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Influence of smoking on physical function, physical activity, and cardiovascular health parameters in patients with symptomatic peripheral arterial disease: A cross-sectional study

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The aim of this study was to analyze the impact of smoking on physical activity, walking capacity, and cardiovascular health in patients with symptomatic peripheral arterial disease (PAD). This cross-sectional study included 180 patients with symptomatic PAD. Patients were classified into 3 groups according to smoking history: smoker (n = 39), ex-smoker (n = 113), and never smoker (n = 28). Physical activity levels, physical function, walking capacity, and cardiovascular health parameters (clinical blood pressure, arterial stiffness, and heart rate variability) were assessed. Smoker patients presented higher sympathetic modulation to the heart (low frequency of heart rate variability: smokers, 71 ± 17 nu; ex-smokers, 53 ± 32 nu; never smokers, 49 ± 21 nu, P < .05) and sympathovagal balance (smokers: 2.44 ± 2.76, ex-smokers: 1.14 ± 1.74, never smokers: 1.04 ± 0.99, P < .05) and lower parasympathetic modulation to the heart (high frequency of heart rate variability: smokers, 29 ± 27 nu; ex-smokers, 47 ± 32 nu; never smokers, 51 ± 21 nu, P < .05) than other patients. In conclusion, nonsignificant differences were observed on physical activity levels, physical function, blood pressure, and arterial stiffness (P > .05). Smoking impairs cardiac autonomic modulation in patients with symptomatic PAD. (J Vasc Nurs 2019;37:106-112)

INTRODUCTION

Peripheral arterial disease (PAD) affects more than 200 million people around the world.[1] Intermittent claudication (IC), the main symptom of PAD, is defined as muscle discomfort in the legs caused by physical activity and relieved by short periods of rest.[2] Symptomatic PAD is associated with important functional and cardiovascular alterations, including walking impairment,[3,4] low physical activity level,[5,6] sedentary behavior,[7] increased blood pressure,[8] arterial stiffness,[9] and cardiac autonomic dysfunction.[10]

Smoking is a main risk factor for PAD development,[11] being prevalent in 35% of patients.[12] In these patients, smoking brings several consequences. For example, patients with PAD who smoke have 3-fold more chance to develop IC symptoms than nonsmokers.[13] In addition, smoker patients with PAD present shorter onset claudication distance during treadmill test,[14] impaired cardiopulmonary dynamics at peak exercise,[14] lower calf muscle hemoglobin oxygen saturation,[15] and lower physical activity level.[16]

In subjects without PAD, smoking impairs physical fitness, physical activity levels, and cardiovascular function.[17,18] In patients with PAD, few studies analyzed the role of smoking on walking capacity and presented controversial results, in which some studies have observed negative effects of smoking on walking capacity[16,19] and another study did not.[3] On the other hand, the influence of smoking on physical activity levels and cardiovascular parameters is unknown in patients with PAD. The aim of this study was to analyze the impact of smoking on physical function, physical activity, and cardiovascular health in patients with symptomatic PAD.

METHODS

Recruitment

This cross-sectional study follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)

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checklist.[20] Patients with symptomatic PAD (eg, IC) were recruited at a tertiary hospital in São Paulo, SP, Brazil. This study was approved by the human research ethics committee, and each patient was informed of the risks and benefits involved in the study and signed a written informed consent for participation.

Patients

Patients were included if they met the following criteria: 1) aged 40 to 90 years; 2) presence of IC symptoms (Rutherford stages II and III in one or both legs); 3) ankle-brachial index ≤ 0.90; 4) absence of critical limb ischemia or rest pain, noncompressible vessels, and amputated limbs and/or ulcers.

Data collection

Data collection was performed between September 2015 and March 2018. Demographic information (age and sex), smoking history, comorbid conditions (obesity, hypertension, diabetes, dyslipidemia, and heart disease), physical function, physical activity level, and cardiovascular health parameters (clinical blood pressure, arterial stiffness, and heart rate variability) were assessed. Obesity was de fined as body mass index > 30 kg/m^2. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of antihypertensive medication. Diabetes was defined as fasting blood glucose > 126 mg/dL or use of hypoglycemic medication. Dyslipidemia was defined as triglycerides ≥ 150 mg/dL, low-density lipoprotein cholesterol ≥ 160 mg/dL, total cholesterol ≥ 200 mg/dL, or high-density lipoprotein cholesterol ≤ 40 mg/L (men) and ≤ 50 mg/dL (women) or use of lipid-lowering medication. Coronary artery disease was defined as a history of myocardial infarction or surgical procedures or use of antiangina medication.

