

Remodeling Pattern and Ventricular Function in Rats Exposed to Cigarette Smoke

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Abstract

Background: The relevance of the remodeling pattern in the model of rats exposed to cigarette smoke is not known.

Objective: Analisar a presença de diferentes padrões de remodelação nesse modelo e sua relação com a função ventricular. Analyzing the presence of different remodeling patterns in this model and its relation with the ventricular function.

Methods: Smoking rats (n=47) have been divided according to the geometry pattern, analyzed by echocardiogram: normal (normal mass index and normal relative wall thickness), concentric remodeling (normal mass index and increased relative wall thickness), concentric hypertrophy (increased mass index and increased relative wall thickness) and eccentric hypertrophy (increased mass index and normal relative wall thickness).

Results: Smoking rats presented one of the following geometry patterns: normal pattern, 51%; eccentric hypertrophy; 32%; concentric hypertrophy, 13% and concentric remodeling, 4%. The normal and eccentric hypertrophy groups presented smaller ejection fraction values and fractional shortening than the concentric hypertrophy group. Thirteen animals (28%) presented systolic dysfunction detected by the ejection fraction and by fractional shortening.

In the single regression analysis, geometry patterns and mass index could not predict ventricular dysfunction ($p < .$). On the other hand, the increased relative thickness of the wall could predict ventricular dysfunction in the single regression analysis ($p < 0,001$) and in the multiple regression analysis after adjustment to the mass index ($p = 0,003$).

Conclusion: Rats exposed to cigarette smoke presented one of the four different remodeling patterns. Among the geometric variables analyzed, only the increased relative thickness of the left ventricle wall could predict ventricular dysfunction in this model. (Arq Bras Cardiol 2010;94(2): 209-212)

Key Words: Remodelling; geometry ; ventricular function; smoking.

Introduction

Remodeling refers to gene, molecular, cellular and cardiac interstitial variations, which clinically manifest by changes in size, mass, geometry and heart function, in response to a given aggression¹⁻³. The remodeling process plays a key role in the ventricular dysfunction physiopathology. By reacting to a given aggression, genetic, structural and biochemical changes result in a progressive deterioration of heart functions⁴⁻⁶.

A relevant aspect is that in patients with high blood pressure, it was found that secondary remodeling to arterial hypertension may result in different geometry patterns. Using the mass index and the left ventricle (LV) wall relative thickness, the patients were divided into four different geometry patterns: normal (normal mass index and

normal relative thickness), concentric remodeling (normal mass index and increased relative thickness), concentric hypertrophy (increased mass index and increased relative thickness) and eccentric hypertrophy (increased mass index and normal relative thickness). An important data to be considered is that the remodeling pattern predicted cardiovascular events⁷.

Recently, various studies reported that the exposure to cigarette smoke causes cardiac remodeling in rats, damaging their ventricular function⁸⁻¹⁵. Nevertheless, the importance of the cardiac remodeling pattern, in this model, is not known. Hence, the purpose of this study was to analyze the presence of different remodeling patterns ventricular functions in the model rats exposed to cigarette smoke.

Methods

The experimental protocol of this paper has been approved by the Ethics Commission on Animal Experimentation (CEEA) of our institution. It complies with the Ethic Principles on Animal Experimentation adopted by the Brazilian Board of Animal Experimentation.

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Protocol and experimental groups

Male Wistar rats weighing 200g to 230g were divided into 2 experimental groups: 1) group C, n=30 - composed of animals not exposed to cigarette smoke; 2) group F, n=47 - composed of animals exposed to cigarette smoke for a period of 2 months.

Later, the animals of group F have been classified according to the remodeling pattern: normal (normal mass index and normal relative thickness), concentric remodeling (normal mass index and increased relative thickness), concentric hypertrophy (increased mass index and increased relative thickness) and eccentric hypertrophy (increased mass index and normal relative thickness).

To expose the animals to cigarette smoke, we used a method standardized in our laboratory⁸⁻¹³. During the first week, the smoke was released at a rate of 5 cigarettes, twice a day in the afternoon with resting intervals of 10 minutes. The number of cigarettes was increased to a rate of 10 cigarettes/30 minutes, twice in the morning and twice in the afternoon, until the completion of the study.

