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Cardiovascular Rehabilitation in Peripheral Artery Disease: Clinical Impact and Pathophysiological Mechanisms

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Sandra Marisa Pereira Magalhães

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

SANDRA MARISA PEREIRA MAGALHÃES

CARDIOVASCULAR REHABILITATION IN PERIPHERAL ARTERY DISEASE: CLINICAL IMPACT AND PATHOPHYSIOLOGICAL MECHANISMS

Tese de Candidatura ao grau de Doutor em Ciências Médicas; Programa Doutoral da Universidade do Porto (Instituto de Ciências Biomédicas Abel Salazar)

Orientador: Professor Doutor Henrique Cyrne Carvalho
Professor Catedrático
Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

Co-orientador: Professor Doutor Mário Santos
Professor Associado Convidado
Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

Co-orientadora: Professora Doutora Sofia Gonçalves Viamonte
Professora Catedrática Convidada
Faculdade de Medicina da Universidade de Aveiro.

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“The only limit to our realization of tomorrow will be our doubts of today.”

Franklin D. Roosevelt

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ABBREVIATIONS AND ACRONYMS

6MWT:	6-minute walk test
ABI:	Ankle-brachial index
ADMA:	Asymmetric dimethylarginine
AEx:	Arm-ergometry exercise
ARMEX:	Arm-ergometry versus treadmill supervised exercise on cardiorespiratory fitness and walking distances in patients with peripheral artery disease trial
BMI:	Body mass index
CAD:	Coronary artery disease
CRP:	C-reactive protein
CPET:	Cardiopulmonary exercise test
CRF:	Cardiovascular risk factors
CVRP:	Cardiovascular rehabilitation program
DALYs:	Disability-adjusted life years
eNOS:	Endothelial nitric oxide synthase
EPCs:	Endothelial progenitor cells
FITT:	Frequency, Intensity, Time, and Type
FMD:	Flow-mediated dilation
HADS:	Hospital Anxiety and Depression Scale
HBE:	Home-based exercise
HR:	Heart rate
HRQoL:	Health-related quality of life
hsIL-6:	High-sensitivity interleukin-6
IC:	Intermittent claudication
IL:	Interleukin
MCS:	Mental component summary
MET:	Metabolic equivalents
MWD:	Maximal walking distance
MWT:	Maximal walking time
NO:	Nitric oxide
PAD:	Peripheral artery disease
PCS:	Physical component summary
PFWD:	Pain-free walking distance
RCT:	Randomized clinical trials

RPE:	Rating of perceived exertion
ROS:	Reactive oxygen species
SET:	Supervised exercise training
SF-36:	Short Form Health Survey-36
TEx:	Treadmill exercise
VE/VCO_2:	Minute ventilation/carbon dioxide production
VO_2:	Oxygen uptake
VT-1:	First ventilatory threshold
VEGF:	Vascular endothelial growth factor
WIQ:	Walking Impairment Questionnaire
WIQd:	Walking Impairment Questionnaire distance

ABSTRACT

Background: Lower extremity peripheral artery disease (PAD) is a common condition that significantly affects functionality, quality of life, and prognosis. Despite its high prevalence and strong association with adverse clinical outcomes, PAD remains frequently underdiagnosed and undertreated, receiving less research attention than other major cardiovascular diseases. Treadmill-supervised exercise training, combined with risk factor management and optimal medical therapy, is the first-line treatment for patients with intermittent claudication. However, concerns have been raised regarding the negative impact of repeated near-maximal pain on patient adherence. While treadmill exercise significantly improves walking distances, it does not consistently lead to substantial increases in peak oxygen uptake (VO_2 peak), with evidence suggesting that arm-ergometry may be more effective in enhancing VO_2 peak compared to other exercise modalities.

Aims: This thesis aims to compare arm-ergometry supervised exercise training (AEx) with a standard treadmill protocol (TEx) in terms of cardiorespiratory fitness, walking distances, walking economy, health-related quality of life (HRQoL), mental health, cardiovascular risk factors (CRF), and plasma biomarkers in patients with symptomatic PAD.

Methods: The ARMEX trial was a single-center, single-blinded, parallel-group, non-inferiority study that enrolled patients with symptomatic PAD. Patients were randomized (1:1 ratio) to a 12-week supervised exercise training protocol, either AEx or TEx. The primary endpoint was the change in VO_2 peak after the 12-week intervention, measured during a treadmill cardiopulmonary exercise test (CPET). Secondary outcomes included changes in VO_2 at the first ventilatory threshold (VT-1), ventilatory efficiency (ratio of minute ventilation [VE] to carbon dioxide production [VCO_2], VE/VCO_2), walking distances measured during a CPET and a 6-minute walk test (6MWT), self-reported walking limitations (Walking Impairment Questionnaire), walking economy ($\dot{V}O_2$ during submaximal effort), HRQoL [Short Form 36 Health Survey (SF-36)], mental health (Hospital Anxiety and Depression Scale), CRF (blood pressure, lipid profile, glycated hemoglobin, body composition, physical activity levels, sedentary time and smoking), as well as inflammatory markers [C-reactive protein (CRP), high-sensitivity IL-6 (hsIL-6)] and endothelial dysfunction markers [asymmetric dimethylarginine (ADMA)].

Results: Fifty-six patients (66 ± 8 yr; 88% male) were randomized (AEx, n = 28; TEx, n = 28). There was no difference between groups in VO_2 peak at 12 weeks (0.75

mL/kg/min; 95% CI, −0.94 to 2.44; p = 0.378), despite a significant increase only in AEx. VO_2 at VT-1 improved in both groups without significant between-group differences, while the VE/VCO_2 slope showed greater improvement in AEx. TEx achieved greater improvements in maximal walking distance as measured by CPET (121.08 m; 95% CI, 24.49–217.66; p = 0.015) and 6MWT (25.08 m; 95% CI, 5.87–44.29; p = 0.012), and better self-perceived walking distance (8.85; 95% CI, 0.10-17.60; p = 0.048). At 12 weeks, $\dot{V}O_2$ between 60 and 240 seconds decreased exclusively in the TEx group, with between-group differences. Participation in the TEx group and a lower baseline body mass index (BMI) were independently associated with greater improvements in walking economy. Improvements in walking economy were inversely correlated with changes in VO_2 peak and positively correlated with both CPET maximal walking distance and self-reported walking distance. The physical component summary (PCS) score of the SF-36 increased in both groups, without between-group differences (1.39; 95% CI, -1.69 to 4.47; p = 0.368). Role-physical and role-emotional domains improved more in TEx, while no between-group differences were observed in the other domains. Changes in PCS were significantly associated with improvements in walking distances. Hospital Anxiety and Depression Scale scores improved in both groups, without between-group differences. This improvement was correlated with self-reported walking distance. Both groups showed a reduction in systolic and diastolic blood pressure, without between-group differences. Significant decreases in total cholesterol and low-density lipoprotein cholesterol were observed only in the AEx group, without between-group differences. Both groups also showed improvements in weight, BMI, waist circumference, waist-to-hip ratio, physical activity levels, and smoking reduction, without between-group differences. CRP levels decreased significantly only in the AEx group following the intervention, without between-group differences (1.11 mg/dL; 95% CI, -1.11 to 16.2; p = 0.051). At 12 weeks, hsIL-6 levels decreased significantly more in the AEx group (4.27 pg/mL; 95% CI, 0.76 to 9.12; p = 0.025). Additionally, at 12 weeks, ADMA levels decreased significantly only in the TEx group, with a significant between-group difference (54.60 ng/mL; 95% CI, 8.92 to 100.28; p = 0.020), favoring the TEx group.

Conclusions: Arm-ergometry was clinically superior, though not statistically superior, to standard treadmill training for improving VO_2 peak. It was similarly effective in improving VO_2 at VT-1 but superior in enhancing ventilatory efficiency compared to treadmill training. In contrast, treadmill training was associated with greater improvements in walking distances and walking economy. Both interventions led to similar improvements in HRQoL, mental health and CRF. Arm-ergometry was more effective in reducing inflammation, while treadmill training resulted in a greater reduction in ADMA levels,

suggesting a stronger impact on endothelial dysfunction. These findings support treadmill training as the first-line choice for improving walking capacity in patients with PAD, while arm-ergometry may be a viable option for selected patients.

Keywords: cardiorespiratory fitness, cardiovascular rehabilitation, cardiovascular risk factors, exercise training, intermittent claudication, peripheral artery disease, quality of life, plasma biomarkers

RESUMO

Introdução: A doença arterial periférica dos membros inferiores (DAP) é uma condição clínica comum que afeta significativamente a funcionalidade, a qualidade de vida e o prognóstico dos doentes. Apesar da sua elevada prevalência e da forte associação com *outcomes* clínicos adversos, a DAP é frequentemente subdiagnosticada e subtratada, recebendo menos atenção na investigação clínica em comparação com outras doenças cardiovasculares. O exercício físico supervisionado em tapete rolante, combinado com o controlo dos fatores de risco cardiovasculares e uma terapêutica médica otimizada, é o tratamento de primeira linha para doentes com claudicação intermitente. No entanto, estudos recentes sugerem que a dor recorrente durante este tipo de exercício pode comprometer a adesão dos doentes a este tipo de treino. Embora o exercício em tapete rolante tenha demonstrado aumentar significativamente as distâncias de marcha, o aumento do consumo de oxigénio no pico do exercício (VO_2 pico) não tem sido demonstrado de forma consistente. Além disso, alguns estudos sugerem que o exercício em cicloergómetro de membros superiores pode ser mais eficaz para promover um aumento significativo deste parâmetro em comparação com outras modalidades de exercício.

Objetivos: Esta tese tem como objetivo comparar o impacto de um programa de exercício físico supervisionado em cicloergómetro de membros superiores (AEx) com o protocolo standard em tapete rolante (TEx) na aptidão cardiorrespiratória, distâncias de marcha, economia da marcha, qualidade de vida relacionada com a saúde (HRQoL), saúde mental, fatores de risco cardiovascular (CRF) e biomarcadores plasmáticos em doentes com DAP sintomática.

Métodos: O ensaio clínico ARMEX foi um estudo unicêntrico, simples-cego, de grupos paralelos e de não inferioridade, que incluiu doentes com DAP sintomática. Os doentes foram randomizados, numa proporção de 1:1, para um programa de exercício supervisionado de 12 semanas, integrando um dos grupos: AEx ou TEx. O outcome primário, com poder estatístico para análise, foi a variação do VO_2 pico após 12 semanas, avaliada através de uma prova de esforço cardiopulmonar em tapete rolante (CPET). Os outcomes secundários incluíram as variações no VO_2 no primeiro limiar ventilatório (VT-1), eficiência ventilatória (relação entre a ventilação por minuto [VE] e a produção de dióxido de carbono [VCO_2], VE/VCO_2), distâncias de marcha obtidas no CPET e no teste de 6 minutos de marcha (6MWT), limitações na marcha auto-percecionadas (Walking Impairment Questionaire), economia da marcha (VO_2 durante

o esforço submáximo), qualidade de vida relacionada com a saúde [Short Form 36 Health Survey (SF-36)], saúde mental (Escala de Ansiedade e Depressão Hospitalar), fatores de risco cardiovascular (pressão arterial, perfil lipídico, hemoglobina glicada, composição corporal, níveis de atividade física, tempo de sedentarismo e tabagismo), bem como marcadores inflamatórios [proteína C-reativa (CRP) e interleucina-6 de alta sensibilidade (hsIL-6)] e marcadores de disfunção endotelial [dimetilarginina assimétrica (ADMA)].

Resultados: Cinquenta e seis doentes (66 ± 8 anos; 88% do sexo masculino) foram randomizados (AEx, n = 28; TEx, n = 28). Ao fim de 12 semanas, a variação do VO_2 pico não apresentou diferenças estatisticamente significativas entre grupos (0,75 mL/kg/min; IC 95%, −0,94 a 2,44; p = 0,378), apesar de se ter registado um aumento significativo apenas no grupo AEx. O VO_2 no VT-1 melhorou em ambos os grupos, sem diferenças significativas entre eles, enquanto o declive VE/VCO_2 apresentou uma melhoria superior no grupo AEx. O grupo TEx obteve uma melhoria mais acentuada na distância máxima de marcha avaliada pelo CPET (121,08 m; IC 95%, 24,49–217,66; p = 0,015), pelo 6MWT (25,08 m; IC 95%, 5,87–44,29; p = 0,012) e na distância de marcha auto-percecionada (8,85; IC 95%, 0,10–17,60; p = 0,048). Às 12 semanas, o VO_2 medido entre os 60 e 240 segundos diminuiu exclusivamente no grupo TEx, com diferenças significativas entre os grupos. A participação no grupo TEx e um índice de massa corporal (IMC) basal mais baixo associaram-se, de forma independente, a uma maior melhoria na economia da marcha**.** As alterações na economia da marcha correlacionaram-se inversamente com as alterações no VO_2 pico e positivamente com a distância máxima de marcha no CPET e com a distância de marcha auto-percecionada. O score do componente físico sumário (PCS) do SF-36 aumentou em ambos os grupos, sem diferenças significativas entre eles (1,39; IC 95%, -1,69 a 4,47; p = 0,368). Os domínios *role physical* e *role emotional* melhoraram mais no grupo TEx, enquanto não foram observadas diferenças entre os grupos nos restantes domínios. As alterações no PCS associaram-se significativamente à melhoria observada nas distâncias de marcha. Os scores da Escala de Ansiedade e Depressão Hospitalar melhoraram em ambos os grupos, sem diferenças entre eles. Esta melhoria correlacionou-se com a distância de marcha auto-percecionada. Ambos os grupos apresentaram uma redução da pressão arterial sistólica e diastólica, sem diferenças entre os grupos. Reduções significativas nos níveis de colesterol total e colesterol LDL foram observadas apenas no grupo AEx, sem diferenças entre os grupos. Além disso, ambos os grupos registaram melhorias no peso, IMC, perímetro abdominal, *ratio* perímetro abdominal/perímetro da anca, níveis de atividade física e redução do

tabagismo, sem diferenças entre os grupos. Os níveis de CRP diminuíram significativamente apenas no grupo AEx após a intervenção, sem diferenças significativas entre os grupos (1,11 mg/dL; IC 95%, -1,11 a 16,2; p = 0,051). Às 12 semanas, os níveis de hsIL-6 diminuíram significativamente mais no grupo AEx (4,27 pg/mL; IC 95%, 0,76 a 9,12; p = 0,025). Além disso, às 12 semanas, os níveis de ADMA diminuíram significativamente apenas no grupo TEx, com uma diferença significativa entre os grupos (54,60 ng/mL; IC 95%, 8,92 a 100,28; p = 0,020), favorecendo o grupo TEx.

Conclusões: O exercício físico em cicolergómetro de membros superiores demonstrou ser clinicamente superior, embora sem significância estatística, em comparação com o treino em tapete rolante no que diz respeito à melhoria do VO_2 pico. Apresentou eficácia semelhante na melhoria do VO_2 no VT-1, mas mostrou-se superior na melhoria da eficiência ventilatória em comparação com o treino em tapete rolante. Em contraste, o treino em tapete rolante foi associado a um maior incremento nas distâncias de marcha e na economia da marcha. Ambas as intervenções resultaram em melhorias semelhantes na qualidade de vida relacionada com a saúde, na saúde mental e nos fatores de risco cardiovascular. O exercício em cicloergémetro de membros superiores revelou-se mais eficaz na redução da inflamação, enquanto o treino em tapete rolante resultou numa maior redução nos níveis de ADMA, sugerindo um impacto mais pronunciado na disfunção endotelial. Estes resultados sustentam o treino em tapete rolante como a primeira escolha para melhorar a capacidade de marcha em doentes com DAP, enquanto o treino em cicloergómetro de membros superiores poderá ser uma opção viável para doentes selecionados.

Palavras-chave: aptidão cardiorrespiratória, biomarcadores plasmáticos, claudicação intermitente, doença arterial periférica, exercício, fatores de risco cardiovascular, qualidade de vida, reabilitação cardiovascular

INTRODUCTION

1. Peripheral Artery Disease: Definition, Epidemiology, Clinical Significance and Management

Peripheral arterial disease is a clinical condition that affects arteries outside of the heart and brain.[1] One subtype is lower extremity peripheral artery disease (PAD), which involves disease of the arteries extending from the distal aorta to the foot and is most commonly caused by atherosclerosis.[1, 2] The scope of this thesis is limited to lower extremity PAD due to atherosclerosis and does not include other causes.

In 2019, the global prevalence of PAD was 1.52%.[3] It was higher in females (2.03%) compared to males (1.01%) and increased with age, reaching 14.91% in individuals aged 80 to 84 years.[3] PAD affects approximately 113 million people aged 40 and older, with 42.6% of cases occurring in countries with low-to-middle sociodemographic indices.[3] Although PAD is more common in females, its overall burden, measured in disability-adjusted life years (DALYs), remains similar between the sexes.[3] The strongest risk factors for PAD include older age, cigarette smoking, and diabetes mellitus.[4] Hypertension and dyslipidemia are also independent risk factors.[4] Modifiable risk factors account for approximately 70% of the total DALYs associated with the global PAD burden.[3] Patients with PAD have a worse prognosis compared to healthy individuals of the same age group, with higher rates of all-cause and cardiovascular mortality, making it a significant public health concern.[5] A systematic review has shown that they have, at least, a comparable risk of all-cause and cardiovascular mortality to patients with vascular disease in other territories.[6] In fact, their risk of major cardiovascular events, such as stroke or acute myocardial infarction, is at least equivalent to those with established coronary disease.[6] These patients are also more likely to have disease in more than one vascular territory and a greater number of uncontrolled cardiovascular risk factors (CRF).[7] Intermittent claudication is the hallmark clinical manifestation of PAD and negatively impacts patients' activities of daily living and mobility.[2] The functional capacity of patients with intermittent claudication is approximately half of age-matched healthy individuals, which corresponds to a functional limitation similar to New York Heart Association class III heart failure.[8] This functional impairment is progressive, with patients reporting a decrease of 8.4 meters per year in self-reported questionnaires assessing maximal walking distance.[9] Patients with PAD frequently avoid physical activity, which leads to a vicious cycle that worsens their functional status and negatively affects their health-related quality of life (HRQoL).[10] The functional disability, morbidity

and mortality and healthcare resources utilization driven by PAD is associated with a high economic impact, exceeding that attributed to coronary and cerebrovascular diseases.[7] Costs are even more relevant in symptomatic patients undergoing revascularization procedures where rates of rehospitalizations and re-interventions are considerable.[7]

Current treatment for PAD focuses on the following main goals: improving functionality by relieving symptoms, reducing the risk of major adverse limb events, and decreasing the risk of major adverse cardiovascular events.[11] Management strategies are categorized into lifestyle modifications, medical management, endovascular therapies, and surgical interventions.[12] Supervised exercise training, combined with risk factor management and optimal medical treatment, is the first-line approach for patients with intermittent claudication.[2, 13] Revascularization procedures should be considered for patients with symptomatic PAD and impaired PAD-related quality of life, following a 3-month period of optimal medical treatment and exercise therapy.[13] This is particularly relevant for patients who continue to experience disabling limb symptoms and are deemed suitable candidates for such interventions.[2, 13] This stepwise approach aims to mitigate the risk associated with invasive treatments and improve overall cost-effectiveness.[2]

Despite its prevalence, impact on adverse clinical outcomes, and economic burden, PAD has been systematically underdiagnosed and has received less research attention and recognition compared to other atherosclerotic diseases such as myocardial infarction and stroke.[14, 15]

2. Impact of Exercise Training on Functional Capacity, Quality of Life, Adverse Events and Mortality in PAD Patients

Over the past three decades, several randomized clinical trials (RCT) have consistently shown that treadmill-based supervised exercise training enhances walking performance in patients with PAD.[16] Previous meta-analyses have confirmed that exercise training significantly improves functional capacity, including increases in maximal walking distance (MWD), pain-free walking distance (PFWD), self-reported walking ability, and aerobic capacity (table 1). A recent umbrella review[17], incorporating sixteen studies and 198 meta-analytic comparisons, concluded that supervised aerobic exercise (walking until moderate to maximum claudication pain) significantly improved walking distances (with MWD increasing by approximately 178 meters and PFWD by 70 meters), self-

reported walking ability [with improvements of 9.22, 8.71 and 8.02 points on distance, speed and stair climbing scores, respectively, as assessed by the Walking Impairment Questionnaire (WIQ)] and aerobic capacity [with a 0.62 mL/Kg/min improvement in peak oxygen uptake (VO_2 peak)] compared to usual care.[17] Based on this substantial body of evidence, international guidelines provide a class I recommendation, supported by level A evidence, endorsing supervised exercise programs for treating symptomatic patients with PAD.[1, 2, 18]

These patients often experience a significant impairment in HRQoL.[19] Research has shown that this impairment is comparable to that observed in individuals with other cardiovascular diseases.[19] Moreover, poor HRQoL is a predictor of long-term survival in this population, offering prognostic value beyond established biomedical risk factors.[20] A recent statement highlighted the need to include HRQoL assessments in evaluating treatment outcomes for all symptomatic PAD patients.[16] This approach aims to determine whether therapies that improve exercise performance also enhance patients' perceptions of their ability to perform daily activities.[16] There is significant heterogeneity in studies assessing the impact of exercise on patients' HRQoL, largely due to the use of different scales and follow-up periods.[21] The aforementioned umbrella review identified three systematic reviews that evaluated the effect of exercise training (walking was the more frequent exercise prescription) on HRQoL, as measured by the Short Form Health Survey-36 (SF-36) and SF-20 questionnaires, compared to usual care.[17] The three systematic reviews found significant improvements in the SF-36 physical component summary (PCS) score [MD: 1.24 (9 studies)[22]; MD: 2.15 (5 studies)[21]; MD: 2.76 (3 studies)[23]] but not in the mental component summary (MCS) score (in one study[21], the MCS improvement was no longer observed when a random-effects model was applied). The authors concluded that future trials should explore various modes and components of exercise prescriptions to determine which specific elements most effectively improve HRQoL.[21-23]

In patients with PAD, reduced exercise capacity, measured in metabolic equivalents (MET) during a treadmill exercise test, is a strong predictor of cardiovascular and all-cause mortality.[24] Each additional MET achieved is associated with a 17% reduction in total mortality and a 20% reduction in cardiovascular mortality, after adjusting for age.[24] Additionally, poor baseline performance on the 6-minute walk test (6MWT) is linked to increased mortality, even after adjusting for confounders factors.[25] A recent trial showed that light and moderate-to-vigorous intensity physical activity is associated with 50%, 58% and 66% lower risk of all-cause and cardiovascular mortality in PAD patients with claudication, respectively.[26] The authors of the previously described umbrella review

identified two meta-analyses that reported adverse events and mortality following the implementation of an exercise program compared to usual care.[17] One of these meta-analysis[21] found no evidence of an effect of exercise training compared to usual care on all-cause mortality (5 RCT) or amputation (1 RCT). The other meta-analysis[27] evaluated the adverse events of an exercise program versus usual care and found no significant between-group differences. All included studies in both meta-analyses reported these outcomes as secondary, with a maximum follow-up time of twelve months. Therefore, a longer follow-up period is often necessary to observe meaningful differences in these types of outcomes. Retrospective data has provided some insight into the mortality benefit of exercise for PAD.[28, 29] More randomized studies are needed to clarify the impact of exercise training on mortality, amputation and other cardiovascular and limb events.[17, 21, 27]

Author / Year	Population	Studies included/ Participants	Outcome Measures	Studies and Participants / Outcome	Effect size (95% CI, p value)
Lane 2017[21]	IC due to PAD	32 RCT; 1835 participants	MWD	10 RCT; 500 participants	120.36 m (95% CI 50.79 to 189.92; p<0.00007)
			PFWD	9 RCT; 391 participants	82.11 m (95% CI 71.73 to 92.48; p<0.00001)
			MWT	12 RCT; 577 participants	4.51 min (95% CI 3.11 to 5.92; p<0.00001)
			PFWT	11 RCT; 534 participants	2.93 min (95% CI 1.77 to 4.09; p<0.0001)
			SF-36: PCS	5 RCT; 429 participants	2.15 (95% CI 1.26 to 3.04; p<0.00001)
			SF-36: MCS	4 RCT; 343 participants	3.76 (95% CI 2.70 to 4.82; p<0.00001)
			Mortality	5 RCT; 540 participants	RR 0.92 (95% CI 0.39 to 2.17; p=0.85)
			Amputations	1 RCT; 177 participants	RR 0.20 (95% CI 0.01 to 4.15; p=0.3)
Parmenter 2015[30]	PAD	15 RCT; 1257 participants	WIQ speed	11 RCT	9.60 (95% CI 6.98 to 12.23; p<0.00001)
			WIQ distance	10 RCT	7.41 (95% CI 4.49 to 10.33; p<0.00001)
			WIQ stair-climbing	10 RCT	5.07 (95% CI 3.16 to 6.99; p<0.00001)
			SF-36: PCS score	9 RCT	1.24 (95% CI 0.48 to 2.01; p=0.001)
			SF-36: MCS score	6 RCT	-0.55 (95% CI –1.27 to 0.18; p=0.14)
Fassora 2022[31]	Symptomatic PAD (Fontaine II / Rutherford stages 1–3)	19 RCT; 1132 participants	MWD	18 RCT; 1044 participants	178 m (95% CI 142 to 214; p<0.00001)
			PFWD	13 RCT; 895 participants	103 m (95% CI 81 to 125; p<0.00001)
			VO_2 peak	12 RCT; 665 participants	2.1 mL/kg/min (95% CI 1.3 to 2.8; p<0.00001)
Fakhry 2012[32]	IC due to PAD	25 RCT; 916 participants	MWD	24 RCT; 916 patients	180 m (95%CI, 130 to 230 m)
			PFWD	20 RCT; 708 patients	128 m (95% CI, 92 to 165 m)
Parmenter 2015[22]	PAD	41 RCT; 1938 participants	MWD	22 RCT	41.0 m (95 % CI 28.8 to 53.2; p<0.00001)
			PFWD	18 RCT	68.8 m (95 % CI 54.4 to 83.2; p<0.00001)
			VO_2 peak	19 RCT	0.62 ml/kg/min (95 % CI 0.47 to 0.77; p<0.00001)
			6MWT MWD	8 RCT	34.9 m (95 % CI 25.6 to 44.1; p<0.00001)
			6MWT PFWD	4 RCT	52.7 m (95 % CI 24.7 to 80.6; p=0.0002)

Table 1. Key meta-analyses comparing supervised exercise to usual care. Abbreviations: 6MWT: 6-minute walk test; IC: intermittent claudication; MWD: maximal walking distance; MWT: maximal walking time; PAD: peripheral artery disease; PFWD: pain-free walking distance; PFWT: pain-free walking time; RCT: randomized controlled trial; SF-36 MCS: short form health survey-36 mental component summary; SF-36 PCS: SF-36 physical component summary; VO_2: oxygen uptake; WIQ: walking impairment questionnaire.

