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REVIEW ARTICLE

Effect of Physical Training on Nitric Oxide Levels in Patients with Arterial Hypertension: An Integrative Review

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Abstract

The regular practice of physical exercise as a non-pharmacological treatment of arterial hypertension (AH) has been encouraged due to causing a series of physiological responses in the cardiovascular system, such as the production of vasoactive substances, including nitric oxide (NO). NO is a relaxation factor released by the endothelium, and the decrease in its bioavailability is related to coronary and arterial diseases, such as AH. This study aimed to perform an integrative literature review to elucidate the effect of physical training on NO levels in patients with AH and to establish a relationship between these levels and blood pressure (BP) control. A literature review was was performed by searching PubMed / MEDLINE, Lilacs, Scielo, Cinahl and Embase databases. The search string used was ("arterial hypertension" OR hypertension) AND (exercise OR "physical exercise" OR "aerobic exercise" OR "exercise training" or "physical activity") AND ("nitric oxide"). We included fully available controlled and uncontrolled clinical trials published in English and Portuguese languages in the last 10 years. The review consisted of 16 articles, of which 13 reported an increase in NO production after the physical training intervention, and three studies found no change. In addition, 15 studies observed a reduction in BP after the intervention. In conclusion, regular practice of physical exercises, advocating moderate intensity, can improve NO bioavailability in pre-hypertensive and hypertensive individuals, which seems to be one of the mechanisms responsible for BP reduction.

Keywords

Blood Pressure; Hypertension; Exercise; Physical Conditioning Human; Nitric Oxide; Endothelium Dependent Relaxing Factors; Vasoactive Substances; Cardiovascular System.

Introduction

Arterial hypertension (AH) is characterized as a multifactorial clinical condition and considered one of the main risk factors for cardiovascular morbidity and mortality. In addition to a sustained elevation in blood pressure (BP), AH is also associated with metabolic disorders and functional and structural changes in target organs, which can be aggravated by the presence of other risk factors and is responsible for several other complications.[1]

The practice of physical exercise as a non-pharmacological therapeutic approach to AH has been increasingly encouraged by health professionals, as it causes many physiological responses in body systems, especially in the cardiovascular system.[2] Physical training, when performed regularly, causes important autonomic and hemodynamic adaptations, as well as humoral changes related to the production of vasoactive substances, such as nitric oxide (NO).[3] These changes are responsible for the reduction or even normalization of the BP levels in patients with mild to moderate hypertension, using or not using medications.[1,4,5]

NO, a relaxation factor released by the endothelium,[6] is a gaseous mediator responsible for a variety of physiological phenomena,[7] and a decrease in its

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bioavailability is related to coronary and arterial diseases, among others. In systemic AH, the increase in oxidative stress and endothelial dysfunction promotes a reduction in the bioavailability of NO and its action on the vascular wall, affecting vascular relaxation.[8,9]

In this sense, moderate physical exercise can be an effective non-pharmacological medicated means to increase NO bioavailability and, hence, mediate positive adjustments in the tissues. The main functions of NO in the cardiovascular system include regulation of vascular tone by the vasodilating action on smooth muscle cells; inhibition of platelet activity; leukocyte aggregation; and proliferation of smooth muscle cells in the vascular endothelium,[10] which altogether contribute to BP control and prevention or control of cardiovascular diseases.[3,11,12]

Therefore, for an effective clinical application of physical training in the management of hypertensive individuals, it is necessary to know the effect of different physical exercises on NO and BP levels. In this regard, defining the study population and clarifying issues related to exercise – type (aerobic or anaerobic), intensity and training duration[3,12-14] is crucial to guide the therapeutic approach by health professionals. Therefore, this study aimed to conduct a literature review to elucidate the effect of physical training on NO levels in patients with AH and to establish a relationship between NO levels and BP control in this population.

Methods

An integrative review was performed by searching PubMed / MEDLINE, Lilacs, Scielo, Cinahl and Embase databases, using terms indexed in the DeCS – Health Sciences Descriptors – which was developed from the Medical Subject Headings of the US National Library of Medicine, to allow the use of common terminology in Portuguese, English and Spanish. The search string used in all databases was ("arterial hypertension" OR hypertension) AND (exercise OR "physical exercise" OR "aerobic exercise" OR "exercise training" or "physical activity") AND "nitric oxide".

