Longitudinal Changes in Physical Activity Levels and Cardiovascular Risk Parameters in Patients with Symptomatic Peripheral Artery Disease

Francielly Monteiro,[1] Marilia de Almeida Correia,[2] Breno Quintella Farah,[3] Diego Giuliano Destro Christofaro,[4] Paulo Mesquita Longano de Oliveira,[2] Raphael Mendes Ritti-Dias,[2] Gabriel Grizzo Cucato[1,5]

Hospital Israelita Albert Einstein - Instituto de Educação e Pesquisa,[1] São Paulo, SP – Brazil

Universidade Nove de Julho - Programa de Pós-graduação em Medicina,[2] São Paulo, SP – Brazil

Universidade Federal Rural de Pernambuco,[3] Recife, PE – Brazil

Universidade Estadual Paulista Júlio de Mesquita Filho,[4] Presidente Prudente, SP – Brazil

Northumbria University,[5] Newcastle upon Tyne – United Kingdom

Abstract

Background: Previous cross-sectional studies have demonstrated that physical activity is associated with lower cardiovascular risk in patients with peripheral artery disease (PAD). However, it is not possible to establish causality, and longitudinal design studies are required.

Objective: To analyze the changes in cardiovascular risk parameters and physical activity levels after a 2-year follow-up in patients with symptomatic PAD.

Methods: This study started in 2015. In the first phase, 268 patients were included. In the second phase, after 2 years (median = 26 months), 72 patients were re-evaluated. Cardiovascular risk parameters, such as blood pressure, cardiac autonomic modulation, and arterial stiffness, and physical activity levels were measured at baseline and after 2 years of follow-up. Association among delta changes (values from follow-up – baseline) in physical activity and cardiovascular parameters were analyzed by multiple linear regression. The significance level was set at $p < 0.05$.

Results: Patients reduced their total physical activity levels compared to baseline (baseline = 2257.6 ± 774.5 versus follow-up = 2041 ± 676.2 min/week, $p = 0.001$). After follow-up, ankle-brachial index (0.62 ± 0.20 versus 0.54 ± 0.20, $p = 0.003$), and standard deviation of all RR intervals (43.4 ± 27.0 versus 25.1 ± 13.4 ms, $p < 0.001$) were lower, whereas carotid-femoral pulse wave velocity was higher (9.0 ± 3.0 versus 10.7 ± 3.4 m/s, $p = 0.002$) compared to baseline values. We did not observe any association among delta values of physical activity levels and cardiovascular risk parameters.

Conclusion: Patients with PAD had reduced physical activity levels and impaired cardiovascular risk parameters during 2-year follow-up.

Keywords: Peripheral Arterial Disease. Cardiovascular System. Arterial Pressure. Exercise.

Introduction

Intermittent claudication is the main symptom of peripheral artery disease (PAD), and it is characterized by pain, cramps, or a burning sensation that affects lower limbs during physical activity, especially while walking.[1] Patients with PAD and intermittent claudication symptoms present limited mobility, poor control of cardiovascular parameters,[2,3] and impaired quality of life.[4,5]

Physical activity has been recommended to improve functional capacity and cardiovascular function in these patients.[6-8] In fact, patients with symptomatic PAD and higher levels of physical activity present better functional capacity and a lower risk of cardiovascular mortality compared to sedentary patients.[9,10] However, due to the cross-sectional design of these studies, it is not possible to establish causality, and longitudinal design studies are required. Also, it is unknown whether alterations in these parameters occur during follow-up in PAD patients.

Therefore, this study aimed to analyze the longitudinal changes in physical activity and cardiovascular risk parameters after a 2-year follow-up in patients with PAD. We also analyzed whether changes in physical activity levels are associated with changes in cardiovascular risk parameters after a 2-year follow-up. We hypothesized that changes in physical activity levels would be associated with better cardiovascular risk parameters.

Mailing Address: Gabriel Grizzo Cucato •
Department of Sport, Exercise & Rehabilitation – Faculty of Health and Life Sciences - Northumbria University – Room 318, Northumberland Building Newcastle Upon Tyne – NE1 8ST – United Kingdom
E-mail: gacucato@gmail.com
Manuscript received May 06, 2021, revised manuscript July 28, 2021, accepted September 08, 2021

DOI: https://doi.org/10.36660/abc.20210386

Methods

This is a longitudinal study that started in 2015, consisting of 2 phases. In the first phase of the study, 268 patients were included and submitted to measurements of physical activity (accelerometry), functional capacity, and cardiovascular risk parameters (clinical blood pressure, central blood pressure, cardiac autonomic modulation, and arterial stiffness). After 2 years, all patients included in the first phase were invited to phase 2.

