

Could a high-fat diet rich in unsaturated fatty acids impair the cardiovascular system?

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BACKGROUND: Dyslipidemia results from consumption of a diet rich in saturated fatty acids and is usually associated with cardiovascular disease. A diet rich in unsaturated fatty acids is usually associated with improved cardiovascular condition.

OBJECTIVE: To investigate whether a high-fat diet rich in unsaturated fatty acids (U-HFD) – in which fatty acid represents approximately 45% of the total calories – impairs the cardiovascular system.

METHODS: Male, 30-day-old Wistar rats were fed a standard (control) diet or a U-HFD containing 83% unsaturated fatty acid for 19 weeks. The *in vivo* electrocardiogram, the spectral analysis of heart rate variability, and the vascular reactivity responses to phenylephrine, acetylcholine, noradrenaline and prazosin in aortic ring preparations were analyzed to assess the cardiovascular parameters.

RESULTS: After 19 weeks, the U-HFD rats had increased total body fat, baseline glucose levels and feed efficiency compared with control rats. However, the final body weight, systolic blood pressure, area under the curve for glucose, calorie intake and heart weight/final body weight ratio were similar between the groups. In addition, both groups demonstrated no alteration in the electrocardiogram or cardiac sympathetic parameters. There was no difference in the responses to acetylcholine or the maximal contractile response of the thoracic aorta to phenylephrine between groups, but the concentration necessary to produce 50% of maximal response showed a decrease in the sensitivity to phenylephrine in U-HFD rats. The cumulative concentration-effect curve for noradrenaline in the presence of prazosin was shifted similarly in both groups.

CONCLUSIONS: The present work shows that U-HFD did not impair the cardiovascular parameters analyzed.

Key Words: Cardiovascular; High-fat diet; Obesity; Unsaturated fatty acid

Diet and lifestyle modifications have long been advocated to decrease the risk of cardiovascular disease (CVD) (1), which is one of the main causes of death worldwide (2). Dietary fatty acids of varying chain length and degree of saturation differentially alter plasma lipoprotein profiles and the subsequent risk of developing CVD. A lipoprotein profile imbalance is associated with obesity, among others (3). Obesity, which is characterized by the accumulation of excessive body fat, is considered to be a global epidemic and represents an important public health problem (4,5).

Although the etiology of obesity is complex, distinct risk factors have been implicated in its development, especially hypercaloric intake (6). Recent investigations (7-10) have demonstrated that obesity decreases

Un régime cétogène riche en acides gras non saturés pourrait-il nuire au système cardiovasculaire ?

HISTORIQUE : La dyslipidémie découle de la consommation d'un régime riche en acides gras saturés et s'associe généralement à une maladie cardiovasculaire. Par contre, un régime riche en acides gras non saturés est généralement lié à une amélioration de l'état cardiovasculaire.

OBJECTIF : Explorer si un régime cétogène riche en acides gras non saturés (RC-N), dans lequel les acides gras représentent environ 45 % des calories totales, nuit au système cardiovasculaire.

MÉTHODOLOGIE : Des rats mâles Wistar de 30 jours ont été nourris au moyen d'un régime standard (groupe témoin) ou d'un RC-N contenant 83 % d'acides gras non saturés pendant 19 semaines. Les chercheurs ont analysé l'électrocardiogramme *in vivo*, l'analyse spectrale de la variabilité du rythme cardiaque et les réponses de réactivité vasculaire à la phényléphrine, à l'acétylcholine, à la noradrénaline et à la prazosine dans les préparations de l'anneau aortique afin d'évaluer les paramètres cardiovasculaires.

RÉSULTATS : Au bout de 19 semaines, les rats RC-N présentaient une masse grasse totale, une glycémie de départ et une capacité de transformation des aliments plus élevées que les rats témoins. Cependant, le poids corporel final, la tension artérielle systolique, la surface sous la courbe de glycémie, l'apport calorique et le ratio entre le poids du cœur et le poids corporel final étaient similaires entre les deux groupes. De plus, les deux groupes n'ont démontré aucune altération de l'électrocardiogramme ou des paramètres sympathiques cardiaques. La réponse à l'acétylcholine ou la réponse contractile maximale de l'aorte thoracique à la phényléphrine ne différait pas entre les groupes, mais la concentration nécessaire pour produire 50 % de la réponse maximale était moins sensible à la phényléphrine chez les rats RC-N. La déviation de la courbe concentration-effet cumulative de noradrénaline en présence de prazosine était similaire entre les deux groupes.

CONCLUSIONS : Les présents travaux révèlent qu'un RC-N ne nuisait pas aux paramètres cardiovasculaires analysés.

life expectancy and is related to numerous medical complications such as type 2 diabetes mellitus, dyslipidemia and CVDs. To understand the physiopathology of the abnormalities secondary to obesity, various animal models have been proposed – using either genetic or dietetic approaches (11,12). Although it is clear that genetic factors contribute to the propensity of an individual to become obese, the overconsumption of a high-calorie diet may promote a positive energy balance and lead to the development of overweight and obesity states (13).