Smoking history. Smoking history was evaluated, and patients were divided into 3 groups: current smoker, ex-smoker, and never smoker.

Physical function. A 6-minute walking test was performed in a 30-meter long corridor, following the protocol previously described,[21] to characterize the patients' onset distance and 6-minute walking capacity. Walking impairment questionnaire was used for providing information on walking capacity in 3 domains (distance, speed, and using stairs), as previously described.[3]

A handgrip strength test was performed using a digital dynamometer (CAMRY), following the guidelines of the *American Society of Hand Therapists*.[22] All subjects performed 3 grip tests with both dominant and nondominant hands alternately, and the highest value was used for analysis. This handgrip test presents high reliability in hypertensive patients (intraclass coefficient correlation of 0.98).[23]

The Short Physical Performance Battery—which consists of 3 components of physical performance, standing balance, gait speed, and chair stands—was applied as previously described.[24] The standing balance test accessed the ability to maintain standing posture for 10 seconds with 3 different foot positions, side-by-side stance, semitandem stance (ie, feet close together with the toe of the dominant foot in line with the heel of the opposite foot), and tandem (ie, one foot in front of the other with the toe and the heel in contact), beginning with the side-by-side position. Upon accomplishment, one point was provided for each of side-by-side stand and semitandem stand and one point was given if the tandem stand was held 3 to <10 seconds and 2 points if the tandem stand was held for 10 seconds (minimum of 0 to maximum of 4 points in total for this test of standing balance).

Gait speed was accessed by calculating the time taken to walk 4 meters at their usual speed, and the faster of the 2 trials was recorded for analysis. Participants were encouraged not to use walking aids but were allowed as per participants' discretion. We analyzed 4-meter walking time measurements as continuous variables. Finally, patients were timed from standing to sitting on a chair 5 times with their arms crossed on their chest. We investigated the time to accomplish 5 chair stands as a continuous variable.

Physical activity level (predictors). ActiGraph GT3X or GT3X + accelerometers (ActiGraph) and the ActiLife software (ActiGraph) were used to measure physical activity and sedentary time. For this, each patient was advised to wear the accelerometer for 7 consecutive days, attached to an elastic belt in the right side of the hip, and remove it only for sleeping or water activities, including bath. For analysis, data were considered valid if the patient used it for a minimum of ten hours of daily recordings, for at least 4 days (at least one weekend day). The data were collected in frequency of 30 Hz and were analyzed using 60-second epochs. Periods with consecutive values of zero (with a 2-minute spike tolerance) for 60 minutes or longer were interpreted as "accelerometer not worn" and excluded from the analysis.[25] The time spent in each intensity of physical activity and sedentary time was estimated based on the cut points proposed by Copeland and Esliger,[26] considering sedentary as 0–100 counts/min, light physical activity as 101–1.040 counts/min, and moderate-vigorous physical activity as ≥1.041 counts/min using the vertical axis and analyzed in min/days, adjusting for the number of days and daily hours that the device was worn. For analysis, we used sedentary time, light physical activity, and moderate-vigorous physical activity in terms of 30 minutes/day.

Cardiovascular health parameters. Before all cardiovascular measurements, patients were instructed to 1) eat a light meal before arriving at the laboratory; 2) to avoid moderate-to-vigorous physical activity for at least 24 hours before the visit; and 3) avoid smoking, alcohol, and caffeine ingestion for at least 12 hours. In the laboratory, a rest period of 10 minutes in seated position was required before the measurements. All measurements were taken in a quiet environment. In addition, all data were collected by researchers blinded to the analysis.

Clinical blood pressure was obtained using the OMRON HEM equipment 742 (OMRON Healthcare), and at least 3 consecutive measurements within an interval of 4 mmHg were performed with one-minute interval between measurements. Measurements were performed on both arms with the proper cuff size for arm circumference, and the highest value was taken as reference. Intraclass correlation coefficient for systolic blood pressure was 0.85 and diastolic blood pressure 0.92.[27]

Arterial stiffness was obtained through carotid-femoral pulse wave velocity measurement, using a high-fidelity applanation tonometry (SphygmoCor; AtCor Medical, Australia) and following the guidelines of the Clinical Application of Arterial Stiffness, Task Force III,[28] and of the American Heart Association Scientific Statement: Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness.[29]