The search was conducted between October 2019 and April 2020, covering studies published in the last 10 years, i.e., from October 2009 until the present moment. Fully available controlled and uncontrolled clinical trials published in English and Portuguese languages were included in the review. We selected articles that evaluated the effect of physical training on blood / urinary concentrations of NO or its metabolites, activity of the enzyme nitric oxide synthase (NOS), or BP levels of pre-hypertensive or hypertensive individuals. Studies on acute physical training only and those that included individuals with pulmonary hypertension were excluded.

Two independent researchers participated in the four steps of the review: literature search; duplicate analysis; reading of titles and abstracts; and full reading of each article. In the 3rd and 4th steps, each researcher classified the articles in a binary way, with zero (0) for articles that did not meet the inclusion criteria or had any of the exclusion criteria and one (1) for articles that fulfilled the inclusion criteria. Articles that scored one (1) from both researchers carried on to the next step, and those articles that were already at the fourth step were included immediately. Articles that scored zero from both researchers were immediately excluded. Articles that were assigned zero from one researcher and one (1) from the other researcher were evaluated by a third reviewer to ultimately determine if the article would be included (or moved to the next step) or not.

Results

Figure 1 presents the flow diagram of identification and selection of the articles included in this review, according to the PRISMA flow diagram.[15] A total of 16 articles were included, with the main results described in Table 1.

Population

The number of individuals studied ranged from 11[29] to 60,[23] and mean age was equal to or older than 50 years in eleven articles,[16,18-22,24,26,29-31] between 40 and 50 years in three[25,27,28] and below 30 years in one study.[17] The studies included individuals with stage I or II hypertension (nine articles[16,18,19,22-24,29-31]), prehypertensive and hypertensive individuals (two articles[20,31]), normotensive and hypertensive (three articles[27-29]), prehypertensive, hypertensive and normotensive individuals[25] and only prehypertensive individuals.[17]

Intervention

Aerobic exercise was the most common intervention, identified in 11 of the 16 articles included,[16,18,19,21,25-31] three of which addressed high-intensity aerobic training.[16,18,19] In addition, two studies performed resistance exercise,[20,28] one of which combined aerobic and resistance exercises.[28] Four studies addressed training with different techniques