Sample recruitment, screening, and sizing

Patients were recruited at hospitals in Sao Paulo, Brazil. The inclusion criteria were: age > 45 years of both sexes, ankle-brachial index (ABI) < 0.90 in one or both limbs, and presence of intermittent claudication symptoms. This study was approved by the Institutional Ethics Committee. Before data collection, patients were informed about the procedures involved in the study, and they signed an informed consent form.

Before and after the 2-year follow-up, patients underwent evaluations in 2 visits with an interval of at least 7 days. During the first visit, clinical, socio-demographic, and functional capacity data were obtained, and all patients received a physical activity monitor GT3X+ triaxial accelerometer (Actigraph, Pensacola, FL, USA). During the second visit, measurements of cardiovascular risk parameters such as clinical blood pressure, central blood pressure, cardiac autonomic modulation, and arterial stiffness were obtained. This session started between 1:00 and 2:00 pm, and patients were given the following instructions: eat a light meal, do not exercise at least 24 hours before the day of the evaluation, do not drink any alcoholic or caffeinated drinks, do not smoke 12 hours before the session, and maintain a normal routine of eating and taking their medication.

Physical activity level

Physical activity levels were obtained using a GT3X+ triaxial accelerometer (Actigraph, Pensacola, FL, USA). All patients received instructions to use the accelerometer for 7 consecutive days, removing it only for sleeping or bathing. The device was attached to an elastic belt and fixed to the right side of the hip. For analysis, a minimum of 10 hours of daily physical activity recordings was necessary. They were considered valid if they had at least 4 days of activity: 3 weekdays and 1 weekend day. The data were collected in the frequency of 30 Hz and were analyzed using 60-second epochs. Periods with consecutive values of 0 (with a 2 min spike tolerance) for 60 min or longer were interpreted as "accelerometer not worn" and excluded from the analysis. The average of total time spent at each intensity of physical activity was calculated using the cutoff points specific to older people,[11] adapted by Buman et al.,[12] considering sedentary time as 0 to 99 counts/min; low-light physical activity as 100 to 1040 counts/min, high-light physical activity as 1041 to 1951 counts/min, and moderate to vigorous physical activity as ≥ 1952 counts/min using the vertical axis, analyzed in min/day, adjusting for the time and number of days the device was worn. Additionally, we also calculated the percentage of patients who met the current physical activity recommendations (≥ 150 min/week) at baseline and after 2 years.

Functional capacity

A 6-minute walk test was conducted in a 30-meter long corridor, following the protocol previously described.[13] Two cones were placed 30 meters apart, and patients were instructed to walk as many laps around the cones as possible. They were also instructed to inform when claudication symptoms (pain, discomfort, cramps, and tiredness) occurred in order to determine claudication onset distance. In addition, the total walking distance was defined as the maximum distance completed by the patient at the end of the 6-minute walk test.

Office blood pressure

Office blood pressure was measured using a monitor (HEM-742, Omron Healthcare, Japan), which consists of an electronic and digital arm blood pressure device with automatic deflation and inflation. For this, patients remained in a sitting position for at least 10 minutes. Three consecutive measurements were taken, 1 minute apart, on both arms, with adequate cuff size. The value used was the average of the 3 measurements, as recommended by the Brazilian Society of Cardiology.[14]

Central blood pressure

Central blood pressure was measured by radial artery by pulse wave analysis using the applanation tonometry technique (SphymoCor, AtCor Medical, Australia). After at least 15 minutes of rest in the supine position, 11 seconds of radial central blood pressure wave recording were used. After this procedure, the SphygmoCor ® software derives the ascending aorta pressure wave, equivalent to the pressure wave measured by an invasive catheter, obtaining systolic and diastolic central blood pressure. For better measurement accuracy, only values with indexes greater than 90% were considered valid.

Arterial stiffness

Arterial stiffness was estimated by carotid-femoral aortic pulse wave velocity using the applanation tonometry technique, following the recommendations of the American Heart Association.[15] The carotid-femoral aortic pulse wave velocity was recorded sequentially by transcutaneous transducers positioned above the carotid artery and the right femoral artery, using an applanation tonometry apparatus (Sphygmocor, AtCor Medical, Australia). Electrocardiography recording was obtained simultaneously with carotid-femoral aortic pulse wave measurements as a reference standard for calculating wave transit time. Two surface distances were measured by the investigator: one between the recording point in the carotid artery and the sternal notch (distance 1) and the other between the sternal notch and femoral artery (distance 2). The distance travelled by the pulse wave was calculated as: distance 2 − distance 1. Carotid-femoral aortic pulse wave velocity was calculated as: carotid-femoral aortic pulse wave velocity = ¼ * distance travelled by pulse wave (m) / transit time (s).

