Comparison of morphometry and ventricular function of healthy and smoking young people

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Abstract

Background: Tobacco smoke is one of the most significant risk factors for cardiovascular diseases and damages in the myocardial tissue directly. Cardiac magnetic resonance (CMR) has been used and is a promising tool to evaluate morphometry and cardiac function in humans. The objective of this study was to evaluate associations of smoking with morphometry and cardiac function by CMR technique in young adult smokers.

Methods: Altogether, 49 volunteers (22 smokers and 27 non-smokers) were included in the study. The comparisons between groups were performed by multiple linear regression adjusting for body mass index and gender.

Results: In the morphometric and functional evaluation of the left ventricle, we observed statistical significant lower values of end-diastolic volume (EDV) \( (p = 0.02) \), ejection volume (EV) \( (p = 0.001) \) and indexed ejection volume (IEV) \( (p = 0.007) \) in smokers when compared to no-smoker group. Right ventricle showed statistical significant lower values of EDV \( (p < 0.001) \), end-systolic volume \( (p = 0.01) \), EV \( (p < 0.001) \), IEV \( (p = 0.001) \), indexed end-diastolic volume \( (p = 0.001) \) and major axis \( (p = 0.01) \) in smokers when compared to non-smokers group.

Conclusions: There is a strongly association of smoking in young adult and cardiac function decline, even adjusted by cofounders, which compromises the proper functioning of the heart. Evidence confirms that smoking can directly influence the cardiac function, even without atherosclerosis or other chronic comorbidities, associated with increased risk of cardiovascular diseases.

Keywords: Cardiovascular magnetic resonance, Smoking, Heart, Ventricular function

Background

Smoking is a public health problem worldwide and is the leading cause of preventable death. Approximately 6 million people die every year due to tobacco-related diseases. The prediction is that ten million deaths occur per year in the world in 2030. In Brazil, approximately 200,000 deaths per year are estimated due to smoking [1, 2]. Tobacco smoke is one of the most significant risk factors for cardiovascular diseases and damages myocardial tissue directly [1]. Long-term smoking is associated with considerable metabolic and morphological changes in the heart muscle that can be characterized as smoking cardiomyopathy, including significantly modifications in right and left chambers functions, resulting in diastolic or systolic dysfunctions [3, 4]. However, experimental studies show that exposure to tobacco smoke, which has over 4700 chemical substances, increases the incidence of cardiovascular diseases [4–7]. Another experimental study showed that the toxic effects of tobacco smoke was associated with eccentric hypertrophy, regardless of hemodynamic effects [6]. In addition, the findings were correlated with apoptosis, hypertrophy and myocardial dysfunction [8–10]. A clinical study by Nadruz et al. [11], which evaluated more than 4500 elderly healthy individuals through transthoracic echocardiography showed that active smoking and cumulative exposure to

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cigarettes were associated with subtle changes in the structure and function of the left ventricle, but not evaluated the right chambers’. Besides echocardiography, cardiac magnetic resonance (CMR) has been used and is a promising tool to evaluate morphometry and cardiac function in humans [12]. However, we identified no data in the literature that assess cardiac function of smoking patients without cardiovascular diseases by CMR. Thus, the main objective of this study was to evaluate associations of smoking with morphometry and cardiac function through the CMR technique in young adult smokers.

Methods
Study population
We evaluated 84 individuals of both genders, smokers (active smokers with at least smoking history ≥10 packs-year) and control (never smokers) from an university city close to the center-west region of São Paulo State. In the smoking group, we included subjects with > 18 years old and we excluded those with acute infection diagnosis or in use of medicines in the past 4 weeks, pregnancy, claustrophobia, or any chronic disease such as coronary insufficiency, cardiac insufficiency, systemic arterial hypertension (SAH), diabetes mellitus, dyslipidemia, respiratory, hepatic, renal, psychiatric diseases, cancer and changes in the laboratory tests [hemogram, fasting glycemia, C-reactive protein, triglycerides, total cholesterol or high-density lipoprotein (HDL)] or in the pulmonary function test. We included 22 subjects in the smoking group and 19 were excluded due to the following reasons: one for pregnancy, four for change in laboratory analysis, seven for abnormal lung function and seven withdrew the informed consent form (ICF).