Previous studies have indicated that human obesity promotes electrocardiographic (ECG) changes (14,15) such as prolongation of the QT interval (16,17). This abnormality is considered to be a precursor of malignant arrhythmias and sudden death (18,19). Although QT

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interval lengthening has been found to be associated with obesity (20), the mechanism responsible for such an association remains elusive. Corbi et al (21) found a significant relationship between heart rate-corrected QT intervals, and plasma adrenaline and noradrenaline concentrations, and suggested autonomic nervous system dysfunction as a possible mechanism of the prolonged heart rate-corrected QT intervals in patients with visceral obesity. Moreover, no study has analyzed the ECG and the QT interval in diet models of obesity.

Despite the unequivocal relationship between obesity and CVD, the effect of obesity on vascular function in experimental studies presents divergent results. Although some authors have found attenuated vasorelaxation responses to acetylcholine (ACh) (22), other investigators have verified that obesity does not impair endothelium-dependent vasodilation (23,24). Furthermore, studies examining the contractile responses to adrenergic agonists in different animal models of obesity have yielded contradictory results. Although Naderali et al (22) did not find differences in contractile responses to noradrenaline, other authors (23,24) observed enhanced vascular contractility in diet-induced obesity. Hypercholesterolemia (25), genetic hyperlipidemias (26) or a single high-fat meal (27) decreases endothelial function, suggesting that a regular high-fat diet might lead to endothelial dysfunction.

Administration of a high-fat diet is an experimental model that reproduces many features of human obesity (28,29). Classically, the high-fat diets used in animal models contain a high fraction of saturated fatty acid (approximately 90%), with a low fraction of monounsaturated and polyunsaturated fatty acid (30). However, few studies have tested, at least to our knowledge, whether a high-fat diet rich in unsaturated fatty acids (U-HFD) – containing 83% unsaturated fatty acid – impairs the cardiovascular system after 19 weeks. Thus, in the present study, we examined the ECG profile, the autonomic function and the vascular reactivity of rats fed a U-HFD to assess such a situation.

METHODS

Animal model and experimental protocol

All experiments and procedures were performed consistent with the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health (USA) and were approved by the Botucatu Medical School Ethics Committee, Universidade Estadual Paulista (São Paulo, Brazil).

Thirty-day-old, male Wistar rats were divided into two groups. One group was fed a standard diet (controls; n=10), containing 11.2% of kilocalories from fat, 55.5% from carbohydrate and 33.3% from protein, for 19 consecutive weeks. The other group received a U-HFD (n=9), containing 45.2% of kilocalories from fat, 28.6% from carbohydrate and 26.2% from protein, for 19 consecutive weeks. The U-HFD (4.5 kcal/g) was more calorie rich than the standard diet (3.3 kcal/g) because of the higher amount of energy from fat – composed of 17% saturated and 83% unsaturated fatty acids. All rats were housed in individual cages in an environmentally controlled clean-air room at a mean (\pm SD) temperature of $23\pm 3^\circ\text{C}$, with a 12 h light/dark cycle (lights on at 06:00) and $60\pm 5\%$ relative humidity. Food consumption was measured daily and body weight was determined once a week. Weekly caloric intake was calculated by the average weekly food consumption caloric value of each diet. Feed efficiency, which is the ability to translate calories consumed into body weight, was also evaluated. Initial body weight, final body weight (FBW), heart weight (HW) and the HW/FBW ratio were analyzed.

Body fat

After the animals had been anesthetized (sodium pentobarbital 50 mg/kg intraperitoneal), decapitated and thoracotomized, the fat pads of adipose tissue were dissected and weighed. Total body fat was measured from the sum of the individual fat pad weights: epididymal fat plus retroperitoneal fat plus visceral fat. The adiposity index was calculated as the following (31):

$$\text{Adiposity index} = (\text{total body fat}/\text{FBW}) \times 100.$$

Systolic blood pressure

At the end of the experiment, the systolic blood pressure was assessed by the noninvasive tail-cuff method using an electrophygmomanometer (Narco BioSystems, International Biomedical Inc, USA) (32). The average of two pressure readings was recorded for each measurement.

Insulin-tolerance test

After 19 weeks of low- and high-fat dietary feeding, the rats were fasted for 6 h and subjected to an insulin-tolerance test. To measure glucose, blood samples were drawn from the tip of the tail at baseline and after intraperitoneal administration of regular insulin (Novolin R, Novo Nordisk, Denmark) at a dose of 1.5 IU/kg body weight (33). Subsequently, blood samples were collected at 0 min (basal), 15 min, 30 min, 45 min, 60 min and 90 min. Glucose levels were determined using the Accu-Chek Go Kit glucose analyzer (Roche Diagnostic Brazil Ltda, Brazil). Insulin resistance was determined by the area under the curve for glucose (0 min to 90 min).

ECG

At the start of the 19th week, the rats were anesthetized (ketamine/xylazine 80/20 mg/kg intraperitoneal). Using a surgical procedure, two steel electrodes were implanted subcutaneously near the apex and base of the heart, resulting in a lead placed close to D2. Electrodes were exteriorized through the back of the neck and terminated in a custom-made connector. ECG recordings in the conscious state were made 24 h after the surgical procedure; this was conducted while the unrestricted animals rested quietly in individual cages. Recordings were always started 10 min to 15 min after linking the connector, through flexible cables, to the differential alternating-current amplifier (Model 1700; A-M Systems, USA), and were conducted in all animals for 3 min 10 s (these additional 10 s were recorded to ensure 180 s of artifact-free tachograms; nevertheless, when RR artifacts were removed, it never reached more than 1% of detected intervals). ECG signals were acquired at a sampling rate of 10 kHz and an amplitude resolution of 16 bits (A/D interface Digidata 1322A; Axon Instruments, USA). All recordings were conducted in a constant environment, during the same period of the morning (06:00 to 09:00).