Cardiac autonomic modulation

Cardiac autonomic modulation was assessed by the heart rate variability technique. For this, patients remained at rest, lying down for 15 minutes and the RR intervals were recorded using a heart rate monitor (Polar V800, Polar Electro, Finland). For analysis, the first 5 minutes were excluded, and those with at least 10 minutes of steady signal were considered valid signals. After collection, RR intervals were exported to Kubios HRV program (Biosignal Analysis and Medical Imaging Group, Finland) and then analyzed in time and frequency domains. Time-domain parameters were: standard deviation of all RR intervals (SDNN), root mean square of the squared differences between adjacent normal RR intervals (RMSSD), and percentage of adjacent intervals over 50 ms (PNN50).[16] Frequency domain parameters were obtained by the spectral analysis technique using the autoregressive method. Frequencies between 0.04 and 0.4 Hz were considered physiologically significant; the low-frequency component is represented by oscillations between 0.04 and 0.15 Hz, and the high-frequency component by those between 0.15 and 0.4 Hz. The power of each spectral component was calculated in normalized terms, dividing the power of each band by the total power, from which the very low frequency (< 0.04 Hz) band value was subtracted, and the result was multiplied by 100.[16]

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences software and SPSS/PASW version 20 (IBM Corp, New York, NY, USA). Normality data were analyzed using the Kolmogorov-Smirnov test. Continuous variables were summarized as mean and standard deviation (normal distribution data) or median and interquartile range (non-normal distribution data), whereas categorical variables were summarized as absolute numbers and percentages, with the respective confidence intervals.

Clinical characteristics at baseline and follow-up were compared using the paired t-test or Wilcoxon signed-rank for continuous variables and the McNemar test for categorical variables. Associations among the delta changes (values from follow-up – baseline) in physical activity and cardiovascular parameters were analyzed by multiple linear regression adjusted for sex, age, changes in antihypertensive medication, ABI, weight, and walking capacity, which are classical confounders in PAD.[17-20]

Residual analysis was performed. Homoscedasticity was analyzed by graphical analysis (scatterplot), and adherence to normal distribution was tested using the Kolmogorov-Smirnov test. Multicollinearity analysis was performed assuming variance inflation factors less than 5 and tolerance below 0.20. For analyses, significance level was set at $p < 0.05$.

Results

The recruitment of the study was conducted between September 2015 and November 2017 (Figure 1). In the first phase of the study, 268 patients underwent baseline measurements. In the second phase of the study, 96 patients agreed to participate, and 24 of those patients were not eligible because of missing data on physical activity. Therefore, the final sample of this study comprises 72 patients.

