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Correlations between daily physical activity, functional capacity and vascular health in patients with COPD

Correlações entre a atividade física diária, capacidade funcional e saúde vascular em pacientes com DPOC

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) often leads to complications such as endothelial dysfunction and increased arterial stiffness, which may contribute to cardiovascular morbidity. While active lifestyles have been shown to mitigate these risks, the connection between daily physical activity, functional capacity, and vascular health in COPD patients remains underexplored. **Aim:** this study evaluates the link between endothelial function, arterial stiffness, functional capacity, and daily physical activity in COPD patients. **Methods:** we measured endothelial function in COPD patients using the reactive hyperemia index (RHI) via peripheral arterial tonometry (PAT) and arterial stiffness through pulse wave velocity (PWV) and the augmentation index adjusted for 75 beats per minute (AIx75). We also assessed functional capacity with the six-minute walking test (6MWT) and monitored daily activity using accelerometers. **Results:** among 22 participants (average age 66.5 years, body mass index (BMI) 27.5 kg/m^2, forced expiratory volume in one second (FEV_1) 34.8% predicted, daily step count ranged from 1,660 to 3,561 in 17 subjects. Endothelial dysfunction was noted in six subjects, and arterial stiffness was observed in four subjects. Daily step count significantly correlated with 6MWT distance (p= 0.004). Still, no correlation was found between the number of steps per day and measures of arterial stiffness by PAT (AIx75, %, p= 0.609), PWV (m/s, p= 0.266), and endothelial function (RHI) with PAT (p= 0.700). **Conclusion:** despite a positive correlation between the 6MWT distance and daily step count, our findings do not indicate a relationship between daily physical activity and measures of vascular function (endothelial function and arterial stiffness) in COPD patients with mild or absent vascular impairment.

Keywords: Chronic Obstructive Pulmonary Disease; Vascular Function; Activities of Daily Living.

Resumo

Introdução: a Doença Pulmonar Obstrutiva Crônica (DPOC) frequentemente leva a complicações como disfunção endotelial e aumento da rigidez arterial, o que pode contribuir para a morbidade cardiovascular. Embora estilos de vida ativos tenham sido mostrados para mitigar esses riscos, a conexão entre atividade física diária, capacidade funcional e saúde vascular em pacientes com DPOC permanece pouco explorada. **Objetivo:** este estudo avalia a associação entre função endotelial, rigidez arterial, capacidade funcional e atividade física diária em pacientes com DPOC. **Métodos:** medimos a função endotelial em pacientes com DPOC usando o índice de hiperemia reativa (IHR) através de tonometria arterial periférica (TAP) e rigidez arterial através da velocidade da onda de pulso (VOP) e do índice de aumento ajustado para 75 batimentos por minuto (IA75). Também avaliamos a capacidade funcional com o teste de caminhada de seis minutos (TC6') e monitoramos a atividade diária usando acelerômetros. **Resultados:** entre os 22 participantes (idade média de 66,5 anos, índice de massa corporal (IMC) 27,5 kg/m^2, volume expiratório forçado no primeiro segundo (VEF_1) 34,8% do previsto, a contagem diária de passos variou de 1.660 a 3.561 em 17 sujeitos. Disfunção endotelial foi encontrada em seis sujeitos, e rigidez arterial foi observada em quatro sujeitos. A contagem diária de passos correlacionou significativamente com a distância do TC6' (p= 0,004), mas não foi encontrada correlação entre o número de passos por dia e medidas de rigidez arterial pelo TAP (IA75, %, p= 0,609), VOP (m/s, p= 0,266) e função endotelial (IHR) com TAP (p= 0,700). **Conclusão:** apesar de uma correlação positiva

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entre a distância percorrida no TC6' e a contagem diária de passos, nossos achados não indicam uma relação entre a atividade física diária e as medidas de função vascular (função endotelial e rigidez arterial) em pacientes com DPOC e comprometimento vascular leve ou ausente.

