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Review Article

NITRIC OXIDE BIOAVAILABILITY AND EXERCISE-MEDIATED BLOOD PRESSURE REDUCTION IN HYPERTENSIVE INDIVIDUALS

BIODISPONIBILIDADE DO ÓXIDO NÍTRICO E REDUÇÃO DA PRESSÃO ARTERIAL MEDIADA PELO EXERCÍCIO EM INDIVÍDUOS HIPERTENSOS

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RESUMO

O objetivo deste estudo foi examinar os efeitos agudos e crônicos de exercícios aeróbicos e resistidos sobre a biodisponibilidade do óxido nítrico (NO) e verificar sua relação com a redução da pressão arterial após o exercício em indivíduos hipertensos. **Metodologia:** Foi realizada uma revisão sistemática utilizando as bases de dados eletrônicas MEDLINE (via PubMed), Scopus, Web of Science e Cochrane. Foram incluídos ensaios clínicos randomizados que avaliaram se a biodisponibilidade de NO após o exercício está associada à redução da pressão arterial. **Resultados:** Um total de 11 ensaios clínicos atendeu aos critérios de inclusão, com o tamanho da amostra variando de 17 a 44 indivíduos, sendo 92 homens e 155 mulheres, totalizando 247 participantes. A amostra consistiu em indivíduos diagnosticados com hipertensão arterial sistêmica. Oito estudos focaram em exercícios aeróbicos, enquanto três abordaram o treinamento resistido. Tanto os exercícios resistidos quanto os aeróbicos prolongados foram positivamente correlacionados com o aumento da biodisponibilidade de NO após o exercício, o que resultou em uma redução significativa da pressão arterial em indivíduos hipertensos. A intensidade e a duração do exercício influenciaram diretamente a magnitude desse aumento na biodisponibilidade de NO, potencializando os efeitos benéficos na pressão arterial. **Conclusão:** O aumento da biodisponibilidade do óxido nítrico, promovido tanto por exercícios aeróbicos quanto resistidos, de forma aguda e crônica, foi positivamente associado à redução da pressão arterial pós exercício em pacientes hipertensos.

Palavras-chave: Exercício, Atividade física, Óxido nítrico, Hipertensão, Pressão sanguínea.

ABSTRACT

The aim of this study was to examine the acute and chronic effects of aerobic and resistance exercises on nitric oxide (NO) bioavailability and to assess its relationship with post-exercise blood pressure reduction in hypertensive individuals. **Methodology:** A systematic review was conducted using the electronic databases MEDLINE (via PubMed), Scopus, Web of Science, and Cochrane. Randomized clinical trials that evaluated whether post-exercise NO bioavailability is associated with blood pressure reduction were included. **Results:** A total of 11 clinical trials met the inclusion criteria, with sample sizes ranging from 17 to 44 individuals, comprising 92 men and 155 women, totaling 247 participants. The sample consisted of individuals diagnosed with systemic arterial hypertension. Eight studies focused on aerobic exercises, while three addressed resistance training. Both resistance exercises and prolonged aerobic exercises were positively correlated with increased NO bioavailability following exercise, which resulted in a significant reduction in blood pressure in hypertensive individuals. The intensity and duration of exercise directly influenced the magnitude of this increase in NO bioavailability, enhancing the beneficial effects on blood pressure. **Conclusion:** The increase in nitric oxide bioavailability, promoted by both aerobic and resistance exercises, both acutely and chronically, was positively associated with post-exercise blood pressure reduction in hypertensive patients.

Key-words: Exercise, Physical activity, Nitric oxide, Hypertension, Blood pressure.

Introduction

Systemic arterial hypertension (SAH) accounts for over 50% of cardiovascular events and 17% of deaths worldwide due to elevated blood pressure[1,2]. Furthermore, SAH is a significant risk factor for the development of coronary artery disease and atherosclerosis, increasing the likelihood of ischemic and hemorrhagic strokes[3]. These dysfunctions can arise from imbalances in various systems, including cardiovascular, neural, renal, and endothelial systems, leading to detrimental changes in blood pressure. Understanding the integrated functioning of these systems is essential for developing effective strategies for the control of hypertension[4].

SAH can be managed through the use of antihypertensive medications and lifestyle modifications[5]. Among the available interventions, physical exercise stands out as an effective, low-cost, and easily accessible option that may contribute to the reduction and control of systemic blood pressure in both acutely and chronically hypertensive individuals[5]. Acute responses to exercise-induced blood pressure reduction manifest in two distinct patterns: an immediate decrease immediately after exercise and a sustained reduction during the first 24 to 48 hours following the session. Additionally, chronic responses are elicited through the implementation of aerobic exercise training programs, leading to long-term improvements in blood pressure regulation[6].