3. CHARACTERISTICS OF THE EXERCISE INTERVENTION: SETTING AND PROTOCOL

Supervised exercise training (SET) is a first-line treatment for patients with symptomatic PAD and is typically conducted in a hospital setting.[33] Several studies have shown that SET is more effective than unsupervised exercise, including home-based exercise (HBE) and walking advice, for treating these patients.[23] A recent meta-analysis demonstrated greater improvement in walking distances after SET compared to HBE in patients with intermittent claudication.[34] However, a sub-analysis including only trials where HBE featured remote monitoring and/or self-monitoring found that the between-group differences were no longer significant.[34] The authors concluded that for HBE to be effective, it should be structured and personalized, following a specific exercise prescription and including proper monitoring.[34] Given the variety of possible monitoring methods, standardization is required, and future research is needed.[34] Structured education programs that include educational sessions and behavioral change techniques (such as motivational interviewing, barrier identification/problem-solving and feedback on performance) have shown potential to improve walking distances and physical activity levels.[33, 35] These programs can equip patients with the knowledge and skills necessary to successfully self-manage their condition.[33]

Based on previous studies and guidelines, the more recommended FITT (frequency, intensity, time, and type) exercise prescription parameters as follows: a frequency of 3 sessions per week, involving intermittent walking at an intensity that induces at least moderate claudication pain, with each session lasting 30 to 60 minutes, over a duration of 12 to 24 weeks (figure 1).[16, 33] Regarding training intensity, most studies use claudication pain severity (assessed with the claudication pain scale) to guide exercise prescription.[33] There is variability among guidelines concerning the recommended level of claudication pain to be precribed.[33] Additionally, most trials do not clearly distinguish between claudication pain intensity and exercise training intensity (measured using percentages of heart rate, VO_2, or the rating of perceived exertion (RPE) on the Borg scale) when describing the interventions.[33] A meta-analysis has provided strong evidence supporting high-pain exercise and some evidence for low-pain exercise compared to usual care.[36] The LITE trial, a multicenter study, found that one year of home-based walking training at a high pain level was more effective than low-pain walking in improving walking performance in patients with PAD.[37] The current consensus is that patients should exercise at a moderate to high level of claudication pain to enhance walking performance.[33] However, evidence comparing the effects of exercise at different pain intensities is lacking.[33] A randomized controlled trial currently underway may offer clarity on this issue in the future.[38] Claudication pain has been identified as a

contributing factor to the low participation rates of PAD patients in SET.[39] A systematic review found that adherence and completion rates were significantly lower for those prescribed exercise at a high claudication pain level compared to low-pain exercise .[40] In this context, a statement from the American Heart Association recommends avoiding repeated near-maximal claudication to mitigate this detrimental impact on adherence levels.[16] Additionally, a statement from the European Society of Cardiology, Vascular Medicine and Vascular Surgery suggests that a more flexible approach, considering patient's needs and preferences, migh achieve a higher level of long-term adherence.[33]

The most commonly used supervised exercise protocol involves interval treadmill walking until the patient experiences moderate to near-maximal leg pain, prompting them to stop, and then resuming walking once the pain resolves.[16] This protocol has demonstrated a greater increase in walking distances, however, most studies compared this protocol with usual care or other treadmill protocols, rather than with alternative modes of exercise.[41] A systematic review found ten RCTs that compared other exercise modalities with traditional walking exercise and reported no clear difference between alternative modes of exercise and supervised walking exercise regarding MWD and PFWD. The authors also noted that the certainty of this evidence was low and that more RCTs with adequate methodological quality are needed to provide more robust evidence.[42] In addition, while the standard treadmill protocol significantly increases walking distances, it does not consistently lead to significant improvements in cardiorespiratory fitness, specifically VO_2 peak,[22] which is one of the most robust and validated cardiovascular surrogate markers. A review, in PAD patients, that included this parameter as a primary outcome found that arm-ergometry leads to a greater increase in VO_2 peak compared to other modes of exercise.[22] Resistance exercise has been shown to increase walking distances in this population compared to usual care.[43, 44] However, this improvement appears to be less than that achieved by walking exercise.[43, 44] A meta-analysis revealed that if resistance training is performed at high-intensity, these differences are no longer significant.[43]

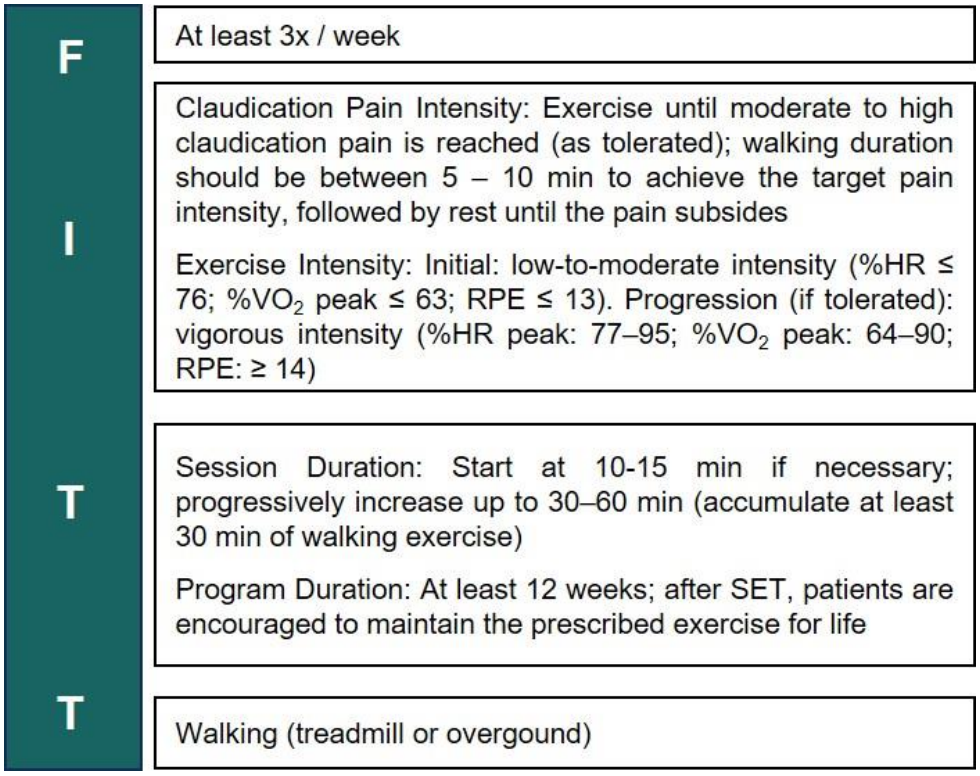

Figure 1. Recommended FITT (Frequency, Intensity, Time, and Type) aerobic exercise prescription parameters for patients with peripheral artery disease. Abbreviations: HR: heart rate; VO_2: oxygen uptake; RPE: rating of perceived exertion; SET: supervised exercise training.

4. Pathophysiological Mechanisms Underlying Exercise Benefits

The pathophysiological mechanisms by which exercise improves functionality, particularly walking capacity, in patients with intermittent claudication, are not yet fully understood.[10, 45, 46] Current evidence suggests multiple chronic adaptations result from exercise training, as discussed below (figure 2).[10, 45, 46] Understanding the pathways through which exercise improves clinical outcomes may offer new possibilities for developing preventive measures or drugs targeting the pathophysiological mechanisms of PAD.

4.1 Hemodynamic response / Calf blood flow

Traditionally, the functional limitation in PAD has been attributed to decreased blood flow caused by obstructive arterial atherosclerotic disease. Fixed atherosclerotic plaques, indicated by a decreased ankle-brachial index (ABI), are certainly a precipitating factor leading to functional abnormalities in PAD.[46] However, numerous findings have shown that the pathophysiology of functional decline and improvement with exercise involves

other mechanisms.[47] Several studies have revealed an inconsistent association between the severity of the obstruction, assessed by ABI or magnetic resonance imaging, and functional status in PAD.[48, 49] Although exercise increases walking distances, this improvement has not been correlated with hemodynamic measures.[46] A systematic review of 33 randomized controlled trials (involving 1237 subjects, 698 of whom underwent exercise training) revealed no significant improvement in various hemodynamic assessments after exercise training, including resting ABI, post-exercise ABI, resting arterial calf blood flow, and reactive hyperemia blood flow post-ischemia.[50] The authors highlight the need for additional research on resting calf blood flow and resting toe pressure because of their association with symptom improvement.[50] Therefore, the functional improvement does not appear to be fully explained by an anatomical model of increased blood flow.

4.2 Hemorheological response

Peripheral vascular resistance throughout the vascular tree is regulated not only by the diameter of resistance vessels but also by the rheological behaviour of the blood. Hemorheology is determined by a complex interplay of several interconnected factors including blood viscosity, plasma viscosity, haematocrit, erythrocyte deformability, erythrocyte aggregation, and fibrinogen concentration.[51] Several hemorheological abnormalities are observed in PAD, such as increased blood and plasma viscosity (due to higher haematocrit, plasma fibrinogen levels, and leukocyte count) and decreased erythrocyte deformability.[52] Exercise has been shown to reduce blood and plasma viscosity and increase erythrocyte deformability, thereby facilitating oxygen delivery to ischemic skeletal muscle in this population.[53-55]

4.3 Angiogenesis

One of the main chronic adaptations induced by exercise training, especially endurance training, is an increase in capillarity in active muscle through a process of angiogenesis, which enlarges the capillary-tissue exchange surface.[56] Several studies in healthy individuals have shown that exercise training leads to a significant increase in the number of capillaries, with this increase primarily varying according to the type of muscle fiber.[57] Exercise has been shown to elevate levels of angiogenic growth factors, including vascular endothelial growth factor (VEGF).[57] Some trials have demonstrated lower capillary density in the calf muscles of patients with PAD.[58, 59] This capillary density has been correlated with indicators of exercise tolerance, such as VO_2 peak, maximal walking time (MWT) and pain-free walking time (PFWT).[59] Animal models of lower limb ischemia subjected to an exercise training protocol demonstrated an improvement of

approximately 43% in regional blood flow, as indicated by an increase in the diameter of collateral vessels and in levels of VEGF.[47] In humans with PAD, data on the angiogenic response to exercise is inconsistent. One group of researchers observed an increase in capillary density following an exercise program; however, this was not accompanied by a significant increase in angiogenic factors such as VEGF-A.[58] A recent review found conflicting evidence and no clear indication that exercise training leads to a significant increase in capillary density in the gastrocnemius muscle of patients with PAD.[60] Further studies are needed to clarify the role and significance of exercise on this biological mechanism in PAD.

Endothelial progenitor cells (EPCs) are bone marrow-derived cells that promote angiogenesis and vascular repair.[61] They hold prognostic clinical value and serve as biomarkers for cardiovascular disease.[61] A systematic review examining the acute and chronic effects of various exercise modalities on EPCs in patients with cardiovascular and metabolic diseases concluded that both the clinical condition and the exercise modality influence the degree of EPC mobilization and the magnitude of long-term increases in EPC levels.[62] Additionally, a meta-analysis demonstrated that exercise training effectively mobilizes EPCs from the bone marrow into circulation in patients with cardiovascular disease.[63] The authors identified only one study in PAD population that showed a significant increase in EPC levels after 3 and 6 months of supervised exercise training.[64] A recent randomized trial involving a structured HBE training for PAD patients over 12 weeks showed a significant increase in circulating EPCs.[65] Moreover, there was a significant positive correlation between the change in EPC levels and walking capacity, as assessed by PFWT time and MWT, in the exercise group.[65] Therefore, the mobilization of EPCs may contribute to walking improvement in PAD patients participating in a structured exercise program.

4.4 Endothelial function

The vascular endothelium plays a crucial role in maintaining vascular homeostasis and is responsible for important functions such as vasodilatation, anti-platelet activity, anticoagulation, fibrinolysis, anti-inflammatory responses, and antiproliferation.[66] Endothelial dysfunction is a key pathophysiological event in the development and progression of atherosclerosis.[66] Flow-mediated dilation (FMD) is a non-invasive method frequently used to assess endothelial function.[67] This parameter is significantly reduced in PAD and serves as an independent predictor of cardiovascular risk.[68]

Several studies have demonstrated that exercise significantly improves endothelial dysfunction, as assessed by FMD, in various pathologies.[69-71] Several mechanisms have

been proposed to explain the enhancement of FMD resulting from exercise: increased bioavailability of nitric oxide (NO), a potent endogenous vasodilator, through the upregulation of endothelial nitric oxide synthase (eNOS) expression and the reduction of its degradation/inactivation by reactive oxygen species (ROS);[72] and an increase in antioxidant capacity through the upregulation of antioxidant enzymes (such as superoxide dismutase, glutathione peroxidase and catalase) while decreasing the expression of oxidizing enzymes (such as nicotinamide adenine dinucleotide phosphate oxidase and xanthine oxidase).[73]

In patients with PAD, some studies have demonstrated a significant increase in FMD,[74, 75] while others have not.[76] A recent meta-analysis revealed that exercise training resulted in a significant 20% increase in brachial artery FMD among patients with PAD.[77] Subgroup analyses indicated that moderate-intensity exercise had a greater effect on FMD compared to vigorous-intensity exercise.[77] Additionally, some studies have shown a reduction in asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase.[64, 76]

4.5 Neurohumoral axis

The autonomic nervous system plays a key role in the pathophysiology of many cardiovascular diseases, with the clinical significance and prognostic implications of sympathetic hyperactivation being well documented.[78] PAD has also been associated with autonomic dysfunction.[79] Neural regulation of the cardiovascular response to exercise involves the interaction of central command, the autonomic nervous system, baroreflexes, and local mechanisms, such as the exercise pressor reflex. The acute cardiovascular response to dynamic exercise leads to increases in heart rate, blood pressure, myocardial contractility, and peripheral vascular resistance, all mediated by a sympathetic activation.[80] In active muscles, metabolically mediated vasodilation occurs to meet increased local oxygen demands.[80] Chronic adaptations to exercise include increased parasympathetic activity[81] and decreased sympathetic activity, resulting in a reduction in resting heart rate, increased heart rate variability, improved baroreflex function, decreased blood pressure and peripheral vascular resistance.[78, 80] In PAD, reduced blood flow to the active muscles leads to an exaggerated blood pressure response to dynamic exercise. The heightened exercise pressor reflex, which promotes sympathetic activation, has been identified as the primary mechanism explaining this hypertensive response.[82] Additionally, a deregulation of the arterial baroreflex may contribute to the commonly observed hypertensive response during exercise.[83] Futhermore, an abnormal response in total peripheral resistance has been noted, as it does not decrease during exercise in patients with PAD.[84] It has been suggested that the

increased accumulation of metabolites and the heightened sensitivity of muscle afferents to mechanical and metabolic stimuli in the more ischemic environment of exercising muscles in patients with PAD may contribute to progressively higher levels of sympathetic outflow.[84]

Exercise training has been shown to prevent the exaggerated exercise pressor reflex in certain conditions, such as chronic heart failure[85, 86] acute myocardial infarction[87] and hypertension.[87] However, further studies on PAD are needed to confirm this effect.

4.6 Mitochondrial and Muscle function

Studies in animals and humans have demonstrated mitochondrial abnormalities in the skeletal muscle of the lower limbs exposed to ischemia.[88] Some trials have reported a decrease in mitochondrial activity, particularly in electron transport chain activity[89] and in the expression of oxidative phosphorylation proteins.[90] In patients with PAD, there is an early accumulation of intermediate oxidative metabolism products, such as acylcarnitines and lactate, suggesting insufficient oxidative metabolism.[91] Recent advances suggest the existence of mutations in mitochondrial DNA in PAD, particularly in the ischemic limb.[92] The most common deletion was associated with the loss of genes encoding subunits of the respiratory chain complexes.[93] Gastrocnemius muscle biopsies from patients with PAD demonstrated a significant increase in mitochondrial heteroplasmy compared to control subjects.[94] PAD is also associated with histopathologic changes in calf muscle, including increased fatty infiltration and fibrosis, smaller cross-sectional area, lower capillary density, increased levels of apoptosis, denervation of distal motor axons, fiber atrophy and a reduced number of type I fibers.[88] Exercise has been shown to decrease levels of acylcarnitines and lactate and increase oxygen extraction in the lower limbs.[47] Exercise has also been shown to significantly increase the amount of angular and target muscle fibers, supporting the hypothesis that it induces an adaptive response involving gastrocnemius denervation and reinnervation.[91] Additionally, there was a significant increase in glycolytic enzymes, suggesting a shift in energy metabolism towards glycolysis.[91] A randomized clinical trial revealed a significant increase in the proportion of slow oxidative myosin heavy chain type I within the gastrocnemius myofibers among patients who performed supervised treadmill exercise training, compared to those in the control group.[95] The impact of exercise on mitochondrial activity has yielded inconsistent results.[60] While certain trials have shown increases in both citrate synthase activity and mitochondrial complex II activity, others have not.[60]

4.7 Inflammation and Oxidative stress

Atherosclerosis is a chronic inflammatory disease, as confirmed by experimental and clinical evidence.[96] PAD patients have increased levels of inflammatory biomarkers, which have been associated with disease progression, the occurrence of cardiac and lower limbs arterial events, and the acceleration of functional decline.[97] Assessing inflammation is challenging, as it involves multiple cells, mediators and pathways. Analysing the effects of exercise on inflammation adds further complexity because the impact depends on resident macrophages, which exert different effects based on the tissue in which they reside.[98] Regular exercise is associated with a significant anti-inflammatory effect.[99] Several explanatory mechanisms have been suggested in the literature, including the reduction of visceral fat, leading to a decrease in proinflammatory adipokines; an increase in interleukin-6 (IL-6) concentration produced by contracting muscles, which raises circulating levels of anti-inflammatory cytokines (IL-10 and IL-1RA) and stimulates cortisol production by adrenal glands; activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, resulting in the release of cortisol and catecholamines; inhibition of adipose tissue infiltration by monocytes and macrophages, and phenotypic switching of macrophages within adipose tissue (mechanisms not completely clarified in humans); decreased expression of Toll-like receptors in monocytes and macrophages, consequently inhibiting the production of pro-inflammatory cytokines; reduction in the percentage of inflammatory monocytes (CD14+;CD16+) compared to the classical population; and an increase in the number of circulating regulatory T cells, which suppress the immune response.[99] Some studies have shown an acute increase in inflammatory markers and oxidative stress following exercise in patients with PAD, particularly with high-intensity exercise.[100] However, studies assessing the chronic effects of exercise have demonstrated an anti-inflammatory action in several chronic diseases.[98] In patients with PAD, previous trials have reported that supervised treadmill exercise reduces circulating vascular and inflammatory biomarkers, including intercellular adhesion molecule-1,[101] soluble vascular cell adhesion molecule-1,[102] E-selectin,[101] IL-6[103] and C-reactive protein (CRP).[102] However, findings from studies examining the effect of exercise training on inflammatory biomarkers in PAD patients have been inconsistent. A recent systematic review found no significant improvements in CRP, IL-6, or TNF-α levels.[77] Differences in exercise prescription parameters, such as intensity, frequency, mode, and duration, likely account for this disparity in results.

Low concentrations of ROS are crucial for cell survival, smooth muscle cell proliferation, angiogenesis, and homeostasis.[104] Endogenous antioxidant systems keep these ROS

levels low.[104] However, under pathological conditions, excessive ROS surpasses the capacity of antioxidant systems, leading to impaired vascular function.[104] Patients with PAD exhibit a higher abundance of ROS in skeletal muscle compared to healthy controls.[105] Some studies suggest that exercise may enhance oxidative stress and improve the antioxidant response.[102, 103]

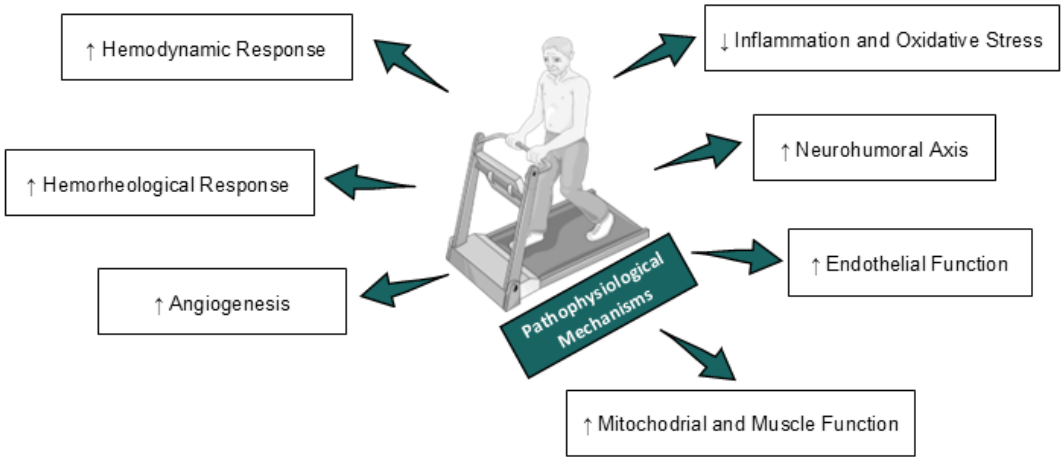

Figure 2. Pathophysiological mechanisms through which exercise improves functionality in patients with peripheral artery disease. This figure contains modifed images from Servier Medical Art (https://smart.servier.com) licensed by a Creative Commons Attribution 3.0 Unported License.

5. CARDIOVASCULAR REHABILITATION PROGRAMS

Cardiovascular rehabilitation is a comprehensive intervention that includes established core components which encompass patient assessment, CRF management and control, physical activity counseling, exercise prescription, nutritional guidance, psychosocial support, and structured follow-up aimed at achieving rehabilitative goals and secondary prevention in both the short and long term.[106] The effectiveness of these programs is well-established for individuals with coronary artery disease (CAD) and heart failure, leading to significant improvements in cardiorespiratory function and quality of life, as well as reduced re-hospitalization rates.[106] However, decreased mortality rates have only been confirmed in CAD patients. [106]

PAD is a well-established indication for integrating a cardiovascular rehabilitation program (CVRP).[106] These programs, which feature individualized prescriptions of supervised exercise combined with risk factor modification strategies, have the potential

to alter the clinical trajectory of PAD by reducing symptoms, improving functionality and lowering the risk of future cardiovascular events. Recent guidelines identify CVRP as an ideal setting for treating PAD patients.[18] However, these patients are referred only in a minority of cases, typically when they share common features with other cardiovascular conditions.[106] Previous trials indicate that PAD patients are less likely to initiate and complete a CVRP compared to those with CAD.[29, 107] Some reports have compared improvements in functional capacity between the two groups,[29, 107] while others suggest a lower increase in VO_2 peak following exercise training in PAD patients.[108] Devrome et colleagues demonstrated a similar improvement in mortality rates for PAD patients compared to those without PAD.[29] However, evidence supporting CVRP for these patients remains limited, as only a small number of randomized controlled trials have been conducted.[29,109]

6. Exercise programs for PAD: Implementation, Challenges, and Future Research Directions

Despite strong evidence, supervised exercise programs are still underused.[33] Few centers offer these programs for this specific population, and the situation varies from country to country across Europe.[110] Even when programs are available, a systematic review found that only about 1 in 3 screened individuals are considered suitable and willing to participate in this particular intervention.[39] The main reasons for non-inclusion were: inability to walk on a treadmill (35%), lack of interest or refusal to participate by the patient (31%), associated comorbidities that prevent exercise (16%), and travel or access constraints for exercise sessions (11%).[39] Additionally, up to one-third of patients who enroll fail to complete the program due to a lack of motivation, with pain experienced during exercise being a significant factor.[39] Finding strategies to overcome these barriers and identify enablers that promote exercise participation is essential.[111]

Some of the research priorities for exercise interventions outlined in the American Heart Association statement include comparing different exercise training modalities, incorporating functional and quality-of-life outcomes in all intervention studies to gain a broader understanding of the impact of exercise on patients' lives, identifying the biological pathways through which exercise improves walking performance, and conducting studies within real-world clinical populations.[16]

AIMS

The current thesis aimed to compare the impact of a cardiovascular rehabilitation program that incorporates supervised arm-ergometry exercise training with a standard treadmill protocol among patients with symptomatic PAD.

The primary aim was to compare the impact of these two interventions on cardiorespiratory fitness, while the secondary objectives included comparing their effects on walking distances, walking economy, CRF, HRQoL, symptoms of anxiety and depression, and plasma biomarkers.

The specific objectives and corresponding papers were as follows:

- To compare an arm-ergometry supervised exercise training with a standard treadmill protocol on cardiorespiratory fitness [VO_2 peak (primary outcome), VO_2 at first ventilatory threshold (VT-1) and minute ventilation/carbon dioxide production (VE/VCO_2) slope] and in walking distances (PFWD and MWD) among symptomatic patients with PAD. **(Paper 1)**
- To compare an arm-ergometry supervised exercise training with a treadmill protocol on walking economy and identify the clinic characteristics and outcomes that were associated with walking economy improvement. **(Paper 2)**
- To compare the effects of an arm-ergometry supervised exercise training program with a treadmill protocol on HRQoL and mental health among symptomatic patients with PAD. Additionally, to assess the relationships between intervention-induced changes in the physical component summary (PCS) score of Short Form Health Survey-36 (SF-36) and walking performance outcomes, as well as the relationships between intervention-induced changes in Hospital Anxiety and Depression scale (HADS) scores and walking performance outcomes. **(Paper 3)**
- To compare the impact of an arm-ergometry supervised exercise training with a standard treadmill protocol on CRF in symptomatic PAD patients. **(Paper 4)**
- To compare an arm-ergometry supervised exercise training with a standard treadmill protocol on inflammation and endothelial function biomarkers among symptomatic patients with PAD. **(Paper 5)**

METHODS

This thesis includes the ARMEX trial and four secondary analyses derived from it. The specific methodologies and approaches for each study are thoroughly detailed in the articles that comprise this thesis. However, some general aspects are outlined below:

1. Trial Design

The ARMEX trial was a single-center, single-blinded, parallel-group, non-inferiority, randomized clinical trial. Consecutive patients with PAD and intermittent claudication, referred to the Cardiovascular Rehabilitation Unit, were invited by a physician to participate. Prior to final eligibility determination, all participants underwent a treadmill CPET. Enrollment was conducted between January 2017 and April 2023. Eligible patients were randomized to either an AEx or a TEx protocol over 12 weeks.

2. Participants

Adults aged 18 years or older, diagnosed with symptomatic PAD and referred to the Cardiovascular Rehabilitation Unit, were recruited. The inclusion criteria were as follows: (i) ability to walk at a minimum speed of 3.2 km/h; (ii) capability to participate in a supervised 12-week exercise program; and (iii) no changes in PAD medication (cilostazol, pentoxifylline, statins, or antiplatelet therapy) for at least three months prior to enrollment. Medication remained unchanged throughout the intervention period. Exclusion criteria included: (i) PAD classified as Leriche-Fontaine stages I, III or IV; (ii) a revascularization procedure within the previous 12 months; (iii) the presence of other chronic conditions that impaired exercise capacity more than PAD; (iv) an acute cardiovascular event within 3 months prior to enrollment; and (v) clinical contraindications for exercise participation, as defined by current guidelines.[112]

3. Randomization and Allocation

Randomization was conducted using a computer-generated random number sequence with a 1:1 allocation ratio and block sizes of four patients. A member of the research team, who was not directly involved in patient recruitment or assessment, was responsible for the randomization and allocation process.

4. Interventions

Exercise sessions were conducted twice weekly and included a 10-minute warm-up, 40-minutes of treadmill walking or arm-ergometry, 1-2 sets of 12-15 repetitions of ten

resistance exercises (Borg rating of perceived exertion (RPE) 12 – 13) (squats, leg extension, leg curls, leg abduction, calf rises, chest press, lateral rises, biceps curls, triceps extension and seated row) and a 10-minute cooldown. Sessions were led by a physiotherapist and supervised by a physician, both experienced in cardiovascular rehabilitation. Heart rate was continuously monitored during sessions using electrocardiographic telemetry and recorded every five minutes, along with Borg RPE scale ratings for both exercise prescriptions. In the TEx group, patient-reported claudication pain severity was also recorded.

Additionally, all patients received nutritional and psychological interventions in accordance with international guidelines.[106] They were also encouraged to engage in at least two 30-minute home exercise sessions per week, with a weekly log kept to monitor unsupervised exercise.

4.1 Treadmill Supervised Exercise Training

The treadmill exercise prescription followed a previously established standard protocol.[113] The initial training intensity was determined based on the baseline CPET and was defined as the incline at which claudication pain first occurred, with a starting speed of 3.2 km/h. Patients walked until they experienced moderate claudication pain (3 – 4 of 5 on the claudication scale), at which point they stopped to rest until the pain fully subsided before resuming walking. Progression occurred when a patient could walk at a given workload for at least 8 minutes before experiencing a pain level of 3 or 4 out of 5 on claudication scale. Adjustments were made in the following session. First, grade increased by 2% increments until 10%. Next, the speed increased in 0.3 km/h increments until reaching 4.8 km/h. Then, grade was increased again in 2% increments up to 15%, (the last increment was 1%). After that, speed continued to increase in 0.3 km/h increments as tolerated.

4.2 Arm-Ergometry Supervised Exercise Training

The arm-ergometry exercise prescription followed the established guidelines for this population.[112] During the first two weeks, patients exercised at 50%–60% of VO_2 peak (RPE: 12–13). From weeks 3 to 6, intensity increased to 60%–70% of VO_2 peak (RPE: 13), and from weeks 7 to 12, intensity further increased to 70%–80% of VO_2 peak (RPE: 13–14).

RESULTS (ORIGINAL PAPERS)

The results of this thesis are presented in the following original papers, which have been either published or submitted for publication. The author has actively contributed to their conceptualization, execution, analysis, interpretation and writing.

Paper 1: **Effect of arm-ergometry versus treadmill supervised exercise on cardiorespiratory fitness and walking distances in patients with peripheral artery disease: the ARMEX randomized clinical trial.**

Sandra Magalhães, Mário Santos, Sofia Viamonte, Fernando Ribeiro, Joana Martins, Cristine Schmidt, Daniel Martinho-Dias, Henrique Cyrne-Carvalho

J Cardiopulm Rehabil Prev. 2024;44(5):353-360. doi:10.1097/HCR.0000000000000878

JCR2024: IF:3.3; Q1: Rehabilitation; Percentile JCI: 87

SciMAGO2023: SJR:1.18; Q1: Cardiology and Cardiovascular Medicine

Paper 2: Walking economy after an arm-ergometry versus a treadmill supervised exercise program in patients with peripheral artery disease: findings from the ARMEX trial.

Sandra Magalhães, Mário Santos, Sofia Viamonte, Fernando Ribeiro, Joana Martins, Cristine Schmidt, Daniel Martinho-Dias, Henrique Cyrne-Carvalho

Heliyon. 2025;11(3), e42275. doi.org/10.1016/j.heliyon.2025.e42275

JCR2024: IF:3.4; Q1: Multidisciplinary; Percentile JCI: 79.1

SciMAGO2023: SJR:0.62; Q1: Multidisciplinary

Paper 3: Effect of arm-ergometry versus treadmill supervised exercise on health-related quality of life and mental health in patients with peripheral artery disease: secondary outcomes from the ARMEX Trial.

Sandra Magalhães, Mário Santos, Sofia Viamonte, Fernando Ribeiro, Joana Martins, Cristine Schmidt, Henrique Cyrne-Carvalho

J Patient Rep Outcomes. 2025;9(1):15. doi:10.1186/s41687-025-00847-8

JCR2024: IF:2.4; Q2: Health Policy & Services; Percentile JCI: 58.5

SciMAGO2023: SJR:0.87; Q2: Health Informatics

Paper 4: Comparing arm-ergometry and treadmill exercise training on cardiovascular risk factors in peripheral artery disease: secondary analysis of the ARMEX trial.

Sandra Magalhães, Mário Santos, Sofia Viamonte, Fernando Ribeiro, Joana Martins, Cristine Schmidt, Henrique Cyrne-Carvalho

Int Angiol. 2025; online ahead of print. doi:10.23736/S0392-9590.25.05364-7

JCR2024: IF: 1.5; Q3: Pheripheral Vascular Disease; Percentile JCI: 30.2

SciMAGO2023: SJR:0.41; Q3: Cardiology and Cardiovascular Medicine

Paper 5: Arm-ergometry versus treadmill exercise in patients with peripheral artery disease: inflammatory and endothelial outcomes in the ARMEX Trial.