Palavras-chave: Doença Pulmonar Obstrutiva Crônica; Função Vascular; Atividades da Vida Diária.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, associated with several systemic manifestations, including musculoskeletal impairment, endothelial dysfunction, and arterial stiffness[1]. Individuals with COPD present sedentary behavior due to clinical characteristics and specific comorbidities, preventing them from reaching satisfactory levels of physical activity like the general population[2].

A recent study found that more daily steps are significantly associated with lower mortality in adult individuals[3]. In addition, evidence points to the importance of counting daily steps as a determinant of health status and risk of exacerbation in individuals with COPD[4]. The limitation in physical activities of daily living (PADL) in COPD becomes evident compared to older adults without the disease[5,6]. Furthermore, arterial stiffness is an independent risk factor and predictor of cardiovascular morbidity and mortality. Also, the abnormal reactive hyperemia index (RHI) is associated with a higher risk of coronary events[7].

Vascular impairment and reduced daily step count are linked to poorer functional status and elevated cardiovascular risk, which exacerbate the health burden in COPD patients. In this population, respiratory limitation causes physical inactivity and deconditioning, worsening endothelial dysfunction, which reduces functional capacity, makes daily living activities difficult, and perpetuates inactivity, creating a vicious cycle of deterioration.

Despite this, research into the relationship between endothelial function, arterial stiffness, and physical activity in COPD is limited. This study evaluates the correlation between endothelial function, arterial stiffness, and functional status, as determined by the six-minute walk test (6MWT) distance and daily step count in COPD patients.

METHODS

Study design and participants

This cross-sectional study was conducted between March 2019 and February 2020 and was interrupted by the COVID-19 pandemic. The study protocol was approved by the Ethics Committee for Research on Human Beings of the Santa Casa de Misericórdia of Porto Alegre, Rio Grande do Sul and Universidade Federal de Ciências da Saúde de Porto Alegre (protocol numbers 40078114.9.0000.5335 and 15181419.1.0000.5345). All participants signed the Informed Consent Form.

Individuals aged ≥ 40 years, diagnosed with COPD (staging 2 to 4, according to the degree of airflow obstruction)[1], smoking history of ≥ 20 pack-years, and clinical stability in the month before the start of the assessments were included. Current smokers, individuals with any pulmonary disease other than COPD, neurological, orthopedic, cardiovascular comorbidities (acute myocardial infarction in the last year, untreated cardiac arrhythmias, and severe pulmonary hypertension), or a condition that compromised any of the study evaluations were excluded. The participants were recruited from the waiting list to participate in a pulmonary rehabilitation program at the Pavilhão Pereira Filho of Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) in Porto Alegre, Brazil, and were not undergoing pulmonary rehabilitation.

Sample characterization

The study protocol was conducted in two days, with an interval between each assessment of seven days. On the first day, participants underwent sociodemographic and anthropometric evaluations, in addition to pulmonary function, standardized by the American Thoracic Society (ATS)/European Respiratory Society (ERS)[8].

Functional capacity

The 6MWT was performed according to the protocol recommended by the ATS, and the predicted value was calculated for the Brazilian population[9].

Physical activity level

Participants were instructed to use an accelerometer for seven consecutive days to measure the number of steps per day. The daily steps were evaluated by the Actigraph® GT3X accelerometer (Pensacola, FL, USA), with which the participants were monitored for 12 h for seven consecutive days. Participants wore the GT3X (setup: 1-s epoch) over their right hip during the day. They were advised that the use should be started soon after waking up and that they should maintain their daily routine while using the device. The ActiLife 6 software (Pensacola, FL) was used to analyze the collected data. Only weekdays were considered for analysis, and a minimum of two valid days of analysis were considered. Valid days were those with eight hours of measurement.