The ECG parameters measured were PR, QT, RR and QRS intervals. Data were analyzed using Clampfit 10.1 (Axon Instruments, USA).

The assessment of cardiac autonomic control was made using heart rate variability (HRV) analysis, and the signal processing in the present study was performed using MATLAB-based algorithms (MathWorks, USA). ECGs were first band-pass filtered (2 Hz to 300 Hz) and, after R-wave peak detection, 180 s tachograms were generated, containing all heart period fluctuations within this time segment. In the time domain, the following indexes were obtained: mean RR interval, SD of the RR intervals, and square root of the mean squared differences of successive RR intervals. For spectral (frequency domain) analysis of HRV, tachograms were resampled to equal intervals by the spline cubic interpolation method at 10 Hz, and the linear trend was removed. Power spectrum was obtained using a fast Fourier transform-based method (Welch's periodogram: 256 points, 50% overlap and Hamming window). Two frequency bands were determined: low frequency (LF; 0.2 Hz to 0.8 Hz) and high frequency (HF; 0.8 Hz to 2.5 Hz). Power (in ms^2) was estimated as the area under the spectrum within these frequency ranges.

Vascular reactivity

The animals were sacrificed by decapitation under sodium pentobarbital (50 mg/kg intraperitoneal) anesthesia. The thoracic aortas were removed, cleaned of connective tissue and prepared for isometric tension recording. The aortas were cut into 2 mm to 3 mm rings that were placed in a vertical chamber filled with saline solution composed of 120 mM NaCl, 5.9 mM KCl, 1.2 mM MgCl_2 , 1.2 mM NaH_2PO_4 , 18 mM NaHCO_3 , 1.2 mM CaCl_2 and 11 mM glucose (pH 7.4), and oxygenated with carbogen gas mixture (95% O_2 , 5% CO_2) at $37\pm 0.5^\circ\text{C}$. Each ring was mounted between two hooks in which one hook was attached to a force transducer (Grass model FT-03, Grass Technologies, USA) whose signal was conditioned by a Cyberamp (Axon Instruments Inc, USA);

TABLE 1
General and nutritional characteristics of study rats

Variables	Group	
	Control diet (n=10)	U-HFD (n=9)
Initial body weight, g	153±1	152±1
Final body weight, g	516±10	537±22
Food consumption, g/day	28.4±0.3	22.6±0.3*
Caloric intake, g × kcal/day	83.9±1.5	82.6±3.3
Feed efficiency, %	3.25±0.04	3.49±0.09*
Systolic blood pressure, mmHg	136±4	128±4
Glucose, mg/dL	88±1	95±1*
AUC	5082±95	5278±92
Epididymal fat, g	6.06±0.47	9.44±1.13*
Retroperitoneal fat, g	5.98±0.46	12.60±1.05*
Visceral fat, g	1.49±0.14	2.44±0.23*
Total body fat, g	13.5±0.8	24.5±2.3*
Adiposity index, %	2.64±0.18	4.51±0.29*

Data presented as mean ± SEM. *P<0.05 versus controls (Student's t test for independent samples). AUC Area under the curve for glucose (insulin-tolerance test); U-HFD High-fat diet rich in unsaturated fatty acids

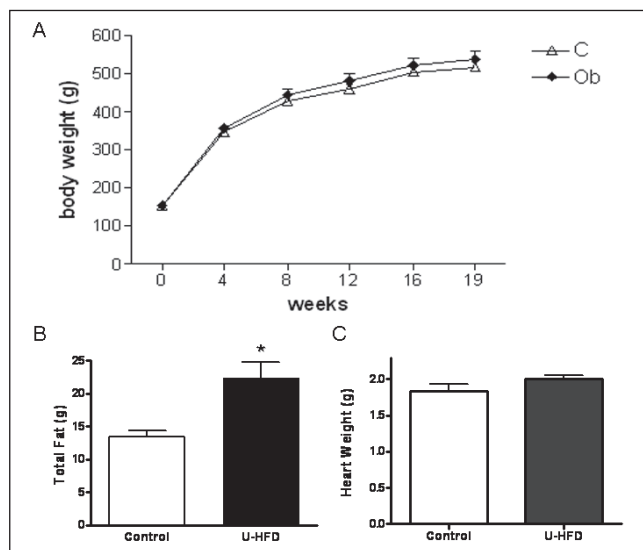


Figure 1 **A** After 19 weeks, no difference in body weight was observed. **B** The high-fat diet rich in unsaturated fatty acids (U-HFD) group showed higher total body fat than the control group. **C** There was no difference in heart weight between the groups. Results are expressed as means with SEMs. Control diet (C; n=10) and U-HFD (Ob; n=9). *P<0.005