In the control group, we included subjects aged > 18 and those who presented a history of never use of any tobacco product. The exclusion criteria were the same from the smoker group. Altogether, 27 subjects were included in the control group and 16 were excluded due to the following reasons: one for SAH, one for previous bariatric surgery, one for endometriosis, one for claustrophobia, one for diabetes, one did not sign the ICF, five for laboratory analysis changes and five for pulmonary function changes.

All participants included in this study signed the informed consent form approved by the Research Ethics Committee of the Clinical Hospital of Botucatu Medical School.

Data source
All subjects of the research were evaluated through clinical history and complete physical examination. Smoking history (packs-years) and current smoking state were investigated and complemented by assessing intensity of nicotine dependence (Fagerström Test) [13] and confirmation of active smoking was accomplished through carbon monoxide (CO) measurement in the exhaled air through a standardized technique with specific equipment (Micro+ Smokerlyzer, Bedfont, England, UK) [14, 15]. Physical activity was assessed by International Physical Activity Questionnaire (IPAQ) short version [16].

Spirometry was performed (only to assess inclusion and exclusion criteria) in a computerized portable system with pulmonary function (Ferraris KOKO, Louisville, CO, USA), according to American Thoracic Society criteria [17]. We measured forced vital capacity (FVC) in liters (L) and forced expiratory volume in the first second (FEV1) in liters (L) and calculated ratio of the two measures (FEV1/FVC). Measures were obtained before and 20 min after administration of 400 mcg of salbutamol dosed as bronchodilator medication. FVC and FEV1 values were also expressed in percentage of the reference values [18].

All participants of the research underwent CMR examination, which were carried out in the 3-T MR device (Magnetom Verio, Siemens AG, Health care Sector, Erlangen, Germany) according to the study protocol. The localizers were obtained through image cut sequences of the heart to the programming of sequences of posterior images. Images on cine-MRI in short and long axes of the left ventricle (LV) using the Steady-State Free Precession sequence were used for calculations of ventricular volumes and functions. The T1 mapping (that allows measuring fibrosis areas in the myocardial tissue) was performed by the Modified Look-Locker Inversion Recovery – MOLLI sequence with motion correction, not available for purchase (Work-in-progress – WIP). T1 mapping were obtained through diastole, in the middle segment of the short axis of the left ventricle and through images of four cameras. The T2 mapping (that allows measuring areas of edema and inflammation in the myocardial tissue) was obtained in the middle segment of the left ventricle.

After acquisition of these images, gadolinium contrast was injected (Gadolinium DTPA – 0.15 mmol/kg) and new images of late enhancement were obtained after 15 min using the phase-sensitive inversion-recovery – PSIR sequence in the short and long axes of the LV and also the T1 maps at the same anatomical plans.

Analysis of images
Ventricular function, volumes and mass of the LV were calculated through the Ventricular Function Argus software (Siemens AG, Healthcare Sector). All volumes and ventricular mass were indexed to the body surface area [19]. Using standardized segmentation of the left ventricle we split the T1 mapping into sixteen myocardial segments for T1 time measurements independently [20]. The Apex (segment 17) was not analyzed due to the impossibility of avoiding partial volume effect in this
segment. Regions of interest (ROIs) were drawn in the pre-contrast image and then copied to the post-contrast images. Calculation of the extracellular volume (ECV) was carried out manually, using the T1 measures before and 15 min after administration of the intravenous contrast [12]. The T2 measurement was performed with the “ROIs” positioned in the interventricular septum to avoid that any increases in the native T1 result from edema.