The changes in systemic blood pressure resulting from physical exercise may be attributed to the inhibition of sympathetic activity and a reduction in circulating levels of angiotensin II, adenosine, and endothelin. These factors contribute to decreased peripheral vascular resistance and increased baroreflex sensitivity[7]. Additionally, vasodilating substances play a significant role in modulating systemic blood pressure, promoting a clinical outcome characterized by reduced blood pressure due to the vasodilatory effect of nitric oxide (NO)[8].

The expression of vasodilating factors, such as nitric oxide (NO), appears to induce an increase in the bioavailability of NO post-exercise, a factor that promotes vasodilation and contributes to blood pressure reduction. Therefore, physical exercise, whether aerobic or resistance-based, seems to influence the reduction of blood pressure and the increase in the bioavailability of NO[9,10].

NO acts as a regulator of endothelial function and mediates endothelium-dependent vasodilation, primarily produced by endothelial nitric oxide synthase (eNOS), which is part of a family of enzymes responsible for synthesizing NO from L-arginine[11]. Several mechanisms contribute to the increase in NO bioavailability, with physical exercise emerging as a viable alternative that yields promising results in inducing NO production[6]. This increase in NO can occur acutely or chronically when associated with physical exercise and appears to have a positive relationship with the control of SAH[9]. However, to date, there are no systematic reviews evaluating the relationship between increased NO bioavailability and reduced blood pressure in hypertensive patients across various clinical trials in the literature.

This study is therefore justified by the need to thoroughly explore the acute and chronic effects of different types of physical exercise on nitric oxide (NO) bioavailability and its correlation with blood pressure reduction in hypertensive individuals. Understanding this relationship could not only enrich scientific knowledge but also provide practical guidelines for the implementation of exercise programs as an effective strategy for managing hypertension, thereby promoting cardiovascular health in an accessible and sustainable manner.

Given this scenario, the aim of this study was to examine the acute and chronic effects of aerobic and resistance exercises on nitric oxide (NO) bioavailability and to verify its relationship with post-exercise blood pressure reduction in hypertensive individuals.

Methods

This systematic review was registered in PROSPERO (CRD42021271705), the international database of systematic reviews in health and social care from the Center for Reviews and Dissemination at the University of York. The review was conducted using the electronic databases MEDLINE, via PubMed, in addition to Scopus, Web of Science, and Cochrane. Randomized clinical trials that investigated the relationship between the increase in nitric oxide (NO) bioavailability after exercise and the reduction of blood pressure in hypertensive individuals were included in the study, without restrictions on language or publication period. The exclusion criteria were duplicate articles, studies that used exogenous administration of substances to stimulate NO production, studies that did not include