Sandra Magalhães, Mário Santos, Sofia Viamonte, Manuel Teixeira, Fernando Ribeiro, Henrique Cyrne-Carvalho

J Cardiopulm Rehabil Prev [Submitted for publication]

Original Investigation

Effect of Arm-Ergometry Versus Treadmill Supervised Exercise on Cardiorespiratory Fitness and Walking Distances in Patients With Peripheral Artery Disease

THE ARMEX RANDOMIZED CLINICAL TRIAL

Sandra Magalhães, MD; Mário Santos, PhD; Sofia Viamonte, MD; Fernando Ribeiro, PhD; Joana Martins, MD; Cristine Schmidt, PhD; Daniel Martinho-Dias, MD; Henrique Cyrne-Carvalho, PhD

Purpose: To compare arm-ergometry and treadmill supervised exercise training on cardiorespiratory fitness and walking distances in patients with peripheral artery disease (PAD).
Methods: ARMEX was a single-center, single-blinded, parallel group, non-inferiority trial enrolling symptomatic patients with PAD. Patients were randomized (1:1 ratio) to a 12-wk arm-ergometry (AEx) or standard treadmill (TEx) supervised exercise training protocol. The powered primary end point was the change in peak oxygen uptake (VO_2) at 12 wk, measured on a treadmill cardiopulmonary exercise test (CPX). Secondary outcomes included changes in VO_2 at the first ventilatory threshold (VT-1), ventilatory efficiency (ratio of minute ventilation [VE] to carbon dioxide production [VCO_2], VE/VCO_2), walking distances by CPX and 6-min walking test (6MWT), and self-reported walking limitations.
Results: Fifty-six patients (66 ± 8 yr; 88% male) were randomized (AEx, n = 28; TEx, n = 28). At 12 wk, VO_{2peak} change was not significantly different between groups (0.75 mL/kg/min; 95% CI, −0.94 to 2.44; P = .378), despite a significant increase only in AEx. VO_2 at VT-1 improved in both groups without between-group differences, and VE/VCO_2 slope improved more in AEx. The TEx attained greater improvements in walking distance by CPX (121.08 m; 95% CI, 24.49-217.66; P = .015) and 6MWT (25.08 m; 95% CI, 5.87-44.29; P = .012) and self-perceived walking distance.
Conclusions: Arm-ergometry was noninferior to standard treadmill training for VO_{2peak}, and treadmill training was associated with greater improvements in walking distance. Our data support the use of treadmill as a first-line choice in patients with PAD to enhance walking capacity, but arm-ergometry could be an option in selected patients.

Key Words: cardiovascular rehabilitation • exercise training • intermittent claudication • peripheral artery disease • upper extremity

Author Affiliations: *Department of Physical and Rehabilitation Medicine, Centro Hospitalar Universitário de Santo António, Porto, Portugal (Dr Magalhães); UMIB—Unit for Multidisciplinary Research in Biomedicine, ICBAS—School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal (Drs Magalhães, Santos, and Cyrne-Carvalho); Department of Cardiology, Centro Hospitalar Universitário de Santo António, Porto, Portugal (Drs Santos and Cyrne-Carvalho); Physiology Laboratory, Immuno-Physiology and Pharmacology Department, ICBAS—School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal (Dr Santos); CAC ICBAS-CHUP—Centro Académico Clínico Instituto de Ciências Biomédicas Abel Salazar—Centro Hospitalar Universitário de Santo António, Porto, Portugal (Drs Santos and Cyrne-Carvalho); ITR—Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal (Drs Santos and Cyrne-Carvalho); Centro de Reabilitação do Norte, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal (Dr Viamonte); Institute of Biomedicine—IBIMED and School of Health Sciences, University of Aveiro, Portugal (Dr Ribeiro); Department of Angiology and Vascular Surgery, Centro Hospitalar Universitário de Santo António, Porto, Portugal (Dr Martins); Research Centre in Physical Activity, Health and Leisure, CIAFEL, Faculty of Sport, University of Porto, Porto, Portugal (Dr Schmidt); Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Porto, Portugal (Dr Schmidt); Department of Community Medicine, Information and Decision in Health, Faculty of Medicine, University of Porto, Porto, Portugal (Dr Martinho-Dias); CINTESIS – Center for Health Technology and Services Research (Dr Martinho-Dias); and Family Health Unit Ao Encontro da Saúde, ACES Santo Tirso-Trofa, Trofa, Portugal (Dr Martinho-Dias).*

All authors meet the 4 ICMJE criteria for authorship.

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Correspondence: *Sandra Magalhães, MD, Department of Physical and Rehabilitation Medicine, Centro Hospitalar Universitário de Santo António, Largo Professor Abel Salazar, 4099-001 Porto, Portugal (mag.sandra@gmail.com).*

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Peripheral artery disease (PAD) is a condition with a worldwide prevalence of 6% in individuals over 25 yr, which corresponds to 236 million people.[1] Patients with PAD have a worse prognosis with higher all-cause and cardiovascular mortality compared to healthy individuals of the same age group.[2]

Supervised exercise training is currently considered a first-line treatment in patients with PAD with intermittent claudication,[3] with interval treadmill walking to near-maximum leg pain being the most used protocol.[4,5] However, concerns about the potential negative impact of the repeated near-maximal pain on patient adherence to the exercise program were highlighted in a recent scientific consensus.[3] In addition, there is evidence supporting the improved adherence of patients with PAD to non-traditional exercise programs.[6] Regarding efficacy, a recent systematic review[7] concluded that, for patients with PAD with intermittent claudication, there is no clear difference between alternative exercise programs and supervised walking exercise regarding walking distances. Due to the small sample size and risk of bias concerns, the certainty of the evidence was judged to be low, and the authors point out the importance of conducting high-quality intervention trials.[7]

Despite leading to significant increases in walking distances, the standard exercise protocol on a treadmill does not lead, consistently, to significant increases in peak oxygen uptake (VO_{2peak}), which is one of the most robust and

KEY PERSPECTIVE

- Arm-ergometry was similarly effective to the standard treadmill protocol in improving peak oxygen uptake (VO_2) and VO_2 at the first ventilatory threshold but was superior to improving ventilatory efficiency (the ratio of minute ventilation to carbon dioxide production).
- Treadmill exercise training is associated with greater improvements in walking distances.
- Treadmill exercise training should be the first-line choice to improve walking distances.
- Arm-ergometry can be an option for selected patients who are unable to perform long walks or intolerant to exercise-induced leg pain.

validated cardiovascular surrogate markers.[8] A systematic review that looked at this parameter as a primary outcome showed that arm-ergometry seems to be associated with a greater increase in VO_{2peak} compared to other exercise modes.[8] With this background, the ARMEX randomized clinical trial was designed to compare arm-ergometry supervised exercise training (AEx) with a standard treadmill protocol on VO_{2peak} and walking distances among patients with symptomatic PAD.

METHODS

TRIAL DESIGN

The ARMEX was a single-center, single-blinded, parallel group, non-inferiority, randomized clinical trial. Consecutive patients with PAD with intermittent claudication referred to the Centro Hospitalar Universitário do Porto were invited to participate in the trial by a physician and then referred to a treadmill cardiopulmonary exercise test (CPX) prior to a final decision about eligibility. The enrollment occurred from January 2017 to April 2023 (the duration of the study was extended due to the coronavirus disease-2019 pandemic). Eligible patients were randomized either to an AEx or a treadmill walking exercise protocol (TEx) over 12 wk. The study was conducted according to the recommendations of the Declaration of Helsinki and approved by the Ethics Committee of Centro Hospitalar Universitário de Santo António and School of Medicine and Biomedical Sciences of the University of Porto [2016-053 (047-DEFI/046-CES)]. Written informed consent was obtained from all participants. The present manuscript was structured according to the Consolidated Standards of Reporting Trials Statement for randomized trials of Nonpharmacological Treatment.[9]

PARTICIPANTS

Patients with PAD older than 18 yr old referred to the Cardiovascular Rehabilitation Unit were prospectively enrolled in the trial. Peripheral arterial disease was diagnosed through a clinical history and physical examination and confirmed by an ankle-brachial index ≤0.90 and/or a decrease in the ankle-brachial index of ≥10% after a symptom-limited treadmill stress test. The inclusion criteria were as follows: (i) patients able to walk at a speed of at least 3.2 km/hr; (ii) able to participate in a supervised exercise program for 12 wk; and (iii) no change in medication for PAD (cilostazol, pentoxifylline, statin, and antiplatelet therapy) for at least 3 mo prior to study enrollment. The medication remained unchanged during the study intervention period. The exclusion criteria are provided in the Supplemental Digital Content, available at: http://links.lww.com/JCRP/A527.

RANDOMIZATION AND ALLOCATION

Randomization was performed with a computer-based random number generator using a 1:1 allocation ratio for block sizes of 4 patients. Randomization and allocation were undertaken by a member of the research team (C.S.) that was not directly involved in the recruitment or patient assessment.

OUTCOME MEASURES

Outcomes were measured at baseline and at the end of intervention (12-wk). The primary endpoint was change in VO_{2peak} evaluated on a treadmill CPX. Secondary outcomes included changes in VO_2 at first ventilatory threshold (VT-1); ventilatory efficiency (ratio of minute ventilation [VE] to carbon dioxide production [VCO_2], VE/VCO_2 slope); maximal walking distance (MWD) and pain-free walking distance (PFWD) evaluated in CPX; walking distances evaluated in a 6-min walking test (6MWT); and self-reported walking limitations evaluated in the Walking Impairment Questionnaire (WIQ) taking into account distance, speed, and stair climbing scores. Patients were asked weekly about exercise performed at home. A detailed description of the assessment procedures is provided in the Supplemental Digital Content, available at: http://links.lww.com/JCRP/A527.

DROPOUT, ADHERENCE RATES, AND EXERCISE SESSION PARAMETERS

The dropout rate was calculated in both groups. The adherence rate was calculated based on the number of sessions performed in relation to the number of sessions planned. The duration and $\%VO_{2peak}$ achieved by patients during the aerobic component of the exercise program were calculated as described in the Supplemental Digital Content, available at: http://links.lww.com/JCRP/A527.

INTERVENTIONS

Exercise sessions consisted of twice-weekly sessions comprising 10-min warm-up, 40-min treadmill intermittent walking or arm-ergometry, resistance exercises, and 10-min cooldown, led by a physiotherapist and under medical supervision, both with experience in cardiovascular rehabilitation. A detailed description of each exercise prescription for both intervention groups is provided in the Supplemental Digital Content, available at: http://links.lww.com/JCRP/A527. Additionally, all patients received nutritional and psychological intervention according to the international guidelines.[10] All patients were encouraged to exercise at home at least twice a week for 30 min. A weekly record of unsupervised exercise was made as described in the Supplemental Digital Content, available at: http://links.lww.com/JCRP/A527.

STATISTICAL ANALYSIS

The distribution of the data was assessed with the Shapiro-Wilk test and via visual inspection of histograms. Continuous data are reported as mean ± SD, mean differences (95% CI), or median (IQR), and categorical data are reported as frequencies (%). Within-group comparisons, from baseline to 12 wk, were performed using a paired-samples *t* test or Wilcoxon signed rank test. Differences between groups in the change from baseline to the end of the study were tested using ANCOVA, adjusting for baseline

value. A statistical significance of $P < .05$ was assumed. IBM SPSS statistics version 29.0 (IBM Corp) was used to perform statistical analyses. The sample size calculation is provided in the Supplemental Digital Content, available at: http://links.lww.com/JCRP/A527.

DATA AVAILABILITY

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

RESULTS

A total of 59 patients were referred to our cardiovascular rehabilitation consultation and assessed for eligibility (Figure 1). One patient refused to participate in the study, and 2 patients did not meet the inclusion criteria. As such, 56 patients (66.0 ± 8.4 yr; 88% male) were enrolled and randomized to the AEx (n = 28) and TEx (n = 28) groups. Of these, 51 patients (AEx, n = 25; TEx, n = 26) completed the intervention. Four patients (AEx, n = 1; TEx, n = 3) were excluded from primary outcome analysis due to the absence of data (CPX was not available during a period of the coronavirus disease-2019 pandemic), but they were included in the analysis of the remaining outcomes. Baseline participant characteristics were well balanced between groups and are described in Table 1.

Adherence to exercise sessions was 91% (AEx, 87%; TEx, 92%; $P = .311$) (Table 2). The VT-1 could not be determined in 4 patients (2 patients in each group). Only 1 patient (in the TEx group) did not reach the heart rate corresponding to VT-1 during the exercise sessions. All the remaining patients achieved this goal. The mean duration per session of the aerobic component of the exercise program was superior in the AEx group, with a significant between-group difference of 6.94 min (95% CI, 6.09-7.78; $P < .001$) (Table 2). The median of $\%VO_{2peak}$ achieved by patients during the aerobic component of exercise was similar in both groups ($P = .258$) (Table 2). The percentage of patients who complied with the recommendation to exercise at home was also similar in both groups (AEx, 76%; TEx, 69%; $P = .588$) (Table 2).

PRIMARY OUTCOME

At 12 wk, VO_{2peak} increased significantly in AEx (1.73 ± 2.65 mL/kg/min, $P = .004$) but not in TEx (0.66 ± 2.98 mL/kg/min, $P = .30$), without significant between-group difference (0.75 mL/kg/min; 95% CI, −0.94 to 2.44; $P = .378$) (Table 3, Figure 2). Individual peak VO_2 changes from baseline to after intervention for the AEx and TEx groups are provided in Figure 3.

SECONDARY OUTCOMES

VO_2 at VT-1 increased significantly in both groups without significant between-group difference (0.58 mL/kg/min; 95%

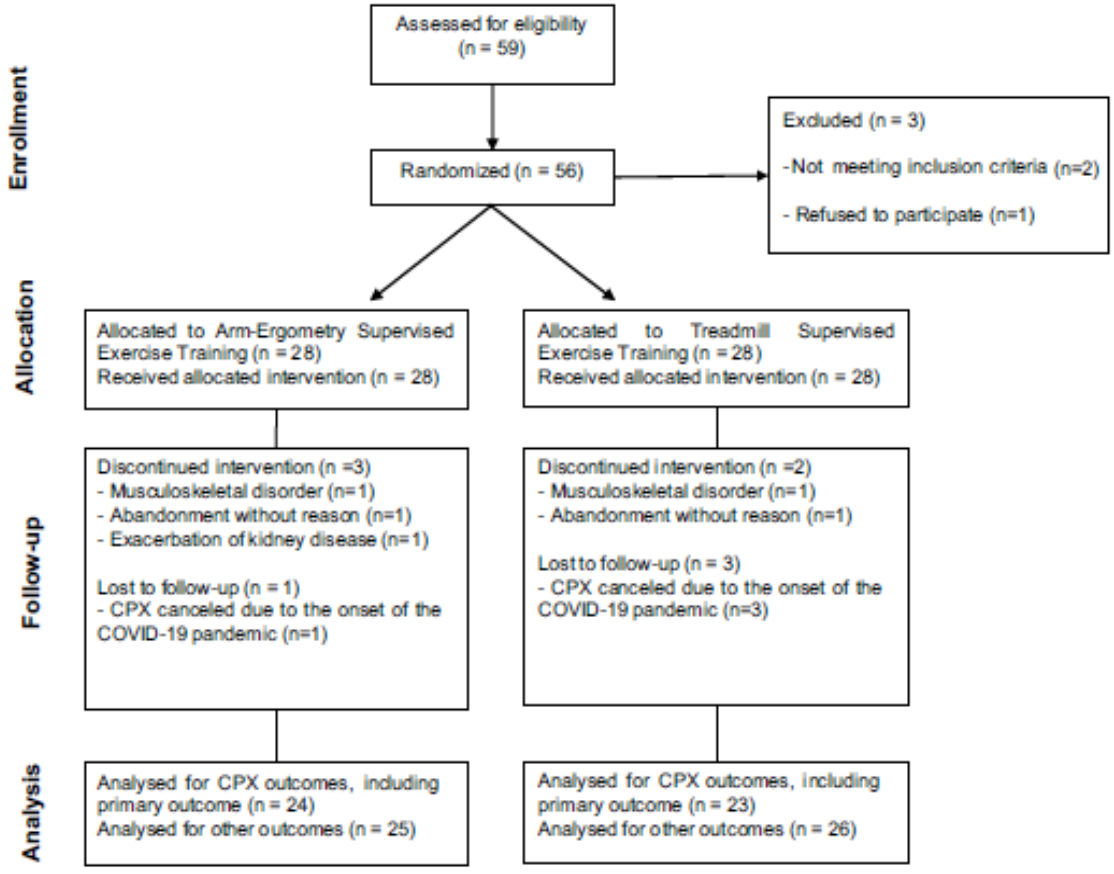

Figure 1. Modified CONSORT flow diagram for patients with peripheral artery disease in the ARMEX randomized clinical trial. COVID-19, coronavirus disease-2019; CPX, cardiopulmonary exercise test.

Table 1

Baseline Characteristics Overall and by Treatment Group in Patients With Peripheral Artery Disease in the ARMEX Randomized Clinical Trial[a]

Variable	Overall n = 56	Arm-Ergometry n = 28	Treadmill n = 28	*P* Value
Age, y	66 ± 8.4	67 ± 7.8	64 ± 8.9	.468
Male	49 (88)	25 (89)	24 (86)	.725
White	56 (100)	28 (100)	28 (100)	NA
Lowest resting ABI	0.66 ± 0.13	0.69 ± 0.11	0.62 ± 0.15	.156
Prior leg revascularization	12 (21)	3 (11)	9 (32)	.180
Comorbidities				
Coronary heart disease	26 (46)	15 (54)	11 (39)	.488
Cerebrovascular disease	4 (7)	2 (7)	2 (7)	.967
Heart failure	5 (9)	3 (11)	2 (7)	.605
COPD	5 (9)	3 (11)	2 (7)	.605
Cardiovascular risk factors				
Dyslipidemia	47 (84)	22 (79)	25 (89)	.406
Diabetes mellitus	25 (45)	13 (46)	12 (43)	.683
Hypertension	48 (86)	22 (79)	26 (93)	.202
Physical inactivity	43 (77)	24 (86)	19 (68)	.157
Obesity	10 (18)	5 (18)	5 (18)	.884
Smoking status				
Current	17 (30)	10 (36)	7 (25)	.485
Previous	34 (61)	17 (61)	17 (61)	.867
Never smoked	5 (9)	1 (4)	4 (14)	.172
Medication				
Acetyl-salicylic acid	47 (84)	22 (79)	25 (89)	.243
Statins	56 (100)	28 (100)	28 (100)	NA
Beta-blockers	35 (63)	21 (75)	14 (50)	.055
ACEi /ARB	43 (77)	21 (75)	22 (79)	.679
Antiplatelet agent	18 (32)	10 (36)	8 (29)	.485
Anticoagulants	10 (18)	7 (25)	3 (11)	.243
Pentoxifylline	14 (25)	7 (25)	7 (25)	.931
Cilostazol	6 (11)	2 (77)	4 (14)	.413

Abbreviations: ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; NA, not applicable.
[a]Data are presented as mean ± SD or n (%).

CI, −0.52 to 1.68; P = .296). VE/VCO_2 slope improved significantly only in the AEx group with significant between-group difference (2.37; 95% CI, 0.17-4.56; P = .035) (Table 3, Figure 2). Walking distances on CPX improved in both groups after intervention with a significant between-group difference of 121.08 m (95% CI, 24.49-217.66; P = .015) for MWD and 95.16 m (95% CI, 6.33-183.99; P = .036) for PFWD in favor of the TEx group (Table 3, Figure 2). Walking distances evaluated in 6MWT also improved in both groups after intervention; the improvement was higher in TEx, resulting in a significant between-group difference in the mean change in the MWD (25.08 m; 95% CI, 5.87-44.29; P = .012) and PFWD (50.35 m; 95% CI, 6.06-94.64; P = .027) (Table 3, Figure 2). At 12 wk, WIQ scores increased in both groups. WIQ distance improved more in TEx (8.85; 95% CI, 0.10-17.60; P = .048). There were no between-group differences in WIQ speed (Table 3, Figure 2) or WIQ stair climbing (Table 3, Figure 2).

DISCUSSION

To the best of our knowledge, this is the first trial comparing the impact of arm-ergometry with treadmill exercise in symptomatic patients with PAD on VO_{2peak} as a primary outcome, a robust and validated surrogate marker for cardiovascular mortality.[11] Consistent with previous studies, we observed a statistically and clinically meaningful improvement of VO_{2peak} at 12 wk only in arm-ergometry group.[12,13] In contrast, the increase of VO_{2peak} in the treadmill group was not statistically significant. This observation is also in line with previous studies that have conflicting data, some showing a significant increase[14,15] and others not.[16,17] The observed change from baseline in VO_{2peak} in both groups (TEx, 0.66 mL/kg/min; AEx, 1.73 mL/kg/min) is clinically relevant because in symptomatic patients with PAD, changes in VO_{2peak} of 0.4, 1.1, and 1.7 mL/kg/min are considered to have a small, moderate, and large clinical importance, respectively.[18] Higher intensity, longer duration, and arm-ergometry exercise were predictors of an increased VO_{2peak} change.[8] The prescription in the treadmill group is determined by the pain that forces the patient to stop, which may occur before the $\%VO_{2peak}$ goal. However, in our sample, the median of VO_{2peak} achieved in exercise sessions was not different between groups. In addition, only 1 patient, in the TEx group, did not reach the heart rate corresponding to VT-1 during the exercise sessions. Therefore, we can assume that all the remaining patients, in both groups, achieved sufficient exercise intensity to promote cardiovascular adaptations. The treadmill protocol was interval training, and due to pain, the total duration of aerobic exercise per session was slightly inferior. This may have contributed to the

Table 2

Adherence and Exercise Session Parameters by Treatment Group in Patients With Peripheral Artery Disease in the ARMEX Randomized Clinical Trial[a]

	Arm-Ergometry	Treadmill	*P* Value[c]
Adherence (supervised exercise)[b]	86.9 (81.8, 100)	91.7 (88.7, 100)	.311
Aerobic exercise time, min/session	39.7 ± 0.59	32.7 ± 2.02	<.001
$\%VO_{2peak}$ achieved per aerobic exercise session[b]	77.5 (72.8, 80.2)	79.6 (73.6, 84.4)	.258
Unsupervised exercise, % patients performed	19 (76)	18 (69)	.588

Abbreviation: VO_{2peak}, peak oxygen uptake.
[a]Data are presented as mean ± SD, median (IQR), or n (%).
[b]Variables with non-normal distribution.
[c]*P* value from independent samples *t* test (variables with normal distribution), Mann-Whitney *U* test (variables with non-normal distribution), and chi-square test (categorical variables).

Table 3

Primary and Secondary Outcomes and Between-Group Differences in Patients With Peripheral Artery Disease in the ARMEX Randomized Clinical Trial[a]

	Arm-Ergometry			Treadmill				
	Baseline	Final	Change From Baseline	Baseline	Final	Change From Baseline	Between-Group Difference in Change[d]	*P* Value[d]
CPX	n = 24			n = 23				
VO_{2peak}, mL/kg/min	13.81 ± 3.1	15.55 ± 3.57[c]	1.73 ± 2.65	15.4 ± 3	16.06 ± 3.75	0.66 ± 2.96	0.75 (–0.94 to 2.44)	.378
VO_2 at VT-1, mL/kg/min	9.92 ± 2.42	11.73 ± 2.5 [c]	1.81 ± 1.82	10.9 ± 2.6	11.9 ± 2.62[c]	0.96 ± 2.01	0.58 (–0.52 to 1.68)	.296
VE/VCO_2 slope	37.20 ± 4.96	32.19 ± 4.58[c]	–5.02 ± 4.49	33.38 ± 5.1	32.54 ± 4.09	–0.84 ± 3.83	2.37 (0.17-4.56)	.035
MWD, m	301.3 ± 176.7	401.6 ± 215.5[c]	100.3 ± 161.74	351.31 ± 201.93	571.65 ± 273.55[c]	220.34 ± 160.23	121.08 (24.49-217.66)	.015
PFWD, m[b]	150 (71.3, 227.3)	182.89 (123.3, 333.3)[c]	72.87 (–13.4, 113.4)	166.22 (89.6, 256.7)	256.7 (209.3, 390)[c]	117.1 (40, 227.6)	95.16 (6.33-183.99)	.036
6MWT	n = 25			n = 26				
MWD, m	352.96 ± 68.48	391.21 ± 66.58[c]	38.25 ± 27.57	376.74 ± 97.74	435.04 ± 81.67[c]	58.30 ± 45.7	25.08 (5.87-44.29)	.012
PFWD, m[b]	188 (91, 267.5)	194.3 (124.8, 342.5)[c]	34.1 (5, 71.5)	192.95 (130.8, 244.3)	265 (169.6, 357.3)[c]	74.5 (17, 123.4)	50.35 (6.06-94.64)	.027
WIQ	n = 25			n = 26				
WIQd, %[b]	27.56 (14.8, 49.9)	48.86 (19.1, 67)[c]	13.85 (3.7, 24)	17.22 (7.8, 49.4)	48.15 (27.2, 73.9)[c]	18.9 (8, 34.9)	8.85 (0.10-17.60)	.048
WIQs, %	26.78 ± 12.73	35.87 ± 14.78[c]	9.09 ± 7.83	25.21 ± 3.82	37.84 ± 3.47[c]	12.62 ± 9.47	3.30 (–1.45 to 8.06)	.169
WIQsc, %[b]	27.56 (14.8, 49.9)	48.86 (19.1, 67)[c]	12.5 (0, 25)	41.67 (16.7, 66.7)	54.17 (36.5, 66.7)[c]	8.33 (0, 25)	1.86 (–7.57 to 11.30)	.693

Abbreviations: CPX, cardiopulmonary exercise test; MWD, maximal walking distance; PFWD, pain-free walking distance; 6MWT, 6-min walking test; VE/VCO_2, ratio of minute ventilation [VE] to carbon dioxide production [VCO_2]; VO_{2peak}, peak oxygen uptake; VT-1, first ventilatory threshold; WIQ, Walking Impairment Questionnaire; WIQd, WIQ distance; WIQs, WIQ speed; WIQsc, WIQ stair climbing.

[a]Data are presented as mean ± SD, mean (95% CI), or median (IQR).

[b]Variables with non-normal distribution. Wilcoxon signed rank test was performed for within-group comparisons.

[c]Significantly different from baseline, $P < .05$.

[d]Treatment difference and *P* value from ANCOVA model, adjusting for baseline value.

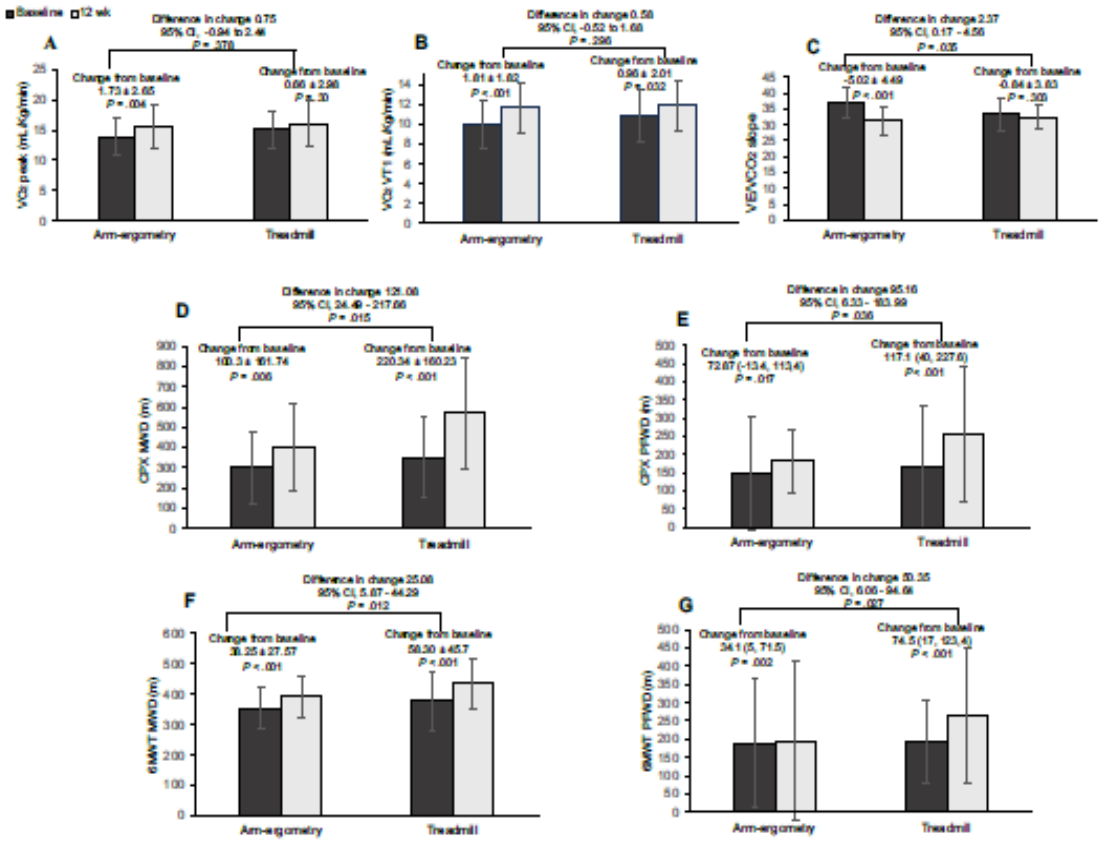

Figure 2. Change in (A) VO_{2peak}, (B) VO_2 at VT-1, (C) VE/VCO_2 slope, (D) CPX MWD, (E) CPX PFWD, (F) 6MWT MWD, and (G) 6MWT PFWD at baseline and 12 wk by treatment group in patients with peripheral artery disease in the ARMEX randomized clinical trial. Data are presented as mean ± SD, mean (95% CI), or median (IQR). CPX, cardiopulmonary exercise test; VE/VCO_2, ratio of minute ventilation [VE] to carbon dioxide production [VCO_2]; VT-1, first ventilatory threshold; MWD, maximal walking distance; PFWD, pain-free walking distance; VO_{2peak}, peak oxygen uptake; 6MWT, 6-min walking test; VE/VCO_2 slope, ventilatory efficiency.

lower VO_{2peak} increase. Our AEx group started the intervention with a lower VO_{2peak} than the TEx group, which gives them a greater possibility of increasing with exercise training. However, the VO_{2peak} improvement remained significant and clinically superior in the AEx group after adjustment for the baseline value.

