Original Article

Effects of Beta-carotene and Smoking on Heart Remodeling after Myocardial Infarction

Leonardo A. M. Zornoff, Daniella R. Duarte, Marcos F. Minicucci, Paula S. Azevedo, Beatriz B. Matsubara, Luiz S. Matsubara, Álvaro O. Campana, Sergio A. R. Paiva

Faculdade de Medicina de Botucatu da Universidade Estadual de São Paulo, Botucatu, SP - Brazil

Summary

Objective: To analyze the effects of beta-carotene on the ventricular remodeling process following myocardial infarction (MI) in rats exposed to cigarette smoke.

Methods: After acute myocardial infarction (AMI), the animals were divided into four groups: 1) Group C, 24 animals that were given standard diet; 2) Group BC, 26 animals that were given beta-carotene; 3) Group ECS, 26 animals that were given standard diet and were exposed to cigarette smoke; and 4) Group BC+ECS, 20 animals that were given beta-carotene and were exposed to cigarette smoke. After six months, a morphofunctional study was performed. We used a 5% significance level.

Results: As regards diastolic areas (DA) and systolic areas (SA), the values for the BC group were higher than those for the C group. If DA/body weight (BW) and SA/BW are considered, the values for group BC+ECS were higher than the values for group C. As regards the fractional area change, we observed significant differences between ECS (lower values) and C (higher values) and between BC (lower values) and C (higher values). Differences between groups regarding infarction size were not observed. The ECS group presented higher values for myocyte cross-section area (MCA) than control animals. Additionally, the BC+ECS group presented higher MCA values than the BC, ECS and C groups.

Conclusion: After myocardial infarction, smoking and beta-carotene intensified the heart remodeling process; harmful effects of the remodeling process were heightened when the two treatments were used in conjunction. (Arq Bras Cardiol 2007;89(3):135-141)

Key words: Betacarotene; smoking; myocardial infarction; ventricular remodeling.

Introduction

Cardiovascular diseases rank first among the causes of death in Brazil, and account for 32% of the total deaths[1]. Among cardiovascular diseases, myocardial infarction stands out as the pathology with the highest mortality rate[2].

Smoking is thought to have an influence on the prevalence of myocardial infarction by means of several mechanisms, including atherosclerotic injury, increase in platelet aggregation, increase in the levels of adhesion molecules and fibrinogen and vasoconstriction[3,4].

Although the association between exposure to smoke and myocardial infarction is universally accepted, the direct effects of smoking or of compounds produced during cigarette burning on the heart are less known. In the heart aggression model that involves exposure to cigarette smoke, our group observed that dietary supplementation with beta-carotene mitigated the heart remodeling process induced by

cigarette smoke exposure in rats, partly because of its ability to reduce oxidative stress[5].

In a recent study carried out in our laboratory, exposure to cigarette smoke for six months after AMI led to intensification in remodeling[6]. In this context, it is important to consider that oxidative stress is accepted as one of the most important modulators of post-AMI ventricular remodeling[7-9]. Thus, antioxidant substances such as beta-carotene might mitigate this process.

Considering that cigarette smoke exposure intensifies post-infarction heart remodeling process, we advance the hypothesis that the administration of beta-carotene could mitigate alterations relating to post-AMI heart remodeling in rats exposed to cigarette smoke. Therefore, the objective of this study was to analyze the effects of beta-carotene supplementation on the heart remodeling process in rats submitted to experimental myocardial infarction and exposed to cigarette smoke.

Methods

Myocardial infarction - The experimental protocol of this study was approved by the Animal Experiment Ethics Committee of our institution and complies with the Animal

Experiment Ethical principles adopted by the Brazilian College for Animal Experiments.

We used male Wistar rats, from Unicamp's Laboratory Animal Facility. The animals were kept in cages for recovery, and fed on standard commercial feed and water ad lib, with controlled light (12-hour cycles), temperature (approximately 25° C) and humidity.

Myocardial infarction was produced according to the method previously described[10]. After AMI, animals were observed for a six-month period.