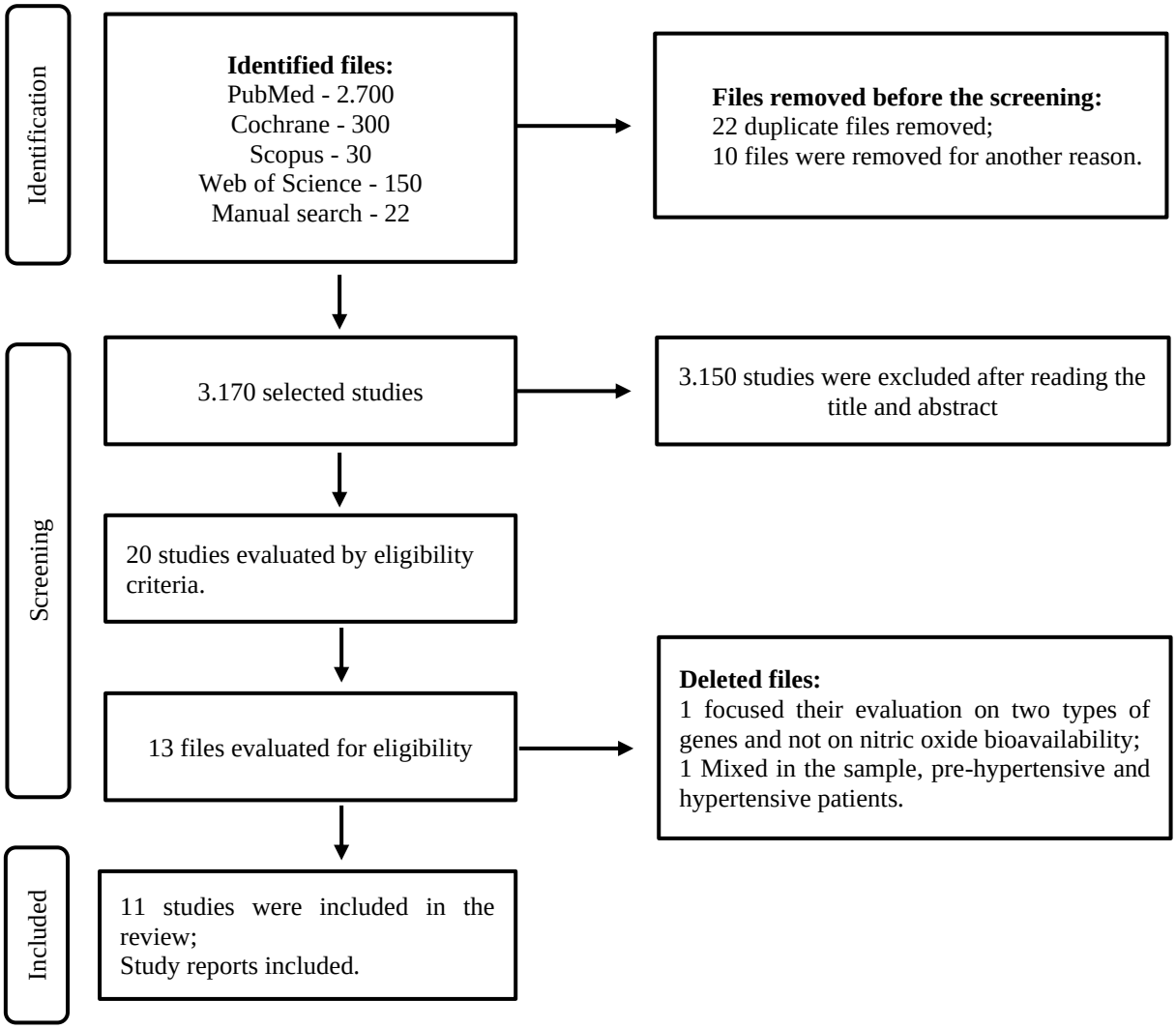
hypertensive individuals in the sample, Studies in which there was administration of phosphodiesterase-5 inhibitors, nitrates, nitric oxide synthase enzyme inhibitors and vasoconstrictors, and research that employed animal models.

The process of identifying methodological aspects and extracting data from the articles was performed by two independent reviewers. The selection of studies was carried out in two stages. The first stage involved reading the title and abstract from the predetermined keywords. In the second stage, the full reading of the articles was carried out and the inclusion and exclusion criteria were analyzed. After analysis of eligibility, data were extracted and a file containing the variables of interest was built using Microsoft Excel, version of the year 2010. To increase the chances of identifying eligible articles, a manual search was performed, in addition to reading the bibliographic references of the selected articles. The results of all selection steps were compared, and disagreements were resolved by consensus between the two reviewers.

The descriptors were identified from the Mesh search, in addition to the use of keywords from the articles related to the topic. Pubmed's search strategy and its respective descriptors: ((((((Nitric Oxide[Title/Abstract]) OR (Nitric Oxide[MeSH Terms])) OR (Oxide, Nitric[MeSH Terms])) OR (Nitric Oxide, Endothelium-Derived[MeSH Terms])) OR (Nitric Oxide Synthase[Title/Abstract])) OR (Nitric Oxide Synthase[MeSH Terms]))) AND (((Exercises[MeSH Terms]) OR (Exercises[Title /Abstract]))). Similar search strategies were used in the Web of Science, Scopus, and Cochrane bibliographic databases, and duplicates were identified and excluded in all databases (Figure 1)

Study characteristics such as the number of participants, metabolic changes, types of exercise performed (resistance or aerobic), and primary and secondary outcomes were done manually.

Figure 1- PRISMA diagram showing articles on the bioavailability of NO and exercise.



Source: Authors

To assess the methodological quality of the selected studies, the Physiotherapy Evidence Database (PEDro) scale was used. The PEDro scale is a reliable and objective tool that helps to identify which of the RCTs are likely to be externally (criteria 1) and internally (criteria 2–9) valid and could have sufficient statistical information to make their results reliable (criteria 10 and 11). Each article was evaluated by two independent reviewers using the eleven-item checklist to produce a maximum score of 10 (the sum of points awarded for criteria 2–11). Points are awarded only when a criterion is fully met (Table 1).