Statistical analysis
We used the Statistical Package for Social Sciences (SPSS) 17.0 (Inc, Chicago, IL, USA). Descriptive analysis of the results was performed, and the data are presented in absolute numbers, percentage and/or in mean and standard deviation and median and 25/75 percentile. For the comparison between two groups (smoker and control), the Student’s t test was used for parametric distribution variables and the Mann-Whitney test for the nonparametric distribution variables. We used multiple linear regression analysis to compare control vs smokers adjusted by gender and body mass index (BMI). We used multiple linear regression analysis with robust standard errors when the normality was not assumed. All models considered control group as a comparator. Therefore, the coefficient needs to be interpreted as an estimated mean difference between smoking group and control group, such as, when the coefficient is negative, the smoking group presented lower values compared to control group. We considered a 5% significance level.

Results
General characteristics of the 49 subjects are presented on Table 1. The smokers showed an average smoking history of 17.7 ± 6.7 packs-years and 32% of these showed a high degree of nicotine dependence. The smokers had significantly smaller stature and higher body mass index and as expected, the CO mean in exhaled air was higher in the smoking group compared to the control group. IPAQ did not show statistical significance between groups.

When we compared morphometric and functional variables of the LV between both groups, we observed significantly lower values of ejection volume (EV) and the indexed ejection volume (IEV) (Table 2). When the model was adjusted for gender and BMI using multiple linear regression analysis to compare both groups, we observed statistical significant lower values of EV, IEV and end-diastolic volume (EDV) in smoker group compared to control group (Table 3).

Comparing morphometric and functional variables of the right ventricle (RV) of smokers and controls, we observed statistical significantly lower values of EV, IEV, EDV, indexed end-diastolic volume (IEDV) and major axis in smokers (Table 4). Adjusting the model by BMI and gender using multiple linear regression analysis we identified EV, IEV, EDV, IEDV, end-systolic volume (ESV) and major axis statistical significantly lower values in smoker group when compared to control group (Table 5).

The left atrium and the aorta variables did not show statistically significant alterations between the groups (Table 6). None of subjects of this study presented alterations on maps T1 or T2.

Discussion
The main finding was to identify reduced left and right cardiac function in active smoking in young smokers

Table 2 Functional and morphometric evaluation of the LV by cardiac magnetic resonance imaging between control group and smokers

| Variables     | Non-smoker (n = 27) | Smoker (n = 22) | P value |
|---------------|---------------------|----------------|---------|
| EF (%)        | 63.7 ± 5.47         | 61.5 ± 4.58    | 0.14    |
| EDV (mL)      | 144 ± 30.9          | 130 ± 24.4     | 0.09    |
| ESV (mL)      | 52.9 ± 17.2         | 50.3 ± 12.5    | 0.56    |
| EV (mL)       | 90.9 ± 16.6         | 79.5 ± 15.9    | 0.02    |
| LVM (g)       | 117 ± 28.4          | 116 ± 30.0     | 0.95    |
| IEDV (mL/m²)  | 75.6 ± 10.4         | 71.0 ± 8.73    | 0.10    |
| IESV (mL/m²)  | 27.6 ± 6.75         | 27.5 ± 5.51    | 0.94    |
| IEV (mL/m²)   | 47.9 ± 5.92         | 43.5 ± 5.32    | 0.009   |
| ILVM (g/m³)   | 61.6 ± 10.6         | 63.4 ± 10.4    | 0.54    |
| IVS (mm)      | 10.0 (9.00–11.0)    | 9.00 (8.00–10.2)| 0.20   |
| LVPW (mm)     | 8.70 ± 1.81         | 8.45 ± 2.01    | 0.65    |
| LVESD (mm)    | 52.9 ± 5.33         | 51.3 ± 4.14    | 0.26    |
| LVESD (mm)    | 34.1 ± 3.92         | 34.0 ± 3.98    | 0.96    |

EF: ejection fraction, EDV: end-diastolic volume, ESV: end-systolic volume, EV: ejection volume, LVM: left ventricular mass, IEDV: indexed end-diastolic volume, IESV: indexed end-systolic volume, IEV: indexed ejection volume, ILVM: indexed left ventricular mass, IVS: interventricular septum, LVPW: left ventricular posterior wall, LVESD: left ventricular end-diastolic diameter, LVESD left ventricular end-systolic diameter. The data are expressed as mean ± standard deviation (parametric distribution) or mean 25 and 75 percentiles (non-parametric distribution)