Experimental groups - Forty-eight hours after the AMI the animals were placed in four experimental groups: 1) Group C, n = 24 - formed by animals that were given the diet mentioned above, with no beta-carotene supplements and with no exposure to cigarette smoke; 2) Group BC, n = 26 - formed by animals that were given beta-carotene, in the form of crystal added to and mixed with the diet, at a dosage of 500 mg of beta-carotene/kg of feed, with no exposure to cigarette smoke; 3) Group ECS, n = 26 - formed by the animals that were given feed with no beta-carotene supplementation and were exposed to cigarette smoke; and 4) Group BC+ECS, n = 20 - formed by animals that were given beta-carotene in the same form as Group BC and were exposed to cigarette smoke. The amount of feed offered to the "non smoking" groups (C and BC) was adjusted according to the daily intake observed in the "smoking" groups (ECS and BC+ECS).

Exposure to smoke - In order to expose the animals to cigarette smoke we used the method proposed by Wang et al[11], that had been standardized in our laboratory[5,7]. At the end of the period of the experimental study, the animals had been exposed to the smoke of 40 cigarettes/day.

Morphological and functional assessment through echocardiogram - Six months after the myocardial infarction, the surviving animals were submitted to echocardiographic study. We used a Hewlett-Packard (Sonos 2000 model) or Philips (TDI 5500) model, equipped with a 12-MHz electronic transducer. The heart structures were measured according to the recommendations of the American Society of Echocardiography[12] which have been validated for the infarcted rat model[13]. Diastolic (DA) and systolic areas (SA) were measured using the bidimensional mode, by means of planimetry and adjusted for the animals' body weight (BW). The left ventricular systolic function was assessed by calculating the variation fraction of the area (FAC=DA-SA/DA x 100)[13].

Functional assessment by means of the isolated heart - Between one and three days after the echocardiographic study, the animals were administered sodium pentobarbital (50 mg/kg) and heparin (1,000 UI) intraperitoneally and were submitted to in vitro functional study using the isolated heart technique. In this preparation, where the heart operates in isovolumetric conditions, we obtained the values for systolic pressure (SP), for the positive derivative (dp/dt) and negative derivative (-dp/dt) of the maximum pressures[14].

Morphometric study - After the functional study, heart tissue samples were fixated in a 10% formol solution for a 48-hour period, according to the method previously described[15], to measure the myocyte cross-section area (MCA) and the interstitial collagen fraction (IC).

The extent of infarcted muscle, as well as of viable muscle in the endocardial and epicardial circumferences was determined by planimetry. Infarction size was calculated by dividing endocardial and epicardial ventricular circumferences in the infarcted area by total endocardial and epicardial circumferences. The measurements were taken in cross-sectional planes of the left ventricle, five to six millimeters from the apex, assuming that in this region the planes present a linear relation with the sum of the measurements of the areas of all the heart planes[16,17].

Statistical method - As regards morphological and functional variables, we employed analysis of variance (ANOVA) of one and two factors. In the one-way ANOVA, three degrees of freedom were applied to identify differences between treatments. If there was significant interaction between factors ($p < 0.05$), multiple comparisons were carried out using Tukey test. When there was no interaction ($p > 0.05$), the variables studied were tested as to the effects of the factors separately. The results were presented as mean values and standard errors (SE) of mean for the four groups studied (C, BC, ECS and BC+ECS). The level of significance adopted was 5%.

SigmaStat for Windows v 2.03, a statistics software package developed by SPSS, was employed to analyze the one and two-way ANOVA tests.

Results

Tables 1 and 2 summarize the results of the echocardiographic study. Considering the one-way ANOVA analysis, we observed differences between the groups regarding the ratio of left atrial diameter (LA) adjusted for BW, A-wave, heart rate (HR), DA/BW on the short axis, SA/BW on the short axis and FAC. As regards DA/BW and SA/BW, the values for Group BC were higher than those found for Group C. As regards the A-wave and FAV, the values found for Group BC were lower than those found for control animals. As regards LA/BW, DA/BW and SA/BW, the values for Group BC+ECS were higher than those found for Group C. As regards HR, the values for ECS and those for BC+ECS alike were higher than those for C.