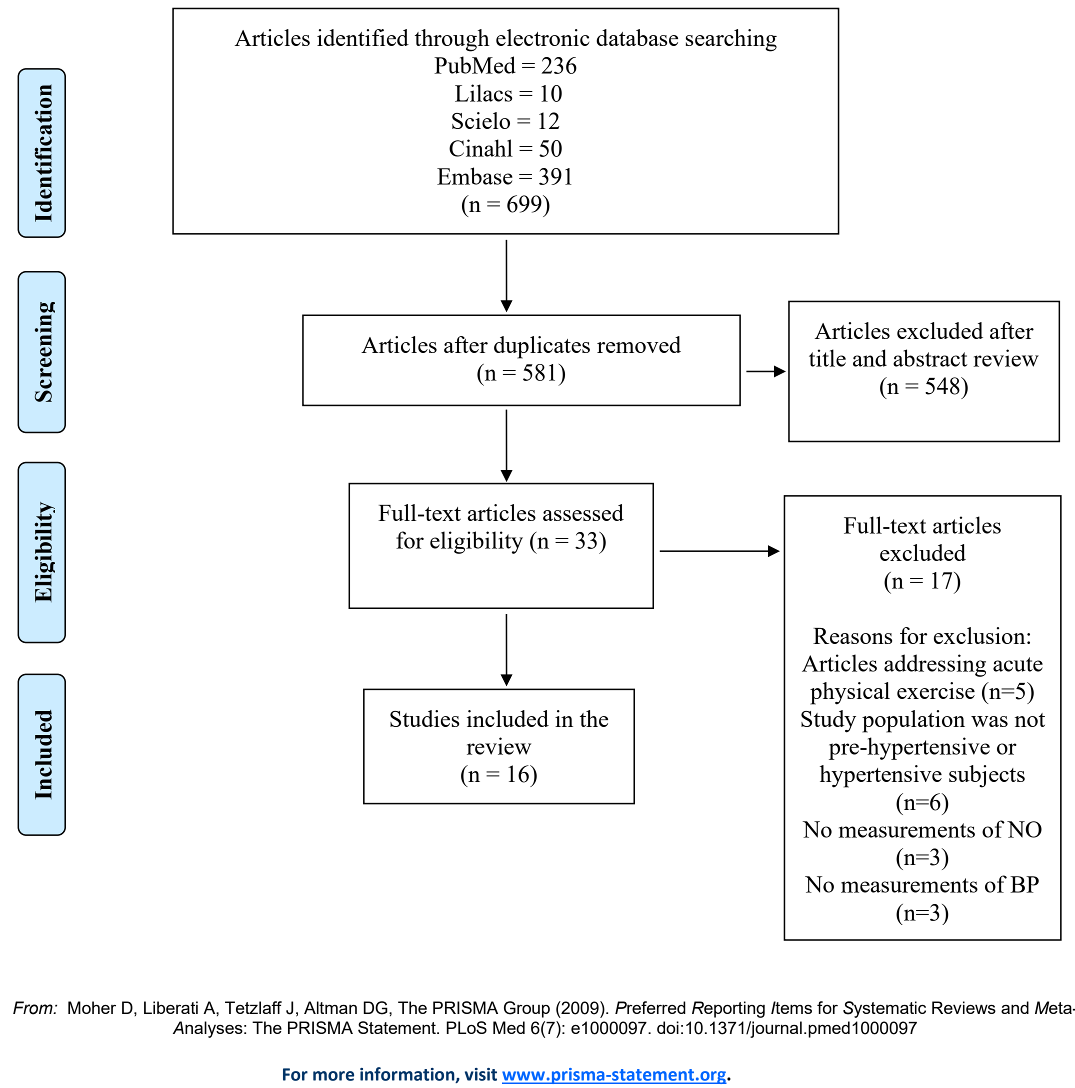

Figure 1 – PRISMA Flow diagram of article selection and inclusion/exclusion process.
BP: Blood Pressure; NO: Nitric Oxide

such as vibrating platform,[22] yoga,[23] Tai Chi practice[24] and mat Pilates.[17]

In the studies that used aerobic physical training, different parameters and percentages were used to measure training intensity, ranging from 60% to 100% of maximum heart rate (HR_{max}),[23,25,27,30] 30% to 100% of maximum oxygen consumption (VO_{2max}),[18,24,27,29] 50% to 90% of HR_{max} reserve[19,28,31] and between 11 and 13 points on Borg's rating scale of perceived exertion.[21]

Duration of exercise training varied between six[18,19] and 24 weeks,[25,29,30] most often three to four days a week,[16-19,21,22,25-31] with sessions from 20 min[25,26] to 60 minutes.[17,22-24,29,31]

Outcomes

Regarding the effect of physical exercise on NO, 13 out of the 16 studies analyzed reported an increase in NO or NOS production after the intervention.[16-26,29,31] In these cases, exercise modality, time and intensity was not homogeneous throughout the studies. The other three studies found no change.[27,28,30]

With respect to BP, only one article carried out with African American individuals did not report a reduction in this variable after the intervention, most likely because the parameters of normotensive and hypertensive individuals were analyzed together. Despite this, there