Table 3 Comparison between groups (smokers and controls) by multiple linear regression of morphometric and functional variables of LV adjusted by gender and body mass index

| Variables         | Coeficiente (95%CI) | P value |
|-------------------|---------------------|---------|
| EF (%)            | −2.59 (−5.62;0.44)  | 0.09    |
| EDV (mL)          | −14.7 (−27.1;2.37)  | 0.02    |
| ESV (mL)          | −2.35 (−10.1;5.34)  | 0.54    |
| EV (mL)           | −12.4 (−19.3;−5.37) | 0.001   |
| LVM (g)           | −1.05 (−11.3;9.12)  | 0.83    |
| IEDV (mL/m²)      | −4.25 (−9.48;0.98)  | 0.11    |
| IESV (mL/m²)      | 0.29 (−3.21;3.79)   | 0.87    |
| IEV (mL/m²)       | −4.44 (−7.63;1.26)  | 0.007   |
| ILVM (g/m²)       | 2.15 (−2.31;6.62)   | 0.34    |
| IVS (mm)³        | −0.42 (−1.14;0.61)  | 0.41    |
| LVPPW (mm)        | −0.35 (−1.31;0.60)  | 0.46    |
| LVEDDD (mm)      | −1.59 (−4.36;1.18)  | 0.25    |
| LVESD (mm)        | −0.07 (−2.21;2.07)  | 0.95    |

EF ejection fraction, EDV end-diastolic volume, ESV end-systolic volume, EV ejection volume, LVM left ventricular mass, IEDV indexed end-diastolic volume, IESV indexed end-systolic volume, IEV indexed ejection volume, LVPPW indexed left ventricular mass, IVS interventricular septum, LVPPW left ventricular posterior wall, LVEDDD left ventricular end-diastolic diameter, LVESD left ventricular end-systolic diameter. Multiple linear regression reference group: controls. The coefficient needs to be interpreted as an estimated mean difference between smoking group and control group, such as, when the coefficient is negative, the smoking group presented lower values compared to control group.

Table 4 Functional and morphometric evaluation of the RV by cardiac magnetic resonance imaging between control group and smokers

| Variables         | Non-smoker (n = 27) | Smoker (n = 22) | P value |
|-------------------|---------------------|----------------|---------|
| EF (%)            | 63.7 ± 5.47         | 61.5 ± 4.58    | 0.14    |
| EDV (mL)          | 140 ± 36.5          | 114 ± 29.7     | 0.01    |
| ESV (mL)          | 60.2 ± 21.5         | 49.5 ± 15.8    | 0.05    |
| EV (mL)           | 79.7 ± 18.5         | 64.4 ± 16.0    | 0.004   |
| IEDV (mL/m²)      | 73.4 ± 14.1         | 61.8 ± 10.6    | 0.003   |
| IESV (mL/m²)      | 31.3 ± 8.83         | 27.0 ± 6.64    | 0.06    |
| IEV (mL/m²)       | 42.1 ± 8.28         | 35.0 ± 5.53    | 0.001   |
| Major axis (mm)   | 81.0 ± 10.6         | 72.5 ± 9.04    | 0.005   |
| Minor axis (mm)   | 45.0 (40.0–53.0)    | 42.0 (38.7–45.2)| 0.30 |

EF ejection fraction, EDV end-diastolic volume, ESV end-systolic volume, EV ejection volume, IEDV indexed end-diastolic volume, IESV indexed end-systolic volume, IEV indexed ejection volume. Data are expressed as mean ± standard deviation (parametric distribution) or median with 25 and 75 percentiles (non-parametric distribution).

risk factor with 14% current smokers and 47% never smokers, presented that current smokers were younger than never-smokers and the association of smoking status and vascular dynamics and function was similar with our results, an unexpected lack of association between smoking and vascular distensibility evaluated by carotid ultrasound and aortic MRI [21]. In the same cohort, but analyzing the relationship of left ventricular mass and geometry to incident cardiovascular events showed that patient who had coronary heart disease were current or former smokers and increase values of LV mass/ LV volume ratio was predictive of incident of coronary heart disease [22].