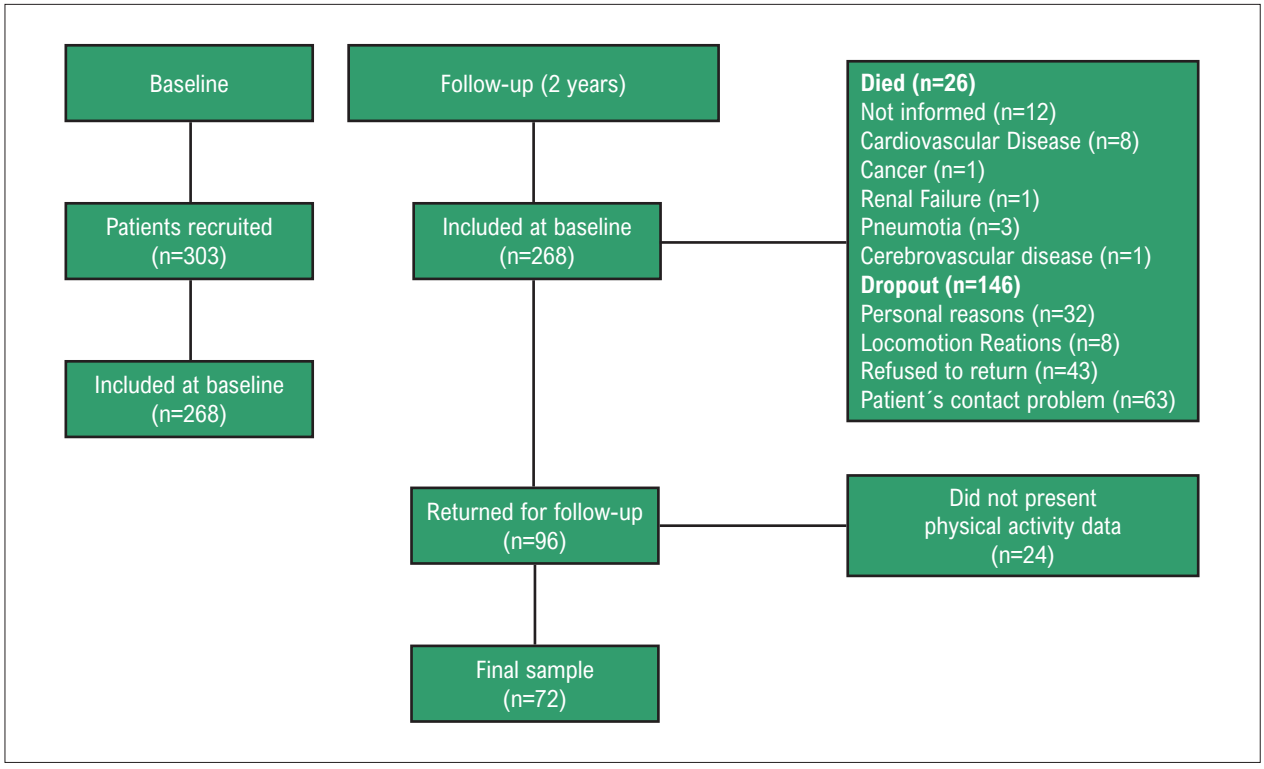

Figure 1 – *Flowchart of the study.*

Table 1 shows the clinical characteristics of patients at baseline and follow-up. After 2 years, we observed a decrease in ABI during follow-up.

Table 2 shows data on total physical activity at the baseline and follow-up period. After 2 years, we observed a significant reduction in time spent in total physical activity and an increase in sedentary time compared to baseline values.

Table 3 shows data on cardiovascular risk parameters at baseline and follow-up. We observed an increase in carotid-femoral pulse wave velocity and a decrease in SDNN in follow-up when compared to baseline values.

We did not observe any association between sedentary time and physical activity with delta values of office and central blood pressure (Table 3), arterial stiffness indicators,

Table 1 – Clinical characteristics of patients with peripheral artery disease (n = 72)

Variables	Baseline	Follow-up	p
Weight (kg)	74.5±13.5	73.7±12.9	0.128
Body mass index (kg/m²)	27.5±4.4	27.3±4.0	0.357
Ankle-brachial index	0.62±0.20	0.53±0.20	0.004
Six-minute walk test	350±90	364±105	0.257
Comorbid conditions			
Diabetes mellitus (%)	42.3	47.2	0.375
Hypertension (%)	82.9	86.1	0.500
Dyslipidemia (%)	84.5	91.8	0.063
Obesity (%)	26.3	38.0	0.359
Coronary artery disease (%)	34.8	40.3	0.523
Stroke (%)	15.7	21.9	0.125
Heart failure (%)	13.2	15.9	0.607
Cancer (%)	11.8	9.9	0.998
Medication			
Antiplatelet (%)	89.7	84.5	0.549
ACE inhibitor (%)	23.9	2.8	0.001
Angiotensin-receptor antagonist (%)	27.9	28.2	0.727
Calcium-channel blocker (%)	22.1	26.8	0.508
Diuretic (%)	41.2	32.4	0.648
Beta-blockers (%)	50.0	26.8	0.007
Statins (%)	92.6	90.1	0.774
Hypoglycemics (%)	47.1	42.3	0.727
Peripheral vasodilator (%)	29.4	47.9	0.004

Data presented as mean ± standard deviation or relative frequency. ACE: angiotensin-converting enzyme.

Table 2 – Physical activity level of patients at baseline and follow-up (n = 72)

Variables	Baseline	Follow-up	p
Sedentary time	4178 (962)	4442 (809)	0.001
Low-light PA (min/week)	2055 (904)	1851 (662)	0.001
High-light PA (min/week)	2257.6 ± 774.5	2041 ± 676.2	0.001
Moderate to vigorous PA (min/week)	85 (177)	41 (79)	0.001
Total PA (min/week)	2257.6 ± 774.5	2041 ± 676.2	0.001
Met PA recommendations (n, %)	6 (7.8)	3 (3.9)	0.250

Data presented as median (interquartile range) or as mean ± standard deviation. PA: physical activity.