Table 1 – Characteristics of the included studies

AUTHOR/ YEAR	POPULATION (n)	EXERCISE PROTOCOL	NO/NOS and BP RESULTS	OTHER RELEVANT RESULTS
Jo et al., 2020[16]	Hypertensive individuals of both sexes with metabolic syndrome (n=34) Moderate and continuous training group (MICT): n=17 (6 men; 11 women) High-intensity interval training group (HIIT): n=17 (12 men; 5 women) Age: MICT: 51.8 ± 8.5 years HIIT: 49.9 ± 7.3 years	• Duration: 8 weeks • Frequency: 3 times/week • Intensity: - MICT: 5 min warm-up at 40% of the reserve heart rate (RHR) followed by 35 min of continuous jogging at 60% of the RHR. - HIIT: 5 min warm-up at 40% of the reserve heart rate (RHR) and 5 min warm- up at 60% of continuous jogging at 60% of the RHR, followed by five 3 min breaks at 80% of the RHR with a 3 min active recovery at 40% of the RHR between each break.	Significant increase in plasma NOx levels for HIITG only. Significant reduction in SBP and DBP for both groups.	HIIT had greater effect than MICT in reducing resting HR, in dilatation mediated by flow, and in the epicardial fat thickness.
Wong et al., 2020[17]	Pre-hypertensive obese women (n=28) Control group (CG): n=14 Exercise group (EG): n=14 Age: CG: 23 ± 1 years EG: 22 ± 1 years	CG: 12 weeks without exercise EG: *Mat Pilates** • Duration: 12 weeks • Frequency: 3 times/week • Intensity: increasing degree of difficulty and complexity of the exercise and increasing number of repetitions starting from 6 in the first week to 10 repetitions in the last week. • 60 min per session (10 min of warm-up, 40 min of general conditioning with *Mat Pilates* exercises * and 10 min of stretching and cooling). * Exercises with 1 series of 6 to 10 repetitions with emphasis on diaphragmatic breathing with abdominal activation.	Significant increase in plasma NOx levels and significant reduction in brachial and aortic pressures (SBP, DBP, MAP and pulse pressure) in the EG.	Reduction in systemic arterial stiffness and % body fat in EG.
Fiorenza et al, 2019[18]	Hypertensive and normotensive adult and elderly men (n=37) Normotensive group (NG): n=13 Hypertensive group (HG): n=24 Age: NG: 58.4 ± 2.5 years HG: 60.8 ± 1.5 years	Both groups submitted to high-intensity interval training (HIIT): • Duration: 6 weeks • Frequency: the weekly frequency increased from 2 times (weeks 1 and 2) to 3 times (weeks 3 to 6) • Intensity: HIIT with five intervals consecutive of 1 min divided into 30, 20 e 10 seconds at an intensity corresponding to 30%, 50% and 100% of VO_{2max}. respectively. • 20-28 min per session (7 min of moderate warm-up and 10-15 min of training with the first and second weeks being 2 sets of 5 min; and from the third week onwards, 3 series of 5 min).	Significant increase in muscle eNOS levels in both groups after training. GH presented lower values of muscle eNOS both pre- and post-training. Significant reduction in SBP, DBP and MAP in GH.	Partial reversal of hypertension-related impairments in muscle mitochondrial renewal in GH.

Izadi et al., 2017[19]	Hypertensive elderly individuals of both sexes (n=30). CG: n=15 (6 women; 9 men) EG: n=15 (7 women; 8 men) Age: 61.70 (± 5.78) years	CG: encouraged to keep their daily activities without exercise training for 6 weeks. EG: HIIT in ergometric bike. • Duration: 6 weeks. • Frequency: 3 times/week • Intensity: 3 min warm up at 40% of the RHR, 35 min of high-intensity training (10 x 1.5 min intervals in 85-90% of the RHR with 2 min active pauses at 50-55% of the RHR between the intervals) and 5 min of relaxation at 40% of the RHR.	Significant increase in plasma NOx levels and significant decrease in SBP/ DBP in EG (HIIT).	Increased plasma levels of apelin and decreased plasma levels of endotelin-1 in EG.
Tomeleri et al, 2017[20]	Pre-hypertensive and hypertensive elderly women (n=30). CG: n=15 EG: n=15 Age: CG: 67.3 ± 4.6 years EG: 69 ± 6.6 years	CG: 12 weeks without exercise EG: supervised resistance training. • Duration: 12 weeks • Frequency: 2 times/week • Intensity: loads were established according to 1RM; 1 series of 10-15 repetitions and 8 types of exercises.	Significant increase in plasma NOx levels with negative correlation between NO and SBP and significant reduction in SBP, DBP and MAP the in GE.	Increased strength and skeletal muscle mass and decreased% body fat in EG.
Cruz et al, 2017[21]	Individuals of both sexes with resistant hypertension for more than 5 years (n=44) CG: n=16 (7 women; 9 men) EG: n=28 (14women; 14 men) Age: CG: 54.4 ± 1.2 years EG: 52.4 ± 1.5 years	CG: 12 weeks without exercise EG: Heated pool training • Duration: 12 weeks • Frequency: 3 times/week • Intensity: Borg scale between 11 and 13. • 5 min warm-up, 20 min of resistance exercise, 30 min of walking and 5 min of cooling/stretching.	Significant increase in plasma NO levels and significant reduction in clinical and 24-hour SBP and DBP in EG.	Decreased levels of norepinephrine, adrenaline, endothelin-1 and plasma renin activity in EG.
Wong et al, 2016[22]	Overweight or obese women in the postmenopausal period, some with stage I hypertension (n=41). Whole-body vibration training (WBVT) + Placebo: n=14 L-citrulline supplementation: n=14 WBVT + L-citrulline: n=13 Age: 58 ± 4 years	WBVT + Placebo: whole-body vibration training + 8 capsules of maltodextrin. • Duration: 8 weeks • Frequency: 3 times/week • Intensity: the volume was increased progressively: ↑Vibration intensity: frequency between 25-40 Hz and 1-2 mm amplitude. ↑Exercise set duration: 30-60s ↑Series number: 1-5 ↑Training session duration: 11-60 min ↓Rest period duration: 30-60s between the sets. Static and dynamic exercise for legs in 60 min' sessions. L-citrulline: 6 g/day and L-citrulline ingested as 750 mg capsules. WBVT + L-citrulline: combined the two interventions.	Significant increase in plasma NOx levels in the three groups. There was no difference between the interventions. Significant reduction in brachial and aortic pressures (SBP, DBP, ABP and pulse pressure).	Reduced augmentation index in BP pulse in groups submitted to WBVT.