As regards FAC in the two-way ANOVA analysis, significant differences were observed between ECS (lower values) and C (higher values) and between BC (lower values) and C (higher values). Additionally, there was significant interaction between the groups, suggesting that the effect of smoke depended on beta-carotene. Therefore, FAC values were higher for Group BC + ECS than for the animals submitted to isolated treatments (fig. 1). As regards other variables, no interactions were observed. Since no significant interactions occurred between factors (exposure to cigarette smoke and beta-carotene dietary supplements), it is understood that the effects of a factor did not depend on the other one. Thus, the values of LA/BW, DA/BW on the long axis, DA/BW on the short axis and SA/BW on the short axis were higher, and the values of the A and E-wave were lower for animals receiving beta-carotene supplements (BC and BC+ECS) than for animals that did not receive beta-carotene supplements (C and ECS). As regards HR, the values for smoking animals (ECS and BC+ECS) were higher than those observed for non-smoking animals (C and BC).

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Table 1 - Echocardiographic study: cavity diameters and transmitral flow velocity

Groups	n	LVDD/BW (mm/kg)	EDVE (mm)	LVWT/ EDD	LA/BW (mm/kg)	E (cm/s)	A# (cm/s)	E/A
C	13	20.5 ± 1.0	1.46 ± 0.08	0.13 ± 0.009	12.3 ± 1.0[a]	75.4 ± 7.0	3.60 ± 0.20[a]	2.73 ± 0.73
BC	11	23.8 ± 1.0	1.24 ± 0.06	0.12 ± 0.010	15.0 ± 1.1[ab]	69.4 ± 5.4	2.82 ± 0.15[b]	5.06 ± 0.74
ECS	11	23.4 ± 1.7	1.39 ± 0.10	0.13 ± 0.010	14.3 ± 1.0[ab]	80.4 ± 3.8	3.01 ± 0.31[ab]	4.56 ± 1.03
BC+ECS	9	22.4 ± 0.9	1.47 ± 0.05	0.14 ± 0.007	17.1 ± 1.4[b]	61.8 ± 5.7	2.89 ± 0.23[ab]	4.88 ± 1.16
P1 (3DF)		0.156	0.102	0.281	0.041	0.160	0.032	0.220
P2 – Effect of ECS (1DF)		0.523	0.343	0.310	0.078	0.826	0.242	0.388
P3 – Effect of BC (1DF)		0.312	0.354	0.857	0.019	0.038	0.042	0.166
P4 – ECS x BC interaction (1DF)		0.064	0.055	0.120	0.996	0.275	0.132	0.291

Values expressed as mean ± SE, n - number of rats; # - logarithmic transformation; C - control; BC - beta-carotene; ECS - exposure to cigarette smoke; LV - left ventricle; LVDD - LV diastolic diameter; BW - body weight; LVWT - LV posterior wall thickness at diastole; LA - left atrium; E - peak velocity in the fast ventricular filling stage; A - peak velocity during atrial contraction. P1 - P value in the one-way ANOVA analysis with three degrees of freedom (DF); P2 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of ECS; P3 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of BC; P4 -P value in the two-way ANOVA analysis with one degree of freedom for the effect of BC and ECS interaction. ab: different letters indicate statistically significant differences in the one-way ANOVA analysis (Tukey Test).

Table 2 - Echocardiographic study: cavity diameters, heart rate and ventricular function

| Groups	n	HR (beat/min)	DALA/BW (cm²/kg)	SALA/BW (cm²/kg)	DASA/BW (cm²/kg)	SASA/BW (cm²/kg)	FAC
C	13	248 ± 9[a]	2.03 ± 0.13	1.45 ± 0.13	1.57 ± 0.12[a]	1.05 ± 0.10[a]	31.9 ± 2.6 *§ [a]
BC	11	281 ± 10[ab]	2.43 ± 0.10	1.87 ± 0.10	2.09 ± 0.08[b]	1.61 ± 0.08[b]	23.6 ± 1.3 § [b]
ECS	11	302 ± 12[b]	2.06 ± 0.12	1.65 ± 0.12	1.90 ± 0.14[ab]	1.32 ± 0.11[ab]	25.5 ± 2.3*[ab]
BC+ECS	9	310 ± 12[b]	2.21 ± 0.11	1.61 ± 0.10	2.02 ± 0.10[b]	1.52 ± 0.10[b]	26.2 ± 1.6[ab]
P1 (3DF)		0.001	0.056	0.074	0.006	<0.001	0.023
P2 – Effect of ECS (1DF)		<0.001	0.424	0.773	0.261	0.348	0.343
P3 - Effect of BC (1DF)		0.065	0.024	0.111	0.006	<0.001	0.063
P4 – ECS x BC interaction (1DF)		0.276	0.291	0.059	0.072	0.068	0.030