Vascular function

On the second day, endothelial function/arterial stiffness was assessed using peripheral arterial tonometry (PAT) and arterial stiffness by pulse wave velocity (PWV). Measurements were taken in a sitting chair position after

resting for at least 10 min. They took place in a silent room with an ambient temperature of 20-22 °C. Data collection occurred in the morning, and participants were instructed to fast for at least eight hours. Moreover, they were asked to suspend vitamins, anti-inflammatory drugs, caffeine, and alcoholic beverages and not perform physical exercise in the 24 h preceding the assessment. In addition, they were instructed to maintain their usual medications.

Endothelial function and arterial stiffness were assessed non-invasively using peripheral arterial tonometry (PAT) by EndoPAT 2000 device (Itamar Medical Ltd, Caesarea, Israel). This device consists of a plethysmograph that records the digital amplitude of the arterial pulse wave by pneumatic probes placed on the index fingers. The protocol was performed by interrupting blood flow for five min (inflation of a cuff placed in the forearm). After this time, the cuff pressure was released, resulting in increased flow and induction of reactive hyperemia. Pulse response amplitude was electronically recorded on both index fingers and digitally analyzed by the computer system, calculating the natural logarithm of the reactive hyperemia index (RHI).

RHI measured endothelial function and arterial stiffness expressed by the augmentation index adjusted for 75 beats per minute (AIx75). Normal endothelial function was defined by an RHI > 0.51. Values ≤ 0.51 were considered endothelial dysfunction (according to Itamar product information). Arterial stiffness is normal by an AIx between -30% and -10%, increased arterial stiffness by an AIx between -10% and 10%, and abnormal by an AIx above 10%[10].

Arterial stiffness in the brachial artery was assessed non-invasively by oscillometric measurement in the upper limb with the Mobil-O-Graph® 24 h PWA device (IEM, Stolberg, Germany). This device uses three automated and consecutive measures (blood pressure, central systolic and diastolic pressures, AIx75, and PWV), already validated by the British Hypertension Society (BHS), and results were expressed as the average of the measurements obtained. The variables used for analysis were AIx75 (AIx reference values used in PAT) and PWV (≥ 10m/s), a cutoff point based on Brazilian hypertension guidelines[11].

Statistical analysis

The sample size was calculated using G*Power Software 3.1.9.7, expecting a minimum bivariate correlation coefficient (Spearman's correlation coefficient; ρ) of 0.6 between the number of steps per day and RHI and considering a two-tailed significance level of 5% and 80% of power, a minimal of 19 individuals would be needed. Data normality was checked with the Shapiro-Wilk test. The data distribution presents mean and standard deviation or median (interquartile range) results. Correlations were tested using the Pearson or Spearman test according to the data distribution. Correlations were considered very weak (<0.3), weak (0.3 - 0.49), moderate (0.5 - 0.69), strong (0.7 - 0.89), or very strong (>0.9)[12]. Statistical significance was defined as $p<0.05$. Data were analyzed using SPSS 20.0 (SPSS, Chicago, IL, USA), and graphs were constructed using GraphPad Prism 7 software (Graph-Pad Software, San Diego, CA, USA).

RESULTS

Twenty-two individuals were recruited and evaluated, and there was a loss of follow-up in specific evaluations due to dropouts and interruptions from the protocol (COVID-19 pandemic, personal reasons, and collection failure), observed in Figure 1. Endothelial function and arterial stiffness were assessed by PAT in nineteen individuals, being 19.9 ± 13.6% in the AIx75 measure and 0.73 ± 0.29 in the RHI, and evaluated by PWV in twelve individuals, with 9.5 ± 1.1m/s and 29.1 ± 9% in the AIx75. Furthermore, four individuals presented values above 10m/s in the PWV assessment (33.3%). The number of daily steps was assessed in seventeen individuals, being 2.519 (1.660-3.561), and eleven individuals walked less than 350 m in the 6MWT.