Table 1 - Classification of methodological quality of the studies included in this systematic review, using the PEDro Scale.
Source: Authors.

		Items from the PEDro Scale										
Autor	**Score**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Nyberg et al.[12]	7	Y	N	N	Y	N	N	Y	Y	Y	Y	Y
Izade et al.[13]	6	Y	N	N	Y	N	N	N	Y	Y	Y	Y
Turky et al.,[14]	9	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Yan et al.,[15]	9	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Higashi et al.[16]	7	Y	N	N	Y	N	N	Y	Y	Y	Y	Y
Olher et al.[17]	6	Y	N	N	Y	N	N	N	Y	Y	Y	Y
Orsano et al.[18]	7	Y	N	N	Y	Y	N	N	Y	Y	Y	Y
Santana et al.[19]	8	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y
Coelho et al.[20]	8	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y
Zaros et al.[21]	6	Y	N	N	Y	N	N	Y	Y	Y	N	Y
Cruz et al.[22]	7	Y	N	N	Y	Y	N	N	Y	Y	Y	Y

Source: Authors.

Results

A total of 11 clinical trials met the inclusion criteria, with sample sizes ranging from 17 to 44 participants, including 92 men and 155 women, for a total of 247 individuals. All participants were diagnosed with systemic arterial hypertension. In terms of age, two studies focused on elderly individuals, while five involved young hypertensive patients. The physical exercise protocols employed both aerobic and resistance exercises. Eight studies involved aerobic exercises, five of which used a cycle ergometer, two used walking as an intervention, and one was conducted in an aquatic environment. Resistance exercises were the focus of the remaining three studies, where isometric exercises, muscle power training, and both traditional and high-speed resistance training were utilized.

The duration of the aerobic exercise sessions ranged from 20 to 60 minutes, with intensities between 50% and 100% of maximum heart rate (HRmax). Two studies employed high-intensity aerobic exercise (85% to 90% of HRmax)[12,13]. Six studies used moderate intensity, ranging from 50% to 75% of HRmax[14-16,19]. The weekly frequency of physical exercise was from 2 to 7 days, and four studies performed the evaluations right after the exercise session and six of them evaluated the changes from 6 to 12 weeks after the beginning of the intervention. In one of the studies where resistance exercise was used, the evaluation was performed right after a submaximal isometric exercise session, consisting of 4 sets of 1-minute duration, using 30% of the voluntary capacity of maximum contraction, in the leg press and bench press exercises[17]. Two studies that used resistance exercises compared traditional resistance training with methods such as power training or high-speed resistance training[18,20].

The control groups were either instructed to avoid specific exercise interventions or received the same conventional treatment as the experimental groups. The characteristics of each study are summarized in Table 2.

Table 2. The characteristics of each study.

Author/year	n (sample)	Groups	Training Protocol	Results
Higashi et al.[16]	12 M e 3 W hypertensive patients with a mean age of 44 years	G1 – aerobic G2 – CON	**I**: 30 min walk (50% VO2) 5 to 7 times a week for 12 weeks	There was no significance ↑ of NO post-exercise and there was a significance ↓ of SBP and DBP in G1
Zaros et al.[21]	11 W postmenopausal hypertensive patients with a mean age of 50 years	G1 – aerobic	3 days a week, each 60-minute session for 6 months at moderate intensity (50% heart rate reserve)	There was a significance ↑ of NO bioavailability and a significant ↓ of SBP and DBP
Nyberg et al.[12]	10 M e 11 W hypertensive and sedentary with a mean age of 46 years	G1 – aerobic G2 – CON	I: Cycle ergometer 2-3x per week + additional cycling or running session 1x per week for 8 weeks	There was a 30% ↑ NO bioavailability and a significant ↓ of SBP and DBP in G1
Turky et al.[14]	25 W hypertensive patients aged between 40 and 50 years	G1 – aerobic G2 – CON	I: 20min walk (60 to 75% Fcmax); 3x a week for 8 weeks	There were ↑ 30.4% and 8% of NO in G1 and G2, respectively, and ↓ of SBP and DBP in 16.2% and 9.5% in G1 and 3% for both in G2
Santana et al.[19]	23 W hypertensive patients with a mean age of 65 years and treated with hydrochlorothiazide	G1 - high-intensity exercise G2 - moderate intensity exercise G3 – CON	Cycle ergometer I: (1) exercise test with constant load for 20 min, at an intensity corresponding to 90% of the anaerobic threshold; 2) maximal incremental test;	There was ↓ SBP and PAM in G1 and G2 compared to G3, obtaining more significance ↓ in G1. NO ↑ significantly in G1 compared to pre-exercise and in G1 and G2 compared to G3

