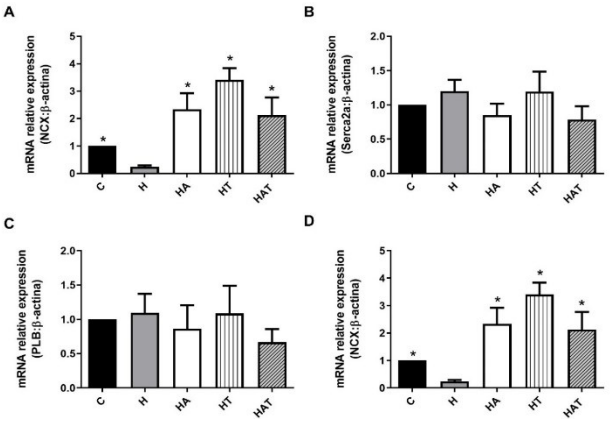

Figure 2. Expression of genes responsible for Ca^{2+} homeostasis in left ventricular cardiomyocytes of experimental animals. C, Control. H, High-fat Diet. HA, High-fat Diet + Açai. HT, High-fat Diet + AET. HAT, High-fat Diet + Açai + AET. Data are presented as mean and mean standard error. ANOVA one way with Tukey post-hoc or Kruskal-Wallis with Dunn's post hoc analysis were performed. *, difference to H group.

Figure 3 depicts the evaluation of left ventricular inflammation through the measurement of IL-6 and IL-10 gene expression. Concerning IL-6, no significant differences were observed between the evaluated groups (ANOVA one-way - $p > 0.05$) (Figure 3A). Notably, IL-10 exhibited elevation specifically in HT group (3.11 ± 2.15) compared to H group (0.91 ± 0.16) (ANOVA one-way - $p = 0.0221$) (Figure 3B).

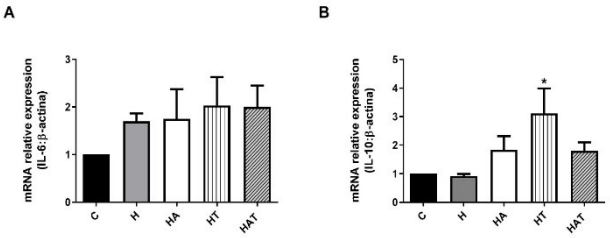

Figure 3. IL-6 and IL-10 mRNA expression in the left ventricle of experimental animals. C, Control. H, High-fat Diet. HA, High-fat Diet + Açai. HT, High-fat Diet + AET. HAT, High-fat Diet + Açai + AET. Data are presented as mean and mean standard error. ANOVA one way with Tukey post-hoc or Kruskal-Wallis with Dunn's post hoc analysis were performed. *, difference to H group.

Discussion

In this study, the influence of the association of treatments with AET and supplementation with açai on Ca^{2+} homeostasis and inflammatory parameters of the heart of rats

submitted to a high-fat diet was verified. The results show that AET increased the gene expression of RyR2, NCX and IL-10. Açai treatment increased NCX mRNA levels. The combination of treatments did not enhance the isolated effects.

The animals in the HT and HAT groups showed low body weight gain and increased TTF at the end of the intervention period. It is known that continuous aerobic exercise causes cardiovascular and neuromuscular adaptations, increasing running capacity (Kemi, Ellingsen, Smith, & Wisloff, 2008). In addition, AET increases energy expenditure, improving body weight control, as observed in the study (Burke et al., 2017). Other researches involving the use of the AET observed similar behaviors regarding body weight gain and TTF (Lavorato et al., 2021; Paulino et al., 2010).

The present study showed a reduction in NCX gene expression in the LV of animals that consumed a high-fat diet. Diastolic dysfunction can be induced by increased collagen content and damage to proteins such as SERCA2a and NCX (Lima-Leopoldo et al., 2014). It was observed that obese rats showed increased NCX protein levels, with reduced expression of microRNA-1, which targets the NCX mRNA, corroborating the findings of this work (Silveira et al., 2017). Our study only looked at mRNA levels, which does not necessarily reflect protein expression.