Seven subjects presented systemic arterial hypertension, and all were in anti-hypertensive drug treatment. All patients reported the use of an inhaled long-acting bronchodilator. There was no reported change in prescribed medication during the protocol. Endothelial dysfunction assessed by EndoPAT (RHI ≤ 0.51) was observed in six subjects (31.6%) and arterial stiffness in four subjects (21.1%) (AIx75 between -10% and 10%). The participants' characterization is detailed in Table 1.

The number of steps per day significantly correlated with the 6MWT (Spearman r= 0.666; p= 0.004; Figure 2A), but no correlation was found between the number of steps per day and measures of arterial stiffness by PAT (AIx75,%) (Spearman r= 0.138; p= 0.609; Figure 2B), PWV (m/s) (Spearman r= -0.347; p= 0.266; Figure 2C) and endothelial function (RHI) with PAT (Spearman r= -0.104; p= 0.700; Figure 2D).

Additionally, we conducted secondary analyses to explore the relationship between the two methods for assessing arterial stiffness, and no correlation was observed between the measurements, PWV (m/s) and PAT (AIx75,%) (Pearson r = 0.372; p = 0.233) and the AIx75 (%) of the PWV and PAT (Pearson r = 0.142; p = 0.659).

DISCUSSION

The current study found few cases of endothelial dysfunction (31.6%) and arterial stiffness (21.1%) in a sample of patients with COPD. The number of steps per day was low, at 2,519, and the distance values walked in the 6MWT were close to the normal range, at 69.6% predicted. However, half of the participants walked less than 350 meters. Additionally, our study found no correlation between the number of daily steps and endothelial function, as assessed by PAT, nor with arterial

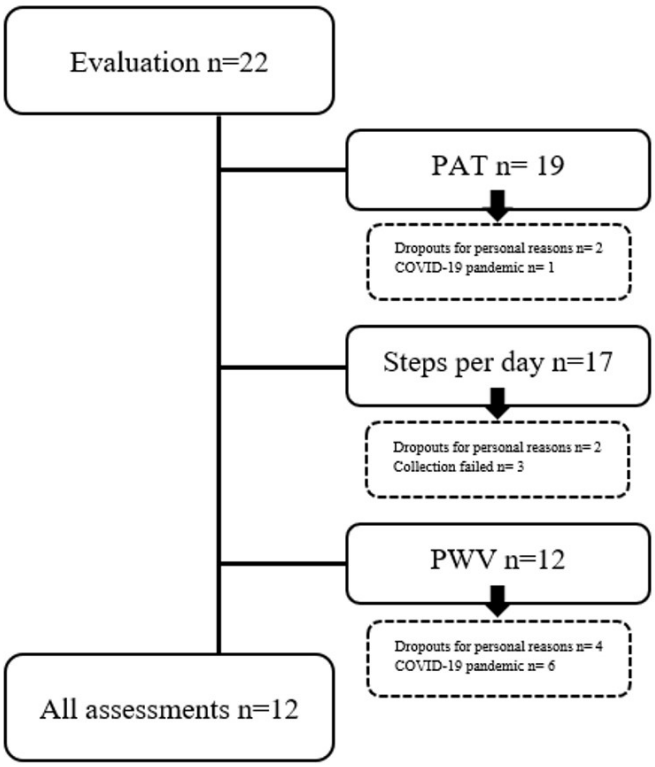

Figure 1. Flow diagram.
Caption: PAT: peripheral arterial tonometry; PWV: pulse wave velocity.