Coelho-Júnior et al.[20]	21 W hypertensive patients with a mean age of 67 years	G1 –RT G2 – ST G3 – CON	Resistance training vs power training group (A single training session 3 sets of 8 repetitions in 8 different exercises	There was ↓ of BP during 35 minutes for G2 compared to pre-exercise. NO ↑ levels in G1 and G2
Cruz et el.[22]	23 M e 21 W resistant hypertensives aged between 40 and 65 years	G1 - training in an aquatic environment G2 - CON	I: 60 min, 3x a week, during 12 weeks of training	There was a significance ↓ of SBP and DBP and a significant ↑ of NO in G1. No changes in G2
Orsano et al., 2018[18]	15 W hypertensive patients with a mean age of 60 years	G1 – Traditional RT G2 - RT at high speed	I: Traditional resistance training group x high-speed resistance group 3 sets of 10 repetitions, performing 10 different exercises	There was no significant difference in SBP and DBP in an acute form, however, there was ↑ NO bioavailability in G1 compared to G2
Izade et al., 2018[13]	17 M e 13 W hypertensive patients with a mean age of 61 years and treated by drug therapy	G1 – HIIT G2 – CON	Cycle ergometer I: 35min total, divided into 10x1.5min intervals at 85-90% Fcmax, each interval 2 min of active rest at 50-55% FCR; 3x per week for 6 weeks C: No training	There was ↑ NO bioavailability ↓ of SBP and DBP in G1 compared to G2
Olher et al., 2020[17]	12 M e 12 W hypertensive and sedentary with a mean age of 41 years	G1 – RT isometric G2 – CON	I: Hypertensive group: Exercise session consisting of 4 sets of submaximal contractions for each exercise lasting 1 min at 30%	There was a significant ↓ SBP and a significant ↑ NO in G1 compared to G2

			of MVIC and 2 min rest interval. (leg press and bench press)	
Yan et al.[15]	18 M stage 1 hypertensive patients aged between 30 and 50 years	G1 – aerobic	Two training sessions were randomly performed on a cycle ergometer. One of the times performed at a moderate intensity of 40% ~ 50% of your HRR for 20 minutes (session E20), and in the other session the duration was 40 min (session E40)	NO ↑ levels significantly post-exercise, however, there was no difference between one session and another. PAD and PAS ↓ after both sessions

Note: CON - control; **RT** – resistance training; **M** – Man; **W** – woman; **NO** – nitric oxide; **SBP** – systolic blood pressure; **DBP** – diastolic blood pressure; ↑ - increase; ↓ - reduction; **MAP** – mean arterial pressure; **ST** - strength training; **Fcmax** - maximum heart rate; **MVIC** – maximum voluntary isometric contraction; **HRR** – reserve heart rate.
Source: Authors.

The dynamics of blood pressure and changes in nitric oxide (NO) bioavailability in the acute phase, immediately after exercise, were examined in five studies. Two of these studies used aerobic exercises on a cycle ergometer. Yan et al.)[15] found that, in 20-minute sessions (E20), systolic blood pressure (SBP) measured 6 minutes after exercise (140 ± 11.25 mmHg) was not significantly different from the resting value (140.44 ± 12.70 mmHg). However, in the 40-minute session (E40), SBP 6 minutes after exercise (126.78 ± 5.62 mmHg) was 14 mmHg lower than the resting value (140.33 ± 10.32 mmHg) ($P < 0.01$). Regarding nitric oxide synthase (NOS) bioavailability, no difference in plasma levels between the pre- and post-exercise sessions. However, the increase in NO levels in the E40 session (24.47%) was significantly greater than in the E20 session (9.24%) ($P < 0.01$)[15].

In the study by Santana et al.[19], two exercise intensities were compared: a constant-load test of 20 minutes at an intensity corresponding to 90% of the anaerobic threshold (AT), and a maximal incremental test (IT). Blood pressure reductions were observed in both protocols, with systolic blood pressure (SBP) decreasing from 122.9 mmHg to 119.6 mmHg in the IT group, and from 121 mmHg to 118 mmHg in the AT group. Although both exercise sessions reduced SBP and mean arterial pressure compared to the control group, higher-intensity exercise (IT) was more effective in lowering post-exercise SBP. In terms of nitric oxide (NO) bioavailability, the IT group showed a more pronounced increase (from 300 μM to 400 μM), although both exercise sessions significantly elevated nitrite (NO2-) levels compared to the control group[19].