The VO_2 at VT-1 was associated with walking tolerance in patients with intermittent claudication.[19] This outcome has been considered a useful indirect marker of oxidative metabolism, obtained noninvasively and with low-intensity exercise.[19] Consistent with a previous study,[16] we found a significant improvement in both groups, without significant between-group differences. The VE/VCO_2 slope improved more in arm-ergometry group, and the VE/VCO_2 slope is prognostically significant in a number of cardiovascular conditions.[20]

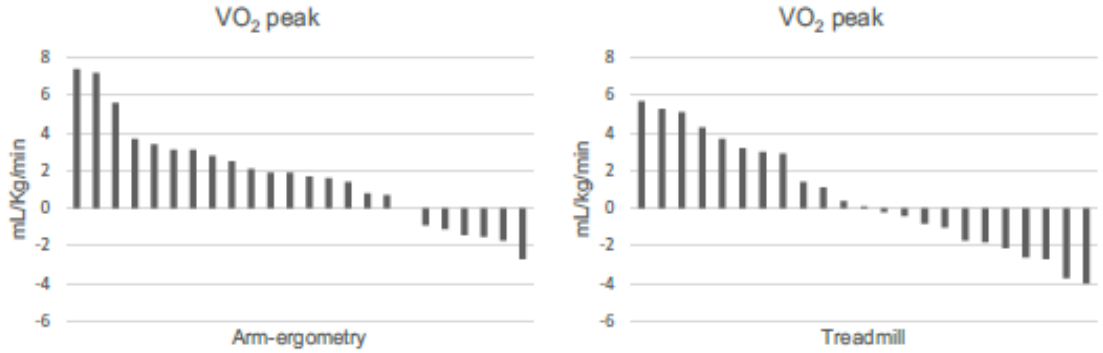

Figure 3. Individual change in VO_{2peak} from baseline to the end of the 12-wk intervention in both exercise groups in patients with peripheral artery disease in the ARMEX randomized clinical trial. VO_{2peak}, peak oxygen uptake.

Many of our patients who improved in walking distances did not improve in VO_{2peak} at the end of the intervention. This outcome depends a lot on performance at maximal effort and many of these patients stop at the treadmill CPX, due to pain, before reaching that level of effort. Therefore, other outcomes (eg, VO_2 at VT-1 and VE/VCO_2 slope) that depend on a submaximal level of exertion may be more appropriate to assess cardiorespiratory fitness in more symptomatic patients with PAD.

CPX walking distances improved in both groups. Several randomized controlled trials have shown improvement in MWD and PFWD after a treadmill[21] or an arm-ergometry[22] exercise program in patients with PAD. CPX walking distances were significantly superior in the TEx group. To the best of our knowledge, there is only 1 pilot study that performed this comparison, and the authors reported a tendency toward a greater increase in MWD in the treadmill group and in PFWD in the arm-ergometry group.[23]

We also studied 6MWT distances because these outcomes showed a greater correlation with walking in daily life and should be considered as a different walking capacity measure.[24] These outcomes have been shown to predict rates of mobility loss and mortality and improve in response to therapeutic interventions and are not associated with a learning effect when repeated testing is performed.[3] We observed a statistically and clinically meaningful improvement in 6MWT distances[18] in both groups, which is in accordance with the previous reports.[22] To the best of our knowledge, this is the first study that performed a comparison between treadmill and arm-ergometry exercise on 6MWT distances in PAD population, and we observed a superior increase in TEx. The minimal clinically important differences for WIQ scores are 6% for WIQ distance, 4% for WIQ speed, and 6% for WIQ stair climbing.[18] Both interventions produced statistically and clinically meaningful increases in WIQ scores. Data on the impact of exercise training on these outcomes are scarce.[25,26] To the best of our knowledge, this is the first study that compared the impact on WIQ scores of a treadmill program versus an arm-ergometry exercise program in a PAD population. This tool has been shown to be effective in assessing the effect of treatment in patients with intermittent claudication[27] and to be an independent predictor of all-cause and cardiovascular mortality.[28] We observed a higher increase in the patient-perceived walking distance in the TEx group.

Speculatively, the clinically greater increase in VO_{2peak} and the smaller improvements in assessed or self-perceived walking distances in the arm-ergometry group suggest a predominance of central cardiorespiratory adaptation. The absence of pain during arm-ergometry exercise may allow for a greater stimulus for cardiorespiratory improvement.[8] The walking distances improvement, although inferior, was also clinically significant in this exercise group.[18] These results corroborate the well-known cross-transfer effects of aerobic exercise training, defined as an adaptation from trained to untrained musculature.[29] Exercise training targeting upper body muscles can improve the exercise capacity of muscle groups not directly involved in the training effort.[29] However, the absence of lower-limb skeletal muscle metabolic adaptations after arm-ergometry exercise likely explains the observed differences in walking distances compared to treadmill training.[30]

Previous trials have indicated that improvements in walking performance, during the first weeks after treadmill exercise training, are more closely related to an improvement in walking economy, namely improvements in gait biomechanics; and later improvements are more related to an increase in VO_2 peak.[31,32] In addition, as previously mentioned, the exercise program duration has been shown to impact the improvement of this outcome, with programs lasting 13 to 24 wk demonstrating greater efficacy than those lasting 12 wk or fewer.[8] Thus, to achieve a more significant increase in VO_{2peak} in the treadmill group, we would have to prolong the intervention. It would be interesting for future trials to explore the combination of both exercise modalities incorporating a duration sufficient to enhance cardiorespiratory fitness, because this approach appears to lead to significant improvement in various outcomes.

Further research is needed to understand the systemic and local mechanisms underlying these changes, namely changes in endothelial vascular function, inflammation, and muscle biological adaptations. However, we consider that the results of this study may contribute to a better clinical practice in cardiovascular rehabilitation programs.

LIMITATIONS OF THE STUDY

Our study has some limitations that must be acknowledged. The nature of the intervention and study design did not allow the blinding of the patients and professionals involved in the exercise supervision and monitoring. We tried to mitigate the potential bias by choosing an objective primary end point assessed by a researcher blinded to the allocation of the participants. Another limitation is the larger SD of the primary end point (VO_{2peak} change) compared to the one used for sample size calculation, so we cannot exclude the presence of a type II error due to lack of statistical power. The lack of a long-term follow-up period must be highlighted. However, the existing reports suggest a progressive fade out over time, explained by the decreasing compliance to exercise and not a qualitative difference when comparing short- to long-term results.[33,34] The intensity prescribed in AEx was determined on a treadmill CPX rather than an arm-ergometry exercise test. In healthy individuals, peak upper-limb aerobic power is generally 70% of that measured for the lower limbs due to the smaller amount of active skeletal muscle.[35] However, in patients with PAD, VO_{2peak} values in arm-ergometry, leg-ergometry, and treadmill have shown similar values.[36,37] These theoretical considerations reflect the real and pragmatic challenges of arm-ergometry exercise prescription. Therefore, we believe they did not affect the internal validity of our trial. For a more accurate assessment of physical activity levels outside the intervention, it would have been more appropriate to use accelerometers, which are the gold standard method for the evaluation of these parameters.[38]

CONCLUSIONS

The ARMEX trial showed that arm-ergometry exercise led to a clinically significant increase in VO_{2peak}, which is a robustly validated prognostic marker in cardiovascular disease—the main cause of death of patients with PAD. The trial also observed improvements in VO_2 at VT-1 and VE/VCO_2 slope (other important cardiorespiratory fitness outcomes), walking distance, and self-reported walking distance. The standard treadmill protocol remains superior for increasing walking distances in patients with intermittent claudication. These findings support the use of treadmill as a first-line mode of exercise in patients with intermittent claudication but also supports arm-ergometry as a complementary or alternative option, particularly for well-selected patients who are unable to engage in long walks or intolerant to exercise-induced leg pain.

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SUPPLEMENTAL DIGITAL CONTENT 1

eMETHODS

PARTICIPANTS

We prospectively enrolled patients with peripheral artery disease (PAD) older than 18 years old referred to the Cardiovascular Rehabilitation Unit. Exclusion criteria included: i) PAD Leriche-Fontaine stages I, III or IV; ii) a revascularization procedure during the previous 12 months; iii) other chronic conditions causing exercise impairment more than PAD; iv) acute cardiovascular event less than 3 months prior to enrollment; and v) clinical contraindications for physical exercise practice, according to current guidelines.[1]

OUTCOME MEASURES

VO_2 peak and CPX distances

Patients performed a graded cardiopulmonary exercise test (CPX), in a treadmill (Medisoft, Model 870C®), using the Gardner-Skinner protocol with a constant speed at 3.2 Km/h and a 2% increase in grade every 2 min until the maximal claudication pain that resulting in an inability to walk any further. [2] Respiratory gas exchange measurements were performed with a calibrated stationary metabolic cart system (Geratherm® Respiratory Ergostik, under BLUE CHERRY®) and were obtained breath-by-breath and averaged every 30 seconds. Heart rate and blood pressure were recorded at regular intervals throughout the test. Oxygen uptake (VO_2) peak was determined as the highest VO_2 achieved during the exercise test. VO_2 at first ventilatory threshold (VT-1) was determined using the ventilatory equivalents method. Ventilation

per carbon dioxide slope (VE/VCO_2 slope) was assessed using all data from exercise. All the tests were interpreted by the same physician (M.S.), who was blinded to patients' intervention allocation.

6-Minute Walk Test distances

The 6-minute walk test was performed according to a standardized protocol.[3] Patients walked up and down a 30-meter corridor marked every 3 meters for 6 minutes after specific instructions to cover as much distance as possible. Participants were allowed to rest if needed, but the stopwatch continued during rest periods.

Walking Impairment Questionnaire scores

The Walking Impairment Questionnaire (WIQ) is a PAD-specific measure of self-reported walking limitations with 3 domains: walking distance (WIQd), walking speed (WIQs), and stair climbing (WIQsc).[4] Each domain is scored on a 0 to100 scale, on which 0 represents the most extreme limitation, and 100 represents no difficulty walking long distances, walking rapidly, or climbing 3 stair flights, respectively.

INTERVENTIONS

Exercise sessions consisted of twice-weekly sessions comprising 10-min warm-up, 40 min treadmill intermittent walking or arm-ergometry, 1-2 sets of 12-15 repetitions of ten resistance exercises (Borg rating of perceived exertion (RPE) 12 – 13) (squats, leg extension, leg curls, leg abduction, calf rises, chest press, lateral rises, biceps curls, triceps extension and seated row) and 10-min cooldown, led by a physiotherapist and under medical supervision, both with experience in cardiovascular rehabilitation.

Treadmill Supervised Exercise Training

The treadmill exercise prescription followed the standard protocol previously described.[5] The initial treadmill training intensity was established using the baseline CPX and was defined as the grade that brings on the onset of claudication pain, with the initial speed set at 3.2 km/h. Patients walked to a moderate claudication pain level (3 – 4 of 5 on claudication scale), stopped and rested until the claudication pain completely resolved and then resumed walking. Progression occurred if a patient was able to walk at a workload for 8 minutes or more before experiencing a pain level 3 or 4 of 5 on claudication scale; this progression was made in the following session. First, grade increased by 2% increments until 10%; then speed increased by 0.3 km/h increments until 4.8 km/h; then grade was once more increased by 2% increments up to 15% (the last increment was 1%); and then increases in speed by 0.3 km/h increments as tolerated. Heart rate was continuously monitored during sessions using electrocardiographic telemetry and recorded every 5 min with the Borg RPE scale and patient-reported claudication pain severity.

Arm-Ergometry Supervised Exercise Training

The arm-ergometry exercise prescription followed the guidelines for this population.[1] In the first two weeks, patients performed exercise at 50% – 60% of VO_2 peak (RPE:12-13); from the 3rd to 6th weeks intensity increased to 60% – 70% VO_2 peak (RPE 13); and from the 7th to 12th weeks intensity increased to 70% – 80% VO_2 peak (RPE 13-14). Heart rate was continuously monitored during sessions using electrocardiographic telemetry and registered along with the Borg RPE scale.

Exercise Sessions Parameters

We recorded the duration of aerobic exercise performed in each exercise session. To quantify the $\%VO_2$ peak achieved by patients during the aerobic component of exercise we calculated the mean of heart rate achieved in each exercise session and checked the corresponding $\%VO_2$ peak in the CPX performed by each patient.

Monitoring of unsupervised exercise

Patients were asked weekly about exercise performed at home. It was made a record of the mode and time of exercise realized. Patients were considered to have performed unsupervised exercise if they completed moderate-intensity exercise for at least 30 min per session for at least 2x/week. Recorded exercise was analyzed as a dichotomous variable (yes or no).

STATISTICAL ANALYSIS

The sample size was calculated assuming a noninferiority margin of 1.5 mL/Kg/min, a previously published[6] pooled standard deviation of 1.8 mL/Kg/min, a power of 0.80, a 1-sided 0.05 level of significance, and equal participant allocation to the 2 treatment groups. With these specifications, 27 participants per group were required to accommodate for a 15% attrition rate.

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Research article

Walking Economy after an Arm-ergometry versus a Treadmill Supervised Exercise program in patients with Peripheral Artery Disease: Findings from the ARMEX trial

Sandra Magalhães [a,b,*], Mário Santos [b,c,d,e,f], Sofia Viamonte [g], Fernando Ribeiro [h], Joana Martins [i], Cristine Schmidt [j], Daniel Martinho-Dias [k,l,m], Henrique Cyrne-Carvalho [b,c,e,f]

[a] Department of Physical and Rehabilitation Medicine, Centro Hospitalar Universitário de Santo António, Porto, Portugal
[b] UMIB - Unit for Multidisciplinary Research in Biomedicine, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal
[c] Department of Cardiology, Centro Hospitalar Universitário de Santo António, Porto, Portugal
[d] Physiology Laboratory, Immuno-Physiology and Pharmacology Department, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal
[e] CAC ICBAS-CHUP – Centro Académico Clínico Instituto de Ciências Biomédicas Abel Salazar – Centro Hospitalar Universitário de Santo António, Porto, Portugal
[f] ITR - Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal
[g] Centro de Reabilitação do Norte, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal
[h] Institute of Biomedicine – iBiMED and School of Health Sciences, University of Aveiro, Portugal
[i] Department of Angiology and Vascular Surgery, Centro Hospitalar Universitário de Santo António, Porto, Portugal
[j] Research Centre in Physical Activity, Health and Leisure, CIAFEL, Faculty of Sport, University of Porto, Porto, Portugal
[k] Department of Community Medicine, Information and Decision in Health, Faculty of Medicine, University of Porto, Porto, Portugal
[l] CINTESIS – Center for Health Technology and Services Research, Portugal
[m] Family Health Unit Ao Encontro da Saúde, ACES Santo Tirso-Trofa, Trofa, Portugal

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ABSTRACT

Background: Peripheral artery disease (PAD) significantly affects patient prognosis, leading to a rapid decline in physical function and health-related quality of life. PAD impacts walking economy, causing higher oxygen uptake during submaximal walking, which is crucial for evaluating walking performance and aerobic endurance.

Research question: How do arm-ergometry supervised exercise training (AEx) and treadmill exercise training (TEx) compare in their effects on walking economy, and what clinical characteristics and outcomes influence the degree of this improvement?

Methods: This study is an ancillary investigation of the ARMEX trial, a single-center, single-blinded, parallel groups, noninferiority randomized clinical trial. Patients with symptomatic PAD were randomized (1:1 ratio) either to a 12-week AEx or TEx. Walking economy was measured by oxygen uptake (VO_2) during submaximal effort during the treadmill cardiopulmonary exercise test (CPET).

Results: Fifty-six patients (66 ± 8.4 years; 87.5 % male) were enrolled and randomized: AEx (n = 28) and TEx (n = 28). At 12-weeks, VO_2 at 60 until 240 s decreased only in TEx. Between-group

* Corresponding author. Department of Physical and Rehabilitation Medicine, Centro Hospitalar Universitário de Santo António, Largo Professor Abel Salazar, 4099-001, Porto, Portugal.
E-mail address: mag.sandra@gmail.com (S. Magalhães).

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differences were found at 60 until 240 s favoring TEx. Exercising in the TEx group and lower baseline body mass index (BMI) were independently associated with a greater improvement in walking economy. Changes in walking economy were inversely correlated with changes in VO_2 peak and positively correlated with CPET maximum walking distance and self-reported walking distance.

Significance: Treadmill exercise improved walking economy more than arm-ergometry in patients with PAD. Individuals with a higher BMI experience less improvement in walking economy with exercise training and might require specialized interventions.

1. Introduction

Peripheral artery disease (PAD) is a prevalent condition with significant implications for prognosis [1]. Patients with PAD experience a fast decline in physical function over time, leading to a decline in health-related quality of life [2].

Walking economy is defined as the metabolic cost of ambulation and patients with PAD have a higher oxygen uptake than predicted during submaximal walking [3]. Efficiency or oxygen cost of exercise is one of the three pivotal factors influencing aerobic endurance performance; the other two factors are maximal oxygen uptake and lactate threshold [4]. Therefore, walking economy stands as an important measure for assessing the walking performance of patients with PAD [5]. An altered gait pattern has been posited as one of the proposed underlying mechanisms for reduced economy [6]. Several studies indicate that individuals with PAD exhibit slower movement, shorter strides, decreased cadence, and compromised balance, resulting in a heightened risk of falls compared to healthy individuals [7,8]. During the gait cycle, individuals with this condition experience an extended stance phase and a reduced swing phase [7]. These impairments are evident even before the emergence of claudication pain but intensify following its onset [6]. A recent review on biomechanical research revealed that patients with PAD demonstrated a sluggish walking pattern and that they exhibited a significantly reduced forward push-off during the late stance phase [9]. The authors concluded that the evidence suggest that gait alterations primarily stem from vascular insufficiency and subsequent muscle damage [9]. Muscle weakness in specific groups, such as posterior thigh and shin muscles, has been identified [10]. The decline in strength and endurance of lower limb muscles results from histological and metabolic alterations, including muscle fiber atrophy, diminished muscle area, increased fat infiltration and decreased mitochondrial activity [11].

Supervised treadmill exercise training until claudication pain is a first-line treatment to patients with claudication. Consistently, this intervention has demonstrated significant benefits in enhancing walking distances [12]. Nonetheless, a recent scientific consensus has underscored concerns regarding the potential adverse effects of recurrent near-maximal pain on patients' adherence to the exercise program [12]. Moreover, evidence supports better adherence to non-traditional exercise programs [13], and the current guidelines already recommend walking to moderate pain as an option for exercise prescription in these patients [14,15]. The ARMEX trial (Arm-ergometry versus Treadmill Supervised Exercise on Cardiorespiratory Fitness and Walking Distances in patients with Peripheral Artery Disease) was a prospective, single-blinded randomized clinical trial comparing an arm-ergometry supervised exercise training with a standard treadmill protocol on VO_2 peak and in walking distances among patients with symptomatic PAD [16]. The primary results of the trial showed that arm-ergometry was noninferior to the standard treadmill training regarding the VO_2 peak, but treadmill training was associated with greater improvements in walking distances. However, few studies have assessed the impact of an exercise training program on walking economy in patients with PAD. Therefore, in this secondary analysis of the ARMEX trial, we aimed to compare an arm-ergometry supervised exercise training with a treadmill protocol on walking economy and identify the clinic characteristics and outcomes that were associated with walking economy improvement. We hypothesize that in patients with symptomatic PAD, supervised arm-ergometry exercise training will be as effective as the standard treadmill exercise training in improving walking economy.

2. Materials and methods

2.1. Study design

This was an ancillary study of the ARMEX trial, that was a single center, single-blind, parallel groups, noninferiority randomized clinical trial (1:1), comparing the efficacy of AEx versus TEx training on improving cardiorespiratory fitness and walking distances in patients with PAD with claudication over 12-weeks [16]. Consecutive patients with PAD with claudication referred to the Cardiovascular Rehabilitation Unit of our hospital were invited to participate in the trial by a physician and then referred to a treadmill cardiopulmonary exercise test prior to a final decision about eligibility. The enrollment occurred between January 2017 and April 2023 (the duration of the study was extended due to the COVID-19 pandemic). Eligible patients were randomized either to an arm-ergometry supervised exercise training (AEx) or a treadmill walking exercise protocol (TEx) over 12-weeks. The study was conducted according to the recommendations of the Declaration of Helsinki and approved by the Ethics Committee of Centro Hospitalar Universitário de Santo António and School of Medicine and Biomedical Sciences from University of Porto [2016-053 (047-DEFI/046-CES)]. The trial was retrospectively registered at the ISRCTN registry: ISRCTN54908548. Written informed consent was obtained from all participants. The present manuscript was structured according to the Consolidated Standards of Reporting Trials (CONSORT) Statement for randomized trials of Nonpharmacological Treatment [17].

2.2. Participants

Patients with PAD older than 18 years old referred to the Cardiovascular Rehabilitation Unit were prospectively enrolled in the trial. Inclusion and exclusion criteria were previously reported [16] and are provided in supplemental material.

2.3. Randomization and allocation

Randomization was performed with a computer-based random number generator using a 1:1 allocation ratio for block sizes of four patients. Randomization and allocation were undertaken by a member of the research team (C.S.) who was not directly involved in the recruitment or patients' assessment.

2.4. Outcomes assessments

2.4.1. Walking economy, VO_2 peak and CPET distances

Patients performed a graded cardiopulmonary exercise test (CPET), on a treadmill (Medisoft, Model 870C®), using the Gardner-Skinner protocol with a constant speed at 3.2 Km/h and a 2 % increase in grade every 2 min until the maximal claudication pain that resulting in an inability to walk any further [18]. During the CPET, participants were not allowed to hold onto the handrails while walking. Respiratory gas exchange measurements were performed with a calibrated stationary metabolic cart system (Geratherm® Respiratory Ergostik, under BLUE CHERRY®) and were obtained breath-by-breath and averaged every 30 s. Heart rate and blood pressure were recorded at regular intervals throughout the test. Walking economy was evaluated by analyzing oxygen uptake during submaximal exertion (VO_2). These assessments were carried out at 30-s intervals over a 240-s duration during the CPET, as previously described [19]. To ensure the analysis reflected submaximal effort, only VO_2 values with a corresponding Respiratory Exchange Ratio (RER) below 1.0 were included. For each patient, baseline VO_2 measured at various CPET times was compared to the VO_2 recorded at the conclusion of the intervention, conducted at the same testing time. This assessment preserved consistency in the distance covered, therefore, following the intervention, the patient with a lower VO_2 will exhibit better walking economy. Predictive equations have been developed to estimate the caloric expenditure of walking in healthy population. The American College of Sports Medicine predictive equation for walking is one of the most widely used ($VO_2 = 3.5+(0.1*speed)+(1.8*speed*grade)$) [20]. We applied this equation to compute the predicted VO_2 for every 30-s interval assessed and subsequently compared them with the values observed within our sample. Oxygen uptake (VO_2) peak was determined as the highest VO_2 achieved during the exercise test. The pain-free walking distance (PFWD) and maximal walking distance (MWD) were recorded. All the tests were interpreted by the same physician (M.S.), who remained unaware of the intervention allocation assigned to each patient.

2.4.2. Walking impairment questionnaire scores

The Walking Impairment Questionnaire (WIQ) is a PAD-specific assessment tool designed to evaluate self-reported walking limitations across three domains: walking distance (WIQd), walking speed (WIQs), and stair climbing (WIQsc) [21]. Each domain is rated on a scale from 0 to 100, where 0 signifies the highest degree of limitation, and 100 signifies no difficulty in walking long distances, walking rapidly, or climbing three flights of stairs, respectively. Patients filled out this questionnaire both before and after the intervention.

2.5. Dropout and adherence rates

Dropout rate was calculated in both groups. Adherence rate was calculated based on the number of sessions performed in relation to the number of sessions planned. Patients were asked weekly about exercise performed at home.

2.6. Interventions

Exercise sessions consisted of twice-weekly sessions comprising 10-min warm-up, 30–40 min treadmill intermittent walking or arm-ergometry, resistance exercises and 10-min cooldown, led by a physiotherapist and under medical supervision, both with experience in cardiovascular rehabilitation. A detailed description of each exercise prescription for both intervention groups was previously published [16] and is provided in supplemental material. Additionally, all patients received nutritional and psychological intervention according to the international guidelines [22]. All patients were encouraged to exercise at home at least twice weekly, for 30 min. A weekly record of unsupervised exercise was made.

2.7. Statistical analysis

The current study examined secondary outcomes of the ARMEX trial, and therefore, no sample size was calculated a priori. Data distribution was evaluated using both the Shapiro-Wilk test and via visual inspection of histograms. Continuous data are reported as mean ± standard deviation, mean differences (95 % CI) or as the median (interquartile range) and categorical data as frequencies (percentage). For the analysis of submaximal VO_2 values (every 30 s), we used paired-samples t-tests to compare within groups from baseline to 12 weeks. Differences between groups in the change from baseline to the end of the study were assessed using ANCOVA, with adjustment for baseline values.

Univariate linear regression models were applied to identify potential predictors before conducting the stepwise regression analysis. The stepwise regression model was then used to identify independent predictors (e.g., demographic data, cardiovascular risk factors, comorbidities, ankle-brachial index (ABI), PAD classification, body mass index (BMI), and exercise training group) of walking economy improvement, with VO_2 at 180 s as the outcome variable. A combination of forward selection and backward elimination methods was used. A probability of F to enter ≤ 0.05 and a probability of F to remove ≥ 0.10 were used as selection criteria for the stepwise regression procedure.

The association between changes in walking economy and changes in CPET MWD, CPET PFWD and WIQ was examined using a Pearson bivariate correlation test. The change of VO_2 at 180 s was chosen as the time point for conducting these associations, according to previous studies [23].

Statistical significance of $p < 0.05$ was assumed. IBM SPSS statistics version 29.0 (IBM Corp., Armonk, NY, USA) was used to perform statistical analyses.

3. Results

Fifty-nine patients were referred to our cardiovascular rehabilitation consultation and assessed for eligibility (Fig. 1). One patient refused to participate in the study and two patients did not meet the inclusion criteria. Fifty-six patients (66 ± 8.4 years; 87.5 % male) were enrolled and randomized: AEx (n = 28) and TEx (n = 28). Of these, 51 patients (AEx, n = 25; TEx, n = 26) completed the intervention. Four patients (AEx n = 1, TEx n = 3) were excluded from primary outcome analysis due to the absence of data (CPET was not available during a period of the COVID-19 pandemic), but they were included in the analysis of the remaining outcomes. Adherence to exercise sessions was 91.3 % (AEx: 86.9 % vs. TEx: 91.7 %; $p = 0.311$). The percentage of patients who complied with the recommendation to exercise at home was similar in both groups (AEx: 76 %; TEx: 69.2 %; $p = 0.59$). Baseline participant's characteristics were well balanced between groups and are described in Table 1.

All submaximal VO_2 values were normally distributed. At the baseline, submaximal VO_2 values (walking efficiency) were similar in both intervention groups and were higher than those predicted by the ACSM walking equation for a healthy population (Fig. 2A). After the intervention, walking economy improved in TEx, i.e. VO_2 values at 60sec until 240sec significantly decreased in TEx (Table 2) and were closer to estimated values for healthy in ACSM walking equation (Fig. 2B). In AEx group, VO_2 decreased but without statistical significance (Table 2) and was further away from estimated values for healthy (Fig. 2B). Between-groups differences were found at 60sec until 240sec favoring TEx (Table 2).

Exercise group ($r^2 = 0.411$, $p < 0.001$), obesity or overweight ($r^2 = 0.130$, $p = 0.026$) and BMI ($r^2 = 0.108$, $p = 0.044$) were significantly associated with changes in VO_2 at 180 s. In the stepwise regression analysis, only exercise in the TEx group ($\beta = 2.968$, $p <$

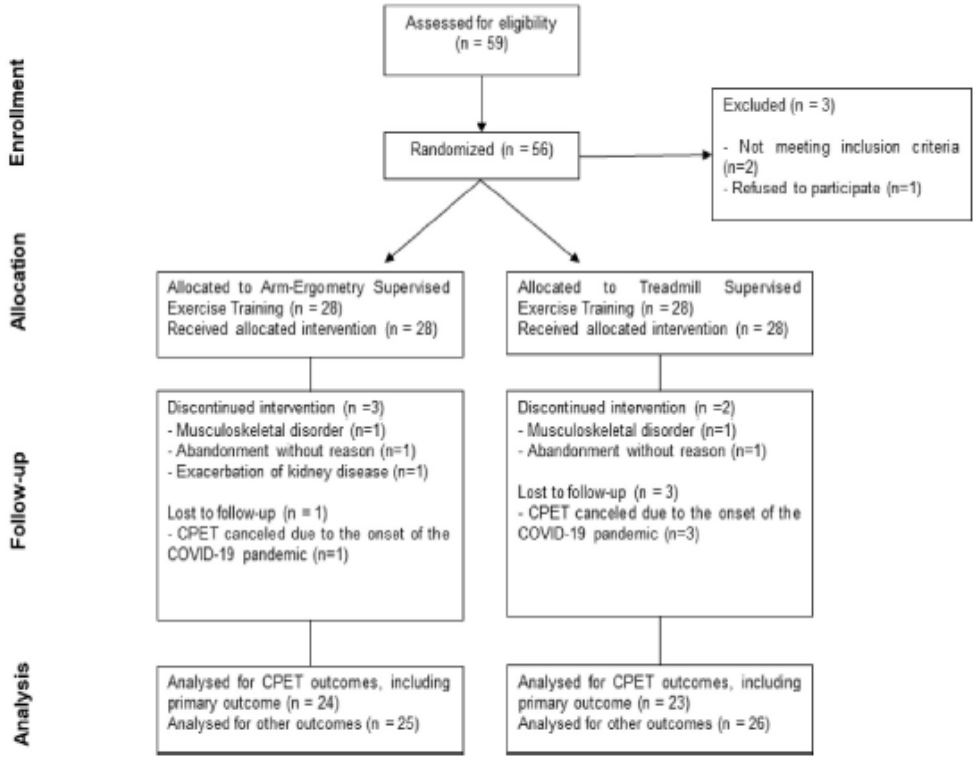

Fig. 1. Modified CONSORT flow diagram for individual randomized controlled trials of nonpharmacologic treatments. CPET: cardiopulmonary exercise test.