Morphologic and functional evaluation by echocardiogram

Twenty-four hours past the end of the observation period, the animals underwent echocardiographic study. A Philips equipment (model TDI 5500) provided with multifrequency transducer was used up to 12 MHz. Cardiac structures were measured according to the recommendations of the American Society of Echocardiography/ European Association of Echocardiography¹⁶. The measurements were made by the same observer, who did not know which groups the animals belonged to. For the relative wall thickness of the LV, the following formula was used: $(RWT = 2 \times \text{posterior wall thickness (WT)} / \text{diastolic diameter})$. The relative wall thickness was considered increased when > 0.42 ¹⁶. For the mass index (LVMI), the following formula was used: $LVM = LVM/BW$, considering $LVM = \{[LVDD + (2 \times WT)^3 - (LVDD)^3] \times 1.04\} / 1000$ and BW is the body weight of the animal. The mass index was considered increased when > 1.733 . This value corresponds to the values above the percentile 75% found in the control animals. To issue a diagnosis on systolic ventricular dysfunction, we considered the values below 49% for the shortening percentage and below 0.87 for the ejection fraction. These values correspond to the values below the percentile 25% found in the control animals.

Statistic method

The comparisons were made by one-way ANOVA, complemented by Tukey test, when the data presented normal distribution. When the data did not present normal distribution, the comparisons between the groups were made by Kruskal-Wallis test. The data were expressed in mean \pm standard deviation (for normal distribution) or average with percentiles 25 and 75 (for non normal distribution). The analysis of ventricular dysfunction prediction factors was made by simple regression analysis. The significance level was 5%. Statistic analysis were made with the program SigmaStat for Windows v3.5 (SPSS Inc, Chicago, IL).

Results

Considering the geometric pattern of control animals, 20 animals presented normal pattern, 5 had eccentric hypertrophy, 2 presented concentric hypertrophy and 3 had concentric remodeling. Concerning the cardiac dimension measures, the results of control animals were: LVDD (7.13 ± 0.68 mm), posterior wall thickness (1.39 ± 0.27 mm) relative wall thickness (0.40 ± 0.14) and mass index (1.5 ± 0.31 g/kg).

Considering our rats exposed to cigarette smoke, the animals presented one of the four geometry patterns, in the following percentages: normal pattern, 51%; eccentric hypertrophy; 32%; concentric hypertrophy, 13% and concentric remodeling, 4%. As only two animals presented the concentric remodeling pattern, these animals were not included in the other analyses.

The echocardiogram results, according to the remodeling pattern, are shown in Table 1. We can observe that the left atrium diameter was bigger in the eccentric hypertrophy than in the normal pattern. The normal and eccentric hypertrophy patterns presented higher ventricular cavity values than the concentric hypertrophy group, both in the systole and in the diastole. Concerning the LV mass index, the animals belonging to the hypertrophy group (concentric and eccentric hypertrophy) presented higher values than the normal group. Concerning the LV wall relative thickness, the animals falling under the normal pattern presented lower values than the concentric hypertrophy pattern. Considering the systolic function, the normal and eccentric hypertrophy groups presented smaller ejection fraction values and fractional shortening than the concentric hypertrophy group. There were no differences between the groups related to the diastolic function.

Considering the smoking animals, thirteen (13) animals (13) presented systolic dysfunction detected by the ejection fraction and by fractional shortening. These animals presented only two geometry patterns: 61% presented normal geometry pattern and 39% presented eccentric hypertrophy pattern.

As to the ventricular dysfunction prediction factors, we analyzed the influence of the mass index, the wall relative thickness and the geometry pattern. In the single regression analysis, geometry patterns and mass index could not predict ventricular dysfunction ($p < .$). On the other hand, the increased relative thickness of the wall could predict ventricular dysfunction in the single regression analysis ($p < 0.001$) and in the multiple regression analysis after adjustment to the mass index ($p = 0,003$).

Discussion

Several studies showed that the exposure to cigarette smoke results in cardiac remodeling, in the rat model, with a drop in the systolic function indexes⁸⁻¹⁵. Considering the lack of information on the relevance of remodeling pattern in the model of rats exposed to cigarette smoke, the purpose of this study was to analyze the presence of different remodeling patterns and its relation with ventricular function in this model.