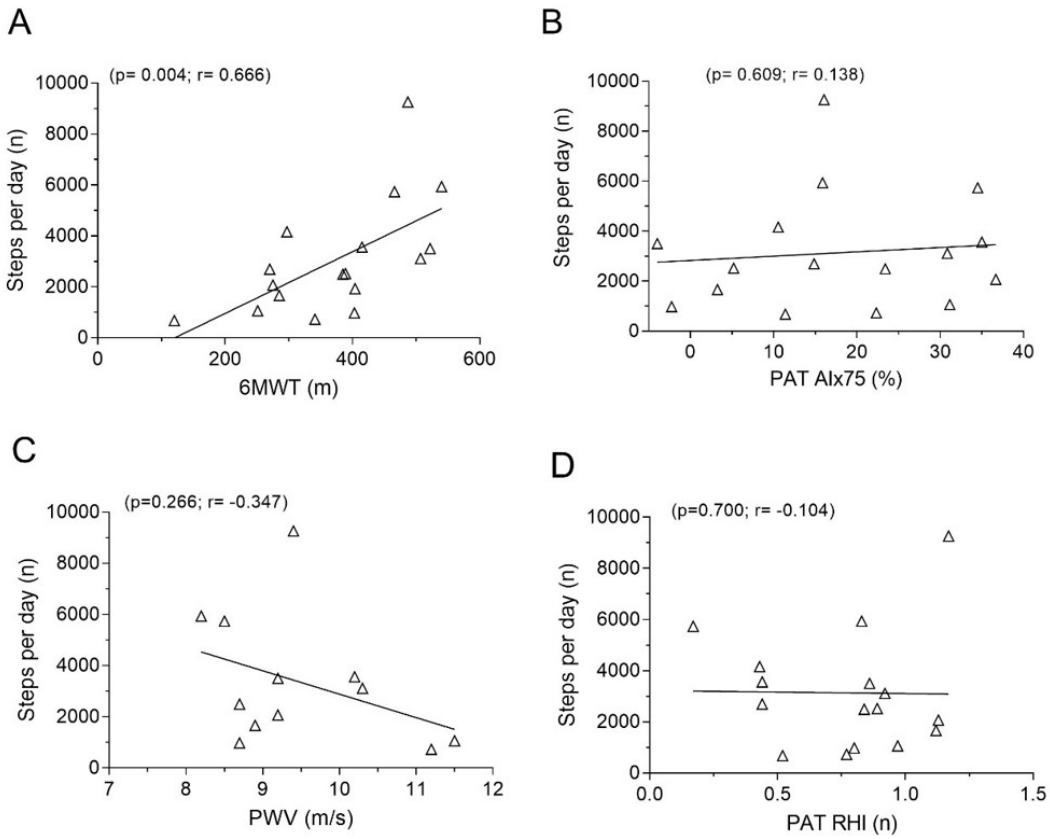

Figure 2. Correlations between outcomes.
Caption: RHI: natural logarithm of the reactive hyperemia index; PAT: peripheral arterial tonometry; AIx75: augmentation index adjusted for 75 beats per minute; PWV: pulse wave velocity; 6MWT: distance walked in the six-minute walking test. (A) seventeen individuals analyzed (n=17); (B) sixteen individuals analyzed (n=16); (C) twelve individuals analyzed (n=12); (D) sixteen individuals analyzed (n=16).

Table 1. Clinical, functional, and performance characteristics.

Characteristics	n=22
Age, years	66.5 ± 9.39
Men – n, %	12 (54.5)
BMI, kg/m²	27.5 ± 4.49
Pack-years	58.1 ± 24
FEV_1/FVC	0.46 (0.37-0.53)
FEV_1, L	0.79 (0.67-1.06)
FEV_1, % pred	34.8 (23.4-45)
FVC, L	1.95 (1.56-2.43)
FVC, % pred	61.1 (47-70.2)
GOLD 2, n, %	5 (22.7)
GOLD 3, n, %	9 (41)
GOLD 4, n, %	8 (36.3)
6MWT, m	365.7 ± 113.9
6MWT, % pred	69.6 ± 21.9

Data are given as mean ± standard deviation or median (25th – 75th quartiles). BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; %pred: percentage of the predicted value; 6MWT: distance walked in the six-minute walking test.

stiffness, as assessed by PWV, in patients with COPD. To the best of our knowledge, this is the first study to evaluate vascular function and the number of daily steps, and both conditions may be additional risk factors in COPD.