Table 1
Baseline characteristics overall and by exercise group.

Variable	Overall n = 56	Arm-ergometry n = 28	Treadmill n = 28
Age, y	66 ± 8.4	67 ± 7.8	64 ± 8.9
Male	49 (87.5)	25 (89.3)	24 (85.7)
Lowest resting ABI	0.66 ± 0.13	0.69 ± 0.11	0.62 ± 0.15
Prior leg revascularization	12 (21.4)	3 (10.7)	9 (32.1)
Comorbidities			
Coronary Heart disease	26 (46.4)	15 (53.6)	11 (39.3)
Cerebrovascular disease	4 (7.1)	2 (7.1)	2 (7.1)
Heart Failure	5 (8.9)	3 (10.7)	2 (7.1)
COPD	5 (8.9)	3 (10.7)	2 (7.1)
Cardiovascular risk factos			
Dyslipidemia	47 (83.9)	22 (78.6)	25 (89.3)
Diabetes mellitus	25 (44.6)	13 (46.4)	12 (42.9)
Hypertension	48 (85.7)	22 (78.6)	26 (92.9)
Physical inactivity	43 (76.8)	24 (85.7)	19 (67.9)
Obesity	10 (17.9)	5 (17.9)	5 (17.9)
Smoking status			
Current	17 (30.4)	10 (35.7)	7 (25)
Previous	34 (60.7)	17 (60.7)	17 (60.7)
Never smoked	5 (8.9)	1 (3.6)	4 (14.3)
Medication			
Acetyl-salicylic acid	47 (83.9)	22 (78.6)	25 (89.3)
Statins	56 (100)	28 (100)	28 (100)
Beta-blockers	35 (62.5)	21 (75)	14 (50)
ACEi/ARB	43 (76.8)	21 (75)	22 (78.6)
Antiplatelet agent	18 (32.1)	10 (35.7)	8 (28.6)
Anticoagulants	10 (17.9)	7 (25)	3 (10.7)
Pentoxifylline	14 (25)	7 (25)	7 (25)
Cilostazol	6 (10.7)	2 (7.1)	4 (14.3)

Data are mean ± SD or n (%). ABI: ankle-brachial index; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; COPD: chronic obstructive pulmonary disease.

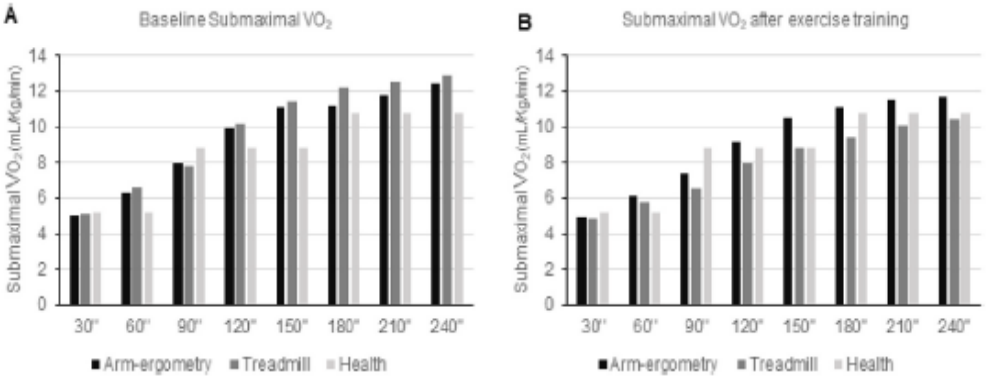

Fig. 2. Walking Economy (assessed by submaximal oxygen uptake at 30-s periods during the cardiopulmonary exercise test)) compared against values predicted using the American College of Sports Medicine equations for a typical healthy population. A: baseline evaluation; B: Evaluation after 12 weeks of supervised exercise training. VO_2: oxygen uptake.

0.001) and BMI ($\beta = 0.186$, $p = 0.014$) remained significant predictors, accounting for 50.5 % of the improvement in walking economy. The regression equation was Y (changes in VO_2 at 180 s) = −8.119 + 2.968 x Group (TEx = 0, AEx = 1) + 0.186 x BMI.

Change in walking economy exhibited an inverse correlation with the change in VO_2 peak and a positive correlation with CPET MWD and WIQd (Table 3).

4. Discussion

To the best of our knowledge, this is the first study that compared walking economy after an arm-ergometry exercise training program versus a treadmill exercise protocol across different time points during the submaximal oxygen uptake assessment in patients with PAD. Previously, this type of evaluation was considered a more detailed analysis compared to assessing walking economy at a single time point during a test [19]. The single-point evaluation increases the probability of patients heavily relying on anaerobic pathways and hyperventilation, potentially compromising the determination of energy expenditure [19]. At baseline, consistent with

Table 2
Submaximal VO_2 at 30 s until 240 s in both intervention groups.

	Arm-ergometry n = 24			Treadmill n = 23			Unadjusted[a] Between-group Difference in Change	*p* value[a]	Baseline adjusted[b] Between-group Difference in Change	*p* value[b]
	Baseline	Final	Change from baseline	Baseline	Final	Change from baseline				
Submaximal VO_2										
VO_2 *30″*	4.98 ± 1.31	4.97 ± 1.14	−0.02 ± 1.32	5.07 ± 0.80	4.83 ± 0.66	−0.27 ± 0.78	0.25 (−0.88 – 0.38)	0.428	0.20 (−0.3 – 0.7)	0.428
VO_2 *60″*	6.32 ± 1.15	6.10 ± 0.94	−0.18 ± 1.15	6.61 ± 1.29	5.75 ± 1.01*	−0.9 ± 1.04	0.72 (0.082–1.36)	0.028	0.51 (0.008–1.02)	0.047
VO_2 *90″*	7.95 ± 1.54	7.4 ± 1.47	−0.47 ± 1.34	7.81 ± 1.5	6.55 ± 0.87*	−1.33 ± 1.33	0.86 (0.077–1.64)	0.032	0.84 (0.23–1.45)	0.009
VO_2 *120″*	9.9 ± 1.98	9.18 ± 1.98	−0.44 ± 1.88	10.2 ± 1.9	8.00 ± 1.0*	−2.39 ± 1.51	1.95 (0.89–3)	<0.001	1.5 (0.6–2.41)	0.002
VO_2 *150″*	11.07 ± 2.17	10.49 ± 2.18	−0.58 ± 1.84	11.42 ± 2.04	8.84 ± 1.11*	−2.73 ± 1.7	2.15 (1.02–3.27)	<0.001	1.9 (0.99–2.81)	<0.001
VO_2 *180″*	11.19 ± 2.16	11.11 ± 2.30	−0.08 ± 1.57	12.23 ± 2.27	9.45 ± 1.33*	−2.96 ± 2.08	2.89 (1.7–4.07)	<0.001	2.31 (1.25–3.36)	<0.001
VO_2 *210″*	11.78 ± 1.98	11.51 ± 2.21	−0.27 ± 1.80	12.53 ± 2.25	101.1 ± 1.06*	−2.69 ± 1.99	2.42 (1.07–3.77)	<0.001	1.79 (0.64–2.95)	0.003
VO_2 *240″*	12.5 ± 2.13	11.71 ± 2.23	−0.79 ± 1.72	12.86 ± 2.18	10.4 ± 1.44*	−2.64 ± 1.9	1.86 (0.52–3.20)	0.008	1.49 (0.32–2.66)	0.014

Data are mean ± SD or mean (95 % CI). *Significantly different from baseline, $p < 0.05$.
[a] Treatment difference and *p* value from unpaired *t*-test.
[b] Treatment difference and *p* value from ANCOVA model, adjusting for baseline value. VO_2: submaximal oxygen uptake.

Table 3
Associations between changes in the walking economy (change in VO_2 180) and changes in peak oxygen uptake, walking distances and self-reported walking limitations.

Change in outcomes	Change in VO_2 180[a]					
	Overall n = 41		Arm-ergometry n = 19		Treadmill n = 22	
	r	*p value*[a]	*r*	*p* value	*r*	*p value*[a]
VO_2 peak	0.48	0.003	0.60	0.011	0.46	0.036
CPET MWD	−0.35	0.034	−0.05	0.837	−0.21	0.368
CPET PFWD	−0.24	0.142	−0.09	0.708	−0.09	0.719
WIQd	−0.39	0.017	−0.22	0.389	−0.29	0.195
WIQs	−0.03	0.843	0.07	0.780	0.03	0.915
WIQsc	0.14	0.408	−0.14	0.591	0.19	0.423

MWD: maximal walking distance; PFWD: pain-free walking distance; VO2: oxygen uptake; WIQ: walking impairment questionnaire; WIQd: WIQ distance; WIQs: WIQ speed; WIQsc: WIQ stair climbing.
[a] *p value* from Pearson bivariate correlation test. CPET: cardiopulmonary exercise test

findings from other studies in this population, both intervention groups exhibited higher submaximal VO_2 values than predicted [3]. We demonstrated a significant and superior improvement in walking economy after a 12-week treadmill exercise training program. Few studies have evaluated walking economy after treadmill exercise training in patients with PAD and the majority have reported results consistent with ours [19,24]. We identified two studies that analyzed submaximal oxygen uptake following arm-ergometry exercise training in a population with PAD, and similarly, the authors did not observe a significant improvement in this parameter [23,25]. Additionally, we found a significant and superior improvement in walking distances in the treadmill group [16]. Maximal walking distance evaluated in CPET and self-reported walking distance were correlated with improvements in walking economy. Consequently, the enhancement in walking distances following the 12-week treadmill exercise program can be partially attributed to the improvement in walking economy. Previous trials have outlined that the enhancement in walking performance during the initial weeks following treadmill exercise training was more related to an improvement in walking economy, particularly due to an enhancement in gait biomechanics, while later improvements were more associated with an increase in VO_2 peak [26,27].

The improvement in walking distances after a 12-week arm-ergometry exercise program cannot be explained by the same mechanism, since, as mentioned previously, we did not find an improvement in walking economy in this group. These results corroborate previous findings in healthy individuals, suggesting that cross-transfer effects (i.e., improved exercise performance during activities involving untrained limbs) primarily stem from central mechanisms. Conversely, non-transferable effects are likely attributable to adaptations within the trained muscles, thus accounting for local adaptations [28]. A trial that studied cross-transfer effects in patients with claudication after an arm-ergometry exercise training program demonstrated that the enhancement in walking performance was coupled with improved oxygen delivery to the lower limbs [25]. We observed that 12 weeks of arm-ergometry exercise training led to a significant improvement in VO_2 peak, whereas the increase in the treadmill group did not reach statistical significance [16]. Other studies conducted on this population support the observed increase in VO_2 peak following arm-ergometry [29]. We found a negative correlation between improvement in walking economy and changes in VO_2 peak. This inverse relationship has been documented in other populations and appears to be partly influenced by fiber type distribution (type I muscle fibers are associated with improved exercise economy, while type II muscle fibers are linked to reduced economy); however, additional factors, such as walking biomechanics, have also been suggested to potentially play a significant role [30,31]. Therefore, the improvement in walking performance after 12 weeks of arm-ergometry exercise training is likely more closely associated with an increase in VO_2 peak, potentially reflecting either an augmentation in muscle oxygen delivery or an enhancement in muscle oxidative metabolism. Further research is necessary to elucidate the mechanisms underlying improvements in walking performance among patients with PAD following both modalities of exercise training. Nonetheless, the findings of this study offer a contribution to the existing body of knowledge on this topic by highlighting potential distinct pathways through which these training modalities may enhance walking performance.

Patients with a higher BMI experienced less improvement in walking economy with exercise training. Consequently, exploring alternative exercise modalities, such as arm-ergometry, which enhance walking distances through mechanisms other than walking economy, could offer greater potential benefits for some of these patients. Both exercise interventions demonstrate improvements in different outcomes that influence walking performance among individuals with PAD. Future research should explore the potential synergistic effects of combining these interventions to enhance overall therapeutic benefits.

4.1. Limitations of the study

This was an ancillary study, therefore, our sample size was calculated based on expected improvement in the primary endpoint (VO_2 peak) derived from previously published data, rather than being specifically tailored for this outcome. Further studies with a larger sample size will be necessary to support our findings regarding this outcome. All patients enrolled in the study presented with claudication (Fontaine stage II), implying that the findings may not be applicable or representative of other stages of the disease. To conduct a more accurate assessment of walking economy, employing a steady-state exercise protocol would be preferable. However, previous studies have demonstrated that in some patients with PAD, despite the exercise intensity remaining constant in such protocols, there is an increase in oxygen uptake, hindering the attainment of a true steady-state condition [6]. Future research should

include both exercise test protocols to comprehensively assess this outcome. Additionally, we must acknowledge that the effects observed in this study may be partly explained by adaptation to treadmill familiarization.

5. Conclusion

Treadmill exercise improved walking economy more than arm-ergometry in symptomatic patients with PAD. The observed enhancement in walking distances after the treadmill exercise program can be attributed, at least partially, to the improvement in walking economy. Patients with a higher BMI showed less improvement in walking economy following exercise training, highlighting the need for tailored attention and specialized interventions in their care.

CRediT authorship contribution statement

Sandra Magalhães: Writing – original draft, Formal analysis, Data curation, Conceptualization. Mário Santos: Writing – review & editing, Validation, Supervision, Conceptualization. Sofia Viamonte: Writing – review & editing, Conceptualization. Fernando Ribeiro: Writing – review & editing, Formal analysis. Joana Martins: Writing – review & editing, Supervision. Cristine Schmidt: Writing – review & editing, Methodology. Daniel Martinho-Dias: Formal analysis, Data curation. Henrique Cyrne-Carvalho: Writing – review & editing, Validation, Supervision, Conceptualization.

Ethics approval and consent to participate

The trial was approved by the Ethics Committee of Centro Hospitalar Universitário de Santo António and School of Medicine and Biomedical Sciences from University of Porto [2016-053(047-DEFI/046-CES)]. Written informed consent was obtained from all participants.

Data availability statement

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e42275.

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Effect of arm-ergometry versus treadmill supervised exercise on health-related quality of life and mental health in patients with peripheral artery disease: secondary outcomes from the ARMEX trial

Sandra Magalhães[1,2*], Mário Santos[2,3,4,5,6], Sofia Viamonte[7], Fernando Ribeiro[8], Joana Martins[9], Cristine Schmidt[10] and Henrique Cyrne-Carvalho[2,3]

Abstract

Background Peripheral artery disease (PAD) negatively affects walking performance, health-related quality of life (HRQoL) and mental health. Exercise training is recommended as a first-line treatment for PAD, with potential impact on all these outcomes, but the optimal program design is not completely ascertained. The aim of this study was to compare arm-ergometry (AEx) and treadmill supervised exercise training (TEx) on HRQoL and mental health in patients with PAD.

Methods This was an ancillary study of the ARMEX trial, a single-center, single-blinded, parallel group, randomized clinical trial, enrolling symptomatic PAD patients referred to a cardiovascular rehabilitation program (CRP). Participants were randomized (1:1) to a 12-week AEx or TEx, along with the core components of a CRP (nutritional and psychological support). Participants completed the short form 36 Health Survey and the Hospital Anxiety and Depression scale before and after the intervention. Differences between groups in the change from baseline to the end of the study were analyzed using ANCOVA, adjusted for baseline values, or the Mann-Whitney U test.

Results Fifty-six patients (66 ± 8.4 years; 87.5% male) were included: AEx ($n = 28$) and TEx ($n = 28$). Physical functioning, role-physical, bodily-pain, general health, mental health and physical component summary (PCS) significantly improved in AEx group. In the TEx group, physical functioning, role-physical, bodily-pain, vitality, social functioning, role-emotional and PCS significantly improved. Role-physical and role-emotional improved more in TEx, with no between-group differences in the other domains. Changes in PCS were significantly associated with changes in walking distances. Hospital Anxiety and Depression scale scores improved in both groups, without between-group differences. This improvement was associated with self-reported walking distance.

*Correspondence:
Sandra Magalhães
mag.sandra@gmail.com

Full list of author information is available at the end of the article

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Conclusion Both exercise protocols improved HRQoL and mental health in patients with symptomatic PAD, highlighting exercise-based programs as important treatment strategies for this population.

Trial registration number ISRCTN54908548 (retrospectively registered).

Keywords Cardiovascular rehabilitation, Exercise therapy, Intermittent claudication, Mental health, Peripheral artery disease, Quality of life

Introduction

Peripheral artery disease (PAD) is a prevalent condition associated with adverse clinical outcomes, including decreased physical fitness and impaired functional status [1].

Health-related quality of life (HRQoL) is a multidimensional concept that reflects an individual's subjective assessment of their physical, mental, emotional, and social well-being and functioning [2]. Previous research has shown that patients with PAD experience diminished HRQoL, similar to that of individuals with other cardiovascular conditions [3]. Poor HRQoL predicts long-term survival in this population, providing prognostic value beyond established biomedical risk factors [4]. A recent statement highlighted the importance of incorporating HRQoL assessment in treatment outcomes for all symptomatic PAD patients, to ascertain whether therapies that improve exercise performance also enhance patient's perception of improvement in the performance of daily life activities [5].

Due to the chronic debilitating nature of PAD, mental health conditions such as depression and anxiety are also more prevalent [6]. The PORTRAIT registry, a multicenter international study, enrolled 1275 patients with PAD and reported a 14.1% prevalence of depression symptoms and 8.3% prevalence of anxiety [6]. Patients at a higher risk of mental health issues were typically younger, female, financially strained, with less social support and worse perceived health status [6]. The increased mental health burden in PAD has been shown to negatively impact outcomes, including health status trajectories, post-revascularization results, and the risk of amputation, long-term mortality, and cardiovascular events [7]. As a first-line treatment, exercise training requires a lifestyle change, and mental health issues can hinder individuals' ability to adhere to exercise regimens and effectively manage their chronic condition [8]. It has been established that evaluating mental health in clinical practice is crucial, and addressing these conditions should be an integral component of comprehensive PAD management [7]. Therefore, promoting therapeutic strategies that enhance HRQoL and mental health in patients with PAD becomes essential, and supervised walking exercise has previously been demonstrated to improve HRQoL in this clinical setting [9, 10]. A meta-analysis suggested that exercise training may be effective in alleviating anxiety and depression symptoms in patients with coronary heart disease [11]. However, there is a lack of studies in the literature that have evaluated the impact of exercise training on mental health in patients with PAD. Cardiovascular rehabilitation (CR) is a multidisciplinary intervention with well-recognized core components, and a position paper from the European Society of Cardiology recognizes PAD as a qualifying diagnosis for this type of intervention [12]. However, only a small percentage of patients with PAD are currently referred to CR, typically when they have additional cardiovascular conditions [13]. The evidence for CR programs (CRP) in patients with PAD remains limited due to the lack of randomized controlled trials [14].

Several researchers emphasized the importance of conducting high-quality intervention trials that compare different exercise modalities and identify the most effective elements for improving outcomes in symptomatic PAD patients [10, 15]. The ARMEX trial (Arm-ergometry versus Treadmill Supervised Exercise on Cardiorespiratory Fitness and Walking Distances in patients with Peripheral Artery Disease) was a prospective, single-blind, randomized clinical trial comparing arm-ergometry supervised exercise training with a standard treadmill protocol on peak oxygen consumption (VO_2 peak) and in walking distances among patients with symptomatic PAD [16]. The primary results of this trial indicated that arm-ergometry was noninferior to treadmill training for VO_2 peak, but treadmill training led to greater improvements in walking distances [16]. However, there is limited data on the impact of these different exercise modalities on HRQoL and mental health. The pain experienced by patients using the standard treadmill protocol has been identified as a potential barrier to adherence [17]. Additionally, evidence suggests that patients with PAD demonstrate better adherence to exercise programs that do not involve pain [18]. Arm-ergometry appears to be a promising modality for improving both HRQoL and mental health in these patients, as it does not cause pain and has been shown to promote pleasurable feelings in this population [19]. Given this background, we aimed to compare the effects of an arm-ergometry supervised exercise training protocol with a treadmill protocol on HRQoL and mental health in symptomatic PAD patients. This study derived from a pre-specified secondary analysis of the ARMEX trial. Additionally, this explanatory analysis sought to

assess the relationships between intervention-induced changes in the physical component score of short form 36 Health Survey (SF-36) and walking performance outcomes, as well as the relationships between intervention-induced changes in Hospital Anxiety and Depression scale (HADS) scores and walking performance outcomes.

Methods

Study design

The ARMEX trial was a prospective single-center, single-blind, parallel group, noninferiority randomized clinical trial (1:1), comparing the efficacy of arm-ergometry (AEx) versus treadmill exercise (TEx) training on improving cardiorespiratory fitness and walking distances in PAD patients with intermittent claudication over 12-weeks [16]. The current study encompasses a pre-specified secondary analysis from this randomized clinical trial.

PAD patients with intermittent claudication consecutively referred to our hospital's Cardiovascular Rehabilitation Unit were recruited. Eligible patients underwent a treadmill cardiopulmonary exercise test (CPET) before a final decision regarding final eligibility and randomization was made. The enrollment occurred between January 2017 and April 2023.

Eligible patients were randomized either to an arm-ergometry supervised exercise training (AEx) or a treadmill walking exercise protocol (TEx) over 12-weeks. The study was conducted according to the recommendations of the Declaration of Helsinki and with approval from the Ethics Committee of Centro Hospitalar Universitário de Santo António and School of Medicine and Biomedical Sciences at the University of Porto [2016-053(047-DEFI/046-CES)]. All participants provided written informed consent prior to their inclusion in the study. The current manuscript was organized following the guidelines outlined in the Consolidated Standards of Reporting Trials (CONSORT) Statement for randomized trials of nonpharmacological treatments [20].

Participants

Adults aged 18 years and above diagnosed with symptomatic PAD and referred to the Cardiovascular Rehabilitation Unit were recruited. The criteria for inclusion and exclusion were previously described [16].

Randomization and allocation

As previously reported [16], randomization was performed with a computer-based random number generator using a 1:1 allocation ratio for block sizes of four patients. Randomization and allocation were undertaken by a member of the research team (C.S.) who was not directly involved in the recruitment or patients' assessment.

Outcomes

Health-related quality of life

To evaluate HRQoL the SF-36 was use, considering the eight domain scores. Four of the subscales are related to physical health: physical functioning (PF), role physical (RP), bodily pain (BP) and general health (GH); and the remaining four scales are related to mental health: vitality (VT), role emotional (RE), social functioning (SF) and mental health (MH). Domain scores range between 0 and 100, with higher scores reflecting better QoL. These scores were Z-transformed and weighted to calculate physical component summary (PCS) and mental component summary (MCS) scores [21].

Anxiety and depression

Patient-reported symptoms of anxiety and depression were measured using the HADS [22]. This questionnaire comprises seven questions for anxiety and seven questions for depression that score for two different subscales: anxiety (HADS-A) and depression (HADS-D). Each item is answered by the patient on a four-point (0–3) response category so the possible scores ranged from 0 to 21 for each one subscale. Lower scores reflect a lower symptom presence [23].

Walking performance outcomes

The assessment of CPET walking outcomes and 6-minute walk test (6MWT) distances was conducted as previously described [16].

Dropout and adherence rate

Dropout rate was calculated in both groups. Adherence rate was calculated based on the number of sessions performed in relation to the number of sessions planned.

Interventions

Exercise sessions consisted of twice-weekly sessions comprising 10-min warm-up, 30 to 40 min treadmill intermittent walking or arm-ergometry, resistance exercises and 10-min cooldown, led by a physiotherapist under medical supervision. All patients were monitored with an electrocardiographic telemetry system during the sessions, ensuring that all safety protocols for the intervention were followed. A detailed description of the exercise prescriptions for both intervention groups has been previously reported [16]. Additionally, all patients received nutritional individual counselling and psychological intervention (weekly group sessions) according to the international guidelines for the core components of an outpatient CRP [12]. All patients were encouraged to exercise at home at least twice a week for 30 min. Patients were asked weekly about exercise performed at home. It was made a record of the mode and time of exercise realized. Patients were considered to have performed

unsupervised exercise if they completed moderate-intensity exercise for at least 30 min per session for at least 2x/week. Recorded exercise was analyzed as a dichotomous variable (yes or no).

Statistical analysis

The present study investigated secondary outcomes of the ARMEX trial, thus, no sample size was calculated a priori. The distribution of the data was assessed with the Shapiro-Wilk test and via visual inspection of histograms. Continuous data are reported as mean ± standard deviation, mean differences (95% CI) or as the median (interquartile range) and categorical data as frequencies (percentage). For within-group comparisons, from baseline to 12 weeks, were performed paired-samples t test or Wilcoxon signed-rank test. Differences between groups in the change from baseline to the end of the study were tested using ANCOVA, adjusting for baseline value or Mann-Whitney U test.

To assess the relationships between changes in the physical component score of SF-36, changes in HADS scores, and changes in walking performance outcomes after the intervention, the Pearson correlation test was used for variables with a normal distribution, while the Spearman Correlation test was employed for variables with a non-normal distribution.

Statistical significance of $p<0.05$ was assumed. IBM SPSS statistics version 29.0 (IBM Corp., Armonk, NY, USA) was used to perform statistical analyses.

The effect size for the outcomes was calculated using appropriate statistical methods. For normally distributed variables, effect size was determined using partial eta squared (η^2) from the ANCOVA. For non-normally distributed variables, effect size was calculated based on the Mann-Whitney U test. Additionally, a post-hoc power analysis was conducted using G*Power 3.1 to assess the observed power of the statistical tests performed.

Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

Fifty-nine patients referred to CR consultation were assessed for eligibility (Fig. 1). One patient refused to participate in the study and two patients did not meet the inclusion criteria. Fifty-six patients (66 ± 8.4 years; 87.5% male) were enrolled and randomized into two groups: AEx ($n=28$) and TEx ($n=28$). Of these, 51 patients (AEx, $n=25$; TEx, $n=26$) completed the intervention. As shown in Fig. 1, three patients in the AEx group discontinued the exercise program: one due to an exacerbation of lumbar spondyloarthritis, one due to an exacerbation of chronic kidney disease, and one for an unknown reason. In the TEx group, two patients discontinued the intervention: one due to an exacerbation of hip osteoarthritis, and one for an unknown reason.

Exercise session adherence was 91.3% (AEx: 86.9% vs. TEx: 91.7%; $p=0.311$). The percentage of patients who complied with the recommendation to exercise at home was also similar in both groups (AEx: 76%; TEx: 69.2%; $p=0.59$). No adverse events were reported during the exercise sessions for any of the patients included in this analysis. Baseline participants' characteristics and between-group comparisons are described in Table 1.

At baseline, in both groups, the four domains of the SF-36, related to physical health (PF, RP, GH and BP) had lower scores than the four subscales related to mental health (VT, SF, RE and MH). These results are depicted in Table 2. After the 12-week exercise training intervention, PF, RP, BP, GH and MH increased significantly in the AEx group, and PF, RP, BP, VT, SF and RE increased significantly in the TEx group. RP and RE improved more in TEx, with no between-group differences in the other domains (Table 2; Fig. 2). The PCS increased in both groups, without between-group differences (1.39; 95% CI, -1.69 to 4.47; $p=0.368$) (Table 2; Fig. 2); the MCS remained unchanged in both groups, without between-groups difference (1.45; 95% CI, -3.29 to 6.20; $p=0.541$). Change in PCS was significantly associated with changes in CPET pain-free walking distance (PFWD) ($r=0.294$, $p=0.043$), 6MWT maximal walking distance (MWD) ($r=0.351$, $p=0.012$) and Walking Impairment Questionnaire distance (WIQd) ($r=0.312$, $p=0.026$).

HADS-A and HADS-D scores improved in both groups, without between-group differences (0.21; 95% CI, -1.03 to 1.44; $p=0.741$ and 0; 95% CI, -1 to 2; $p=0.509$, respectively) (Table 2; Fig. 2). Changes in HADS-A and HADS-D were associated with changes in WIQd (r = -0.352, $p=0.011$ and r = -0.353, $p=0.011$, respectively).