contractile response was displayed and stored in a computer for future analysis using Axoscope software (Axon Instruments Inc). Preparations were stabilized under 1 g resting tension for 2 h. After the equilibrium period, the integrity of the endothelium was tested by the addition of ACh (10 μ M) after precontraction with phenylephrine (PE; 10 μ M). The endothelium was considered to be intact if the Ach-induced relaxation of the precontracted aorta was greater than 80%. The aortic rings were then washed and equilibrated for another 40 min period before initiating the experimental protocol. Increasing concentrations of PE (1 nM to 10 μ M) were added to the tissue bath. When the contractile response to PE reached a plateau, ACh was added in a cumulative manner (1 nM to 10 μ M). Also, to assess the contribution of the α_1 -adrenergic receptors in the aortas of both control and U-HFD rats, cumulative concentration-effect curves for noradrenaline were generated for isolated aortas in the absence or presence of the reversible α_1 -antagonist prazosin (10^{-8} M).

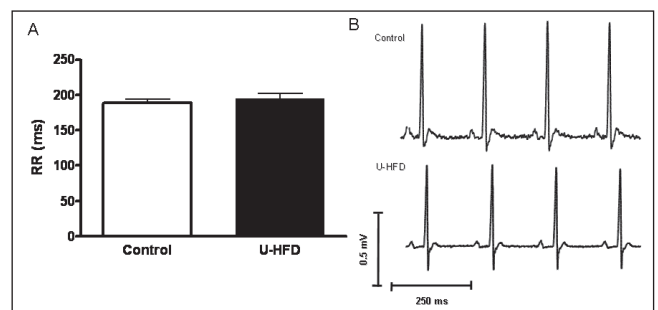


Figure 2 Representative electrocardiograms in conscious rats. **A** Bar graph showing no difference in RR interval between the groups. Results are expressed as means with SEMs. **B** Representative traces of electrocardiograms from both groups. Control diet (n=10) and high-fat diet rich in unsaturated fatty acids (U-HFD; n=9). P>0.05 for comparison between groups

TABLE 2
Electrocardiogram parameters

Interval	Group	
	Control diet (n=10)	U-HFD (n=9)
PR	44.3±1.9	44.4±1.9
QRS	20.3±0.6	19.9±0.7
RR	189±5	195±6
QT	72.4±3.3	65.0±2.6
Heart-rate corrected QT	167±8	146±7

Data presented as mean ± SEM. There was no statistical difference between groups (Student's t test for independent samples). U-HFD High-fat diet rich in unsaturated fatty acids

Statistical analysis

Values were compared between groups using the Student's t test. The mean weekly body weight and the insulin-tolerance test were analyzed by repeated-measures two-way ANOVA and complemented by Bonferroni's post hoc test for multiple comparisons. Contraction responses are expressed as the percentage of maximal PE-induced contraction. Relaxation responses are expressed as the percentage relaxation of the precontraction induced by 10 μ M PE. Concentration-response curves were analyzed by nonlinear regression using GraphPad Prism version 4.0 (GraphPad Software Inc, USA). Both the maximal contraction or maximal relaxation (E_{max}) and the concentration necessary to produce 50% of maximal response (EC_{50}) were determined. Data are presented as mean ± SEM.

RESULTS

General characteristics of rats

The general characteristics of the rats are shown in Table 1. There was no difference between groups in the evolution of body weight after 19 weeks (Figure 1A).

After 19 weeks, the FBW, systolic blood pressure, area under the curve for glucose, and calorie intake were similar between groups. Despite the fact that the U-HFD rats demonstrated less food consumption (P<0.05), their feed efficiency was greater than that of control rats (P<0.03). Furthermore, the adiposity index and plasma glucose concentration were significantly increased in the U-HFD rats (Table 1).

Although FBW was not different between groups, the U-HFD rats showed significantly greater total body fat weight (control 13.5±0.8 g versus U-HFD 24.5±2.3 g, P<0.01; Figure 1B). No difference between groups was observed in HW (control 1.84±0.09 g versus U-HFD 1.99±0.06 g, P>0.05; Figure 1C), nor in the HW/FBW ratio (HW/FBW × 1000) (control 3.57±0.18 versus U-HFD 3.75±0.18, P>0.05).

ECG and HRV

Figure 2 illustrates representative unfiltered tracings of ECG recordings obtained from both control and U-HFD rats. The ECG parameters measured were not statistically different between groups (Table 2).