Table 3 – Cardiovascular risk parameters at baseline and follow-up (n = 72)

Variables	n	Baseline	n	Follow-up	p
Resting HR (bpm)	72	64.4± 11.5	72	67.7 ± 17.2	0.12
Brachial SBP (mmHg)	72	133.3 ± 21.0	73	132.5 ± 21.0	0.69
Brachial DBP (mmHg)	72	73.0 ± 10.2	73	72.7 ± 10.6	0.74
Central BP (mmHg)	62	130.9 ± 22.3	62	128.0 ± 21.4	0.43
Central DBP (mmHg)	62	75.2 ± 9.9	62	74.6 ± 9.8	0.79
PP (mmHg)	62	55.7 ± 182	62	52.5 ± 18.3	0.09
AIx (%)	60	32.3 ± 11.1	60	30.6 ± 13.2	0.59
AIx 75 bpm (%)	60	26.6 ± 9.6	60	26.9 ± 10.6	0.42
Cf-PWV (m/s)	43	8.4 (3.21)	43	11.5 (6.2)	0.01
SDNN (ms)	39	45.6 ± 31.4	39	24.3 ± 13.3	0.01
RMSSD (ms)	39	31.7 (29.2)	39	21.1 (33.8)	0.18
PNN50 (%)	39	5.8 (16.8)	39	3.1 (18.5)	0.23
LF (un)	39	63.2 (32.4)	39	61.4 (24.6)	0.97
HF (un)	39	36.8 (32.4)	39	38.6 (24.6)	0.98
LF/HF	39	1.71 (3.11)	39	1.56 (1.69)	0.69

Data presented as mean ± standard deviation or as median (interquartile range). AIx: augmentation index; BP: blood pressure; Cf-PWV: carotid-femoral pulse wave velocity; DBP: diastolic blood pressure; HF: high frequency; HR: heart rate; LF: low frequency; PNN50: percentage of adjacent intervals over 50 ms; PP: pulse pressure; RMSSD: root mean square of the squared differences between adjacent normal RR intervals; SBP: systolic blood pressure; SDNN: standard deviation of all RR intervals.

and heart rate variability parameters after 2-year follow-up in patients with symptomatic PAD (Tables 4 and 5).

Discussion

The results of this study indicate that important changes in cardiovascular risk parameters and physical activity occurs after 2 years in patients with symptomatic PAD. These changes include increases in the prevalence of comorbid conditions, decreases in lower limb hemodynamic (ABI), increases in arterial stiffness, and reductions in physical activity levels with a concomitant increase in time spent in sedentary behavior.

The results also indicate a marked worsening in the clinical profile in our sample, with an increase in the prevalence of cardiovascular risk factors after a 2-year follow-up. Reduced ABI and heart rate variability and increased arterial stiffness were also observed. As these factors are highly related to cardiovascular mortality,[21-23] the alterations in clinical profile and cardiovascular parameters observed over time in patients with PAD may potentially explain the severe prognosis of these patients. Thus, these results highlight the importance of aggressive secondary prevention strategies, including risk factor modification, antiplatelet therapy, lipid-lowering therapy, antihypertensive treatment, and especially increased physical activity levels.[24,25] In fact, previous studies have shown that regular physical activity improved different health parameters in PAD, such as walking ability, vascular function, inflammation, and calf muscle hemoglobin oxygen saturation.[26-28]

Physical activity guidelines for the general and PAD population recommend engaging in at least 150 minutes of moderate physical activity, 75 minutes of vigorous physical activity, or an equivalent combination of moderate to vigorous physical activity weekly to promote overall health benefits.[24-26] In the present study, during the 2-year follow-up, patients increased their sedentary time 7% while in low-light, high-light, moderate to vigorous, and total physical activity, they decreased 7%, 10%, 38%, and 10%, respectively. In addition, a reduction of 50% of patients who met the recommendations for physical activity guidelines was observed after a 2-year follow-up (7.8% versus 3.9%). These results are alarming since the guidelines for patients with PAD are clear in recommending regular physical activity as an initial clinical treatment.[29,30] Thus, as most of our patients did not modify or even worsened their physical activity levels, this raises the need to explore strategies to understand the barrier and create new strategies to promote engagement in physical activity in these patients.

We did not observe an association between changes in physical activity with any of the cardiovascular parameters during the 2-year follow-up. These results contrast with our initial hypothesis that changes in physical activity would be associated with cardiovascular risk parameters. A possible explanation is that most of our patients were already physically inactive at baseline, and only 3.9% met the minimum physical activity recommendations during the follow-up. Thus, these lower levels of physical activity were not enough to promote changes in cardiovascular risk parameters in patients with PAD during the follow-up period.