Patil et al, 2015[23]	Elderly males with hypertension (n=60) Brisk walking group (BWG): n=30 Yoga Group: n=30 Age: BWG: 69.30 ± 5.93 years Yoga Group: 68.50 ± 4.85 years	BW: brisk walking • Duration: 12 weeks • Frequency: 6 times/week • Intensity: ------ • 60 min session (20 min of stretching, 35 min of brisk-walking and 5 min rest). Yoga Group: Yoga training • Duration:12 weeks • Frequency: 6 times/week • Intensity: ------ • 60 min session (15-20 min posture maintaining exercises and 40-45 min of relaxation/ meditation breathing exercises).	Significant increase in serum NOx levels and significant reduction in SBP and MBP after training with yoga. No change in plasma NOx and BP after brisk walking.	Improved arterial function and cardiac autonomic modulation in the yoga group.
Pan et al, 2015[24]	Individuals of both sexes with stage I and II hypertension and normotensive (n=56) Normotensive control group (NG): n=16 (10 men and 6 women). Hypertensive control group (HG): n=10 (4 men and 6 women). Tai Chi exercise group (TCEG): n=14 (4 men and 10 women). Age: NG: 55.5 ± 3.54 years HG: 56.88 ± 3.95 years HTCG: 56.37 ± 3.95 years	NG: 12 weeks without physical exercise. HG: 12 weeks without physical exercise. TCEG: Tai Chi training • Duration: 12 weeks • Frequency: 6 times/week • Intensity: 60% of the maximum heart rate and/or a perceived effort rate equal 10. 60 min session with body relaxation, maintenance of posture, continuous anzd agile movements, soft and regular breathing.	Significant increase in plasma NOx levels in the TCEG group compared to the HG. HG and TCEG showed lower plasma NOx values both before and after training compared to the NG. Significant reduction in SBP and MAP that correlated with changes in NO levels in the TCEG.	Increased levels of gaseous signaling molecules, such as carbon monoxide and hydrogen sulfate, associated with improved vascular function. Reduced anxiety and improved lipid profile in the TCEG.
Feairheller et al, 2014[25]	African American, pre-hypertensive, hypertensive and normotensive individuals of both sexes (n=26; 21 women, 5 men) Normotensive: n=10 Pre-hypertensive patients: n=9 Hypertensive: n=7 Age: 53.4 ± 6.2 years	All groups were submitted to aerobic training: • Duration: 6 months • Frequency: 3 times/week • Intensity: starting with 20 min sessions at 50% VO_{2max} until reaching 40 min at 65% VO_{2max}. • Sessions of 20 to 40 min.	Significant increase in plasma NOx levels. No changes in SBP, DBP and MBP.	Reduction of fasting triglyceride and blood glucose levels and improvement in vascular function and structure in all groups.