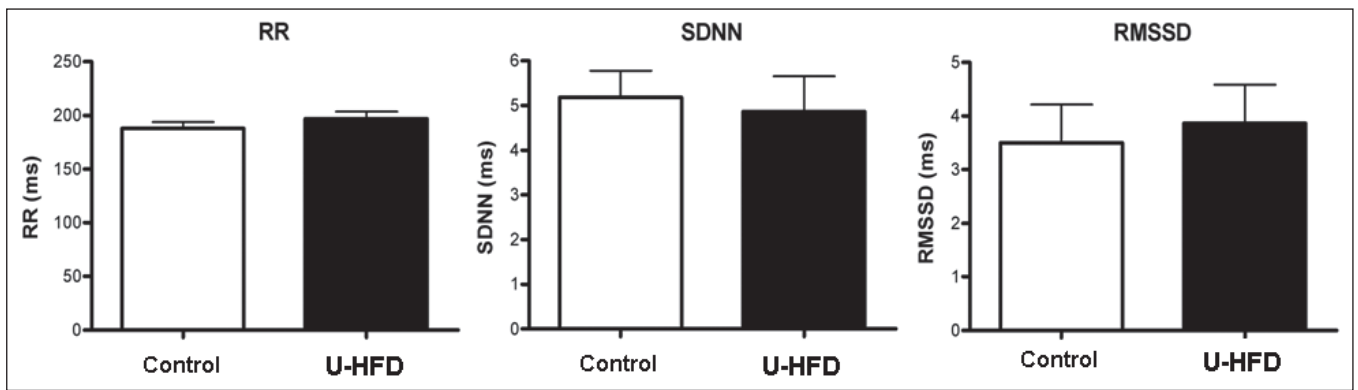


Figure 3 Time-domain heart rate variability indexes for the mean RR interval (RR), the SD of RR intervals (SDNN) and the square root of the mean squared differences of successive RR intervals (RMSSD). Data are presented as means with SEMs. U-HFD High-fat diet rich in unsaturated fatty acids

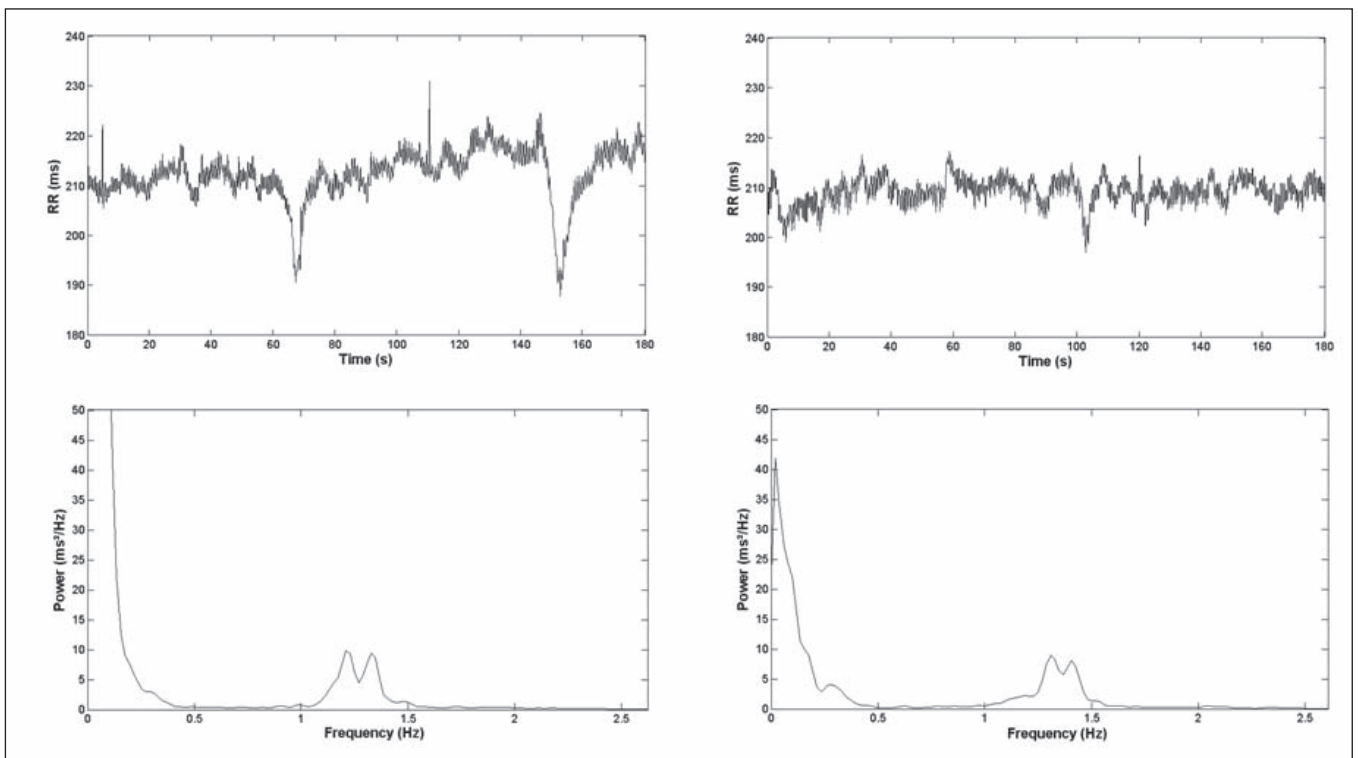


Figure 4 Full-length tachograms (top) and RR power spectra (bottom) from both a representative control rat (left) and a rat fed a high-fat diet rich in unsaturated fatty acids (right)

Time-domain HRV analysis revealed no significant difference between groups for the studied indexes, as illustrated in Figure 3 (mean RR interval: control 187.8 ± 6.2 ms versus U-HFD 196.9 ± 6.7 ms; SD of RR intervals: control 5.2 ± 0.6 ms versus U-HFD 4.9 ± 0.8 ms; square root of the mean squared differences of successive RR intervals: control 3.5 ± 0.7 ms versus U-HFD 3.9 ± 0.7 ms).