Values expressed as mean ± SE, n - number of rats; C - control; BC - beta-carotene; ECS - exposure to cigarette smoke; LV - left ventricle; HR - heart rate; BW - body weight; DALA - LV diastolic long-axis area; SALA - LV systolic short-axis area; DASA - LV diastolic short-axis area; SASA - LV short-axis systolic area; FAC - fractional area change. P1 - P value in the one-way ANOVA analysis with three degrees of freedom (DF); P2 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of ECS; P3 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of BC; P4 -P value in the two-way ANOVA analysis with one degree of freedom for the effect of the BC and ECS interaction. When interactions were observed: * - significant differences between smoking and non-smoking Groups; § - significant differences between Groups receiving BC supplements and not receiving supplements; ab: different letters indicate statistically significant differences in the one-way ANOVA analysis (Tukey Test).

Data relating to the functional study of the isolated heart are shown on table 3. In the one-way ANOVA, differences were observed regarding maximum –dp/dt, since BC values were lower than BC+ECS values. In the two-way ANOVA, there was a statistically significant interaction between smoke and beta-carotene supplements. The analysis of –maximum -dp/dt showed differences between Group BC (lower values) as compared with Group BC+ECS (higher values), and between ECS (lower values) and BC+ECS (higher values). As regards maximum SP, there was a statistically significant interaction between smoking and beta-carotene supplements. In the analysis we observed differences between BC (lower values) and C (higher values) and between BC (lower values) and BC+ECS (higher values). As regards the maximum volume injected into the balloon, there was a statistically significant interaction between smoking and beta-carotene supplements (fig. 2). The analysis showed differences between ECS (lower values) and C (higher values), and between BC (lower values) and BC+ECS (higher values).
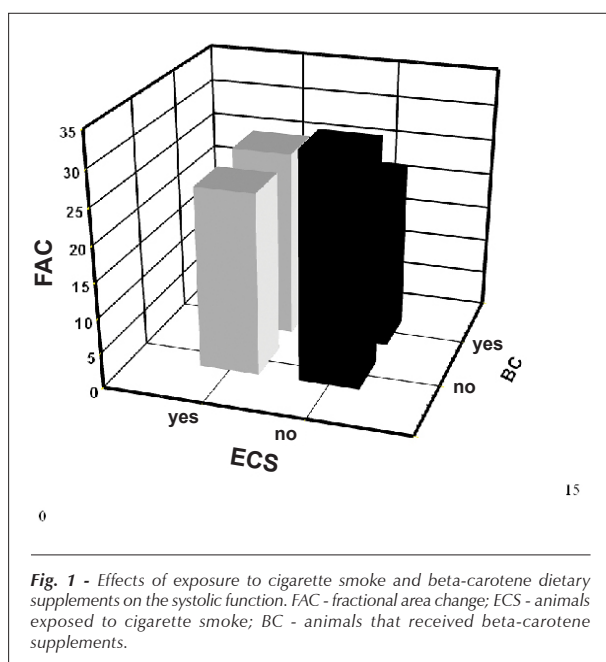
Fig. 1 - *Effects of exposure to cigarette smoke and beta-carotene dietary supplements on the systolic function. FAC - fractional area change; ECS - animals exposed to cigarette smoke; BC - animals that received beta-carotene supplements.*
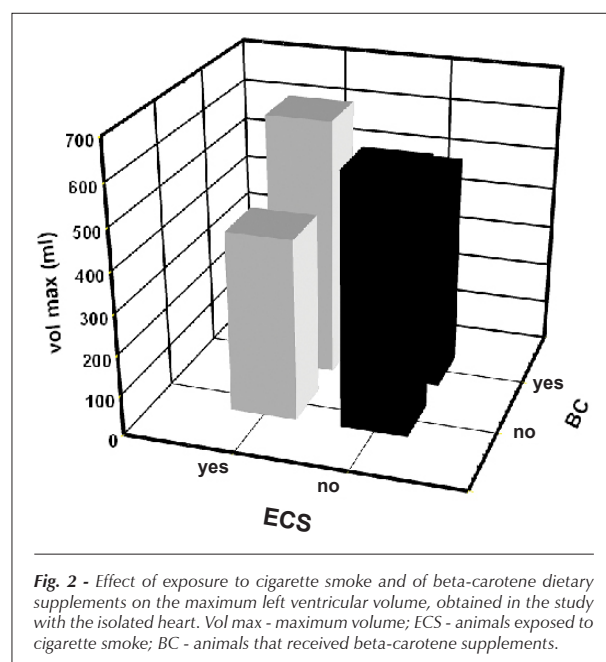
Fig. 2 - *Effect of exposure to cigarette smoke and of beta-carotene dietary supplements on the maximum left ventricular volume, obtained in the study with the isolated heart. Vol max - maximum volume; ECS - animals exposed to cigarette smoke; BC - animals that received beta-carotene supplements.*