Olher et al.[17], the acute effects of resistance exercise were evaluated, showing a significant decrease in systolic blood pressure (SBP) only in hypertensive individuals at 45 and 60 minutes post-exercise (baseline vs. 45 min: $p = 0.03$, $\Delta\% = 4.44\%$; vs. 60 min: $p = 0.018$, $\Delta\% = 5.58\%$). SBP decreased from 131.86 ± 2.54 mmHg to 126.0 ± 2.59 mmHg at 45 minutes ($p = 0.03$) and to 125.93 ± 2.54 mmHg at 60 minutes ($p = 0.018$). Nitric oxide (NO) levels also increased immediately after exercise, but only in hypertensive individuals ($p = 0.008$, $\Delta\% =$

16.44%)[17]. In a comparison of resistance training methods, resistance training was compared with power training. In the muscle power training group, SBP decreased significantly at 10, 15, 30, and 45 minutes post-exercise ($F = 3.7$, $p = 0.001$) compared to rest. However, traditional resistance training was not effective in reducing blood pressure. Both groups, however, demonstrated an increase in NO bioavailability 60 minutes after the sessions[20].

In their study, Orsano et al.[18] evaluated the acute effects of traditional resistance training versus high-speed resistance training on blood pressure reduction and its potential association with increased nitric oxide (NO) bioavailability. Both groups performed three sets of ten repetitions, with the only variation being the speed of execution across ten different exercises. The results indicated that there was no significant difference in systolic blood pressure (SBP) and diastolic blood pressure (DBP) immediately after exercise (up to 30 minutes post-exercise). However, NO bioavailability increased more markedly in the high-speed resistance training group (from 50 to 200 μM) compared to the traditional resistance training group (from 50 to 100 μM).

The follow-up of the sample over longer periods, ranging from 6 to 12 weeks, was conducted in studies utilizing aerobic exercises. High-intensity interval training (HIIT) demonstrated a negative correlation between changes in plasma endothelin-1 and alterations in plasma apelin and nitric oxide synthase (NOS) levels. This suggests that by increasing plasma levels of apelin and NOx, HIIT may effectively reduce arterial blood pressure. In the HIIT group, systolic blood pressure (SBP) decreased from 130 mmHg ± 6.71 to 127 mmHg ± 6.35, while diastolic blood pressure (DBP) decreased from 82.33 mmHg ± 3.71 to 80.20 mmHg ± 3.60. Additionally, NOx bioavailability increased from 19.49 μM ± 1.93 to 46.63 μM ± 7.39 in the exercise group[13]. When using a cycle ergometer at 20 watts during high-intensity training sessions, Nyberg et al.[12] observed a 30% increase in nitric oxide synthase (NOS) bioavailability compared to the pre-training period, which lasted 8 weeks. In addition to the increase in NOS bioavailability, there was a significant decrease ($P < 0.05$) in systolic blood pressure by 9 mmHg and diastolic blood pressure by 12 mmHg at rest in individuals with essential hypertension.

Low- and medium-intensity aerobic exercises were also employed to assess the chronic dynamics of blood pressure. Turky et al.[14], evaluated the effects of walking at an intensity corresponding to 60% to 75% of HRmax for two months, finding that nitric oxide (NO) levels increased by 30.4%, while systolic blood pressure decreased by 16.2% (from 148 mmHg to 124 mmHg). Diastolic blood pressure also decreased by 9.5% (from 94 mmHg to 85 mmHg), and body mass index dropped by 6%[12]. In a study by Higashi et al.[16] participants engaged in walking at an even lower intensity (50% of Fcmax) for 12 weeks, 5 to 7 times a week, which significantly reduced systolic blood pressure by 7 mmHg and diastolic blood pressure by 4 mmHg. Although post-exercise NO bioavailability was higher than pre-exercise levels (NOx increased from 24.6 μM to 26.1 μM), the difference was not statistically significant[14].