Açai restored NCX mRNA levels in the animals' left ventricle. Due to its antioxidant effects, açai could reduce the oxidation of proteins responsible for the intracellular Ca^{2+} transient, promoting changes in gene expression, as observed. It is known that treatment with açai generates changes in the protein expression of proteins involved in Ca^{2+} homeostasis in cardiomyocytes of animal models of myocardial infarction (Zapata-Sudo et al., 2014).

The practice of AET causes cardiac adaptations such as interstitial remodeling, eccentric hypertrophy and improvement in cardiomyocyte contractility (Kemi et al., 2008; Paulino et al., 2010). In fact, AET increased the gene expression of NCX and RyR2 in the LV of animals, showing the benefits of the intervention in the relaxation and contraction of cardiomyocytes.

It is known that the action of inflammatory mediators is associated with the process of cardiac fibrosis induced by high-fat diet. It is believed that the onset of the inflammatory reaction is due to increased cell death of cardiomyocytes, caused, among other factors, by increased oxidative stress. The increased release of chemokines and cytokines induces collagen deposition through the recruitment and activation of fibroblasts (Meléndez et al., 2010). No entanto, o presente estudo não apresentou diferenças na expressão gênica de IL-6 nos ratos tratados com dieta hiperlipídica. The intervention period with the high-fat diet may not have been enough to change this parameter. Furthermore, the treatment may have activated other cytokines and pathways such as IL-1β, TGF-β and p-Smad 3, which are related to the fibrogenic process in the heart (Wang et al., 2015).

The group treated with AET showed increased IL-10 gene expression. It is well established that chronically performed AET generates cardiac adaptations, such as reduced IL-6 release and increased IL-10, in order to provide tissue repair and growth (Benatti & Pedersen, 2015). Corroborating our findings, it was found that mice that underwent AET (swimming) and consumed a high-fat diet showed increased levels of IL-10 protein in the heart, compared to animals that only consumed the high-fat diet (Kesherwani et al., 2015).

The combination of treatments between AET and açai supplementation increased NCX gene expression, with no change in inflammatory parameters. Therefore, the combined treatments failed to enhance the isolated effects in animals submitted to a high-fat diet. It seems that the isolated treatments were enough to change the analyzed variables to a point that could not be improved by their combination. However, further research involving the protein expression of the targets analyzed in our study and other complementary ones are needed for a better understanding of the mechanisms involved.

The study has limitations. One of them is the failure to perform protein analyzes via Western-Blot, to confirm or challenge the results at the genic level. Furthermore, the analysis of other markers of the inflammatory response, such as TNF-α, could improve data interpretation.

Conclusion

The treatments changed parameters of Ca^{2+} homeostasis and inflammation, but the association of interventions did not provide additional effects. The data have clin-ical relevance, as they show possible non-pharmacological treatments for the effects imposed by the high-fat diet.

References

Benatti, F. B., & Pedersen, B. K. (2015). Exercise as an anti-inflammatory therapy for rheumatic diseases—myokine regulation. Nat Rev Rheumatol, 11(2), 86-97.

Bonomo, L. F., Silva, D. N., Boasquivis, P. F., Paiva, F. A., Guerra, J. F. d. C., Martins, T. A. F., ... Oliveira, R. P. (2014). Açai (Euterpe oleracea Mart.) modulates oxidative stress resistance in Caenorhabditis elegans by direct and indirect mechanisms. PloS one, 9(3), e89933.

Browning, J. D., & Horton, J. D. (2004). Molecular mediators of hepatic steatosis and liver injury. The Journal of clinical investigation, 114(2), 147–152.