Under normal conditions, pulmonary vascular compliance is suitable and pulmonary vascular resistance is reactive enough to accept emphatically higher quantities of pulmonary blood flow with minimal increases in pulmonary blood pressure [23]. The pulmonary hypertension was not technically evaluated, however, we can

Table 5 Comparison between groups (smokers and controls) by multiple linear regression of morphometric and functional variables of RV adjusted by gender and body mass index

| Variables         | Coeficiente (95%CI) | P value |
|-------------------|---------------------|---------|
| EF (%)            | −1.37 (−4.62;1.88)  | 0.40    |
| EDV (mL)          | −25.8 (−39.7;−11.1) | <0.001  |
| ESV (mL)          | −9.7 (−17.5;−0.85)  | 0.01    |
| EV (mL)           | −16.1 (−24.4;−7.87) | <0.001  |
| IEDV (mL/m²)      | −10.9 (−17.1;−4.70) | 0.001   |
| IESV (mL/m²)      | −3.51 (−7.13;0.11)  | 0.06    |
| IEV (mL/m²)       | −7.28 (−11.4;−3.16) | 0.001   |
| Major axis (mm)   | −6.96 (−12.2;−1.68) | 0.01    |
| Minor axis (mm)   | −1.66 (−5.07;1.76)  | 0.33    |

EF ejection fraction, EDV end-diastolic volume, ESV end-systolic volume, EV ejection volume, IEDV indexed end-diastolic volume, IESV indexed end-systolic volume, IEV indexed ejection volume. Multiple linear regression reference group: controls. The coefficient needs to be interpreted as an estimated mean difference between smoking group and control group, such as, when the coefficient is negative, the smoking group presented lower values compared to control group.

Table 6 Comparison between groups (smokers and controls) by multiple linear regression of left atrium and aortic variables adjusted by gender and body mass index

| Variables         | Coeficiente (95%CI) | P value |
|-------------------|---------------------|---------|
| LA (mm)           | 0.78 (−2.38;3.95)   | 0.62    |
| RA (mm)           | −0.30 (−2.77;2.17)  | 0.81    |
| descending aorta (mm) | −0.65 (2.86;1.55) | 0.55    |
| ascending aorta (mm) | −0.31 (−1.65;1.04) | 0.65    |

LA left atrium, RA aortic root. Multiple linear regression reference group: controls. The coefficient needs to be interpreted as an estimated mean difference between smoking group and control group, such as, when the coefficient is negative, the smoking group presented lower values compared to control group.
assume our hypothesis to justify the biggest compromis-
ing of the right chamber when comparing with the left
chamber is that the toxic smoke of the cigarette causes
more and/or earlier damage to pulmonary flow leading
to vasoconstriction in the pulmonary arteries due to
presence of oxidative stress and infiltration of the infl-
mamatory process compared to the systemic flow [3].
This continuous cyclical process would be associated
with elevation of pulmonary artery pressure and conse-
cuently bigger effort from the right ventricle, which
would result in reduced value of volume compared to
the control group. This hypothesis is consistent with the
experimental study on mice exposed to tobacco smoke,
which showed that the right ventricle systolic function
presented reduction despite the echocardiogram showed
the left ventricular function as normal. Besides, in this
study, the authors did not identify changes in mitochon-
drial respiration between the fibers of the left and right
chambers that could justify changes only in the right
cardiac function but showed reduced endothelial vaso-
dilatation of the aortic ring [24]. In the same direction,
results of an experimental study in pigs corroborate our
hypothesis. Both groups of pigs, the one exposed to to-
bacco smoke and the one exposed to chronic hypoxia,
showed that these both injuries produced similar in-
creases in elevation of pulmonary artery pressure and in
the right ventricle and that the combination of both
agents had a synergetic effect on these changes. In
addition, distensibility of the aorta was lower than dis-
tensibility of the pulmonary arteries and thickness of the
pulmonary arteries presented thickening, which demons-
trates the direct effect of tobacco smoke on reactivity
and mechanical properties of large pulmonary arteries
and in morphological characteristics of small intrapul-
nomary vessels [25]. However, the literature shows dir-
ectly influence of smoking on vascular stiffness and
arterial age of increased values of serum lipids, contin-
uous activation of sympathetic nervous system and the
rise of blood pressure. These chronic modifications asso-
ciated to smoking leads to an increased risk of cardio-
vascular disease [26].