A sedentary lifestyle, COPD systemic manifestations, and endothelial dysfunction can increase cardiovascular and mortality risks associated with COPD[13]. Daily step counting using pedometers or accelerometers is widely accepted to assess physical activity levels, where the number of daily steps becomes a functional status marker[14].

The number of daily steps has already been described as a significant predictor of mortality in healthy individuals[3], with a recommendation for the general population to perform at least 10,000 steps per day[15]. However, cardiometabolic risks are consistently associated with performing less than 5,000 steps per day[16]. A study that evaluated mortality in individuals with COPD showed that individuals with the worst outcomes achieved an average of 3,006 daily steps[17], which agrees with our study of 2,519 daily steps. There is strong evidence that increasing steps per day ameliorates the heavily impaired endothelial function in patients with severe and very severe COPD[18]. Therefore, daily physical activity and pulmonary rehabilitation based on physical training are crucial to COPD treatment[19].

The average distance in the 6MWT of our sample was 365.7 m and a predicted test value of 69.6%, with the general values being close to the recommended range[9]. However, for patients with COPD, a 6MWT of fewer than 350 m indicates a worse prognosis and mortality[20]. This is a critical fact to be highlighted, as half of the sample in the present study (n=11) covered values below 350 m. Furthermore, when the daily steps were correlated with the 6MWT, we found a significant correlation (r= 0.666), confirming that individuals who walked less on daily activities evaluated by accelerometers had less distance covered in the 6MWT. Similar results were observed in other studies that monitored steps for seven days[21,22].

PAT measures the RHI, an endothelial function marker, allowing measurement during reactive hyperemia[10], which may be associated with coronary blood flow in response to acetylcholine and discriminate individuals with normal and abnormal coronary endothelial function[23]. Our sample had a low prevalence of endothelial dysfunction, which may explain the lack of correlation between daily steps with RHI and AIx75 assessed by EndoPAT. In a previous study, we found no signs of endothelial dysfunction in the participants, and the RHI was 0.79[24], similar to the present study (0.73). However, in two other studies, peripheral endothelial dysfunction was present in more than half of the individuals in the sample, with a mean RHI value of 0.36 and 0.43 ranging from -0.14 to 1.30[25,26]. Thus, endothelial dysfunction may not be present in all individuals with COPD, reinforcing the need for further investigation.

The Mobil-O-Graph 24 h device has been frequently used to assess arterial stiffness since its validation[27]. In addition, a study with patients with obstructive sleep apnea syndrome evaluated PWV and AIx, concluding that arterial stiffness can be considered a possible cause of cardiovascular complications in these patients[28]. Corroborating these findings, a recent study evaluated the impact of cardiovascular risk factors and their interaction with central blood pressure, PWV, and AIx values, and one of the results was that diabetes was directly related to PWV[29]. Although our study did not find a correlation between the number of daily steps and the arterial stiffness parameters, namely AIX75 and PWV (m/s), there is a lack of literature describing the use of these measures in individuals with COPD. This study pioneered the evaluation of PWV using the Mobil-O-Graph device in the COPD population.

A high level of physical activity seems to benefit aspects related to endothelial function[21]. However, we did not find a correlation between daily steps and other variables of endothelial function and arterial stiffness in COPD patients. These results differ from a systematic review and meta-analysis that demonstrated that the number of steps per day was inversely correlated with arterial stiffness measured by PWV in adults and older adults[30]. Corroborating those findings, a recent study showed that arterial stiffness is associated with a worse overall cardiovascular risk profile. In contrast, in the elderly, it is strongly related to isolated systolic hypertension[31]. Therefore, some hypotheses need to be raised. First, most

of the sample did not present values that characterize endothelial dysfunction, this condition being a previous stage for the development of arterial stiffness. It may be a matter of time before the studied individuals exhibit these conditions. Second, there was a low prevalence of arterial hypertension (n=7) in the sample, which could also contribute to the development of arterial stiffness.