Figure 4 illustrates full-length tachograms and RR power spectra from both a representative control rat and a U-HFD rat. HRV analysis in the frequency domain also failed to reveal significant differences between groups, as illustrated in Figure 5 (LF power: control 1.7 ± 0.4 ms² versus U-HFD 1.9 ± 0.6 ms²; HF power: control 5.8 ± 2.6 ms² versus U-HFD 4.4 ± 1.4 ms²; LF/HF ratio: control 0.59 ± 0.2 versus U-HFD 0.57 ± 0.2).

Vascular response

Isometric tension was measured in aortic rings from control and U-HFD rats. The concentration-response curve for PE was shifted slightly to the right in the U-HFD group, although maximal response

was not altered (E_{\max} : control 1.2 ± 0.04 versus U-HFD 1.2 ± 0.08 g, $P > 0.05$) (Figure 6A). The U-HFD aorta was less sensitive to the α_1 -adrenergic agonist as shown by the higher EC_{50} (EC_{50} : control 53.5 ± 8.1 nM versus U-HFD 87.9 ± 8.1 nM, $P < 0.05$).

Vasodilation in response to ACh did not differ between control and U-HFD rats (Figure 6B) (E_{\max} : control $90.1 \pm 2.4\%$ versus U-HFD $86.9 \pm 4.5\%$, $P > 0.05$). EC_{50} was 35.8 ± 4.3 nM and 42.2 ± 9.9 nM ($P > 0.05$), respectively.

In other experiments, the participation of the alpha-adrenergic pathway was investigated. Thus, the cumulative concentration-effect curves for noradrenaline were generated for isolated aortas in the absence or presence of the reversible α_1 -antagonist prazosin (10^{-8} M). In the aortas of both control and U-HFD groups, a significant shift in the presence of prazosin was observed, as shown in Figures 7A and 7B. However, the final response to prazosin was similar for both groups (Figure 7C and Table 3). In addition, no significant differences between groups were found when comparing the EC_{50} of noradrenaline in the presence of prazosin ($P < 0.05$).

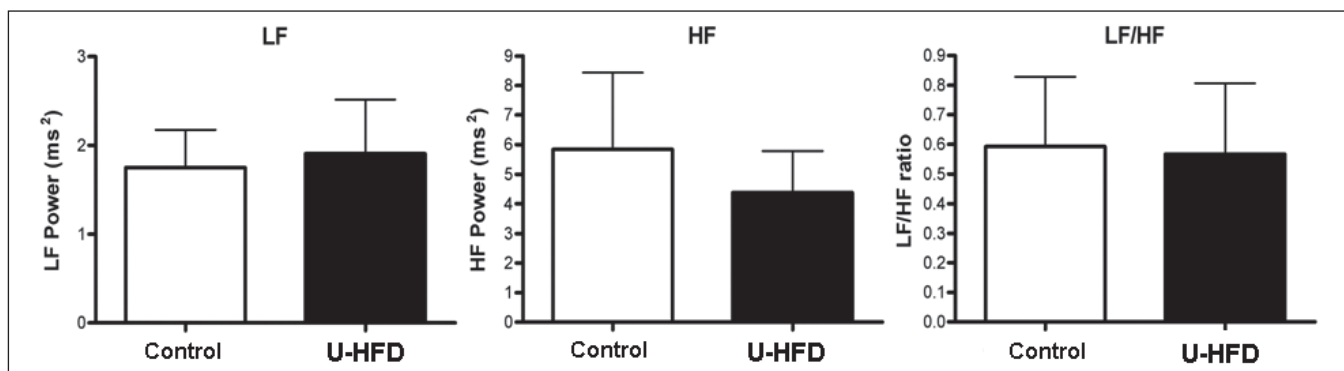


Figure 5 Spectral heart rate variability indexes for low-frequency (LF) RR power, high-frequency (HF) RR power and LF/HF ratio. Data are presented as means with SEMs. U-HFD High-fat diet rich in unsaturated fatty acids