This study is an analysis of a 2-year follow-up, and the results are preliminary and require further investigations at a longer follow-up period and in a larger sample size.

Table 4 – Relationship between sedentary and physical activity with changes in office and central blood pressure after 2-year follow-up in patients with symptomatic peripheral artery disease (n = 72)

Independent variables	Models	Δ Office SBP N=72		Δ Office DBP N=72		Δ Central SBP N=62		Δ Central DBP N=62	
		b	p	b	p	b	p	b	p
Δ Sedentary time (min/week)	Crude	0.045	0.707	-0.079	0.512	0.085	0.518	0.113	0.391
	Adjusted	0.172	0.254	-0.117	0.907	0.235	0.183	0.211	0.230
Δ Low-light PA (min/week)	Crude	-0.075	0.531	0.055	0.646	-0.109	0.407	-0.106	0.419
	Adjusted	-0.193	0.202	0.010	0.947	-0.256	0.146	-0.196	0.275
Δ High-light PA (min/week)	Crude	-0.001	0.933	-0.005	0.274	0.001	0.906	0.002	0.726
	Adjusted	-0.002	0.895	-0.005	0.357	-0.003	0.843	0.002	0.784
Δ MVPA (min/week)	Crude	0.054	0.653	0.039	0.746	-0.042	0.749	-0.122	0.352
	Adjusted	0.250	0.098	0.227	0.120	0.194	0.270	-0.044	0.806

All analyses were adjusted for sex, age, changes in antihypertensive medication, ankle-brachial index, weight, and walking capacity. b: standardized coefficients; DBP: diastolic blood pressure; MVPA: moderate to vigorous physical activity; PA: physical activity; SBP: systolic blood pressure.

Table 5 – Relationship between sedentary and physical activity with changes arterial stiffness indicators and heart rate variability parameters after 2-year follow-up in patients with symptomatic peripheral artery disease (n = 72)

Independent variables	Models	Δ Cf-PWV N=43		Δ AIx N=60		Δ SDNN N=39		Δ LF/HF N=39		Δ LF N=39		Δ HF N=39	
		b	p	b	p	b	p	b	p	b	p	b	p
Δ Sedentary time (min/week)	Crude	-0.148	0.349	0.129	0.331	-0.004	0.557	0.087	0.608	0.001	0.923	-0.001	0.923
	Adjusted	-0.003	0.989	0.100	0.568	-0.007	0.458	-0.061	0.842	-0.002	0.841	0.002	0.841
Δ Low-light PA (min/week)	Crude	0.154	0.330	-0.168	0.203	-0.003	0.596	-0.081	0.634	-0.001	0.837	0.001	0.837
	Adjusted	-0.018	0.936	-0.188	0.279	0.010	0.416	0.066	0.829	0.001	0.911	-0.001	0.911
Δ High-light PA (min/week)	Crude	0.001	0.002	-0.008	0.245	-0.023	0.179	-0.001	0.506	-0.003	0.814	0.003	0.814
	Adjusted	0.002	0.477	-0.006	0.443	-0.019	0.359	-0.002	0.444	-0.021	0.286	0.021	0.286
Δ MVPA (min/week)	Crude	-0.070	0.660	0.150	0.256	0.007	0.901	-0.240	0.153	-0.042	0.352	0.042	0.352
	Adjusted	-0.028	0.897	0.038	0.194	-0.019	0.773	-0.196	0.415	-0.015	0.814	0.015	0.814

All analyses were adjusted for sex, age, changes in antihypertensive medication, ankle-brachial index, weight, and walking capacity. AIx: augmentation index; b: standardized coefficients; Cf-PWV: carotid-femoral pulse wave velocity; HF: high frequency; LF: low frequency; MVPA: moderate to vigorous physical activity; PA: physical activity; SDNN: standard deviation of all RR intervals.

The clinical significance of the present study is that these patients presented impaired cardiovascular profile and reduced physical activity after 2 years, and these results highlight the importance of developing and delivering clinical strategies to tackle these risk factors with the aim of reducing cardiovascular risk in the PAD population.

This study has some limitations that should be mentioned. We had a significant loss of heart rate variability data due to the presence of cardiac arrhythmias or pacemakers, which may have affected the power to infer cause and effect for these variables. In some patients, it was not possible to collect the applanation tonometry data because of a non-detectable femoral pulse (weak or nonexistent pulse). We had high dropout rates during the follow-up period, which may incur a selection bias. On the other hand, strong aspects of our study include the 2-year longitudinal design, more robust analysis of cardiovascular risk parameters, and the objective measurement of physical activity levels.