Table 1 - Echocardiogram data according to geometry

Variable	Normal (n=24)	Hipertrofia excêntrica (n=15)	Hipertrofia concêntrica (n=6)
Weight (g)	386 ± 65 ^a	377 ± 42 ^a	328 ± 65 ^a
HR (bpm/min)	295 ± 39 ^a	292 ± 45 ^a	331 ± 31 ^a
LA (mm)	3.98 ± 0.57 ^a	4.59 ± 0.61 ^b	4.33 ± 0.65 ^{ab}
LVDD (mm)	7.42 ± 0.72 ^a	7.84 ± 0.50 ^a	6.72 ± 0.59 ^b
LVSD (mm)	3.59 ± 0.69 ^a	3.83 ± 0.43 ^a	2.80 ± 0.72 ^b
LVMI (g/kg)	1.51 ± 0.17 ^a	2.00 ± 0.31 ^b	2.10 ± 0.28 ^b
WT (mm)	1.23 ± 0.10 ^a	1.40 ± 0.16 ^b	1.57 ± 0.14 ^c
RWT	0.32(0.30-0.38) ^a	0.35(0.33-0.41) ^{ab}	0.44(0.43-0.45) ^b
EF	0.88 ± 0.04 ^a	0.88 ± 0.02 ^a	0.92 ± 0.03 ^b
FS	52 ± 5.8 ^a	51 ± 3.4 ^a	59 ± 8 ^b
E/A	1.52 ± 0.35 ^a	1.48 ± 0.37 ^a	1.22 ± 0.23 ^a

LA - left atrium diameter; LVDD - left ventricle diastolic diameter; LVSD - left ventricle systolic diameter; WT - diastolic thickness of the posterior wall; RWT - left ventricle relative wall thickness; LVMI - left ventricle mass index; FS - fractional shortening; EF - ejection fraction. The data are expressed in mean ± standard deviation (for normal distribution) or average with percentiles 25 and 75 (for non normal distribution). The presence of different letters indicates statistically significant differences.

The first relevant information of our study was that animals exposed to cigarette smoke presented one of the four geometry patterns described: normal pattern, eccentric hypertrophy, concentric hypertrophy, and concentric remodeling. Nevertheless, we should consider that the mechanisms involved in the geometry pattern variability are not known.

Considering the presence of one of the four different remodeling patterns, an aspect that is worthy of note is that the same phenomenon was observed in clinical studies, in arterial hypertension models^{7,17}. In the case of arterial hypertension, although the mechanisms are not completely clear, the different geometry patterns are explained by the different physiopathological mechanisms for hypertension, with different hemodynamic patterns. Hence, the geometry would depend on the vasoconstriction degree, the intensity of activation of neurohumoral factors and the presence of volume overcharge¹⁷. In our study, however, the animals exposed to cigarette smoke present the same characteristics. Then, our results suggest that in the model of exposure to cigarette smoke, animals with the same characteristics may present different morphological adaptations even if submitted to the same aggression.

Concerning the relevance of the ventricular remodeling patterns, in the Jackson Cohort of the Atherosclerosis Risk in Communities (ARIC) Study, the type of hypertrophy was associated to the type of ventricular dysfunction. Eccentric

hypertrophy was associated to a systolic dysfunction, while concentric hypertrophy was associated to diastolic dysfunction. On the other hand, concentric remodeling was not associated to ventricular dysfunction¹⁸. In the MESA study, however, patients with concentric remodeling presented systolic dysfunction, assessed by means of magnetic resonance¹⁹. Therefore, the association between the geometry and the ventricular dysfunction is still controversial. In our study, only the animals with normal geometry patterns and eccentric hypertrophy presented systolic dysfunction. Another aspect to be considered is that different authors showed that the remodeling pattern may have prognostic implications. This way, in patients with hypertension, the concentric hypertrophy pattern was associated with increased risk of cardiovascular events compared to other geometry patterns²⁰. Additionally, studies suggest that the concentric remodeling is associated to an increased risk of cardiovascular events²¹⁻²⁶. On the other hand, other studies found that geometry was not associated to a worse prognosis²⁷⁻²⁹, suggesting that the relevance of the remodeling pattern in patients with high blood pressure remains undetermined. In our study, the geometry patterns were not factors of prediction of systolic ventricular dysfunction. Therefore, in the model of rats exposed to cigarette smoke, the remodeling pattern did not present relevance in relation to cardiac function.

Another aspect to be considered in our study refers to the importance of the LV relative thickness. In clinical trials with patients with high blood pressure, the mass index was more important than the relative thickness of wall as a prognostic factor²⁹. In patients with acute myocardial infarction, the geometry pattern, the mass index and the relative thickness of the wall were independent prediction factors of death³⁰. In our study, among the geometric variables analyzed, the relative thickness of the wall was the only variable that could predict ventricular dysfunction, emphasizing the importance of such variable in the model of smoking rats.

The conclusion we have drawn is that rats exposed to cigarette smoke presented one of the four different remodeling patterns. Among the geometric variables analyzed, only the increased relative wall thickness of the left ventricle could predict ventricular dysfunction in this model.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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