Table 3 - Data on the isolated heart

Groups	n	V0/BW (ml/g)	SP max (mmHg)	dp/dt max (mmHg/s)	-dp/dt max (mmHg/s)	Vol max (ml)
C	13	0.76±0.12	126±8§	2,387±229	1,294±118[ab]	615±68*
BC	11	0.71±0.05	95±9§*	1,918±284	1,006±161[a]*	517±55§
ECS	11	0.67±0.08	117±9	2,416±318	1,104±124[ab]§	443±32*
BC+ECS	9	0.67±0.03	123±7*	2,630±218	1,614±125[b]§*	629±47§
P1 (3DF)		0.776	0.053	0.271	0.012	0.064
P2 – Effect of ECS (1DF)		0.392	0.259	0.165	0.127	0.578
P3 - Effect of BC (1DF)		0.780	0.144	0.629	0.413	0.414
P4 - ECS x BC interaction (1DF)		0.776	0.036	0.200	0.005	0.011

*Values expressed as mean ± SE, n - number of rats; C - control; BC - beta-carotene; ECS - exposure to cigarette smoke; BW - body weight; V0 - volume where diastolic pressure is equal to zero mmHg; dp/dt max - maximum value for positive pressure derivative; -dp/dt max - maximum value for negative pressure derivative; vol max - maximum volume. P1 - P value in the one-way ANOVA analysis with three degrees of freedom (DF); P2 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of ECS; P3 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of BC; P4 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of the BC and ECS interaction. When interactions were observed: * - significant differences between smoking and non-smoking Groups; § - significant differences between Groups receiving BC supplements and not receiving supplements; ab: different letters indicate statistically significant differences in the one-way ANOVA analysis (Tukey Test).*

Data relating to the morphometric analyses are on table 4. No differences were observed between the groups as regards infarction size. In the one-way ANOVA analysis, we observed differences between the groups regarding BW, RVW/BW, MCA and lung water content, RV and LV. Group ECS presented higher values for RVW/BW and MCA than control animals. Additionally, Group BC+ECS presented higher values for MCA than Groups BC, ECS and C. As regards lung water content, Group ECS presented higher values than Group C (C = 22.0±3.0, ECS = 29.0±2.0; p < 0.05). Additionally,

Group BC+ECS presented higher values for water content in RV (C = 4.63±0.33, BC+ECS = 5.69±0.14; p < 0.05) and LV (C = 5.11±0.25, BC+ECS = 6.81±0.31; p < 0.05) than Group C.

In the two-way ANOVA, we observed interaction as regards PVC/BW and MCA. As concerns RVW/BW, a significant difference was observed between ECS (higher values) and C (lower values). The RVW/BW ratio was smaller for Group BC+ECS than for Group ECS. As for MCA values, values for ECS were higher than for C, values for BC+ECS were higher