Our studied population was asymptomatic smoking
young adults; however, they already presented reduced
value of volume parameter. Changes identified through
the CMR in young smokers can be a useful tool for early
diagnosis of cardiac changes caused by smoking, which
can help behavioral modification of individuals that leads
them to quit smoking. However, we cannot say that the
reduced value of cardiac functional identified in our
sample are definitive. Aggressive cyclic events of smok-
ing and induction for definitive changes may be slow be-
fore morphometry and heart function present clinical
changes as seen in the experimental studies. At this
stage, the heart muscle is still functional and seems
completely fine, but in myocardium, there are rising
signs of degeneration. Cellular hypertrophy and fibrosis
are factors that increase risk of cardiac arrhythmias,
heart attack and even sudden death. Still regarding ex-
perimental studies with similar results, study by Min-
cucci et al. [27], which evaluated rats exposed and not
exposed to tobacco smoke for 2 months, showed that
rats exposed to tobacco smoke presented cardiac remod-
eling characterized by atrium and LV increase and with
decreased systolic function. In addition, they identified
mechanisms associated with systolic function worsening,
with myocyte hypertrophy, change in energetic metab-
olism due to increase in lactate dehydrogenase and reduc-
tion in citrate synthase, and also increase in oxidative
stress (increase in hydroperoxide of lipid proteins and
reduction in the superoxide disproportionation). How-
ever, the present study did not evaluate the possible in-
flammatory mechanisms or oxidative stress that can
demonstrate similarity with the experimental studies.

Thus, other studies in young smokers that quit smok-
ing are required for proof of the benefit of smoking ces-
sation. Our study did not identify muscular fibrosis.
However, CMR images are the only non-invasive
method capable of detecting both modifications simul-
taneously; currently, the interstitial fibrosis is only found
through the cardiac tissue biopsy, an invasive and diffi-
cult to be applied technique. Through obtention of mul-
tiple images of the myocardial fibers, which forms a
movie of the heart functioning, the CMR examination
allows to calculate size of cells of the heart muscle and
quantity of fibrosis. On the other hand, such examin-
ation is still considered expensive and its clinical practice
application is focused on identification of cardiovascular
pathologies with clinical manifestations.

The high accuracy and the smallest variability pre-
ented by MRI measurements are of great importance in
clinical research, being appropriate to perform serial
measurements over time. According to this, the evaluation
of early modification of cardiac function in asymptomatic
smokers can be compared to experimental studies and it
is a tool to evaluate the influence of stopping smoking in
early stages of structural cardiac changes.

Therefore, evidence confirms that smoking is strongly
related to occurrence of cardiovascular events and car-
diac function decline, which compromises the proper
functioning of the heart.

This study has some limitations that need to be ad-
dressed. First, other studies are necessary to confirm our
results, because of the size of the sample is small and
consisting only of young smokers. Second, we did not
confirm the cotinine levels to assess the smoking impact
in possible involved mechanisms. Third, this was a
cross-sectional study that cannot affirm the causality.
There was no follow-up of smokers to evaluate evolution
of cardiac functions and their long-term outcomes. In addition, our study did not evaluate inflammatory or oxidative stress factors associated with the CR mechanism.

**Conclusion**

There is a strongly association of smoking in young adult and cardiac function decline, even adjusted by co-founders, which compromises the proper functioning of the heart. Evidence confirms that smoking can directly influence the cardiac function, even without atherosclerosis or other chronic comorbidities, associated with increased risk of cardiovascular diseases.