Discussion

At baseline, the SF-36 domains related to physical health exhibited lower scores compared to the mental health domains in both intervention groups, consistent with findings from previous studies conducted on PAD population [24]. Few studies have investigated the HRQoL following a 12-week exercise program and reported on the SF-36 domain scores among patients with PAD. We showed a significant improvement in the four physical health domains (PF, RP, BP and GH) as well as in one mental health domain (MH) following a 12-week arm-ergometry exercise program. Two previous trials have evaluated HRQoL after arm-ergometry exercise training in PAD patients. One study [25], conducted over 6 weeks, showed a significant enhancement of PF and RF domains. In the other study [26], at the 6-week follow-up,

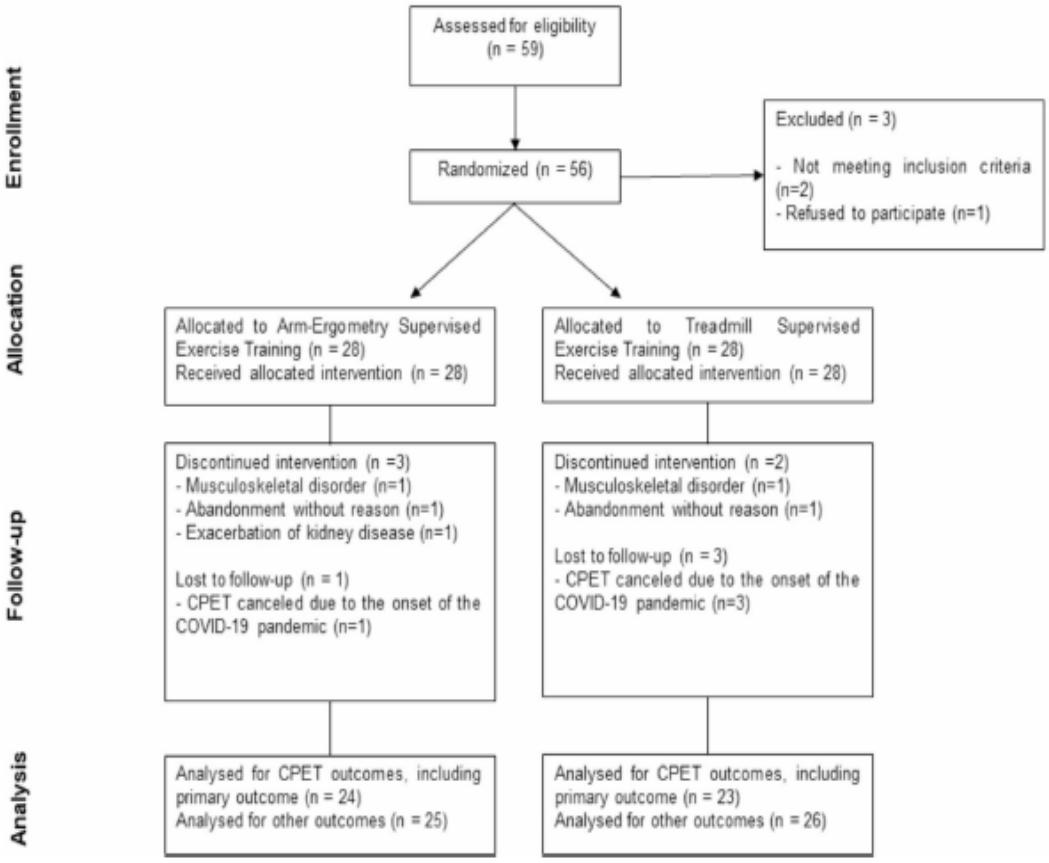

Fig. 1 Modified CONSORT flow diagram for individual randomized controlled trials of nonpharmacologic treatments. Abbreviations: CPET = cardiopulmonary exercise test

no improvement was observed in any domain, but after 24 weeks, significant enhancements were found in PF, BP, GH, VT and MH. To the best of our knowledge, this is the first study to report these results after a 12-week arm-ergometry exercise training; early improvements in HRQoL domains are crucial, as they could significantly impact patient exercise adherence.

In TEx group, a significant improvement in three physical health domains (PF, RP, BP) and three mental health domains (VT, SF, RE) was observed. A meta-analysis encompassing randomized controlled trials comparing exercise versus usual care in PAD patients revealed improvements after a 12-week treadmill exercise in PF, RP and VT domains (2 trials) [9]. A significant increase in most SF-36 domains within both intervention groups was observed in the present trial. These positive results may be related to the incorporation of balance and coordination exercises during the warm-up and cool-down phases of the rehabilitation exercise program, as well as resistance training. A previous trial involving PAD patients demonstrated that the four most significant predictors of the physical function subscale of HRQoL were all patient-based measures of physical function: WIQ speed score, history of stumbling while walking, WIQ stair climbing score, and activities of daily living, specifically bathing [24]. Therefore, incorporating balance and coordination exercises along with resistance training may reduce the risk of falling, enhance autonomy, improve walking speed, and enhance stair climbing abilities, all of which can significantly contribute to improving HRQoL in this population.

The PCS showed a statistically and clinically [27] meaningful improvement in both intervention groups, whereas the increase in MCS did not reach statistical significance. Other studies support our findings [10]. To the best of our knowledge, this is also the first study that compared the HRQoL of PAD patients who performed an arm-ergometry exercise training protocol versus a treadmill protocol. Only RF and RE domains improved more in TEx group, but we must highlight that no significant between-group differences were observed in PCS and MCS subscores. Arm-ergometry appears to be an alternative exercise modality that can enhance HRQoL in the PAD population. The change in the PCS after exercise training correlated with treadmill pain-free walking distance but showed stronger associations with the

Table 1 Baseline characteristics overall and for the two exercise groups

Variable	Overall *n* = 56 Mean ± SD or *n* (%)	Arm-ergometry *n* = 28 Mean ± SD or *n* (%)	Treadmill *n* = 28 Mean ± SD or *n* (%)
Age, years	66 ± 8.4	67 ± 7.8	64 ± 8.9
Male, %	49 (87.5)	25 (89.3)	24 (85.7)
Lowest resting ABI	0.66 ± 0.13	0.69 ± 0.11	0.62 ± 0.15
Prior leg revascularization, %	12 (21.4)	3 (10.7)	9 (32.1)
Comorbidities, %			
Coronary Heart disease	26 (46.4)	15 (53.6)	11 (39.3)
Cerebrovascular disease	4 (7.1)	2 (7.1)	2 (7.1)
Heart Failure	5 (8.9)	3 (10.7)	2 (7.1)
COPD	5 (8.9)	3 (10.7)	2 (7.1)
Cardiovascular risk factors, %			
Dyslipidemia	47 (83.9)	22 (78.6)	25 (89.3)
Diabetes mellitus	25 (44.6)	13 (46.4)	12 (42.9)
Hypertension	48 (85.7)	22 (78.6)	26 (92.9)
Physical inactivity	43 (76.8)	24 (85.7)	19 (67.9)
Obesity	10 (17.9)	5 (17.9)	5 (17.9)
Smoking status			
Current	17 (30.4)	10 (35.7)	7 (25)
Previous	34 (60.7)	17 (60.7)	17 (60.7)
Never smoked	5 (8.9)	1 (3.6)	4 (14.3)
Medication, %			
Acetyl-salicylic acid	47 (83.9)	22 (78.6)	25 (89.3)
Statins	56 (100)	28 (100)	28 (100)
Beta-blockers	35 (62.5)	21 (75)	14 (50)
ACEi /ARB	43 (76.8)	21 (75)	22 (78.6)
Antiplatelet agent	18 (32.1)	10 (35.7)	8 (28.6)
Anticoagulants	10 (17.9)	7 (25)	3 (10.7)
Pentoxifylline	14 (25)	7 (25)	7 (25)
Cilostazol	6 (10.7)	2 (7.1)	4 (14.3)

Abbreviations ABI = ankle-brachial index; ACEI = angiotensin receptor blockers; COPD = chronic obstructive pulmonary disease; SD = standard deviation

6-minute maximum walking distance and self-reported walking distance in the WIQ questionnaire. These results are consistent with previous findings, which suggest a stronger correlation between the improvement in HRQoL and the enhancement in walking performance observed in the 6-minute walk test and the self-reported distance in the WIQ questionnaire [28, 29]. The 6-minute walk test is potentially more reflective of typical walking activities performed daily compared to walking on a treadmill [28, 29].

HADS-A and HADS-D scores improved significantly in both groups after the intervention, without differences between groups. The association of mental symptoms of anxiety and depression with cardiovascular disease is widely recognized and affects prognosis and adherence to treatment [30]. Some reports have also shown a high prevalence of emotional distress in PAD patients, possibly influencing prognosis [31, 32]. Few studies have reported the impact of exercise interventions on anxiety and depression in the PAD population. A previous trial demonstrated no improvement in HADS scores after a community CR program [33]. However, unlike our study, that program did not include a specialized psychological evaluation and intervention [33]. One trial pointed out that the minimal clinically important difference for both HADS anxiety and depression scores, in patients with cardiovascular disease is 1.7 [34]. In present trial, a higher increase was found in both intervention groups for anxiety and depression scores. This improvement was related to the enhancement in self-reported walking distance. Therefore, the improvement in mental symptoms appears to be more closely linked to the individual's perception of enhanced walking ability in daily life rather than to more objective measures of walking performance.

Limitations

This was a secondary analysis, and as such, our sample size was determined based on the expected improvement in the primary endpoint (VO_2 peak) of the ARMEX trial and not specifically calculated for these outcomes. The small sample size for evaluating these outcomes and the overrepresentation of males must be addressed, as they limit the generalizability of the results. The male predominance is a significant concern, as it may not fully reflect the outcomes of the broader population, including females with PAD, for whom sex-based differences in response to supervised exercise therapy have been reported in the literature [35]. Therefore, the findings of this study may not be fully applicable to women or other demographic groups, such as older adults or those from different ethnic backgrounds.

For evaluating HRQoL, we used a generic instrument. However, incorporating a disease-specific survey instrument, such as the short version of the Vascular Quality of Life Questionnaire (VascuQoL6), would have provided a more accurate and relevant assessment, in accordance with recent guidelines [14]. We did not assess the improvement in autonomy in activities of daily living or the risk of falling. Future studies should incorporate performance tests and/or patient-reported outcome measures that address these factors, as they are crucial determinants of HRQoL in this population. Other mental health concerns, such as cognitive performance, sleep disturbances, and attention-deficit/hyperactivity disorders, are also recognized as important outcomes but were not addressed in this study. Future research should involve longer follow-up periods and focus on recruiting a more diverse population, including both sexes, a broader age range, and different ethnic and socioeconomic groups, to enhance the generalizability of the findings. Moreover, it is important to consider factors such as patient preference, exercise adherence, and the

Table 2 Effects of arm-ergometry and treadmill exercise training on SF-36v2 and HADS and groups differences

	Arm-ergometry $n=25$			Treadmill $n=26$			Between-group Difference in Change[a]	p value[a]	Effect Size (Partial Eta Squared η^2)	Observed Power
	Baseline	Final	Change from baseline	Baseline	Final	Change from baseline				
SF-36										
Physical functioning	41.82 ± 15.5	53.8 ± 16.41*	11.98 ± 18.75	44.62 ± 18.81	55.58 ± 18.13*	10.96 ± 13.71	0.23 (-8.1–8.48)	0.955	0.00	0.05
Role-physical†	0 (50)	25 (100)*	0 (25)	0 (25)	37.5 (81.25)*	25 (50)	25 (0–25)††	0.022[b]	0.32	0.19
Bodily-pain†	41(40)	52 (36.5)*	11 (24.5)	41 (30.5)	54.5 (33)*	10 (19.5)	1.75 (-5.5–14)††	0.529[b]	0.09	0.06
General health	36.88 ± 14.45	42.72 ± 13.26*	5.84 ± 12.09	44.73 ± 18.7	45.96 ± 20.72	1.23 ± 15.43	2.25 (-5.33–9.83)	0.553	0.01	0.05
Vitality†	45 (17.5)	50 (17.5)	5 (12.5)	45 (20)	55 (22.5)*	5 (15)	5 (-5–10)††	0.281[b]	0.15	0.08
Social functioning†	62.5 (31.25)	75 (43.75)	12.5 (18.75)	62.5 (25)	75 (27.67)*	12.5 (25)	0 (-12.5–12.5)††	0.779[b]	0.04	0.05
Role-emotional†	33.33 (100)	33.33 (100)	0 (0)	50 (34)	83.5 (41.7)*	16.5 (33.33)	0 (0–33.3)††	0.045[b]	0.28	0.16
Mental health†	52 (30)	68 (24)*	4 (12)	56 (32)	64 (29)	0 (9)	0 (-8–4)††	0.522[b]	0.09	0.06
Physical component summary	31.82 ± 7.64	36.25 ± 7.83*	4.44 ± 5.54	32 ± 8.09	37.78 ± 7.99*	5.78 ± 6.03	1.39 (-1.69–4.47)	0.368	0.02	0.05
Mental component summary	43.81 ± 11.87	45.76 ± 9.82	1.95 ± 7.39	44.42 ± 9.4	47.83 ± 9.23	3.41 ± 9.32	1.71 (-2.38–5.8)	0.405	0.02	0.05
HADS										
HADS – A	8.2 ± 3.58	5.96 ± 3.8*	-2.24 ± 2.49	6.81 ± 3.78	5.08 ± 3.37*	-1.73 ± 2.07	0.21 (-1.03–1.44)	0.741	0.01	0.05
HADS – D†	8 (6)	6 (6)*	-1 (3.5)	6.5 (4.25)	4.5 (5)*	-1 (2.25)	0 (-1–2)††	0.509[b]	0.09	0.06

†Variables with non-normal distribution; Wilcoxon signed-rank test and Mann-Whitney U test were performed for within-group and between-group comparisons, respectively; data are median (interquartile range).
††Hodges-Lehmann estimate (estimate confident interval across groups)

[a]p value from ANCOVA model, adjusting for baseline value, for between-group difference in change. [b]p value from Mann-Whitney U test for between-group difference in change

Data are mean ± SD or mean (95% CI), or †median (interquartile range). *Significantly different from baseline, $p<0.05$

Abbreviations SF-36 = Short form 36 health survey version 2; HADS = Hospital Anxiety and Depression scale; HADS-A – anxiety score; HADS-D – depression score

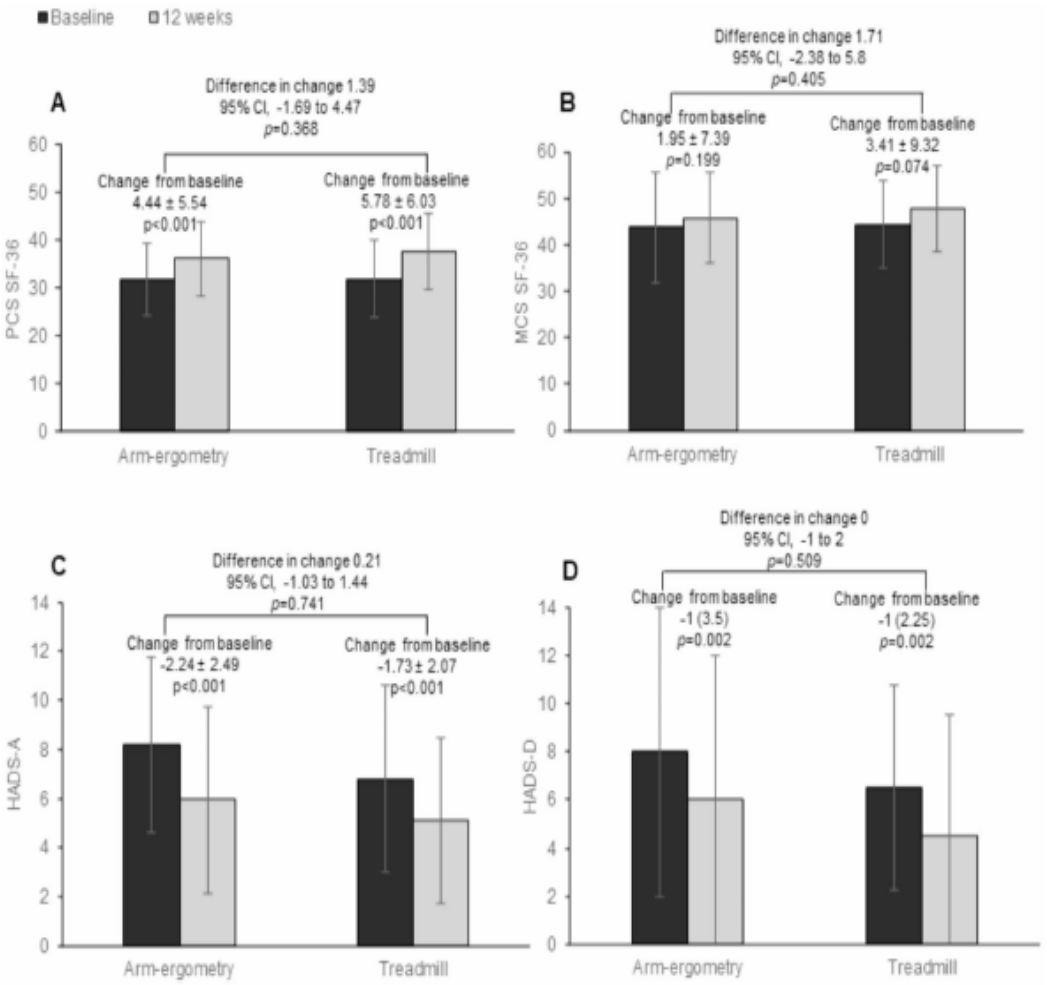

Fig. 2 Change in PCS of SF-36 (**A**), MCS of SF-36 (**B**), HADS-A (**C**) and HADS-D (**D**) from baseline to the end of the 12-week exercise program. Data are presented as mean ± SD, mean (95% CI), or median (IQR). Abbreviations: SF-36 = Short form 36 health survey version 2; PCS: physical component summary score; MCS: mental component summary score; HADS = Hospital Anxiety and Depression scale; HADS-A – anxiety score; HADS-D – depression score

cost-effectiveness of these interventions, as these elements are essential for maximizing long-term adherence and ensuring the widespread application of exercise programs for this population.

Conclusion

Both modes of exercise effectively enhanced HRQoL and reduced anxiety and depression levels in PAD patients, with greater improvements in the physical component.

Assessing and enhancing HRQoL along with addressing mental health concerns are crucial for improving patients' adherence to rehabilitation programs and effectively manage their chronic disease. Hence, both exercise modalities proved to be effective in improving various outcomes, serving as viable treatment options that enhance bodily functions and increase levels of activity and participation in this patient population.

It is important to note that the improvements in HRQoL and mental health outcomes observed in this study are exploratory and may have generalizability limitations. These findings should be interpreted with caution, and future research should investigate these findings further in diverse healthcare settings and populations to determine their broader applicability and ensure relevance across different patient demographics.

Abbreviations

PAD	Peripheral artery disease
HRQoL	Health-related quality of life
AEx	Arm-ergometry exercise training
TEx	Treadmill exercise training
CRP	Cardiovascular rehabilitation program
PCS	Physical component summary
CR	Cardiovascular rehabilitation
VO_2 peak	Peak oxygen consumption
SF-36	Short form 36 Health Survey
HADS	Hospital Anxiety and Depression scale
CPET	Treadmill cardiopulmonary exercise test

CONSORT	Consolidated Standards of Reporting Trials
PF	Physical functioning
RP	Role physical
BP	Bodily pain
GH	General health
VT	Vitality
RE	Role emotional
SF	Social functioning
MH	Mental health
MCS	Mental component summary
HADS-A	HADS anxiety score
HADS-D	HADS depression score
6MWT	6-minute walk test
PFWD	Pain-free walking distance
MWD	Maximal walking distance

Supplementary Information

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Supplementary Material 1

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Author contributions

SM participated in the design of the study, data acquisition, data analysis and interpretation of results; MS, SV, HCC participated in the design of the study and interpretation of results; CS contributed to randomization process; FR contributed to data analysis and interpretation of results. All authors contributed to the manuscript writing. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

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Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Centro Hospitalar Universitário de Santo António and School of Medicine and Biomedical Sciences at the University of Porto [2016-053(047-DEFI/046-CES)]. All participants provided written informed consent prior to their inclusion in the study.

Consent for publication

Not applicable.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author details

[1]Department of Physical and Rehabilitation Medicine, Centro Hospitalar Universitário de Santo António, Porto 4050-011, Portugal
[2]UMIB - Unit for Multidisciplinary Research in Biomedicine, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto 4050-313, Portugal
[3]Department of Cardiology, Centro Hospitalar Universitário de Santo António, Porto 4050-011, Portugal
[4]Pulmonary Vascular Disease Unit, Centro Hospitalar Universitário de Santo António, Porto 4050-011, Portugal
[5]CAC ICBAS-CHUP – Centro Académico Clínico Instituto de Ciências Biomédicas Abel Salazar – Centro Hospitalar Universitário de Santo António, Porto 4050-011, Portugal
[6]ITR - Laboratory for Integrative and Translational Research in Population Health, Porto 4050-600, Portugal
[7]Centro de Reabilitação do Norte, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia 4405-565, Portugal
[8]Institute of Biomedicine – iBiMED and School of Health Sciences, University of Aveiro, Aveiro 3810-193, Portugal
[9]Department of Angiology and Vascular Surgery, Centro Hospitalar Universitário de Santo António, Porto 4050-011, Portugal
[10]Research Centre in Physical Activity, Health and Leisure, CIAFEL, Faculty of Sport, University of Porto, Porto 4200-450, Portugal

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ORIGINAL ARTICLE
ARTERIAL DISEASE

Comparing arm-ergometry and treadmill exercise training on cardiovascular risk factors in peripheral artery disease: secondary analysis of the ARMEX trial

Sandra MAGALHÃES [1, 2] *, Mário SANTOS [2, 3, 4, 5, 6], Sofia VIAMONTE [7], Joana MARTINS [8], Cristine SCHMIDT [9], Fernando RIBEIRO [10], Henrique CYRNE-CARVALHO [2, 3]

[1]Department of Physical and Rehabilitation Medicine, Centro Hospitalar Universitário de Santo António, Porto, Portugal; [2]UMIB - Unit for Multidisciplinary Research in Biomedicine, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal; [3]Department of Cardiology, Centro Hospitalar Universitário de Santo António, Porto, Portugal; [4]Physiology Laboratory, Immuno-Physiology and Pharmacology Department, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal; [5]CAC ICBAS-CHUP - Centro Académico Clínico Instituto de Ciências Biomédicas Abel Salazar, Centro Hospitalar Universitário de Santo António, Porto, Portugal; [6]ITR - Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal; [7]Centro de Reabilitação do Norte, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; [8]Department of Angiology and Vascular Surgery, Centro Hospitalar Universitário de Santo António, Porto, Portugal; [9]Research Center in Physical Activity, Health and Leisure, CIAFEL, Faculty of Sport, University of Porto, Porto, Portugal; [10]Institute of Biomedicine – iBiMED and School of Health Sciences, University of Aveiro, Aveiro, Portugal

*Corresponding author: Sandra Magalhães, Department of Physical and Rehabilitation Medicine, Centro Hospitalar Universitário de Santo António, Professor Abel Salazar, 4099-001 Porto, Portugal. E-mail: mag.sandra@gmail.com

ABSTRACT

Background: Peripheral artery disease (PAD), usually caused by atherosclerosis, is linked to high cardiovascular mortality. In this setting, a multidimensional cardiovascular rehabilitation program (CRP) comprising supervised exercise training can improve cardiovascular risk factors (CRF) control. This study compares the effects of an arm-ergometry supervised exercise training (AEx) with a standard treadmill protocol (TEx) on CRF.

Methods: The ARMEX trial (ISRCTN54908548) was a single-center, single-blinded, parallel groups, noninferiority randomized clinical trial enrolling symptomatic PAD patients referred to a CRP. Participants were randomized (1:1) either to a 12-week AEx or TEx. Changes in blood pressure, lipid profile, glycated hemoglobin, body composition, physical activity levels, sedentary time and number of cigarettes smoked after the CRP were assessed.

Results: Fifty-six patients (66±8.4 years; 87.5% male) were included: AEx (N.=28) and TEx (N.=28). Systolic and diastolic blood pressure decreased in both groups without significant between-group differences. Total cholesterol and low-density lipoprotein cholesterol decreased significantly only in the AEx group, without significant between-group differences. Weight, body mass index, waist circumference, waist/hip ratio and

physical activity levels improved in both groups, without significant b etween-group differences. Smoking reduction was also similar between groups.

Conclusions: A multidimensional CRP, whether involving arm-ergometry or treadmill exercise, improved CRF control in symptomatic PAD patients. Both exercise modalities were equally effective, supporting their use as part of a comprehensive approach in this complex population.

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Key words: Cardiac rehabilitation; Heart disease risk factors; Intermittent claudication; Peripheral artery disease; Upper extremities.

The main underlying cause of lower extremity peripheral artery disease (PAD) is atherosclerosis.[1] In 2015, the worldwide prevalence of PAD among individuals aged 25 years and older was 5.56%, equating to approximately 236 million people.[2] PAD is associated with a worse prognosis and is recognized as an important cause of cardiovascular morbidity and mortality.[3] Despite its prevalence and impact on prognosis, PAD has been underdiagnosed and undertreated compared with other cardiovascular diseases such as myocardial infarction and stroke.[1] Traditional cardiovascular risk factors (CRF) have been linked with PAD, including diabetes, smoking, dyslipidemia, hypertension and physical inactivity.[1] In recent years, several studies have demonstrated a different pattern of association between CRF and atherosclerosis in different vascular territories.[3] Diabetes, smoking and hypertriglyceridemia are particularly strongly linked to PAD.[3]

Supervised treadmill exercise training is a first-line treatment for patients with PAD, supported by multiple randomized clinical trials demonstrating its efficacy in enhancing functional outcomes, such as increasing maximal walking distance and pain-free walking distance.[4]

Cardiovascular rehabilitation is a comprehensive intervention comprising established core components which encompass patient assessment, CRF management and control, counselling on physical activity, exercise prescription, nutritional guidance, psychosocial support, and the establishment of a structured follow-up focused on rehabilitative goals and secondary prevention over the short and long term.[5] The effectiveness of these programs is well established in individuals with coronary artery disease (CAD) and heart failure, resulting in notable improvements in cardiorespiratory function and quality of life, along with decreased rates of re-hospitalization. Reduced mortality rates have been confirmed only in CAD patients.[5] PAD is also a well-established indication for integrating a cardiovascular rehabilitation program (CRP). However, these patients are referred only in a minority of cases, typically when they share common features with other cardiovascular conditions.[5] Previous trials report that PAD patients are less likely to initiate and complete a CRP compared to those with CAD,[6, 7] and few studies have documented the effects of CRP in this population.[6] Some reports have compared enhancements in functional capacity between the two groups,[6, 7] while others suggest a lower increase in VO_2 peak following exercise training in PAD patients.[8] Devrome *et al.* demonstrated a mortality rate improvement in PAD patients of a similar magnitude to those without PAD.[6] Research is also limited regarding the effects of CRP on CRF in this population.[9, 10] Some authors raise doubts whether the amount of exercise in this debilitated population is adequate to induce beneficial changes in CRF,[11] while others emphasize the importance of investigating the effects of alternative pain-free exercise modalities on CRF in this population,[10] in order to change cardiovascular risk profile.

The ARMEX trial (Arm-ergometry *versus* Treadmill Supervised Exercise on Cardiorespiratory Fitness and Walking Distances in patients with Peripheral Artery Disease) was a prospective, single-blind, randomized clinical trial that compared arm-ergometry supervised exercise training with a standard treadmill protocol in terms of VO_2 peak and walking distances in patients with symptomatic PAD.[12] The trial found arm-ergometry noninferior to treadmill training for VO_2 peak, though treadmill

training improved walking distances more. In this secondary analysis of the ARMEX, we aimed to investigate the impact of a CRP incorporating arm-ergometry supervised exercise training compared to a standard treadmill protocol on CRF in symptomatic PAD patients.

Materials and methods

Trial design

The ARMEX trial was a prospective single-center, single-blind, parallel groups, noninferiority randomized clinical trial (1:1), which aimed to compare the efficacy of an arm-ergometry protocol versus treadmill exercise training on cardiorespiratory fitness and walking distances among PAD patients with intermittent claudication over a period of 12-week.[12]

PAD patients with intermittent claudication, consecutively referred to our Cardiovascular Rehabilitation Unit, were recruited. Details about eligibility and enrollment were previously reported.[12] Eligible patients were randomized either to a 12-weeks arm-ergometry supervised exercise training (AEx) or a treadmill walking exercise protocol (TEx). The study was conducted according to the recommendations of the Declaration of Helsinki and approved by the Ethics Committee of Centro Hospitalar Universitário de Santo António and School of Medicine and Biomedical Sciences from University of Porto (2016-053[047-DEFI/046-CES]). The trial was retrospectively registered at the ISRCTN registry: ISRCTN54908548. Written informed consent was obtained from all participants prior to their involvement in the study. The current manuscript was structured according to the guidelines outlined in the Consolidated Standards of Reporting Trials (CONSORT) Statement for randomized trials of Nonpharmacological Treatment.[13]

Participants

Patients with PAD older than 18 years old referred to the Cardiovascular Rehabilitation Unit were enrolled. Inclusion and exclusion criteria were previously provided.[12]

Randomization and allocation

As previously reported,[12] randomization was performed with a computer-based random number generator using a 1:1 allocation ratio for block sizes of four patients. Randomization and allocation were undertaken by a member of the research team (C.S.) who was not directly involved in the recruitment or patients' assessment.

Outcome measures

Blood pressure

Resting brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed from the upper left arm using an automated Dinamap Vital Signs Monitor (Philips SureSigns VM4, Andover, USA) after a 10 minutes rest period, following current recommendations.[14]

Lipid and glycemic biomarkers

A blood sample was collected after a 12 hour fasten period. Following collection, the samples were centrifugated at 4000 rpm in ambient air for 5 minutes. Total cholesterol (TC-C), low-density lipoprotein (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured using the Roche/Hitachi Cobas c 701/702® (Roche Diagnostics, Swiss). Glycated hemoglobin (HbA_{1c}) was assessed using an automated glycohemoglobin analyzer, HLC-723® G11 (Tosoh Bioscience, UK).