Cardiac autonomic modulation was obtained by assessment of heart rate variability. For this, the RR intervals obtained by using a heart rate monitor (V800; Polar Electro, Finland) and at least 5 minutes of stationary R-R interval data were used. All analyses were performed using the Kubios HRV software (Biosignal Analysis and Medical Imaging Group, Joensuu, Finland) by a single evaluator blinded and using the recommendations of the Task Force for Heart Rate Variability.[30] Frequency-domain variables were calculated via the autoregressive method. The signals operating at frequencies

between 0.04 and 0.4 Hz were considered physiologically significant, with the low-frequency (LF) component represented by oscillations between 0.04 and 0.15 Hz and high-frequency (HF) component represented by oscillations between 0.15 and 0.4 Hz. To interpret the results, the LF and HF components were considered sympathetic modulation and vagal modulation of the heart, respectively. LF/HF was defined as the cardiac sympathovagal balance.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software e SPSS/PASW version 20 (IBM Corp, New York, NY). The sample size was estimated based on a previous study that compared the walking capacity between smoker and nonsmoker patients with PAD.[14] Considering a power of 80, an alpha error of 0.05, and an effect size of 0.68, the minimum sample per group was of 35 subjects.

Continuous variables were summarized as mean and standard deviation or median and interquartile range, whereas categorical variables were summarized as relative frequency. Normal distribution was tested using the Shapiro-Wilk test. One-way analysis of variance or Kruskal-Wallis test, followed by Tukey's post hoc or Mann-Whitney *U* test, were used for comparisons between the 3 groups (current smoker, ex-smoker, and never smoker) on physical function and cardiovascular health parameters. For the comparison of heart rate variability among the 3 groups, the use of beta blockers and presence of obesity were used as adjustments. The Bonferroni correction was used, and significance level adopted in all analysis was at $P < .05$.

RESULTS

From the 262 patients enrolled in the present study, 82 were excluded (46 did not perform the 6-min walking test, 14 did not have the ankle brachial index measurement, and 22 did not come back to the second visit); therefore, 180 patients were included in the analyses. Table 1 shows clinical characteristics of the patients. The mean ankle brachial index (0.59 ± 0.19) reflects moderate severity of the disease. Most of the patients presented associated risk factors such as hypertension (83.5%), dyslipidemia (82.6%), and diabetes mellitus (53.4%). Moreover, most of the patients presented a smoking history (84.4%) as current smokers (21.6%) and ex-smokers (62.8%). Smokers presented lower weight, body mass index, and hypertension prevalence; the percentage of men was higher in this group ($P < .05$ for all).

Table 2 shows a comparison of the physical function, physical activity levels, and cardiovascular health parameters among groups (current smoker, ex-smoker, and never smoker) comprising patients with symptomatic PAD. All parameters were similar among groups ($P > .05$).

Figure 1 shows a comparison of the cardiac autonomic modulation among smoker, ex-smoker, and never-smoker patients with symptomatic PAD. Smoker patients presented higher LF and LF/HF and lower HF than ex-smoker and never-smoker patients ($P < .05$).

DISCUSSION

The following are the main results of this study: 1) patients with symptomatic PAD, who are current smokers, had lower vagal modulation and higher sympathetic modulation to the heart than nonsmokers; 2) walking capacity, physical function, physical activity levels, blood pressure, and arterial stiffness were similar among smokers, ex-smokers, and never-smoker patients with PAD.

Previous studies have shown that cardiac autonomic modulation assessed through the Kubios HRV software is an independent and powerful predictor of mortality.[31–33] In this sense, we

TABLE 1

GENERAL CHARACTERISTICS OF PATIENTS WITH SYMPTOMATIC PERIPHERAL ARTERY DISEASE IN THIS STUDY (N = 180)

Variables	*All*	*Smoker*	*Ex-smoker*	*Never smoker*	P
N	180	39	113	28	—
Age (y)	66 ± 10	64 ± 9	66 ± 9	68 ± 10	.196
Ankle brachial index	0.59 ± 0.19	0.57 ± 0.16	0.60 ± 0.20	0.59 ± 0.19	.732
Weight (kg)	72.9 ± 14.4	67.8 ± 15.6*	75.3 ± 13.1	69.8 ± 15.7	.003
Body mass index (kg/m^2)	27.5 ± 4.9	25.2 ± 5.0*	28.3 ± 4.5	27.3 ± 5.0	.002
Male sex (%)	66.5	76.3*	68.1	46.4	.033
Obesity (%)	30.8	20.0	33.0	36.4	.339
Diabetes (%)	53.4	50.0	52.7	60.7	.671
Hypertension (%)	83.5	68.4*	86.4	92.9	.013
Dyslipidemia (%)	82.6	73.7	86.0	81.5	.226
Coronary artery disease (%)	35.1	26.3	39.4	29.6	.280

Data presented as mean ± standard deviation or relative frequency.