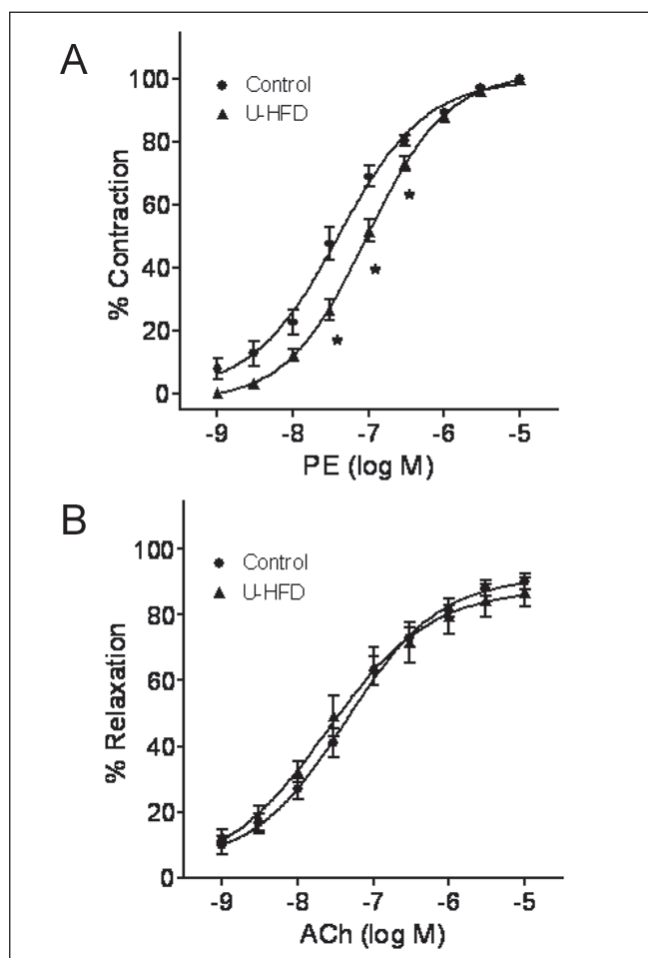


Figure 6 Vascular response to phenylephrine (PE) and acetylcholine (ACh). **A** Representative curves contractile response to PE. **B** Concentration-effect curves for ACh in the aorta with intact endothelium. The concentration-response curves of the aortic rings were generated from control rats and rats fed a high-fat diet rich in unsaturated fatty acids (U-HFD). Each point represents mean \pm SEM, $n=7$. * $P<0.05$ versus the control group

DISCUSSION

The results obtained in the present work show that U-HFD did not impair the cardiovascular parameters evaluated, even though a slightly decreased sensitivity to PE was observed in the aortas from the U-HFD animals.

Although no significant difference between groups was observed in the FBW, the U-HFD was of sufficient intensity and duration to

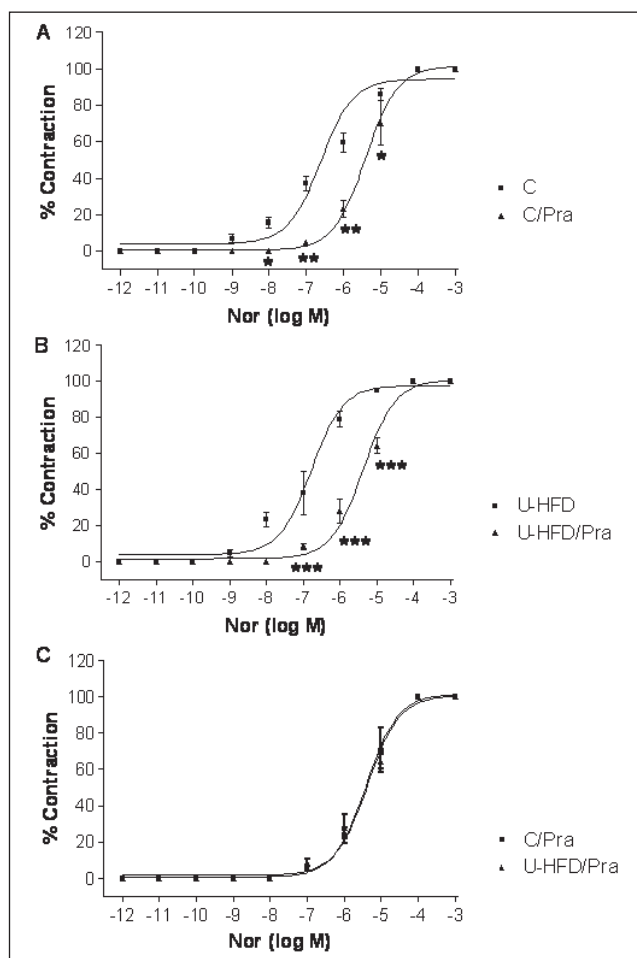


Figure 7 The vascular response to prazosin was similar in both the high-fat diet rich in unsaturated fatty acids (U-HFD) group and the control (C) group. **A** Curves of contractile response to noradrenaline (Nor) in the presence or absence of prazosin (Pra) in an aorta from the control group. **B** Curves of contractile response to Nor in the presence or absence of Pra in aortas from the U-HFD group. **C** Both groups showed similar pharmacological behaviour to Nor in the presence of the alpha-1-antagonist Pra. Each point represents mean \pm SEM, $n=6$. * $P<0.01$; ** $P<0.001$; *** $P<0.0001$ versus C curve

increase both the total body fat (81.5%) and the adiposity index of U-HFD animals (Table 1) (34,35). These results are in agreement with several studies (28-30) regarding high-saturated-fat-diet-induced obesity that found no difference in FBW. On the other hand,

notwithstanding a significant difference in plasma glucose concentration between the groups, the insulin-tolerance test was not able to demonstrate insulin resistance in the U-HFD rats. In this context, a previous study using an insulin resistance diet model showed that rats that were fed polyunsaturated fatty acid (docosahexaenoic acid) had a short QT interval on the ECG (36). Nevertheless, in our study, no changes were observed in this parameter. Because increased heterogeneity of ventricular repolarization favours the development of malignant ventricular arrhythmias, and prolonged QT interval may reflect this inhomogeneity, the effects of an unsaturated fatty acid diet on the QT interval observed here could explain the antiarrhythmic properties of this dietary habit (for more details, see reference 37).