Conclusion

Patients with PAD had reduced physical activity levels and impaired cardiovascular risk parameters after 2 years. In addition, there was no association of changes in physical activity with cardiovascular risk parameters over the 2-year follow-up.

Authors Contribution

Conception and design of the research, Obtaining financing and Critical revision of the manuscript for intellectual content: Ritti-Dias RM, Cucato GG; Acquisition of data: Monteiro F, Correia MA, Oliveira PML; Analysis and interpretation of the data: Monteiro F, Correia MA, Farah BQ, Ritti-Dias RM, Cucato

GG; Statistical analysis: Monteiro F, Correia MA, Farah BQ, Oliveira PML; Writing of the manuscript: Monteiro F, Farah BQ, Christofaro DGD.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by CNPq - 4097072016-3.

Study Association

This article is part of the thesis of master submitted by Francielly Monteiro, from Hospital Israelita Albert Einstein.

References

1. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): A Collaborative Report From the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113(11):463-54. doi: 10.1161/CIRCULATIONAHA.106.174526.
2. Lima AHRA, Chehuen M, Cucato GG, Soares AHG, Askew CD, Barbosa JPAS, et al. Relationship Between Walking Capacity and Ambulatory Blood Pressure in Patients with Intermittent Claudication. Blood Press Monit. 2017;22(3):115-21. doi: 10.1097/MBP.0000000000000243.
3. Germano-Soares AH, Cucato GG, Leicht AS, Andrade-Lima A, Peçanha T, Correia MA, et al. Cardiac Autonomic Modulation Is Associated with Arterial Stiffness in Patients with Symptomatic Peripheral Artery Disease. Ann Vasc Surg. 2019;61:72-7. doi: 10.1016/j.avsg.2019.04.021.
4. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33 Suppl 1:1-75. doi: 10.1016/j.ejvs.2006.09.024.
5. Spronk S, White JV, Bosch JL, Hunink MG. Impact of Claudication and its Treatment on Quality of Life. Semin Vasc Surg. 2007;20(1):3-9. doi: 10.1053/j.semvascsurg.2007.02.003.
6. Ritti-Dias RM, Correia MA, Andrade-Lima A, Cucato GG. Exercise as a Therapeutic Approach to Improve Blood Pressure in Patients with Peripheral Arterial Disease: Current Literature and Future Directions. Expert Rev Cardiovasc Ther. 2019;17(1):65-73. doi: 10.1080/14779072.2019.1553676.
7. Correia MA, Silva GO, Longano P, Trombetta IC, Consolim-Colombo F, Puech-Leão P, et al. In Peripheral Artery Disease, Diabetes is Associated with Reduced Physical Activity Level and Physical Function and Impaired Cardiac Autonomic Control: A Cross-Sectional Study. Ann Phys Rehabil Med. 2021;64(2):101365. doi: 10.1016/j.rehab.2020.01.006.
8. Lane R, Harwood A, Watson L, Leng GC. Exercise for Intermittent Claudication. Cochrane Database Syst Rev. 2017;12(12):CD000990. doi: 10.1002/14651858.CD000990.pub4.
9. Garg PK, Tian L, Criqui MH, Liu K, Ferrucci L, Guralnik JM, et al. Physical Activity During Daily Life and Mortality in Patients with Peripheral Arterial Disease. Circulation. 2006;114(3):242-8. doi: 10.1161/CIRCULATIONAHA.105.605246.
10. Cavalcante BR, Germano-Soares AH, Gerage AM, Leicht A, Tassitano RM, Bortolotti H, et al. Association Between Physical Activity and Walking Capacity with Cognitive Function in Peripheral Artery Disease Patients. Eur J Vasc Endovasc Surg. 2018;55(5):672-8. doi: 10.1016/j.ejvs.2018.02.010.
11. Copeland JL, Esliger DW. Accelerometer Assessment of Physical Activity in Active, Healthy Older Adults. J Aging Phys Act. 2009;17(1):17-30. doi: 10.1123/japa.17.1.17.
12. Buman MP, Hekler EB, Haskell WL, Pruitt L, Conway TL, Cain KL, et al. Objective Light-Intensity Physical Activity Associations with Rated Health in Older Adults. Am J Epidemiol. 2010;172(10):1155-65. doi: 10.1093/aje/kwq249.
13. Ritti-Dias RM, Sant'anna FDS, Braghieri HA, Wolosker N, Puech-Leao P, Lanza FC, et al. Expanding the Use of Six-Minute Walking Test in Patients with Intermittent Claudication. Ann Vasc Surg. 2021;70:258-262. doi: 10.1016/j.avsg.2020.07.047.
14. Malachias MVB, Gomes MAM, Nobre F, Alessi A, Feitosa AD, Coelho EB. 7th Brazilian Guideline of Arterial Hypertension: Chapter 2 - Diagnosis and Classification. Arq Bras Cardiol. 2016;107(3 Suppl 3):7-13. doi: 10.5935/abc.20160152.
15. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension. 2015;66(3):698-722. doi: 10.1161/HYP.0000000000000033.
16. Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93(5):1043-65.
17. Gardner AW, Addison O, Katzel LI, Montgomery PS, Prior SJ, Serra MC, et al. Association Between Physical Activity and Mortality in Patients with Claudication. Med Sci Sports Exerc. 2021;53(4):732-9. doi: 10.1249/MSS.0000000000002526.
18. Kim DJ, Montgomery PS, Wang M, Shen B, Kuroki M, Gardner AW. Patients with Peripheral Arterial Disease with Exaggerated Pressor Response Have Greater Ambulatory Dysfunction Than Patients With Lower Pressor Response. Angiology. 2020;71(8):747-53. doi: 10.1177/0003319720925970.
19. Farah BQ, Ritti-Dias RM, Cucato GG, Chehuen MR, Barbosa JP, Zeratti AE, et al. Effects of Clustered Comorbid Conditions on Walking Capacity in Patients with Peripheral Artery Disease. Ann Vasc Surg. 2014;28(2):279-83. doi: 10.1016/j.avsg.2013.01.020.
20. Farah BQ, Barbosa JPS, Cucato GG, Chehuen MR, Gobbo LA, Wolosker N, et al. Predictors of Walking Capacity in Peripheral Arterial Disease Patients. Clinics. 2013;68(4):537-41. doi: 10.6061/clinics/2013(04)16.
21. Ohkuma T, Ninomiya T, Tomiyama H, Kario K, Hoshide S, Kita Y, et al. Ankle-Brachial Index Measured by Oscillometry is Predictive for Cardiovascular Disease and Premature Death in the Japanese Population: An Individual Participant Data Meta-Analysis. Atherosclerosis. 2018;275:141-8. doi: 10.1016/j.atherosclerosis.2018.05.048.
22. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of Cardiovascular Events and All-Cause Mortality with Arterial Stiffness: A Systematic Review and Meta-Analysis. J Am Coll Cardiol. 2010;55(13):1318-27. doi: 10.1016/j.jacc.2009.10.061.
23. Fang SC, Wu YL, Tsai PS. Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events in Patients with Cardiovascular Disease: A