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Groups	n	BW# (g)	% AMI (%)	LVW# (g)	RVW (g)	LVW/BW (g/kg)	RVW/BW (g/kg)	MCA (μm²)	IC (%)
C	13	6.30 ± 0.03[a]	46.4 ± 1.2	0.572 ± 0.087	0.454 ± 0.064	2.94 ± 0.29	0.814 ± 0.114*[a]	240 ± 3*[a]	4.1 ± 0.2
BC	11	6.14 ± 0.02[b]	48.9 ± 2.0	0.396 ± 0.055	0.497 ± 0.039	2.80 ± 0.16	1.071 ± 0.083[ab]	235 ± 2*[a]	3.8 ± 0.5
ECS	11	6.18 ± 0.05[ab]	47.8 ± 1.5	0.421 ± 0.045	0.607 ± 0.067	2.86 ± 0.22	1.311 ± 0.153*[b]	254 ± 2*§[b]	3.5 ± 0.3
BC+ECS	9	6.15 ± 0.02[b]	50.3 ± 1.7	0.439 ± 0.032	0.476 ± 0.053	2.88 ± 0.10	1.000 ± 0.097[ab]	265 ± 2*§[c]	3.2 ± 0.5
P1 (3DF)		0.003	0.425	0.179	0.334	0.962	0.042	<0.001	0.710
P2 – Effect of ECS (1DF)		0.090	0.407	0.400	0.242	0.979	0.059	0.036	0.310
P3 - Effect of BC (1DF)		0.007	0.145	0.221	0.433	0.761	0.808	0.103	0.617
P4 – ECS x BC interaction(1DF)		0.057	0.993	0.137	0.123	0.718	0.013	0.007	0.965

Table 4 - Morphological data

*Values expressed as mean ± SE, n - number of rats; # - logarithmic transformation; C - control; BC - beta-carotene; ECS - exposure to cigarette smoke; BW - body weight; %AMI - infarction size; LVW - left ventricle weight; RVW - right ventricle weight; MCA - myocyte cross-section, IC - interstitial collagen fraction. P1 - P value in the one-way ANOVA analysis with three degrees of freedom (DF); P2 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of ECS; P3 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of BC; P4 - P value in the two-way ANOVA analysis with one degree of freedom for the effect of the BC and ECS interaction. When interactions were observed: * - significant differences between smoking and non-smoking Groups; § - significant differences between Groups receiving BC supplements and not receiving supplements; ab: different letters indicate statistically significant differences in the one-way ANOVA analysis (Tukey Test).*

than for BC and ECS (fig. 3). As for water content, smoking animals (ECS and BC+ECS) presented higher values than non-smoking animals (C and BC).

Discussion

The objective of this study was to analyze the effects of beta-carotene supplements on the ventricular remodeling process
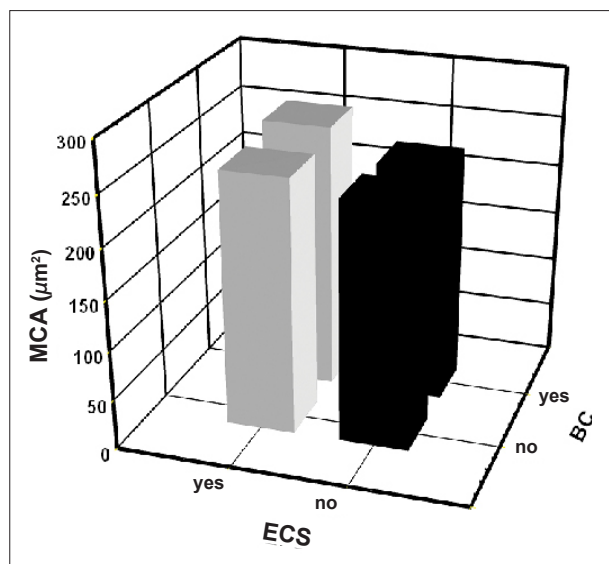

Fig. 3 - *Effect of exposure to cigarette smoke and of beta-carotene dietary supplements on myocyte cross-section. MCA - myocyte cross-section; ECS - animals exposed to cigarette smoke; BC - animals that received beta-carotene supplements.*

following acute myocardial infarction in rats exposed to cigarette smoke. Our hypothesis was that the antioxidant effects of beta-carotene would mitigate post-AMI remodeling process in animals exposed to cigarette smoke. Contrary to our hypothesis, however, our results suggest that beta-carotene intensified the heart remodeling process following infarction in this situation. Additionally, beta-carotene supplements heightened the harmful morphological effects induced by infarction.