Burke, L. M., Ross, M. L., Garvican-Lewis, L. A., Welvaert, M., Heikura, I. A., Forbes, S. G., Mirtschin, J. G., ... Hawley, J. A. (2017). Low carbohydrate, high fat diet impairs exercise economy and negates the performance benefit from intensified training in elite race walkers. The Journal of physiology, 595(9), 2785–2807.

Carneiro-Júnior, M. A., Quintão-Júnior, J. F., Drummond, L. R., Lavorato, V. N., Drummond, F. R, da Cunha, D. N., Amadeu, M. A., ... Natali, A. J. (2013). The benefits of endurance training in cardiomyocyte function in hypertensive rats are reversed within four weeks of detraining. J Mol Cell

Cardiol, 57, 119-28.

Chen, X., Li, H., Wang, K., Liang, X., Wang, W., Hu, X., Huang, Z., & Wang, Y. (2019). Aerobic Exercise Ameliorates Myocardial Inflammation, Fibrosis and Apoptosis in High-Fat-Diet Rats by Inhibiting P2X7 Purinergic Receptors. Frontiers in physiology, 10, 1286.

Drummond, F. R., Soares, L. L., Leal, T. F., Leite, L. B., Rezende, L. M. T., Fidelis, M. R., Lavorato, V. N., ... Natali, A. J. (2023). Effects of voluntary running on the skeletal muscle of rats with pulmonary artery hypertension. Front. Physiol. 14, 1-7.

Gaillard, D., Passilly-Degrace, P., & Besnard, P. (2008). Molecular mechanisms of fat preference and overeating. Annals of the New York Academy of Sciences, 1141, 163–175.

Kemi, O. J., Ceci, M., Condorelli, G., Smith, G. L., & Wisloff, U. (2008). Myocardial sarcoplasmic reticulum Ca^{2+} ATPase function is increased by aerobic interval training. European journal of cardiovascular prevention and rehabilitation: official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 15(2), 145–148.

Kemi, O. J., Ellingsen, O., Smith, G. L., & Wisloff, U. (2008). Exercise-induced changes in calcium handling in left ventricular cardiomyocytes. Frontiers in bioscience: a journal and virtual library, 13, 356–368.

Kesherwani, V., Chavali, V., Hackfort, B. T., Tyagi, S. C., & Mishra, P. K. (2015). Exercise ameliorates high fat diet induced cardiac dysfunction by increasing interleukin 10. Frontiers in physiology, 6, 124.

Lavorato, V. N., Del Carlo, R. J., da Cunha, D. N., Okano, B. S., Belfort, F. G., de Freitas, J. S., da Mota, G. de F., ... Natali, A. J. (2016). Mesenchymal stem cell therapy associated with endurance exercise training: Effects on the structural and functional remodeling of infarcted rat hearts. J Mol Cell Cardiol, 90, 111-119.

Lavorato, V. N., Miranda, D. C., Isoldi, M. C., Drummond, F. R., Soares, L. L., Reis, E. C. C., Pelúzio, M. D. C. G., ... Natali, A. J. (2021). Effects of aerobic exercise training and açai supplementation on cardiac structure and function in rats submitted to a high-fat diet. Food research international (Ottawa, Ont.), 141, 110168.

Lima-Leopoldo, A. P., Leopoldo, A. S., da Silva, D. C., do Nascimento, A. F., de Campos, D. H., Luvizotto, R. A., de Deus, A. F., Freire, P. P., Medeiros, A., Okoshi, K., & Cicogna, A. C. (2014). Long-term obesity promotes alterations in diastolic function induced by reduction of phospholamban phosphorylation at serine-16 without affecting calcium handling. Journal of applied physiology, 117(6), 669–678.

Meléndez, G. C., McLarty, J. L., Levick, S. P., Du, Y., Janicki, J. S., & Brower, G. L. (2010). Interleukin 6 mediates myocardial fibrosis, concentric hypertrophy, and diastolic dysfunction in rats. Hypertension, 56(2), 225–231.