Continuing with the examination of low- and medium-intensity aerobic exercises, Zaros et al. [21] reported that performing aerobic exercises at 50% of HRmax for 6 months resulted in a significant reduction in both systolic and diastolic blood pressure values (from 141/90 mmHg to 123/80 mmHg). This reduction was accompanied by a notable increase in NOx levels, with baseline measurements showing 10 ± 0.9 μM and post-exercise training levels at 16 ± 2 μM. Conversely, when aerobic exercises were conducted in an aquatic environment over a 12-week period, participants experienced a significant reduction in systolic blood pressure (from 163.2 ± 3.5 mmHg to 130.4 ± 2.5 mmHg) and diastolic blood pressure (from 95.1 ± 1.6 mmHg to 80.6 ± 1.9 mmHg). Additionally, a correlation was observed between the increase in NO bioavailability and the reduction in blood pressure[22].

Discussion

The objective of this systematic review was to analyze evidence from randomized clinical trials, which evaluated whether increased post-exercise nitric oxide bioavailability is related to arterial hypotension in hypertensive individuals. The results showed that there was a positive correlation between the reduction in blood pressure associated with the increase in the bioavailability of nitric oxide after physical activity. This correlation seems to occur, as physical training increases the release of NO from the endothelium, which acts as a vasodilator, enhancing blood flow and decreasing blood pressure[23].

The influence of exercise and nitric oxide on systemic arterial hypertension

The SAH population seems to have different characteristics regarding the endothelium's ability to function, with changes that negatively influence blood flow[12]. According to Michael Nyberg et al.[12], individuals with SAH have different responses to exercise than normotensive individuals regarding blood flow. blood, this change is not associated with a reduced capacity of the NO and prostanoid systems, but with an alteration of the endothelium. Hypertensive individuals have a decrease in nitric oxide bioavailability secondary to the increase in the excessive production of reactive oxygen species (ROS)[24].

SAH may be a factor that negatively influences the production of NO secondary to endothelial dysfunction[24]. This alteration in the endothelium's ability to produce NO in hypertensive patients may be associated with increased oxidative stress, which is considered the main mechanism involved in hypertensive patients pathogenesis of endothelial dysfunction[24]. The reduction in the bioavailability of NO occurs through the alteration of its metabolism, which originates from the inactivation, degradation, or presence of NO inhibitors, evidencing a relationship with oxidative stress and a decrease in the bioavailability of NO.

These findings conflict with the findings of the study by Michael Nyberg et al[12] who evaluated a group of hypertensive individuals and a group of normotensive individuals, allowing us to infer those hypertensive individuals had lower blood flow in the leg before performing exercises on a cycle ergometer. However, this reduction in blood flow was not associated with a reduced capacity of vasodilators such as NO but suggests that the reduction in blood pressure in the present study was associated with a training-induced change in the tonic effect of NO on vascular tone[12].

According to the authors of the studies selected in this review,[13-15,17,19,20,22] the types of exercises, whether resistance or aerobic, in addition to the duration of physical activity, longer or shorter, can promote improvement in endothelial function, favoring increased NO bioavailability and possible reduction of blood pressure in hypertensive patients[25].

The mechanism that seems to be responsible for favoring the increase in NO bioavailability in hypertensive individuals, during and after physical activity, is shear stress[13-15,17,19]. This mechanism occurs due to the friction force generated by the blood flow, secondary to an activity that demands greater blood flow[26]. From the increase in blood flow, a cascade of events will occur, which will activate the endothelial nitric oxide synthase, which will stimulate the production of NO that will rapidly diffuse from the endothelial cells to the smooth muscle cells of the blood vessel, as demonstrated in Figure 2.