*Different from ex-smoker and never smoker groups, $P < .033$.

TABLE 2

COMPARISON OF THE PHYSICAL FUNCTION, BLOOD PRESSURE, AND ARTERIAL STIFFNESS AMONG SMOKER, EX-SMOKER, AND NEVER-SMOKER PATIENTS WITH SYMPTOMATIC PERIPHERAL ARTERY DISEASE

Variables	*Smoker*	*Ex-smoker*	*Never smoker*	P
Claudication distance (m)* n = 180	109 ± 122	120 ± 106	120 ± 94	.961
Six-minute walk test (m)* n = 180	339 ± 102	336 ± 131	348 ± 120	.629
Handgrip test (kgf)* n = 180	34 ± 12	34 ± 16	32 ± 13	.780
WIQ—distance (score) n = 180	24 ± 20	19 ± 19	21 ± 18	.490
WIQ—speed (score) n = 180	24 ± 13	23 ± 16	18 ± 12	.331
WIQ—stairs (score) n = 180	27 ± 20	31 ± 26	22 ± 25	.221
Usual 4-meter test (seconds)* n = 177	3.0 ± 1.3	4.0 ± 1.0	4.0 ± 1.5	.224
Fast 4-meter test (seconds)* n = 177	2.0 ± 1.0	2.0 ± 1.0	3.0 ± 1.0	.643
Standing balance (score)* n = 177	4.00 ± 1.25	4.00 ± 1.00	3.15 ± 2.00	.308
Chair stands (s)* n = 168	15 ± 7	15 ± 8	13 ± 8	.680
Light physical activity (min/week)† n = 144	2,326 ± 1,102	2,163 ± 808	2,147 ± 713	.863
Moderate-vigorous physical activity (min/week)* n = 144	73 ± 193	64 ± 124	52 ± 194	.650
Sedentary time (min/week)* n = 144	4,340 ± 1,726	4,590 ± 1,326	4,485 ± 1,398	.896
Systolic blood pressure (mmHg)† n = 177	138 ± 20	135 ± 21	138 ± 19	.628
Diastolic blood pressure (mmHg)† n = 177	73 ± 9	73 ± 10	69 ± 9	.115
Pulse wave velocity (m/s)† n = 128	8.75 ± 2.30	9.36 ± 2.72	9.29 ± 4.66	.408

WIQ = walking impairment questionnaire.

*Data presented as median ± interquartile range.

†Data presented as mean ± standard deviation.

analyzed whether smoking history would affect these cardiovascular parameters in patients with symptomatic PAD. Our results indicated that patients with symptomatic PAD who are current smokers presented lower HF and higher LF and LF/HF, indicating reduced vagal modulation to the heart with a concomitant increase in cardiac sympathetic modulation. These results were maintained even after adjustment for beta-blocker use and obesity, recognized factors associated with cardiac modulation to the heart.[34,35] The underlying mechanism by which smoking affects cardiac autonomic modulation to the heart was investigated previously. A review study[36] suggested that long-term exposure to smoke generates lung oxidative stress and stimulates transient receptor potential vanilloid 1 and ankyrin 1 receptors present on lung afferent C-fibers, leading to reflexively increased efferent cardiac sympathetic nerve activity. In addition, smokers have lower baroreflex sensitivity than nonsmokers, allowing sustained sympathetic activation.[36]

In this study, we also analyzed the impact of smoking in other cardiovascular health parameters such as blood pressure and arterial stiffness. Our findings indicated that smoking history was not associated with blood pressure levels, contrasting with previous studies[17,18] that demonstrated acute adverse effects of smoking on blood pressure levels. However, epidemiological studies have shown inconsistent associations between smoking and high blood pressure levels in non-PAD subjects.[37–39] A potential explanation may be the use of hypertensive medication, which may have attenuated the deleterious effects of smoking on blood pressure.[18] Other explanation is the high arterial stiffness of patients with PAD,[9] one of the main determinants of blood pressure, that is already impaired in patients with PAD. Thus, smoking does not lead to further impairments in blood pressure. This also explains the similar arterial stiffness in patients with different smoking history.[40,41]

Walking capacity and physical function were analyzed, and in contrast with previous studies,[14,42] we showed no effects of