PWV above 10 m/s has been associated with biomarkers of structural changes in the left ventricle chamber and carotid arteries and an increase in cardiovascular mortality[32]. Corroborating these findings, a meta-analysis of 17 studies showed that higher PWV values (≥ 12 m/s) predicted a 102% increase in mortality risk from cardiovascular events. Furthermore, a one m/s increase in PWV was correlated with a 15% increase in cardiovascular risk[33]. When evaluated using the Mobil-O-Graph, we did not find PWV values >12 m/s in any individual. However, four individuals presented values greater than 10 m/s, a reference value indicative of arterial stiffness. These findings are different from those obtained using AIx75 (%). This result differs when we assess arterial stiffness by AIx75 using EndoPAT, where four other individuals had values corresponding to arterial stiffness (AIx75 between -10% and 10%). Furthermore, when we correlated PWV (m/s) and PAT (AIx75), we did not find any significant association ($r = 0.372$; $p = 0.233$). Similarly, between PWV (AIx75) and PAT (AIx75), we did not find a correlation ($r = 0.142$; $p = 0.659$). However, a previous study found that AIx assessed by PAT and AIx derived from synthesized aortic pressure waves (obtained non-invasively through the acquisition of radial artery pressure waveforms) is comparable and reliable due to its high correlation between invasive and non-invasive values, in addition to the lack of proportional bias against invasive assessment[34]. However, one study showed a substantial underestimation and wide dispersion of AIx in the evaluation, which may raise doubts about using AIx to define arterial stiffness[35]. Due to uncertainties regarding the assessment of AIX75 by PAT, we used these secondary analyses to investigate the association between both methods for analyzing arterial stiffness.

The lack of agreement between the arterial stiffness measures in the present study may be caused by the specificity of each assessment method. The AIx75 measures the pressure increase due to the early return of the reflected wave, where the more significant the pulse wave reflections, the greater the AIx75[36], being considered an indirect indicator of arterial stiffness and predictor of cardiovascular events[37]. Meanwhile, PWV is defined by the ratio of the distance between two points in the arterial system (Δx), and the time the wave takes to travel this distance (Δt) is the most used indicator of arterial stiffness due to its good reproducibility[38]. Only one study has simultaneously assessed arterial stiffness using the EndoPAT and Mobil-O-Graph devices in patients over 35 with Type 2 diabetes mellitus and arterial hypertension[39]. Finally, the Mobil-O-Graph was validated for measuring PWV compared to invasive and non-invasive exams[40], unlike EndoPAT, which has not validated the device as a stiffness marker through the AIx75.

The current study's limitations, including a small sample size and participants' diverse lifestyles and occupations, contribute to heterogeneity. Moreover, the research was interrupted by the COVID-19 pandemic. Despite these challenges, the sample generally showed minimal endothelial dysfunction and arterial stiffness. This minimal alteration may explain the lack of correlation between the 6MWT distance and the number of daily steps. To confirm these findings, further research with a larger cohort is essential. We advocate for more in-depth studies to explore the impact of daily step count on vascular health in individuals with COPD at GOLD stages 2 to 4, who may exhibit more significant vascular impairment.

CONCLUSION

Despite a positive correlation between the 6MWT distance and daily step count, the study did not find associations between measures of vascular function (endothelial function and arterial stiffness), functional capacity (6MWT distance), and functional activity (daily step count) in COPD patients with mild or no vascular impairment. The prevalence of endothelial dysfunction (31.6%) and arterial stiffness (21.1%) was relatively low. While daily steps significantly correlated with 6MWT distance, there was no correlation with vascular measures (RHI, PWV, AIx75).

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CONFLICT OF INTEREST

None.

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