Meta-Analysis of Cohort Studies. Biol Res Nurs. 2020;22(1):45-56. doi: 10.1177/1099800419877442.

24. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;69(11):71-126. doi: 10.1016/j.jacc.2016.11.007.

25. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document Covering Atherosclerotic Disease of Extracranial Carotid and Vertebral, Mesenteric, Renal, Upper and Lower Extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763-816. doi: 10.1093/eurheartj/ehx095.

26. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Step-Monitored Home Exercise Improves Ambulation, Vascular Function, and Inflammation in Symptomatic Patients with Peripheral Artery Disease: A Randomized Controlled Trial. J Am Heart Assoc. 2014;3(5):e001107. doi: 10.1161/JAHA.114.001107.

27. Tew G, Nawaz S, Zwierska I, Saxton JM. Limb-Specific and Cross-Transfer Effects of Arm-Crank Exercise Training in Patients with Symptomatic Peripheral Arterial Disease. Clin Sci. 2009;117(12):405-13. doi: 10.1042/CS20080688.

28. Chehuen M, Cucato GG, Carvalho CRF, Ritti-Dias RM, Wolosker N, Leicht AS, et al. Walking Training at the Heart Rate of Pain Threshold Improves Cardiovascular Function and Autonomic Regulation in Intermittent Claudication: A randomized Controlled Trial. J Sci Med Sport. 2017;20(10):886-92. doi: 10.1016/j.jsams.2017.02.011.

29. Kahlmeier S, Wijnhoven TM, Alpiger P, Schweizer C, Breda J, Martin BW. National Physical Activity Recommendations: Systematic Overview and Analysis of the Situation in European Countries. BMC Public Health. 2015;15:133. doi: 10.1186/s12889-015-1412-3.

30. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. JAMA. 2018;320(19):2020-8. doi: 10.1001/jama.2018.14854.