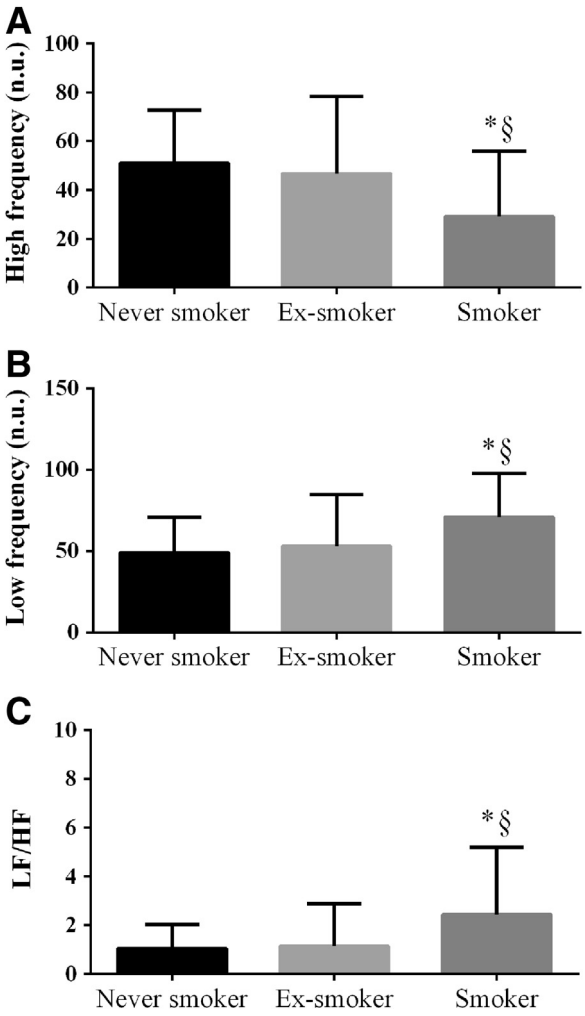

Figure 1. *Comparison of the cardiac autonomic modulation among smoker, ex-smoker, and never-smoker patients with symptomatic peripheral artery disease. Data presented as median ± interquartile range. *Significant difference from never smoker (*P < .05*). §Significant difference from ex-smoker. LF/HF = sympathovagal balance; nu = normalized units.*

smoking history on these parameters in patients with PAD. In fact, Cahan et al[42] showed that smokers walked 61 meters less on the 6-minute walking test than nonsmokers. On the other hand, one study did not find differences in maximal walking capacity between smokers and nonsmokers,[16] whereas another study did not identify smoking as a predictor of walking capacity,[3] demonstrating that the literature is still controversial. Interestingly, studies that observed the influence of smoking on walking capacity reported that smokers had a greater severity of the disease than nonsmokers.[14,42] In the present study, the severity of the disease was similar between smokers, ex-smokers, and never smokers.

Physical activity level was also not influenced by smoking history. Previous studies have shown that walking impairment has been correlated with a number of barriers to physical activity practice,[43] muscular fitness,[44] and daily physical activity levels in patients with PAD.[5] Therefore, the similar walking capacity observed in patients with different smoking statuses explains the similar physical levels observed among these patients.

Limitations and strengths

The cross-sectional design of this study is an evident limitation because no causality can be inferred. In addition, we included only patients with PAD with claudication symptoms, and the results cannot be extrapolated to patients with other stages of the disease. We did not analyze the time of exposure to smoking and the number of cigarettes smoked per year, and these factors may affect the results. The small sample size, particularly in patients who have never smoked, also limits our findings, especially the impossibility to stratify by medication that might have effected performance. Passive smoking also affects functional and cardiovascular variables,[45] but was not analyzed in the present study. Finally, patients with severe cardiac disease and asymptomatic PAD (Rutherford Grade 1, Category 0) or more severe PAD than claudication (Rutherford Grade II, III, and IV) were excluded from the screening; therefore, the results of this study can only be generalized to the current sample of patients.

Smoking has been a main concern in patients with PAD[11] as it is associated with increased cardiovascular risk. The impaired cardiac autonomic modulation observed in current smokers might be a mediator of this increased cardiovascular risk observed in smoker patients with PAD. Studies have shown that exercise training can improve cardiac autonomic control.[46,47] Therefore, smoker patients with PAD should be strongly encouraged to engage in such programs to improve their cardiovascular risk. On the other hand, the fact that smoking did not alter physical function and some of cardiovascular health parameters, clinical markers frequently assessed in these patients, limits the awareness of the consequences of the smoking.

CONCLUSION

Patients with symptomatic PAD who are current smokers had lower vagal modulation and increased sympathetic modulation to the heart, indicating a poor cardiac autonomic modulation to the heart. No association was observed between smoking history and blood pressure, arterial stiffness, physical function, or physical activity.

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