Body composition

Height was measured with the patient standing upright against a wall, with feet positioned hip-width apart; weight was measured using an electronic scale (SECA 769, Hamburg, Germany) and Body Mass Index (BMI) was then calculated. Waist circumference was assessed at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, utilizing a stretch-resistant tape. Hip circumference was measured around the widest portion of the buttocks, with the tape held parallel to the floor. For both measurements, patients stood in an upright position with their feet close together, arms at their sides, and body weight evenly distributed. Patients were asked to relax, and measurements were taken at the end of a normal expiration. Each measurement was conducted twice. If the measurements were within 1 cm of each other, the average was calculated. If the difference between the two measurements exceeded 1 cm, the measurements were repeated.[15] The waist-hip ratio (WHR) was also calculated.

Physical activity levels

The physical activity level was assessed through self-completion of the International Physical Activity Questionnaire – Short Form (IPAQ). This questionnaire collects information on the patient's physical activity over the seven days preceding the test. Data from the IPAQ were converted into metabolic equivalent minutes per week (METs-min/week) in accordance with established guidelines.[16] Physical activity levels can be categorized

as 'high' (>1500 METs), 'moderate' (600-1500 METs), or 'low' (<600 METs). One of the questions specifically pertains to sitting time. The IPAQ has been validated in 12 countries, including Portugal.[17]

Patients used a wearable smartwatch (Polar M200 heart rate monitor, Polar Electro Ltd, Kempele, Finland) to track the number of steps taken per day during a 7-day period. The average number of steps taken was calculated for the week prior to the commencement of the exercise program and the week following its completion.

Smoking status

Former and current smokers were inquired about their daily cigarette intake and the duration of their smoking history.

Dropout and adherence rates

Dropout rate was calculated in both groups. Adherence rate was calculated based on the number of sessions performed in relation to the number of sessions planned.

Interventions

The intervention included a CRP following current guidelines.[5] Exercise sessions comprised twice-weekly sessions, each consisting of a 10-minute warm-up, 40 minutes of intermittent treadmill walking or arm-ergometry, ten resistance exercises and 10-minute cooldown. Exercise protocols were previously published.[12] These exercise sessions were conducted by a physiotherapist under medical supervision, both with experience in cardiovascular rehabilitation. Furthermore, all patients received nutritional and psychological interventions in accordance with cardiac-rehabilitation international guidelines.[5] Current smokers were provided with advice from a physician to quit smoking and were referred to a structured smoking cessation program as needed. All patients were encouraged to exercise at home at least twice a week for 30 minutes. Patients were asked weekly about exercise performed at home. It was made a record of the mode and time of exercise realized. Patients were considered to have performed unsupervised exercise if they completed moderate-intensity exercise for at least 30 min per session for at least 2x/week. Recorded exercise was analyzed as a dichotomous variable (yes or no).

Statistical analysis

The present study investigated secondary outcomes of the ARMEX trial, so, no sample size was calculated a priori. The distribution of the data was assessed with the Shapiro-Wilk Test and *via* visual inspection of histograms. Continuous data are reported as mean and standard deviation, mean differences (95% CI) or as the median (interquartile range) and categorical data as frequencies (percentage). For within-group comparisons, from baseline to 12 weeks, were performed paired-samples *t*-test or Wilcoxon Signed-Rank Test. Differences between groups in the change from baseline to the end of the study were tested using ANCOVA, adjusting for baseline value or Mann-Whitney U Test. Statistical significance of $P<0.05$ was assumed. IBM SPSS statistics version 29.0 (IBM Corp., Armonk, NY, USA) was used to perform statistical analyses.

Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

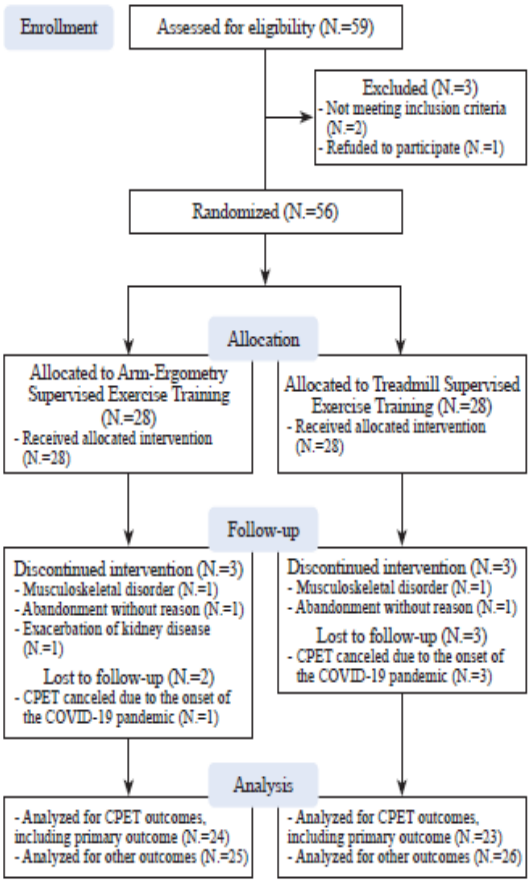

Figure 1.—Modified CONSORT flow diagram for individual randomized controlled trials of nonpharmacologic treatments.
CPET: cardiopulmonary exercise test.

Results

A total of 59 symptomatic PAD patients were referred to our cardiovascular rehabilitation consultation and assessed for eligibility (Figure 1). As previously published,[12] 56 patients (66.0±8.4 years) were enrolled and randomized: AEx (N.=28) and TEx (N.=28). Baseline participant characteristics were well balanced between groups and are described in Table I. In brief, the majority of the patients were male (87.5%), and the average lowest resting ankle-brachial index (ABI) was 0.66±0.13. Prior leg revascularization had been performed in 21.4% of patients. Common comorbidities included coronary heart disease (46.4%), heart failure (8.9%), chronic obstructive pulmonary disease (8.9%) and cerebrovascular disease (7.1%). Cardiovascular risk factors were prevalent, with hypertension (85.7%), dyslipidemia (83.9%) and diabetes mellitus (44.6%) being the most common. A substantial portion of the patients were physically inactive (76.8%), and 30.4% were current smokers. The majority of patients (60.7%) had a history of smoking. Regarding medication, all patients were on statins, and most were prescribed acetyl-salicylic acid (83.9%) and ACE inhibitors/angiotensin receptor blockers (76.8%).

Of the enrolled patients, 51 patients (AEx, N.=25; TEx, N.=26) completed the intervention and were included in this analysis. Exercise session adherence was 91.3% (AEx: 86.9% *vs.* TEx: 91.7%; P=0.311). The percentage of patients who complied with the recommendation to exercise at home was similar in both groups (AEx: 76%; TEx: 69.2%; P=0.59).

After 12 weeks of exercise training SBP and DBP decreased in both groups without significant between-group differences (1.12 mmHg; 95% CI, -4.42 to 6.65 mmHg; P=0.687 and 0.49 mmHg; 95% CI, -4 to 4.98 mmHg; P=0.827, respectively) (Supplementary Digital Material 1: Supplementary Table I) (Figure 2). Regarding the lipid profile, TC-C and LDL-C decreased significantly only in AEx, but without significant between-group differences (Supplementary Table I, Figure 2). HDL-C and TG did not improve after intervention in both groups (Supplementary Table I, Figure 2). In patients with diabetes, HbA1c

TABLE I.—*Baseline characteristics overall and for the two exercise groups.*

Variable	Overall N.=56	Arm-ergometry N.=28	Treadmill N.=28	P value
Age, years	66±8.4	67±7.8	64±8.9	0.468
Male sex	49 (87.5%)	25 (89.3%)	24 (85.7%)	0.725
Lowest resting ABI	0.66±0.13	0.69±0.11	0.62±0.15	0.156
Prior leg revascularization	12 (21.4%)	3 (10.7%)	9 (32.1%)	0.180
Comorbidities				
Coronary heart disease	26 (46.4%)	15 (53.6%)	11 (39.3%)	0.488
Cerebrovascular disease	4 (7.1%)	2 (7.1%)	2 (7.1%)	0.967
Heart failure	5 (8.9%)	3 (10.7%)	2 (7.1%)	0.605
COPD	5 (8.9%)	3 (10.7%)	2 (7.1%)	0.605
Cardiovascular risk factors				
Dyslipidemia	47 (83.9%)	22 (78.6%)	25 (89.3%)	0.406
Diabetes mellitus	25 (44.6%)	13 (46.4%)	12 (42.9%)	0.683
Hypertension	48 (85.7%)	22 (78.6%)	26 (92.9%)	0.202
Physical inactivity	43 (76.8%)	24 (85.7%)	19 (67.9%)	0.157
Obesity	10 (17.9%)	5 (17.9%)	5 (17.9%)	0.884
Smoking status				
Current	17 (30.4%)	10 (35.7%)	7 (25%)	0.485
Previous	34 (60.7%)	17 (60.7%)	17 (60.7%)	0.867
Never smoked	5 (8.9%)	1 (3.6%)	4 (14.3%)	0.172
Medication, %				
Acetyl-salicylic acid	47 (83.9%)	22 (78.6%)	25 (89.3%)	0.243
Statins	56 (100%)	28 (100%)	28 (100%)	NA
Beta-blockers	35 (62.5%)	21 (75%)	14 (50%)	0.055
ACEi /ARB	43 (76.8%)	21 (75%)	22 (78.6%)	0.679
Antiplatelet agent	18 (32.1%)	10 (35.7%)	8 (28.6%)	0.485
Anticoagulants	10 (17.9%)	7 (25%)	3 (10.7%)	0.243
Pentoxifylline	14 (25%)	7 (25%)	7 (25%)	0.931
Cilostazol	6 (10.7%)	2 (7.1%)	4 (14.3%)	0.413

ABI: Ankle-Brachial Index; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; COPD: chronic obstructive pulmonary disease; SD: standard deviation.

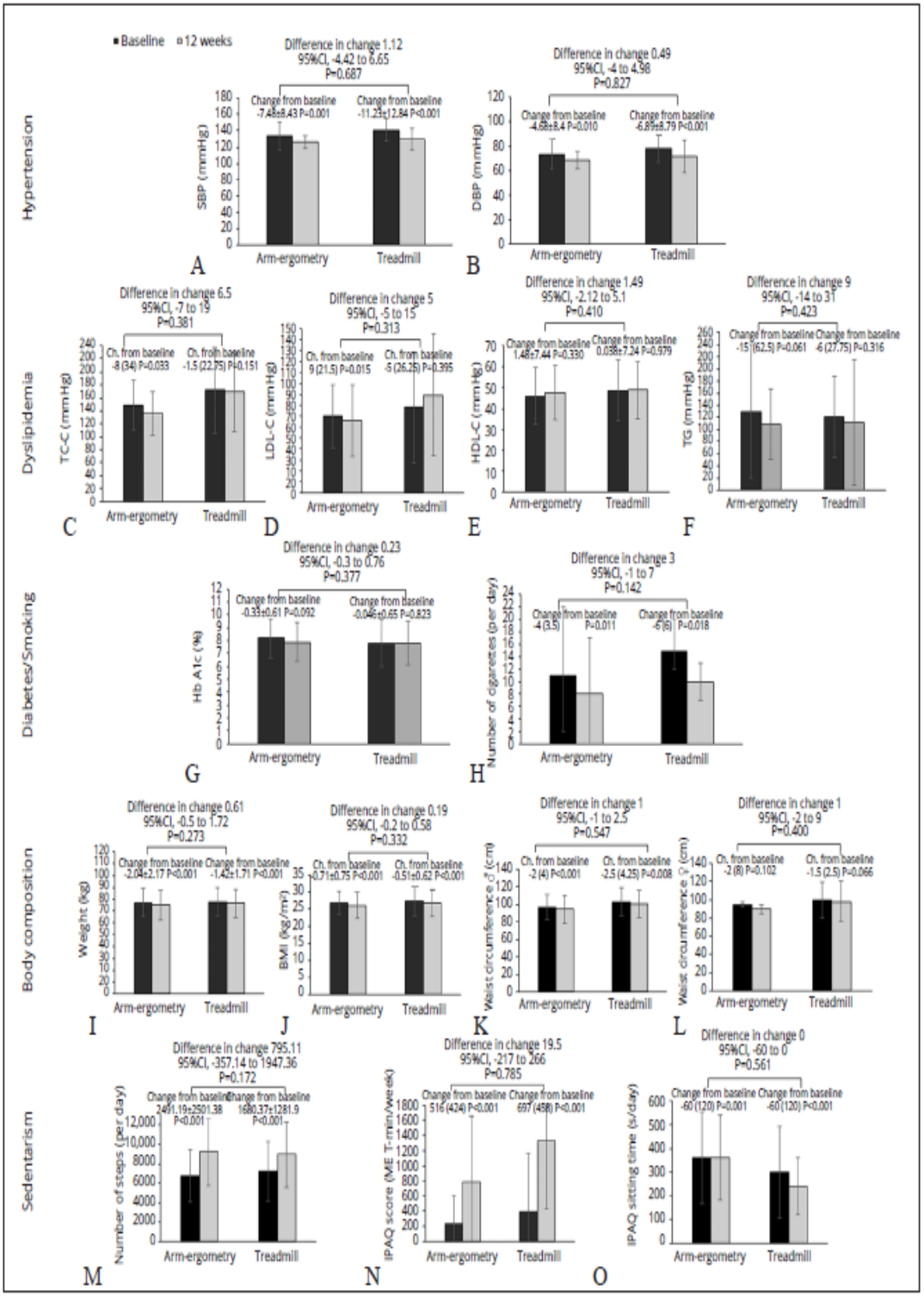

Figure 2.—Change in SBP (A), DPB (B), TC-C (C), LDL-C (D), HDL-C (E), TG (F), HbA_{1c} (G), number of cigarettes (H), weight (I), BMI (J), waist circumference ♂ (K), waist circumference ♀ (L), number of steps (M), IPAQ score (N), IPAQ sitting time (O) from baseline to the end of the 12-week exercise program. A, B, E, G-J, M) Data are mean±SD or mean (95% CI); C, D, F, K, L, N, O) data are median (interquartile range) or mean (95% CI).

BMI: Body Mass Index; DBP: diastolic blood pressure; HbA_{1c}: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol; IPAQ: International Physical Activity Questionnaire; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

did not improve significantly after exercise training in both groups (Supplementary Table I, Figure 2). Regarding body composition, after 12 weeks of intervention, weight, BMI, waist circumference (in males) and waist/hip ratio (in males) improved in both groups, without significant between-group differences (Supplementary Table I, Figure 2). However, waist circumference and waist/hip ratio did not improve in females (Supplementary Table I, Figure 2). Physical activity levels assessed through IPAQ score and the wearable smartwatch increased after the exercise program in both groups, without significant between-group differences (19.5 MET-min/wk; 95% CI, -217 to 266 MET-min/wk; P=0.785 and 795.11 steps/day; 95% CI, -357.14 to 1947.36 steps/day; P=0.172, respectively) (Supplementary Table I, Figure 2). The IPAQ sitting time improved also in both groups, without significant between-group differences (Supplementary Table I). Regarding the smoking habits, after intervention the number of cigarettes smoked (per day) decreased in both groups, without significant between-group differences (3; 95% CI, -1 to 7; P=0.142) (Supplementary Table I, Figure 2).

Discussion

In this secondary analysis of the ARMEX trial, we aimed to compare the effects of AEx *versus* TEx on CRF in patients with PAD. Overall, both exercise modalities demonstrated comparable efficacy in improving blood pressure, body weight, BMI, waist circumference, waist-to-hip ratio, smoking status, and physical activity levels. To the best of our knowledge, this is the first study to compare AEx and TEx in relation to lipid profile, diabetes control, and physical activity levels in this population.

Few studies have investigated the impact of a CRP in CRF control in patients with PAD.[9] In our sample, CRF were highly prevalent, with hypertension exhibiting the highest percentage. These results are consistent with literature findings indicating a poorer CRF profile in PAD patients referred to a CRP compared with patients with CAD.[6, 18] Several previous trials have documented the undertreatment of CRF in patients with PAD.[19] Patient's inadequate awareness of the risk of cardiovascular events associated with PAD and how controlling CRF could mitigate this risk has been identified as a potential explanation for these findings.[19]

In patients with PAD, hypertension is one of the most critical factors influencing the risk of lower extremity amputation.[20] A cross-sectional analysis of the Hungarian ERV study indicated that a low ankle-brachial index is a stronger predictor of mortality in hypertensive patients, even after adjusting for several potential confounders.[20] In the present trial a significant decrease in SBP of 7.5 mmHg in AEx group and 11.2 mmHg in TEx group was observed. A comprehensive analysis of previous randomized trials showed that a reduction of 5 mm Hg in SBP could led to a decrease in the risk of major cardiovascular events by approximately 10%, regardless of prior diagnoses of cardiovascular disease.[21] A meta-analysis that included patients with intermittent claudication that performed walking exercise (such as treadmill, Nordic pole walking, etc.) compared to those receiving usual care, revealed a mean reduction of 8 mmHg in SBP following exercise training.[9] A previous pilot trial[22] has investigated the effect of arm ergometry exercise training on blood pressure in patients with PAD and compared it with a treadmill protocol.[22] The authors found a significant improvement in SBP after 12 weeks of exercise training only in the arm-ergometer group; they reported this result as unexpected and emphasized the need for further studies with larger sample sizes.[22]

We observed a significant decrease in TC-C and LDL-C only in AEx, although without between-group differences. HDL-C and TG did not improve after the intervention in both groups. A systemic review in PAD patients showed no effect on LDL-C, TC, HDL-C or TG following supervised walking exercise training.[10] Another systematic review found a significant decrease in LDL-C and TG at midterm follow-up (6 to 12 months) after walking exercise training.[9] However, at short-term follow-up (6 weeks to 3 months), they also did not find an improvement in lipid profile.[9] Studies have indicated that a minimum volume of weekly aerobic exercise and an energy expenditure >900 Kcal/week are necessary to induce positive changes in lipid profile.[23, 24] In this population, arm-ergometry is associated with painless exercise. In our study, it was performed continuously for 40 minutes without rest periods, potentially resulting in a higher volume of exercise and, consequently, greater energy expenditure.

We did not observe a significant improvement on HbA1c after exercise training. A previously mentioned systematic review identified only three trials that investigated the impact of exercise training on HbA1c levels in patients with PAD and similarly found no significant improvements.[9] None of the studies included arm-ergometry exercise training.[9] Exercise volume has been demonstrated to be a significant determinant of glycemic control in patients with type 2 diabetes who undergo structured exercise programs.[23, 25] More significant reductions in HbA_{1c} are linked to exercise frequency in aerobic exercise and to

the weekly volume of resistance exercise.[25] If we had increased the frequency of supervised exercise sessions, the impact on HbA1c might have been even more substantial in both intervention groups.

We found a significant improvement in all body composition parameters in both intervention groups, without between-group differences. The improvements in waist circumference and waist/hip ratio were not significant in females, likely because the number of female patients included in the study was very small, with only three in the AEx group and four in the TEx group. These results surpassed those observed in the two previously mentioned systematic reviews concerning weight and BMI.[9, 10] None of the studies included in these reviews assessed the effect of exercise on waist circumference and waist/hip ratio, which are important parameters reflecting body fat distribution.[10] The most significant reductions in body weight were observed when exercise training was combined with caloric intake restriction.[23] In the ARMEX trial, patients participated in a multidimensional CRP, which involved evaluation by a nutritionist and the prescription of an individualized plan for each patient. Throughout the exercise program, patients were encouraged to adhere to preventive measures, including compliance with their established nutritional plan. We believe that this comprehensive approach has significantly contributed to our positive results.

Previous research has shown that sedentary behavior, encompassing sedentary time, is linked to a heightened risk of cardiovascular disease morbidity and mortality, distinct from those resulting from physical inactivity.[26] Physical activity levels and sedentary behavior after supervised exercise training are seldomly reported as outcomes in trials related to intermittent claudication treatment. However, if there is an improvement in physical activity levels and reduction in sedentary time following an exercise program, it may lead to long-term cardiovascular risk reduction and improved quality of life.[27] Some studies have indicated that certain patients engaging in a structured exercise program may decrease their non-exercise physical activity, aligning with the well documented concept of behavioral compensation.[26] In patients with PAD, some studies have also demonstrated no enhancement in physical activity levels or reduction in sitting time after a supervised exercise program.[26, 27] However, authors have reported a highly variable response in these outcomes, with some patients experiencing a substantial increase and others even experiencing a decrease.[26, 27] Our results surpassed those reported in these trials; we observed a statistically and clinically significant improvement[28] in the number of steps performed per day following both interventions, without between-group differences. We also demonstrated a significant improvement in weekly physical activity levels and sitting time, assessed by the IPAQ, after both interventions. Patients were provided with an exercise diary in which they recorded the exercise performed at home. Throughout supervised exercise sessions, patients were questioned about their home exercise routines and were motivated to adhere to them. We believe that this continuous encouragement played a pivotal role in achieving our improved results. Several trials have shown that combining activity monitoring with feedback on the results leads to significant increases in physical activity levels.[29]

Smoking in patients with PAD is strongly linked to an elevated risk of disease progression, poorer post-revascularization outcomes, increased hospitalizations, and cardiovascular events.[30] Smoking cessation, as well as smoking reduction, have been highlighted as fundamental therapeutic strategies in these patients.[30, 31] We observed a decrease in the number of cigarettes smoked per day in both exercise groups, without between-group differences.

Limitations of the study

While our study provides valuable insights into the impact of exercise training on CRF control in PAD patients, some limitations should be acknowledged. While we assessed body weight, body mass index, waist circumference and waist/hip ratio to gain insights into body composition, we acknowledge that using a bioelectrical impedance analyzer could have provided a more accurate evaluation of body fat percentage, as demonstrated by other studies in this population.[32] Further studies are needed to clarify our findings, since the impact of exercise training on CRF in PAD patients was considered a secondary outcome in both our study and other trials. Thus, the sample size calculation was based on different primary outcomes. In future research, it would be important to examine the impact of this type of interventions across different subgroups (*e.g.*, current smokers versus non-smokers/previous smokers) and genders. For a more accurate evaluation of physical activity levels and sedentary behavior, it would have been preferable to utilize accelerometers, which are considered the gold standard method for assessing these parameters.[28]

It is challenging to isolate the effects of exercise training from those of nutrition or other preventive strategies in our results. However, no changes in medication were made during the study period. We also acknowledged that the various components of the comprehensive CRP interact synergistically. We aimed to understand how this

intervention works in real-world settings, as it has been suggested by several authors to be the most effective approach for these patients.

Conclusions

Both exercise modalities, when incorporated into a multidimensional program, similarly improved the majority of the evaluated CRF. Arm-ergometry exercise training offers a viable alternative for enhancing CRF in symptomatic PAD patients.

Incorporating PAD patients into a multidimensional CRP is a therapeutic strategy that can yield significant benefits. However, this population has specific challenges, such as lower participation and adherence rates, which need to be addressed. Therefore, special efforts should be made to retain them, potentially through tailored exercise programs and disease-specific education.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Sandra Magalhães, Mário Santos, Sofia Viamonte and Henrique Cyrne-Carvalho contributed to study conception; Cristine Schmidt contributed to randomization process; Sandra Magalhães and Mário Santos contributed to data acquisition, Sandra Magalhães, Mário Santos and Fernando Ribeiro contributed to data analysis and interpretation. Sandra Magalhães wrote the first draft of manuscript; All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Table I.—Effects of arm-ergometry and treadmill exercise training on cardiovascular risk factors and groups differences.

	Arm-ergometry			Treadmill			Between-group difference in change [a]	P value [a]
	Baseline	Final	Change from baseline	Baseline	Final	Change from baseline		
Hypertension								
SBP (mm/Hg)	133.52±17.08	126.04±16.28	-7.48±8.43*	141.04±13.93	129.81±10.98	-11.23±12.84*	1.12 (-4.42 – 6.65)	0.687
DBP (mm/Hg)	73.32±12.15	68.64±7.63	-4.68±8.4*	78.5±10.97	71.62±13.32	-6.89±8.79*	0.49 (-4 – 4.98)	0.827
Dyslipidemia								
TC-C (mg/dL)†	148 (38.5)	136 (33.5)	-8 (34)*	171.5 (66.25)	169 (60.5)	-1.5 (22.75)	6.5 (-7 – 19)††	0.381[b]
LDL-C (mg/dL)†	70 (29)	66 (33)	-9 (21.5)*	78 (51)	89.5 (55.75)	-5 (26.25)	5 (-5 – 15) ††	0.313[b]
HDL-C (mg/dL)	46±13.64	47.48±12.95	1.48±7.44	48.69±14.59	48.73±13.5	0.038±7.24	1.49 (-2.12 – 5.1)	0.410
TG (mg/dL)†	130 (111)	109 (58.5)	-15 (62.5)	120.5 (67)	111.5 (103.5)	-6 (27.75)	9 (-14 – 31)††	0.423[b]
Diabetes mellitus								
HbA1c (%)	8.2±1.49	7.88±1.5	-0.33±0.61	7.82±1.87	7.77±1.67	-0.046 (0.65)	0.23 (-0.3 – 0.76)	0.377
Body composition								
Weight (kg)	77.1±12.01	75.06±12.57	-2.04±2.17*	77.95±11.6	76.53±11.77	-1.42±1.71*	0.61 (-0.5 – 1.72)	0.273
BMI (kg/m^2)	26.86±3.51	26.15±3.77	-0.71±0.75*	27.37±4.18	26.86±4.13	-0.51±0.62*	0.19 (-0.2 – 0.58)	0.332
Waist circumference (cm)♂ †	97.3 (13.5)	94.5 (15.8)	-2 (4)*	103.5 (16.3)	101 (15.3)	-2.5 (4.25)*	1 (-1 – 2.5)††	0.547[b]
Waist circumference (cm)♀ †	95 (3)	90 (5)	-2 (8)	99.5 (19.5)	98 (22)	-1.5 (2,5)*	1 (-2 – 9)††	0.400[b]
Waist / hip ratio ♂ †	1 (0.09)	0.98 (0.11)	-0.01 (0.02)*	1 (0.1)	1 (0.09)	-0.02 (0.04)*	8.1*10^{-5} (-0.016 – 0.017)††	0.953[b]
Waist / hip ratio ♀ †	0.95 (0.1)	0.94 (0.11)	-0.02 (0.07)	0.95 (0.15)	0.97 (0.11)	-0.02 (0.1)	0.03 (-0.041 – 0.16)††	0.629[b]
Physical inactivity / sedentarism								
IPAQ score (MET-minutes/week)†	231 (371.25)	780 (872.5)	516 (424)*	393.5 (768)	1329.5 (897)	697 (458)*	19.5 (-217 – 266)††	0.785[b]
IPAQ sitting time (minutes/day)†	360 (195)	360 (180)	-60 (120)*	300 (195)	240 (120)	-60 (120)*	0 (-60 – 0)††	0.561[b]
N. of steps (per day)	6731.63±2659.59	9222.82±3468.56	2491.19±2501.38*	7251.83±3046	8932.2±3346.14	1680.37±1281.9*	795.11 (-357.14 – 1947.36)	0.172
Smoking status								
N. of cigarettes smoked (per day)†	11 (11)	8 (9)	-4 (3.5)*	15 (5)	10 (3)	-6 (6)*	3 (-1 – 7)††	0.142[b]

†Variables with non-normal distribution; Wilcoxon signed-rank test and Mann-Whitney U test were performed for within-group and between-group comparisons, respectively; data are median (interquartile range). ††Hodges-Lehmann estimate (estimate confident interval across groups).
[a] P value from ANCOVA model, adjusting for baseline value, for between-group difference in change; [b] P value from Mann-Whitney U test for between-group difference in change.
Data are mean±SD or mean (95% CI), or † median (interquartile range). *Significantly different from baseline, P<=0.05.
BMI: Body Mass Index; DBP: diastolic blood pressure, HbA1c: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol; IPAQ: International physical activity questionnaire; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

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Arm-ergometry versus Treadmill Exercise in Patients with Peripheral Artery Disease: Inflammatory and Endothelial Outcomes in the ARMEX Trial

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Corresponding Author:	Sandra Magalhães, MD Centro Hospitalar Universitario de Santo Antonio Porto, PORTUGAL
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Centro Hospitalar Universitario de Santo Antonio
Corresponding Author's Secondary Institution:	
First Author:	Sandra Magalhães, MD
First Author Secondary Information:	
Order of Authors:	Sandra Magalhães, MD
	Mário Santos
	Sofia Viamonte
	Manuel Teixeira
	Fernando Ribeiro
	Henrique Cyrne-Carvalho
Order of Authors Secondary Information:	
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Research Letter

Arm-ergometry versus Treadmill Exercise in Patients with Peripheral Artery Disease: Inflammatory and Endothelial Outcomes in the ARMEX Trial

Plasma Biomarkers in PAD: Arm-Ergometry vs. Treadmill

Sandra Magalhães, MD[a,b*]; Mário Santos, PhD[b,c,d,e,f]; Sofia Viamonte, PhD[g]; Manuel Teixeira, MSc[h]; Fernando Ribeiro, PhD[h] Henrique Cyrne-Carvalho, PhD[b,c,e,f]

[a]Department of Physical and Rehabilitation Medicine, Centro Hospitalar Universitário de Santo António, Porto, Portugal

[b]UMIB - Unit for Multidisciplinary Research in Biomedicine, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal

[c]Department of Cardiology, Centro Hospitalar Universitário de Santo António, Porto, Portugal

[d]Physiology Laboratory, Immuno-Physiology and Pharmacology Department, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal

[e]CAC ICBAS-CHUP – Centro Académico Clínico Instituto de Ciências Biomédicas Abel Salazar – Centro Hospitalar Universitário de Santo António, Porto, Portugal

[f]ITR - Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal

[g]Centro de Reabilitação do Norte, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal

[h]Institute of Biomedicine – iBiMED and School of Health Sciences, University of Aveiro, Portugal

All authors meet the 4 ICMJE criteria for authorship.