Natali, A. J., Turner, D. L., Harrison, S. M., & White, E. (2001). Regional effects of voluntary exercise on cell size and contraction-frequency responses in rat cardiac myocytes. The Journal of experimental biology, 204(Pt 6), 1191–1199.

Paulino, E. C., Ferreira, J. C., Bechara, L. R., Tsutsui, J. M., Mathias, W., Jr, Lima, F. B., Casarini, D. E., Cicogna, A. C., Brum, P. C., & Negrão, C. E. (2010). Exercise training and caloric restriction prevent reduction in cardiac Ca^{2+}-handling protein profile in obese rats. Hypertension, 56(4), 629–635.

Sánchez, G., Araneda, F., Peña, J. P., Finkelstein, J. P., Riquelme, J. A., Montecinos, L., Barrientos, G., ... Donoso, P. (2018). High-Fat-Diet-Induced Obesity Produces Spontaneous Ventricular Arrhythmias and Increases the Activity of Ryanodine Receptors in Mice. International journal of molecular sciences, 19(2), 533.

Pereira, R. R., de Abreu, I. C., Guerra, J. F., Lage, N. N., Lopes, J. M., Silva, M., de Lima, W. G., Silva, M. E., & Pedrosa, M. L. (2016). Açai (Euterpe oleracea Mart.) Upregulates Paraoxonase 1 Gene Expression and Activity with Concomitant Reduction of Hepatic Steatosis in High-Fat Diet-Fed Rats. Oxidative medicine and cellular longevity, 2016, 8379105.

Reeves, P. G., Nielsen, F. H., & Fahey, G. C., Jr (1993). AIN-93 purified diets for laboratory rodents: final report of the American Institute of Nutrition ad hoc writing committee on the reformulation of the AIN-76A rodent diet. The Journal of nutrition, 123(11), 1939–1951.

Schauss, A. G., Wu, X., Prior, R. L., Ou, B., Huang, D., Owens, J., Agarwal, A., ... Shanbrom, E. (2006). Antioxidant capacity and other bioactivities of the freeze-dried Amazonian palm berry, Euterpe oleracea mart. (acai). Journal of agricultural and food chemistry, 54(22), 8604–8610.

Silveira, A. C., Fernandes, T., Soci, Ú. P. R., Gomes, J. L. P., Barretti, D. L., Mota, G. G. F., Negrão, C. E., & Oliveira, E. M. (2017). Exercise Training Restores Cardiac MicroRNA-1 and MicroRNA-29c to Nonpathological Levels in Obese Rats. Oxidative medicine and cellular longevity, 2017, 1549014.

VanWagner, L. B., Wilcox, J. E., Colangelo, L. A., Lloyd-Jones, D. M., Carr, J. J., Lima, J. A., Lewis, C. E., Rinella, M. E., & Shah, S. J. (2015). Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: A population-based study. Hepatology, 62(3), 773–783.

Wang, Z., Li, L., Zhao, H., Peng, S., & Zuo, Z. (2015). Chronic high fat diet induces cardiac hypertrophy and fibrosis in mice. Metabolism: clinical and experimental, 64(8), 917–925.

Zapata-Sudo, G., da Silva, J. S., Pereira, S. L., Souza, P. J., de Moura, R. S., & Sudo, R. T. (2014). Oral treatment with Euterpe oleracea Mart. (açaí) extract improves cardiac dysfunction and exercise intolerance in rats subjected to myocardial infarction. BMC complementary and alternative medicine, 14, 227.

Datos de los autores/as y traductor/a:

Victor Neiva Lavorato	victor.lavorato@unifagoc.edu.br	Autor/a
Denise Coutinho de Miranda	denisecmiranda@gmail.com	Autor/a
Luciano Bernardes Leite	luciano.leite@ufv.br	Autor/a
Marcelo Eustáquio Silva	macesil@gmail.com	Autor/a
Antônio José Natali	anatali@ufv.br	Autor/a
Victor Neiva Lavorato	victor.lavorato@unifagoc.edu.br	Traductor/a