It is known that cardiac autonomic control plays a fundamental role in the maintenance of cardiac electric stability. HRV analysis represents a powerful tool for the assessment of cardiac autonomic control, both in humans and in animal models. Cardiac vagal impairment, detected by reduced high-frequency power in spectral analysis of HRV, consists of a marker of cardiac electrical instability, and has been shown to constitute an independent prognostic factor for ventricular arrhythmia and sudden cardiac death in cardiac patients, and an independent predictor of cardiovascular events in the general population (38-40). The U-HFD model was not accompanied by a change in autonomic function as evaluated by HRV spectral analysis. To our knowledge, no previous work has assessed HRV in U-HFD rats. However, a previous study (41) showed a strong positive association between RR interval and omega (ω)-3 polyunsaturated fatty acid content in cell membranes, suggesting a lower heart rate in subjects with a high intake of ω -3 polyunsaturated fatty acid. This effect helps to explain the mechanism by which unsaturated fatty acids prevent sudden death and arrhythmias. Also, Christensen et al (42) showed a close positive association between ω -3 polyunsaturated fatty acid and HRV in patients suspected of having ischemic heart disease; it may indicate a protective effect of ω -3 polyunsaturated fatty acids against sudden cardiac death. The same group (42) showed increased HRV in postmyocardial infarction patients who received 5.2 g of ω -3 polyunsaturated fatty acid daily for 12 weeks.

Vascular reactivity

Vascular endothelium plays an essential role in the regulation of vascular tone through the synthesis and liberation of many substances, which can be activated by the stimulation of specific receptors by various agonists (43). Activation of muscarinic receptors in the endothelium by Ach increases the production of nitric oxide, which stimulates soluble guanylate cyclase in vascular smooth muscle cells, leading to increased levels of cyclic guanosine monophosphate and consequent relaxation (44). Our study showed that endothelium-dependent relaxation by ACh did not differ between control and U-HFD animals, suggesting a significant alteration in the nitric oxide-induced vasodilation of U-HFD rat aortas. This result is in agreement with experimental studies that did not observe alteration in ACh-induced vasodilation of aortas from mice (23) or rats (24) treated with a diet rich in fat – mainly saturated fatty acid. These findings suggest that different dietary components may or may not have an effect on vasorelaxation. Humans and animals fed high-fat diets, particularly saturated fat, have shown endothelial abnormalities (27,45). On the other hand, the protective effects of high-carbohydrate (low-saturated fat) diets and diets rich in unsaturated fats are contentious (46,47). Although the high-fat diet used in the present study contained a lower amount of saturated fat and a higher amount of unsaturated fatty acid, which is associated with improved cardiovascular risk (48,49), at high levels they could impair endothelial function (46).

In contrast to our results, some studies (50,51) have shown a decrease in endothelium-dependent vasorelaxation and no alteration in the maximal contractile responses to PE in renal arteries from saturated and unsaturated fatty acid-fed rats, compared with control rats, but there was no marked difference between them (50). These authors used a 34.4% unsaturated fatty acid diet over a 24-week period, while our study

TABLE 3
The vascular response to prazosin

Diet	Prazosin use	Maximal response, g	EC ₅₀ ($\times 10^{-6}$ M)
Control	Without prazosin	2.20 \pm 0.40	0.44 \pm 1.4
	With prazosin	2.21 \pm 0.70	2.06 \pm 3.7*
U-HFD	Without prazosin	1.83 \pm 0.65	0.16 \pm 1.8
	With prazosin	1.84 \pm 0.46	5.01 \pm 1.2**

Data presented as mean \pm SEM. * $P < 0.003$ versus control without prazosin; ** $P < 0.001$ versus a high-fat diet rich in unsaturated fatty acids (U-HFD) without prazosin ($n=6$) (Student's t test for paired samples). EC₅₀ Concentration necessary to produce 50% of maximal response

used an 83% unsaturated fatty acid diet over a 19-week period. Therefore, the higher percentage of unsaturated fatty acid and the shorter treatment time used in the present study could explain, at least in part, the divergent results observed here when compared with the work of Yu et al (50).

Furthermore, our results showed that endothelium-intact aorta isolated from U-HFD rats exhibited a slight decrease in sensitivity to PE, observed as a change in the EC₅₀ in response to PE. This response could be explained by an alteration in the α_1 -adrenergic receptors in aortas of U-HFD rats. However, no differences were found in the maximal contraction generated by noradrenaline in aortas from both groups when in the presence of the α_1 -adrenergic receptor antagonist prazosin. The contractile response of aortic rings from U-HFD rats was very similar to the response obtained in the control group; in both groups, the curve shifted to the right as expected, suggesting that the α_1 -adrenergic receptor pathway and density were not impaired by the U-HFD. Thus, the results of the present study suggest that systemic vascular smooth muscle contraction in response to α_1 -adrenoceptor stimulation is conserved after U-HFD.

Furthermore, the results regarding vascular reactivity and control of the autonomic system in the present study were in agreement with the arterial pressure measurement that did not show any differences between the control and the U-HFD groups.

CONCLUSION

The data obtained in the present study indicate that the U-HFD diet increased total adiposity and decreased the vascular sensitivity to PE, but did not impair cardiac electrical and autonomic functions.

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