Heart remodeling can be defined as genetic alterations that result in changes in heart molecules, cells and interstice. These changes can manifest themselves clinically as changes in volume, mass, constitution, geometry and/or heart function[18-20]. Although the ventricular remodeling process after myocardial infarction is highly complex, this term is frequently used as a synonym for cellular growth, evidenced by the increase of ventricular cavity[18-20]. A relevant aspect of this process relates to the fact that ventricular remodeling after myocardial infarction is associated with a worse prognosis, because its presence and intensity are related to fibrosis, progressive ventricular dysfunction, arrhythmias and increased mortality[21].

The mechanisms that modulate the post-infarction remodeling process are not yet fully understood. It is currently accepted that the increase in oxidative stress as a result of the accumulation of reactive oxygen species may be one of the mechanisms that trigger or regulate heart adaptations in response to a certain aggression[22-24]. Therefore, situations characterized by an increase in oxidative stress after infarction could heighten the remodeling process.

An increase in oxidative stress is associated with smoking. We must take into account, however, that few studies analyzed the effects of smoking on the process of ventricular remodeling

after myocardial infarction. Nicotine promoted left ventricular dilation in rats submitted to myocardial infarction. This phenomenon apparently occurs at the expense of the increase in infarct expansion, since thinner infarcted walls have been found in treated animals[25]. In our laboratory, exposure to cigarette smoke for six months resulted in the intensification of remodeling, which was accompanied by the worsening of functional variables[7]. Thus, exposure to cigarette smoke seems to provoke remodeling in normal conditions and in situations involving heart aggression as well.

In this study, animals exposed to cigarette smoke presented increased LV systolic and diastolic dimensions and increased myocyte cross-section as compared with control animals. We can therefore infer that exposure to cigarette smoke intensified the process of ventricular remodeling after infarction, which is in agreement with previously mentioned studies[6,7].

Considering that acute myocardial infarction and exposure to cigarette smoke alike are conditions where there is increase in oxidative stress, we advanced the hypothesis that the administration of beta-carotene would mitigate ventricular remodeling secondary to these aggressions. However, contrary to our hypothesis, animals exposed to both treatments (beta-carotene and exposure to cigarette smoke) presented additional intensification of heart remodeling, attested by the increase in left atrium area and in myocyte cross-section area. Additionally the group that received supplements presented an increase in LV systolic and diastolic sizes as compared with control group animals. So far, the mechanisms that are responsible for these harmful effects of beta-carotene on the post-infarction remodeling process remain unclear. Despite this fact, however, as regards the clinical perspectives of this study, our paper suggests caution in the administration of antioxidants, especially beta-carotene and in the presence of smoking for cardiovascular protection after myocardial infarction.

Heart remodeling invariably causes a progressive decrease of ventricular function. At first, as a consequence of cellular growth, remodeling can contribute to maintain or restore heart function. Chronically, however, biochemical, genetic and structural changes occur that result in progressive ventricular dysfunction. In our study, the functional results are in partial disagreement with this concept. In the group that received beta-carotene supplements, echocardiographic and isolated heart variables confirm left ventricular dysfunction as compared with the control group. In the beta-carotene and smoking group, however, despite intense remodeling, no statistically significant differences were observed as compared with the control group. But we observed function improvement in some of the variables for this group as compared with Group BC. An explanation for this fact may have to do with the acute or chronic effects of exposure to cigarette smoke.

In our study, both the echocardiographic study and the analysis of the isolated heart were performed in the afternoon but the animals had been exposed to cigarette smoke during the morning. We could therefore infer that functional analysis may have been influenced by the acute positive inotropic stimulation of cigarettes. This limitation should be taken into account when interpreting our results. This hypothesis is supported by the fact that smoking animals presented higher heart rates and higher water content in some of the organs analyzed, which is compatible with chronic ventricular dysfunction.

In summary, the data obtained in this study allow the following conclusions: exposure of rats to cigarette smoke after myocardial infarction intensified the heart remodeling process; beta-carotene dietary supplements increased the heart remodeling process caused by experimental myocardial infarction; the harmful effects of the remodeling process were heightened when the two treatments were employed in conjunction.

Potential Conflict of Interest

Sources of Funding

Study Association

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