**Abbreviations**

BMI: Body mass index; CMR: Cardiac magnetic resonance; CO: Carbon monoxide; ECV: Extracellular volume; EDV: End-diastolic volume; ESV: End-systolic volume; EV: Ejection volume; FCV: Forced vital capacity; FEV1: Forced expiratory volume in the first second; HDL: High-density lipoprotein; ICQ: Informed consent form; IEDV: Indexed end-diastolic volume; IV: Indexed ejection volume; IPAQ: International physical activity questionnaire; L: Liters; LV: Left ventricle; ROIs: Regions of interest; RV: Right ventricle; SAH: Systemic arterial hypertension

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**Authors’ contributions**

ANRB participated in the design of the study, performed the statistical analysis, interpreted the findings, and drafted the manuscript. TG contributed to the study design and discussion. SET participated in the design of the study, was involved in revising the manuscript for important intellectual content and gave final approval of the version to be published. PSA, LAMZ, IG participated in critical manuscript revision. EATF, MFB and MFM, SARP and IG participated in funding. JWZ participated in the acquisition of data. All the authors have read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

This study protocol was approved by the Research Ethics Committee of the Clinical Hospital of Botucatu Medical School (approval number: 969.289). This study protocol was approved by the Research Ethics Committee of the Clinical Hospital of Botucatu Medical School (approval number: 969.289). Written informed consent was obtained from each patient. If patients were unable to provide consent due to disease severity or other reasons, informed consent was obtained from relatives or a legal guardian.