*Corresponding author: Sandra Magalhães, Department of Physical and Rehabilitation Medicine, Centro Hospitalar Universitário de Santo António, Largo Professor Abel Salazar, 4099-001 Porto, Portugal. Phone: +351222077550. Fax: +351223320318. E-mail: mag.sandra@gmail.com

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INTRODUCTION

Lower extremity peripheral artery disease (PAD), primarily caused by atherosclerosis involves endothelial dysfunction and inflammation.[1]

Supervised exercise training is a first-line treatment for patients with intermittent claudication.[2] Exercise has been shown to impact key atherosclerotic factors in cardiovascular disease[1], but the mechanisms underlying its benefits in PAD are not yet fully understood.[3] Several local and systemic mechanisms have been proposed, including reduced levels of inflammatory markers, improved endothelial function, enhanced hemorheology, and improved muscle and mitochondrial function in the gastrocnemius muscle.[3] Understanding these pathways could enhance our knowledge of PAD pathophysiology and contribute to the development of new preventive or treatment strategies. This ancillary study of the ARMEX trial aims to compare the effects of arm-ergometry and standard treadmill exercise on inflammation and endothelial function biomarkers in PAD patients.

METHODS

The ARMEX trial was a single center, single-blind, parallel groups, noninferiority randomized clinical trial (1:1), comparing arm-ergometry (AEx) and treadmill exercise (TEx) training for improving cardiorespiratory fitness and walking distances in PAD patients with intermittent claudication over a 12-week period.[4] This pre-specified secondary analysis evaluates plasma biomarkers of inflammation and endothelial function. Consecutive PAD patients were prospectively enrolled and randomized to AEx or TEx.

Recruitment, randomization and ethical details, have been previously described[4] and are available in the supplemental digital content (eMethods).

Inflammation was measured using C-reactive protein (CRP) and high-sensitivity interleukin-6 (hs IL-6), while endothelial function was evaluated through asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor.

Both groups participated in a 12-week comprehensive program, including lifestyle counseling, nutritional and psychological intervention, smoking cessation, and exercise. Outcome measures and exercise prescription details have been previously published[4] and are available in the supplemental digital content 1. Since all variables showed a non-normal distribution, within-group comparisons were performed using the Wilcoxon signed-rank test, while between-group differences analyzed with the Mann-Whitney U test. Statistical significance was set at $P < .05$, and analyses were performed using IBM SPSS vr29.0.

RESULTS

A total of 59 patients were referred and assessed for eligible. Fifty-six patients were enrolled and randomized. Of these, 51 patients (AEx, n=25; TEx, n=26) completed the intervention. Exercise sessions adherence was 91.3% (AEx: 86.9% vs. TEx: 91.7%; $P = 0.31$). Due to a refrigerator malfunction, 8 samples from 7 patients were lost. As such, 44 patients (66 ± 8.6 years; 88.6% male) were included in this secondary analysis (AEx, n=22, TEx, n=22). Baseline characteristics of the participants were well balanced between the groups (please refer to ref. 3 for further details), and the characteristics of patients whose plasma biomarkers were analyzed were also comparable to those excluded. CRP levels decreased significantly only in AEx, without significant between-groups difference

(1.11 mg/dL: 95%CI, -1.11[-16] to 2.99; $P = 0.051$) (Fig.2). At 12 weeks, hsIL-6 decreased significantly more in AEx (4.27 pg/mL; 95% CI, 0.76 to 9.12; $P = 0.025$) (Fig.1).

At 12 weeks, ADMA levels decreased significantly only in TEx (-27.37 ± 88.84 ng/mL, $P = .019$), with a significant between-group difference of 54.60 ng/mL (95% CI, 8.92 to 100.28; $P = .020$) in favor of the TEx group (Fig. 1).

DISCUSSION

The arm-ergometry exercise program produced a greater anti-inflammatory effect than treadmill exercise, as evidenced by a significantly larger decrease in hs IL-6 and a clear trend toward a greater reduction in CRP. In patients with PAD, a meta-analysis reported no significant effect on IL-6 and CRP levels following exercise training.[5] In this review, the majority of interventions involved walking exercise, with none including arm-ergometry.[5] The authors suggested that prolonged treadmill or cycling sessions might damage leg tissue and contribute to chronic inflammation.[5] Exercise seems to induce significant metabolic adaptations in the skeletal muscle of patients with PAD only when the pain threshold is reached.[6] However, the intensity of pain reached may impact inflammatory markers and ROS released.[6] Therefore, the specific threshold at which patients with PAD transition from a beneficial level of ROS to a detrimental level of ROS in skeletal muscle is unknown.[6] Only one study evaluated inflammatory biomarkers, specifically hsCRP levels, after arm-ergometry training in patients with PAD, comparing it with cycle-ergometry and usual care.[7] The authors observed a strong trend toward a decrease in circulating hsCRP levels following arm-cranking exercise; however, this trend did not reach statistical significance.[7] We did not find any trials that evaluated IL-6 levels after arm-ergometry exercise training in this population. In our study, the only difference

in FIIT exercise prescription parameters was the longer duration of the aerobic component in the arm-ergometry group.[4] IL-6, a "myokine" produced by active muscles, plays a key role in training adaptations, with exercise duration being the primary factor influencing its response.[8] Other factors such as intensity, muscle glycogen status, training status, and exercise modality have a lesser impact.[8] Thus, arm-ergometry and its longer duration may have contributed to its anti-inflammatory effects.

Treadmill training led to greater improvement in ADMA levels, aligning with two RCTs showing improved ADMA levels following treadmill training in patients with PAD.[9, 10] One study utilized a combined program of treadmill and resistance training,[10] while the other used only treadmill training.[9] No studies have examined ADMA levels following arm-ergometry training in this population. The previously mentioned meta-analysis found that exercise improves endothelial dysfunction, particularly FMD, but not inflammatory biomarkers.[5] These results are consistent with ours , and the authors suggest that exercise-induced improvement in vascular endothelial function can occur independently of improvements in systemic inflammation.[5] The cycles of ischemia/reperfusion involved in treadmill or walking training may explain their lesser anti-inflammatory impact.[5]

To mitigate potential bias, we blinded the outcome assessors. As an ancillary study, our sample size was based on expected improvements in the primary endpoint (VO_2 peak), rather than inflammatory or endothelial biomarkers. Further studies with larger sample sizes are needed to support our findings.

In conclusion, arm-ergometry was more effective than treadmill exercise in reducing inflammation in symptomatic PAD patients, while treadmill training led to a greater ADMA reduction, indicating a stronger impact on endothelial dysfunction.

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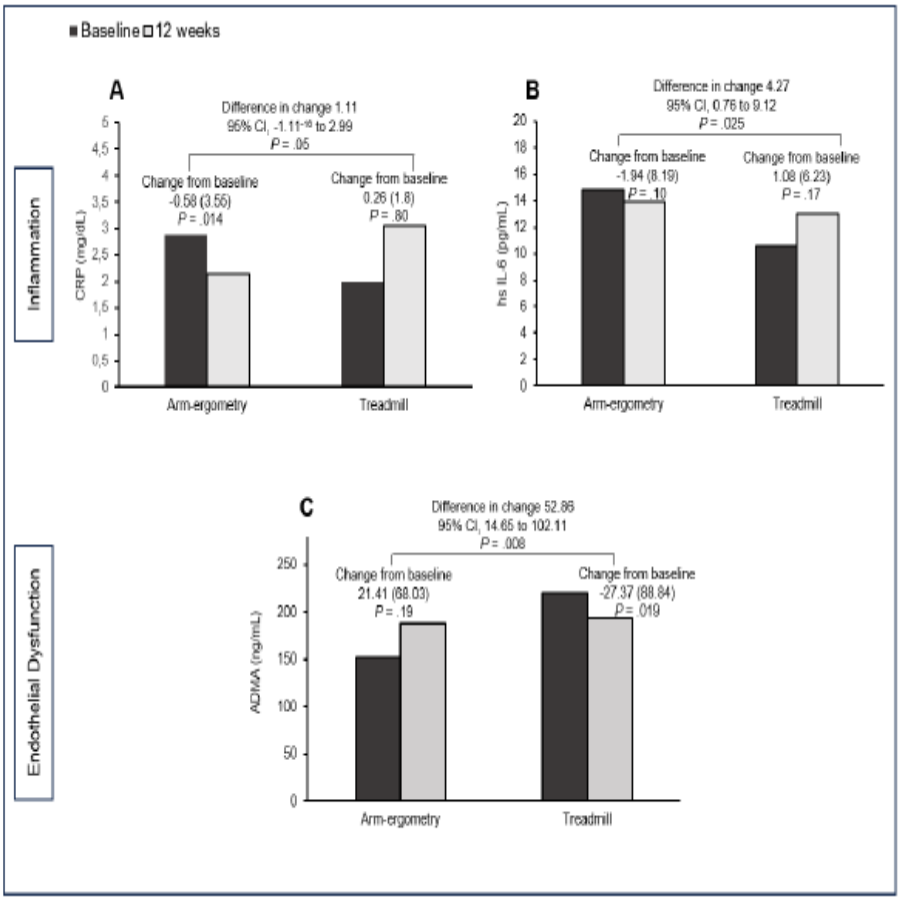
Figure Legend

Fig. 1. Change in CRP (A), hs IL6 (B), ADMA (C) from baseline to the end of the 12-week exercise program. Abbreviations: CRP, C-reactive protein; hsIL6, high-sensitivity interleukin-6; ADMA, asymmetric dimethylarginine.

Figure 1


Baseline 12 weeks
Inflammation
A
Difference in change 1.11
95% CI, -1.11 to 2.99
P = .05
Change from baseline
-0.58 (3.55)
P = .014
Change from baseline
0.26 (1.8)
P = .80
CRP (mg/dL)
Arm-ergometry
Treadmill
B
Difference in change 4.27
95% CI, 0.76 to 9.12
P = .025
Change from baseline
-1.94 (8.19)
P = .10
Change from baseline
1.08 (6.23)
P = .17
hs IL-6 (pg/mL)
Arm-ergometry
Treadmill
Endothelial Dysfunction
C
Difference in change 52.86
95% CI, 14.65 to 102.11
P = .008
Change from baseline
21.41 (68.03)
P = .19
Change from baseline
-27.37 (88.84)
P = .019
ADMA (ng/mL)
Arm-ergometry
Treadmill

SUPPLEMENTAL DIGITAL CONTENT 1

eMETHODS

PARTICIPANTS

We prospectively enrolled patients with peripheral artery disease (PAD) older than 18 years old referred to the Cardiovascular Rehabilitation Unit. PAD was diagnosed through a clinical history and physical examination and confirmed by an ankle-brachial index (ABI) ≤ 0.90 and/or an ABI decrease ≥ 10% after a symptom-limited treadmill stress test. Inclusion criteria were: i) patients able to walk at a speed of at least 3.2 Km/h; ii) able to participate in a supervised exercise program for 12weeks; and, iii) no change in medication for PAD (cilostazol, pentoxifylline, statin and antiplatelet therapy) at least 3 months prior to study enrollment. Medication remained unchanged during the study intervention period.

Exclusion criteria included: i) PAD Leriche-Fontaine stages I, III or IV; ii) a revascularization procedure during the previous 12 months; iii) other chronic conditions causing exercise impairment more than PAD; iv) acute cardiovascular event less than 3 months prior to enrollment; and v) clinical contraindications for physical exercise practice, according to current guidelines.[1]

ETHICAL REQUIREMENTS

The study was conducted according to the recommendations of the Declaration of Helsinki and approved by the Ethics Committee of Centro Hospitalar Universitário de Santo António and School of Medicine and Biomedical Sciences from University of Porto [2016-053(047-DEFI/046-CES)]. The trial was retrospectively registered at the

ISRCTN registry: ISRCTN54908548. Written informed consent was obtained from all participants. The present manuscript was structured according to the Consolidated Standards of Reporting Trials (CONSORT) Statement for randomized trials of Nonpharmacological Treatment.[2]

RANDOMIZATION

Randomization was performed with a computer-based random number generator using a 1:1 allocation ratio for block sizes of four patients. Randomization and allocation were undertaken by a member of the research team who was not directly involved in the recruitment or patients' assessment.

OUTCOMES MEASURES

A blood sample was collected from the antecubital vein of patients who had fasted overnight for at least 12 hours, both before and after the 12-week intervention. Patients were instructed to refrain from smoking for a minimum of 12 hours prior to the blood test. After collection, the samples were centrifuged at 4000 rpm in ambient air for 5 minutes. Changes in CRP were measured using the Roche/CRP4 Cobas c 701/702® analyzer (Roche Diagnostics, Switzerland), according to the manufacturer's instructions. The analyses of CRP were performed by laboratory staff who were not directly involved in the trial, as these measurements are part of routine testing. The remaining serum was stored at -80ºC before being transported on dry ice to the University of Aveiro in Portugal, where enzyme-linked immunosorbent assay analyses for hs IL-6 and ADMA (Elabscience®, USA) were performed. All assessments were conducted blindly by research team members uninvolved in exercise training or the other outcomes evaluations.

INTERVENTIONS

Exercise sessions consisted of twice-weekly sessions comprising 10-min warm-up, 40 min treadmill intermittent walking or arm-ergometry, 1-2 sets of 12-15 repetitions of ten resistance exercises (Borg rating of perceived exertion (RPE) 12 – 13) (squats, leg extension, leg curls, leg abduction, calf rises, chest press, lateral rises, biceps curls, triceps extension and seated row) and 10-min cooldown, led by a physiotherapist and under medical supervision, both with experience in cardiovascular rehabilitation.

Treadmill Supervised Exercise Training

The treadmill exercise prescription followed the standard protocol previously described.[5] The initial treadmill training intensity was established using the baseline CPX and was defined as the grade that brings on the onset of claudication pain, with the initial speed set at 3.2 km/h. Patients walked to a moderate claudication pain level (3 – 4 of 5 on claudication scale), stopped and rested until the claudication pain completely resolved and then resumed walking. Progression occurred if a patient was able to walk at a workload for 8 minutes or more before experiencing a pain level 3 or 4 of 5 on claudication scale; this progression was made in the following session. First, grade increased by 2% increments until 10%; then speed increased by 0.3 km/h increments until 4.8 km/h; then grade was once more increased by 2% increments up to 15% (the last increment was 1%); and then increases in speed by 0.3 km/h increments as tolerated. Heart rate was continuously monitored during sessions using electrocardiographic telemetry and recorded every 5 min with the Borg RPE scale and patient-reported claudication pain severity.

Arm-Ergometry Supervised Exercise Training

The arm-ergometry exercise prescription followed the guidelines for this population.[1] In the first two weeks, patients performed exercise at 50% – 60% of VO_2 peak (RPE:12-13); from the 3rd to 6th weeks intensity increased to 60% – 70% VO_2 peak (RPE 13); and from the 7th to 12th weeks intensity increased to 70% – 80% VO_2 peak (RPE 13-14). Heart rate was continuously monitored during sessions using electrocardiographic telemetry and registered along with the Borg RPE scale.

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DISCUSSION

This thesis explores an alternative, practical, and feasible exercise modality that can be used in patients with PAD, which often faces challenges with traditional walking programs.

In our **first paper**, we compared the impact of an arm-ergometry versus a treadmill supervised exercise training on cardiorespiratory fitness and walking distances. To the best of our knowledge, this was the first trial to compare the impact of these two exercise modalities on VO_2 peak, as a primary outcome, a robust and validated surrogate marker for cardiovascular mortality.[114] We observed a significant incease in VO_2 peak in the AEx group but not in the TEx group, without significant between-groups difference. Neverthless, the recorded change from baseline in VO_2 peak in both groups (TEx: 0.66 mL/kg/min; AEx: 1.73 mL/kg/min) was clinically relevant since changes in VO_2 peak, in symptomatic PAD patients, ranging from 0.4, 1.1, and 1.7 mL/Kg/min are considered to have a small, moderate and large clinical importance, respectively.[115] Therefore, the observed VO_2 peak increase within the AEx group was clinically superior. Concerning the other cardiorespiratory fitness parameters, we found a significant improvement in VO_2 at VT-1 in both exercise groups, without significant between-group differences. Ventilatory efficiency (VE/VCO_2 slope) improved more in the AEx group. Notably, many patients who showed improvements in walking distance did not exhibit a corresponding increase in VO_2peak at the end of the intervention. This outcome largely depends on maximal effort, but many patients discontinue the treadmill CPET due to pain before reaching that level of exertion. Therefore, alternative measures such as VO_2 at VT-1 and the VE/VCO_2 slope, which reflect submaximal exertion, may be more suitable for assessing cardiorespiratory fitness in more symptomatic patients with PAD. Regarding walking distances, we assessed both CPET and 6MWT distances. This approach is based on the well-established understanding that they represent distinct outcomes warranting separate investigation.[116] We observed a statistically and clinically meaningful improvement in both CPET and 6MWT distances in both exercise groups, with a superior increase in the TEx group. We also found a greater improvement in the patient-perceived walking distance (WIQd score) in the TEx group. To the best of our knowledge, only one pilot study has conducted this comparison in CPET distances.[117] However, the ARMEX trial was the first study to undertake this comparison in 6MWT distances and WIQ scores. The authors of the previously mentioned pilot study reported a tendency toward a greater increase in MWD in the treadmill group and in PFWD in the arm-ergometry group.[117] Overall, our findings align with a recent meta-analysis demonstrating that walking

exercise produces greater improvements in walking performance compared to other exercise modalities performed at the same intensity, while alternative modalities, including arm-ergometry, lead to superior increases in VO_2 peak.[31] Both outcomes are desirable, but the extent of improvement depends on specific exercise prescription parameters, including the type of modality used. Speculatively, the clinically greater increase in VO_2 peak observed in the AEx group, combined with smaller gains in both objectively measured and self-perceived walking distances, suggests a predominance of central cardiorespiratory adaptations. The absence of leg pain during arm-ergometry exercise may provide a stronger stimulus for enhancing cardiorespiratory function.[22] Although the improvements in walking distances were less pronounced, they remained clinically significant.[115] These results support the well-established principle of cross-transfer effects in aerobic exercise training, where physiological adaptations in trained muscles also benefit untrained muscle groups.[118] Upper-body training has the potential to improve the exercise capacity of muscles not directly engaged in the activity.[118] However, the absence of local metabolic adaptations in lower-limb skeletal muscles following arm-ergometry likely explains the comparatively smaller improvements in walking distances relative to treadmill training.[119]

In our **second paper**, we compared the effect of these two exercise modalities on walking economy, which is defined as the metabolic cost of ambulation.[120] Aerobic endurance performance is influenced by three factors: maximal VO_2, VO_2 at VT-1, and the submaximal oxygen cost of exercise.[121] In our sample, patients with symptomtic PAD exhibit higher-than-predicted $\dot{V}O_2$ during submaximal walking, resulting in a lower walking economy, consistent with findings from other studies.[122] An altered gait pattern has been suggested as a potential underlying mechanism for reduced walking economy.[123] We observed a significantly greater improvement in walking economy after treadmill exercise training compared to arm-ergometry. Few studies have evaluated this outcome following an exercise program in patients with PAD, but those that have support the improvement in walking economy after treadmill exercise training[124, 125] and the lack of improvement after arm-ergometry exercise.[119, 126] This improvement in walking economy was correlated with both MWD measured by CPET and self-reported walking distance. Consequently, the improvement in walking distances following the 12-week treadmill exercise program can be partially attributed to the enhancement in walking economy, whereas the improvement in walking distances after arm-ergometry cannot be explained by the same mechanism. Previous trials have indicated that improvements in walking performance during the early weeks of treadmill exercise training are primarily driven by enhanced walking efficiency, largely attributed to better gait biomechanics,

whereas later gains are more closely linked to an increase in VO_2 peak.[127, 128] These findings support previous research in healthy individuals, indicating that cross-transfer effects (where improved exercise performance occurs in activities involving untrained limbs) are primarily driven by central mechanisms.[129] In contrast, the specific (non-transferable) effects are likely attributable to adaptations within the trained muscles, reflecting local adaptations.[129] We also observed that patients with a higher BMI experienced less improvement in walking economy with exercise training. Consequently, exploring alternative exercise modalities, such as arm-ergometry, which enhance walking distances through mechanisms other than walking economy, could offer greater potential benefits for some of these patients.

In our **third paper**, we compared the impact of these two interventions on HRQoL and mental health outcomes. The assessment of HRQoL has recently been incorporated into the treatment algorithm for patients with symptomatic PAD in international guidelines,[13] recognizing the importance of including patient-reported outcome measures to capture patients' pain and discomfort, daily functional limitations, and the social and emotional impact of living with the disease.[2] Additionally, evaluating mental health in clinical practice has been deemed crucial, and addressing these conditions should be an integral part of comprehensive PAD management.[130] Arm-ergometry appears to be a promising modality for improving both HRQoL and mental health in these patients, as it avoids pain and has been shown to enhance feelings of well-being in this population.[131] To the best of our knowledge, this is the first study to make this specific comparison in relation to these outcomes. Both intervention groups demonstrated a significant improvement in most SF-36 domains. Only the role-physical and role-emotional domains of the SF-36 showed greater enhancement in the TEx group. However, it is important to note that no significant between-group differences were observed in the PCS and MCS scores. A previous study found that, among patients with PAD, the four strongest predictors of the physical function subscale of HRQoL were all patient-based measures of physical function: WIQ speed score, history of stumbling while walking, WIQ stair-climbing score, and activities of daily living, particularly bathing.[132] The observed improvements in HRQoL in our trial may have been influenced by the inclusion of balance and coordination exercises during the warm-up and cool-down phases of the rehabilitation program, along with resistance training. These exercises may contribute to reducing fall risk, promoting autonomy, improving walking speed, and enhancing stair-climbing ability, factors that, collectively, could play an important role in improving HRQoL in this population. The change in the PCS following exercise training correlated with treadmill PFWD but showed stronger associations with the 6MWT MWD and self-reported walking

distance in the WIQ questionnaire. HADS-A and HADS-D scores improved significantly in both groups after the intervention, without differences between groups. This improvement was associated with the enhancement in self-reported walking distance. Therefore, improvements in outcomes such as MWD measured by the 6MWT, which has been shown to better reflect typical daily walking activities,[116, 133] or the self-reported distance on the WIQ, appear to have a greater impact on HRQoL and mental health in this population than treadmill walking performance.

In our **fourth paper**, we compared the effects of these two exercise modalities on CRF. Research on the impact of CVRP on CRF in patients with PAD remains limited.[134, 135] Some authors question whether the walking exercise that patients with intermittent claudication are able to perform is sufficient to achieve meaningful improvements in CRF,[136] while others highlight the need to explore alternative, pain-free exercise modalities that could potentially modify the cardiovascular risk profile in this population.[135] We observed improvements in the most of the outcomes studied, including blood pressure, body weight, body mass index, waist circumference, waist-to-hip ratio, smoking status, physical activity levels, and sitting time, without between-group differences using either exercise modality. In terms of the lipid profile, improvements in TC-C and LDL-C were noted only in the AEx group, although without between-group differences. In our study, this group performed continuous arm-ergometry exercise for 40 minutes, without rest periods, potentially leading to a higher exercise volume and, consequently, greater energy expenditure. Previous research indicates that a minimum weekly exercise volume and an energy expenditure exceeding 900 Kcal per week are necessary to induce positive changes in the lipide profile.[137, 138] Further studies with larger sample sizes are required to clarify these findings. Overall, our results for CRF control after the CVRP were better than those reported in the literature.[134, 135] In our study, patients participated in a multidimensional CVRP that incorporated several key components, in addition to exercise training, including an evaluation by a nutritionist who developed an individualized plan for each patient, as well as an intervention with a psychologist, which may have enhanced patients' motivation to adhere to preventive measures. Throughout the exercise program, patients were encouraged to follow preventive strategies, including adhering to their prescribed nutritional plan and engaging in home-based exercise. We believe that this comprehensive approach played a crucial role in achieving the positive results observed in our study.

In our **fifth paper**, we compared the effects of arm-ergometry supervised exercise training and a standard treadmill protocol on biomarkers of inflammation and endothelial function in patients with PAD. Inflammation and endothelial dysfunction are key

contributors to the initiation and progression of atherosclerosis and are well-recognized pathophysiological mechanisms in PAD.[10] Our findings demonstrated that arm-ergometry exercise elicited a greater anti-inflammatory response than treadmill exercise, as evidenced by a significantly larger reduction in hsIL-6 and a clear trend toward a more pronounced decrease in CRP. Conversely, we observed a greater improvement in ADMA levels following treadmill training compared to arm-ergometry. A recent meta-analysis investigating the effects of exercise training on inflammatory biomarkers and endothelial function in PAD patients reported a significant improvement in endothelial dysfunction, particularly in FMD, but no significant changes in inflammatory biomarkers (CRP and IL-6).[77] Most interventions in this meta-analysis involved walking exercise, with none including arm-ergometry.[77] The ischemia/reperfusion cycles associated with treadmill or walking training have been cited as one of the main reasons for the lesser impact of this training modality on inflammation.[77] Therefore, exercise-induced improvements in endothelial function and systemic inflammation appear to occur through distinct mechanisms.

FUTURE PERSPECTIVES

As discussed in this thesis, both arm-ergometry and treadmill exercise training have been shown to improve cardiorespiratory fitness and walking distances to varying extents. These outcomes are crucial for the management of patients with PAD and are complementary to one another. Therefore, future research should investigate the potential benefits of combining these two exercise modalities to optimize therapeutic outcomes for PAD patients.

Additionally, future studies should explore the response of specific subpopulations to exercise interventions, such as women, patients with diabetes, and other demographic groups, including older adults and individuals from diverse ethnic backgrounds. These subgroups may exhibit distinct responses to exercise,[139, 140] and understanding these differences could lead to more tailored and effective treatment strategies.

While this thesis primarily focused on the impact of exercise training in patients with intermittent claudication, future research should include asymptomatic patients or those with atypical symptoms, as they may also experience benefits from exercise-based interventions.

Despite the substantial body of evidence supporting the efficacy of SET in symptomatic PAD patients, this approach remains underutilized, with both its availability and compliance being low.[33] Developing strategies to enhance patient participation and long-term compliance is essential. As mentioned, pain has been identified a significant barrier to exercise compliance.[40] For patients who experience pain as a major obstacle, it is crucial to explore and offer pain-free exercise modalities. Assessing patient perspectives and experiences with exercise programs will be critical in understanding their barriers and preferences. Establishing a robust therapeutic partnership between clinicians and patients, with individualized exercise interventions based on patient preferences, may enhance long-term adherence. Further randomized controlled trials are needed to investigate these factors and assess uptake and adherence rates.

An important gap in the literature is the lack of studies incorporating extended follow-up periods to evaluate the sustained long-term effects of SET.[141] Evidence suggests that physical activity levels tend to decline after completing a SET, leading to reductions in walking distances, particularly as measured by the 6MWT.[141] Therefore, supporting patients in transitioning to the maintenance phase of unsupervised exercise after completing SET is essential for sustaining and even improving clinical outcomes. Hybrid programs, which combine an initial hospital-based phase with a subsequent home-based

phase (supported by telemonitoring, activity diaries, logbooks, home visits, phone calls, etc.), may offer additional benefits and warrant further investigation. Long-term follow-up studies will be crucial for comparing the impact of these interventions on key outcomes, including all-cause mortality, cardiovascular mortality, major adverse limb events (such as acute limb ischemia and major amputation), and the need for subsequent revascularization. Evaluating the cost-effectiveness of these interventions is also vital to ensure the sustainable implementation of effective exercise-based rehabilitation programs.

As noted earlier, the pathophysiological mechanisms by which exercise improves clinical outcomes in PAD remain incompletely understood.[10] Further research into these mechanisms may open new therapeutic avenues, including the development of drugs targeting these pathways. Investigating the systemic and local mechanisms underlying these benefits, such as changes in endothelial function, inflammation, and muscle adaptations, will be crucial in advancing our understanding of exercise's role in PAD management.

CONCLUSIONS

The findings and insights presented in this thesis lead to the following conclusions:

The ARMEX trial demonstrated that arm-ergometry exercise resulted in a clinically superior improvement in VO_2 peak compared to treadmill exercise in patients with intermittent claudication, although this difference did not reach statistical significance between the groups. Furthermore, the trial revealed a greater improvement in the VE/VCO_2 slope in the arm-ergometry group, along with a similar improvement in VO_2 at VT-1; both are important indicators of cardiorespiratory fitness. However, the standard treadmill protocol was more effective in improving walking distances, as measured by CPET, the 6MWT, and self-reported distance in this population.

Treadmill exercise was found to improve walking economy more than arm-ergometry. The observed enhancement in walking distances following the treadmill exercise program can, at least partially, be attributed to the improvement in walking economy. Moreover, patients with a higher BMI showed less improvement in walking economy following exercise training, highlighting the need for tailored care and specialized interventions for this group.

When incorporated into a multidimensional program, both exercise modalities effectively enhanced HRQoL, reduced anxiety and depression levels, and similarly improved the majority of the evaluated cardiovascular risk factors.

Arm-ergometry exercise training was more effective than treadmill exercise in reducing inflammation, demonstrating a significantly greater reduction in hsIL-6 levels and a clear trend toward a reduction in CRP. In contrast, treadmill exercise training led to a greater reduction in ADMA levels, indicating a more significant impact on this marker of endothelial dysfunction.

These results support treadmill training as the first-line exercise modality for enhancing walking capacity in patients with PAD. However, arm-ergometry emerges as a viable complementary or alternative option, particularly for well-selected patients unable to engage in long walks or those intolerant to exercise-induced leg pain, as it positively influences various outcomes. Prioritizing patient perspectives and preferences will be essential to fostering sustained long-term adherence to exercise.

Overall, this thesis contributes to improved clinical practice in CVRP for the management of patients with PAD.

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