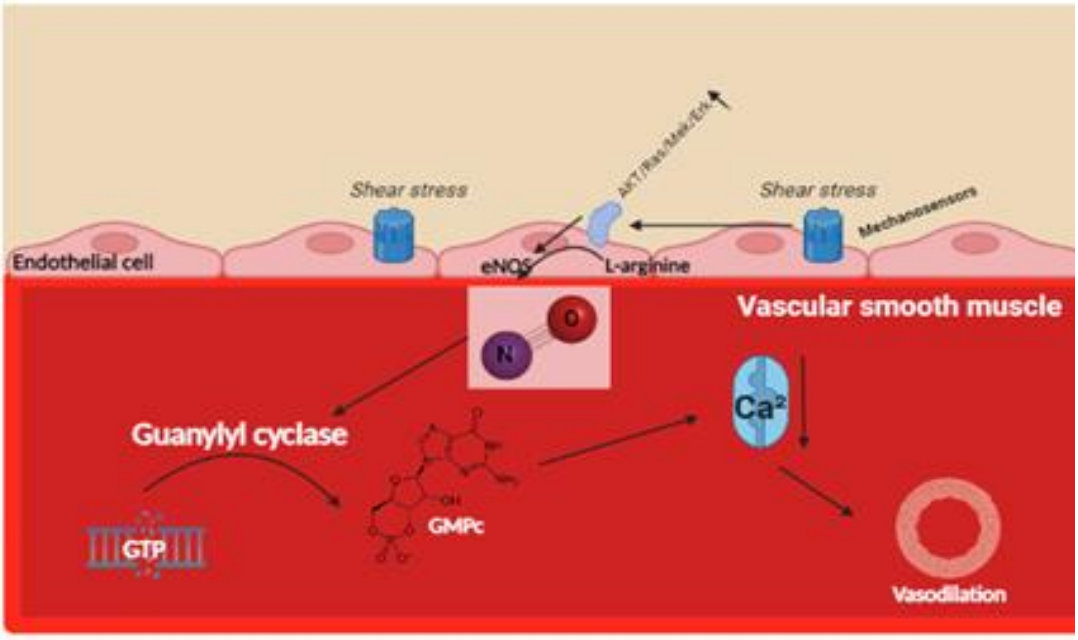


Figure 2. Physical exercise stimulates an increase in blood flow in the vessels, resulting in the "shear stress" mechanism, which will favor an increase in the bioavailability of NO. Then, membrane proteins will be activated through mechanoreceptors, which will phosphorylate nitric oxide synthase (eNOS). The NO produced will migrate to smooth muscle cells, forming cGMP which will have the function of reducing intracellular calcium, this entire cascade of events will result in a decrease in peripheral vascular resistance from the relaxation of vascular smooth muscle.
Source: Authors.

A previous study demonstrated that the stimulus of "shear stress" is responsible for vascular adaptations, favoring the functionality of the artery and remodeling as a function of exercise[27]. The findings reinforce the result of this review, where exercise was responsible for promoting a reduction in BP secondary, among other variables, to the increase in the bioavailability of NO in hypertensive individuals, who seem to have significant vascular alterations that can alter the production of vasodilating substances and NO[13-15,17,19]

The increase in the bioavailability of NO improves vascular function and favors the reduction of BP, in addition to indicating that it is dependent on the execution time of the activity[23]. Physical exercise will favor the synthesis of NO through chemical mechanisms, which will interact, such as acetylcholine and bradykinin, with receptors on endothelial cells[28]. The result of the physical stimulus on the vascular walls causes a greater release of nitric oxide in the blood vessel[29]. Hypertensive individuals seem to benefit when a series of physical exercises are performed with greater volumes and intensities when correlated with NO, this event is the result of a longer duration of the stimulus arising from the shear stress mechanism.

In the study by Yan., et al [15], it was demonstrated when comparing different volumes of aerobic stimuli and observing that the greater volume had better results in terms of increasing NO bioavailability and reducing BP. In the study by Santana et al., 2013[19], the stimulus of greater intensity had more expressive results in increasing the bioavailability of NO and reducing BP. In a previous study, a result regarding exercise intensity and duration was reported. Aerobic exercise, achieved at medium intensity and duration, obtained positive results

for the increase in BP, associated with the increase in the mean NO[29].

The findings in the literature correlating shear stress with increased blood flow corroborate the results found in this study[12,13,15,16,18-20]. Tinkken et al.[27], performed acute and chronic assessments of blood flow from the "shear stress", provided by the performance of handgrip exercise. It was identified that 30 minutes of performing the activity generates changes in blood flow, which are abolished if shear stress does not occur. In addition, 8 weeks of training generated a time-dependent change in vessel remodeling[27].

The increase in NO production seems to be closely linked to physical exercise, regardless of its modality, whether exercise with aerobic characteristics or resistance training, favoring shear stress and, consequently, increasing the bioavailability of NO[12-15,17,19-22]. The duration and intensity of the exercise are shown to be variables that influence the magnitude of the increase in NO production[13,15]. It is already a consensus in the literature that aerobic exercise has a greater effect on BP reduction when compared to resistance exercise in hypertensive individuals, and NO may be one of the factors that contribute to reducing blood pressure. The performance of physical exercise for longer periods favors a longer duration of shear stress, resulting in a more expressive increase in the bioavailability of NO than in activities of short duration[1-4,7,8].

Conclusion

In conclusion, the increase in nitric oxide bioavailability, which occurs through aerobic and resistance physical exercise, both acutely and chronically, was positively associated with the reduction of blood pressure in hypertensive patients. Physical exercise can be an easily accessible intervention tool with good prognoses for hypertensive patients and can also be used to prevent and control blood pressure.

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