**Consent for publication**

All authors have read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

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**References**

1. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease. An update. J Am Coll Cardiol. 2004;43(10):1731–7.
2. World Health Organization (WHO) b. Report on the global tobacco epidemic, 2013.
3. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. Chest. 2007;131(5):1557–66.
4. Kamimura D, Cain LR, Mentz RJ, White WB, Blaha M, Defilippis AP, Fox ER, Rodriguez CJ, Keith RI, Benjamin EJ, Butler J, Bhatnagar A, Robertson RM, Winniford MD, Corea A, Hall ME. Cigarette smoking and incident heart failure: insights from the Jackson heart study. Circulation. 2018;137(24):2572–82.
5. Minicucci MF, Azevedo PS, Polegato BF, Paiva SA, Zornoff LA. Cardiac remodeling induced by smoking: concepts, relevance, and potential mechanisms. Inflamm Allergy Drug Targets. 2012;11(6):442–7.
6. Azevedo PS, Minicucci MF, Matabuba BB, Matabuba LS, Duarte DR, Paiva SAR, Zornoff LAM. Remodeling pattern and ventricular function in rats exposed to cigarette smoke. Arq Bras Cardiol. 2010;94(2):224–8.
7. Al-Arifi MN, Manahy ZH, Alshamrani AA, Korashy HM. Impact of cigarette smoke exposure on the expression of cardiac hypertrophic genes, cytchrome P450 enzymes, and oxidative stress markers in rats. J Toxicol Sci. 2012;37(5):1083–90.
8. Hellestek MK, Benowitz NL, Neese RA, Schwartz JI, Hoh R, Jacob P 3rd, Hsieh J, Fagg F. Effects of cigarette smoking and its cessation on lipid metabolism and energy expenditure in heavy smokers. J Clin Invest. 1994;93:265–72.
9. Cavalcante AGM, Brin PF. O papel do estresse oxidativo na DPOC: conceitos atuais e perspectivas. J Bras Pneumol. 2009;35(12):1227–37.
10. Jacobson O, Malaguti C, Silva JA Jr, Nascimento JML. Envolvimento do tabagismo e apoptose na patogênese da doença pulmonar obstrutiva crônica. Rev Med Minas Gerais. 2011(2):161–8.
11. Nadruz W, Caggett B, Gonçalves A, Queijetia-Roca G, Fernandes-Silva MM, Shah AM, Cheng S, Tanaka H, Heiss G, Kitzman DW, Solomon SD. Smoking and cardiac structure and function in the elderly: the ARIC study (atherosclerosis risk in communities). Circ Cardiovasc Imaging. 2016;9(9):e004950.
12. Van der Meer RW, Donnoms J, Koxenje S, Schär M, Bax JJ, Hammer S, Smit JW, Bijn J, Mier CM. Detection of tobacco smoking with reference to individualization of treatment. Addict Behav. 1978;3(3–4):235–41.
13. Middleton ET, Monice AH. Breath carbon monoxide as an indicator of smoking habit. Chest. 2000;117(3):758–63.
14. Santos UP, Gannam S, Abe JM, Esteves PB, Filho MF, Wakasaa TS, Issa JS, Filho MT, Stelmach R, Cukier A. Emprego da determinação de monóxido de carbono na ar exalado para a detecção do consumo de tabaco. J Bras Pneumol. 2001;27(5):231–6.
15. International Physical Activity Questionnaire (IPAQ). Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ) - short and long forms. 2018. http://www.ipaq.ki.se. Accessed 20 Feb 2018.
16. Standardization of spirometry-1987 update. Statement of the American Thoracic Society. Am Rev Respir Dis. 1987;136(5):1285–98.
17. Pereira C, Bareto S, Simeóes J, Pereira F, Gerster L, Nakatani J. Valores de referência para a espirometria em uma amostra da população brasileira adulta. J Bras Pneumol. 1992;18:10–22.
18. Kankaanpää M, Lehto HR, Pärkkä JP, Kormu M, Viljanen A, Ferrannini E, Knuuti J, Nuutila P, Parkkola R, Iozzo P. Myocardial triglyceride content and epicardial fat mass in human obesity: relationship to left ventricular function and serum free fatty acid levels. J Clin Endocrinol Metab. 2006;91(11):4689–4695.
19. Iozzo P, Lautamaki R, Borra R, Lehto HR, Bucci M, Viljanen A, Parkka J, Lempomaki V, Maggio R, Parkkola R, Knuuti J, Nuutila P. Contribution of glucose tolerance and gender to cardiac adiposity. J Clin Endocrinol Metab. 2009;94(11):4472–82.
20. McLvoy JW, Nasir K, Defilippis AP, Lima JA, Blumeke DA, Hundley WG, Barr RG, Budoff MJ, Szabo M, Navas-Acien A, Polak JF, Blumenthal RS, Post WS, Blaha MJ. The relationship of cigarette smoking with inflammation and subclinical vascular disease: the multi-ethnic study of atherosclerosis. Atherosclerosis. 2013;236(1):1002–10.
21. Blumeke DA, Kronmal RA, Lima JAC, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA study. J Am Coll Cardiol. 2008;52(25):2148–55.
22. Pinsky MR. The right ventricle: interaction with the pulmonary circulation. Crit Care. 2016;20:266.
24. Bowen TS, Aakerøy L, Eisenkolb S, Kunth P, Bakkerud F, Wohlwend M, Ombbostad AM, Fischer T, Wisloff U, Schuler G, Steinshammer S, Adams V, Bronstad E. Exercise Training Reverses Extrapulmonary Impairments in Smoke-exposed Mice. Med Sci Sports Exerc. 2016;49(5):879-887.

25. Ferrer E, Peinado VI, Castañeda J, Prieto-Lloret J, Olea E, González-Martín MC, Vega-Agapito MV, Diez M, Domínguez-Fandos D, Obeso A, González C, Barberà JA. Effects of cigarette smoke and hypoxia on pulmonary circulation in the Guinea pig. Eur Respir J. 2011;38(3):617–27.

26. Mozos I, Maidana JP, Stoian D, Stehlik M. Gender differences of arterial stiffness and arterial age in smokers. Int J Environ Res Public Health. 2017;14(6):565.

27. Minicucci M, Oliveira F, Santos P, Polegato B, Roscani M, Fernandes AA, Lustosa B, Palva S, Zornoff L, Azevedo P. Pentoxifylline attenuates cardiac remodeling induced by tobacco smoke exposure. Arq Bras Cardiol. 2016;106(5):396–403.

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