Turky et al, 2013[26]	Menopausal and hypertensive women (n=25) CG: n=13 EG: n=12 Age: CG: 52.7 ± 2.2 EG: 52.9 ± 2.6	CG: 8 weeks without physical exercise. EG: Aerobic training. • Duration: 8 weeks • Frequency: 3 times/week. • Intensity: 60-75% maximum HR • 5 to 10 min warm up, 20 min of aerobic training, and 5 min of relaxation.	Significant increase in serum NO levels and significant decrease in SBP and DBP in EG.	Significant decrease in BMI values in the EG.
Nyberg et al, 2012[27]	Individuals of both sexes with essential hypertension (HG) and normotensive controls (NG) (n=21) NG: n=11 (6 men; 5 women) HG: n=10 (4 men; 6 women) Age: NG: 46 ± 1 years HG: 47 ± 1 years	Both groups underwent aerobic training in ergometric bike: • Duration: 8 weeks • Frequency: 2 to 3 times/ week; one additional independent training day (jogging or cycling) • Intensity: high intensity	There was no change in plasma NOx in both groups, but there was a significant reduction in SBP, DBP and MAP in HG. HG showed lower plasma NOx values before training, however, during the 20 watts exercise session there was a 30% increase in plasma NOx.	Vascular conductance and blood flow in the leg were lower during exercise in the HG, as well as before and after the training period.
Hansen et al, 2011[28]	Individuals of both sexes with essential hypertension and normotensive controls (n=20) NG: n = 10 (5 men; 5 women) HG: n = 10 (6 men; 4 women) Age: NG: 42.8 ± 2 years HG: 45 ± 2 years	Both groups were submitted to aerobic training + resistance training: • Duration: 16 weeks • Frequency: 3 times a week • Intensity: moderate - 60% VO_{2max} 10 min cycle ergometer warm up (30% to 40% VO_{2max}); 50 min of aerobic exercise (60% VO_{2max}), combined with upper and lower limb strength training (8-10 repetition maximum).	The level of muscle eNOS was not altered by training and was significantly lower in HG compared to NG. There was a significant reduction in MBP in HG.	Decreased thromboxane A2 concentrations and increased prostacyclin and cystathionine gamma lyase enzyme after training.
Zaros et al, 2009[29]	Postmenopausal women with stage 1 hypertension (n=11) Age: 50 ± 4 years.	Aerobic training in cycle ergometer • Duration: 24 weeks • Frequency: 3 times/week • Intensity: 50% of the RHR • 60 min sessions (starting with 20 min and increasing 10 min day until 60 min).	Significant increase in plasma NOx levels and significant decrease in SBP, DBP, HR.	Reduction of resting HR and total cholesterol.

Sturgeon et al, 2009[30]	Individuals of both sexes, pre-hypertensive and stage I hypertensive (n=23). Women were postmenopausal for more than 2 years. Two groups before training: Dippers: n=11 (5 men; 6 women) Non-dippers: n=12 (6 men; 6 women) Three groups after training: Not changed: n=14 Switched from dippers to non-dippers: n=5 Switched from non-dippers to dippers: n=4 Note: non-dippers – absence of a decrease or attenuated decrease in night BP Age: Dippers: 58.3 ± 1.2 years Non-dippers: 58.8 ± 2.1 years	Both groups underwent aerobic exercise training (AEXT) • Duration: 24 weeks • Frequency: 3 times/week – after 10 weeks a 4th session of unsupervised exercises was incorporated to the program. • Intensity: 50% - 70% VO_{2max} • Up to 40 min sessions, starting with 20 min and progressing through the program.	There was no difference in urinary and plasma NOx between the three groups formed after training. AEXT does not seem to promote changes in the oxidative profile of the groups studied. The group that changed from non-dipper to dipper with AEXT showed a significant decrease in MBP, SBP and DBP, while the group that changed from dipper to non-dipper significantly increased BP values.	The group that changed from non-dipper to dipper with AEXT showed a decrease in total cholesterol and LDL-cholesterol values.
De Meirelles et al, 2009[31]	Hypertensive individuals of both sexes (n=19) CG: n=6 EG: n=13 Age: EG: 50 ± 4 years CG: 49 ± 1 years	CG: 3 months without physical exercise. EG: aerobic training on treadmill • Duration: 12 weeks • Frequency: 3 times/week • Intensity: 75-85% of the maximum HR (it was gradually increased after 3 week). 60 min per session (5-10 min warm up/stretching, 40 min walking or running and 5-10 min cool down).	Significant increase in NOS activity and l-arginine transport in platelets and levels of intra-platelet cGMP and significant reduction in SBP and DBP in EG.	Decreased double product, resting HR, % body fat, platelet aggregation and plasma levels of fibrinogen and C-reactive protein and improved lipid profile in EG.

1RM: one repetition maximum; AEXT: aerobic exercise training; BMI: body mass index; BW: brisk-walking; CG: control group; DBP: diastolic blood pressure; EG: exercise group; eNOS: endothelial nitric oxide synthase; HDL-C: high density lipoprotein cholesterol; HG: hypertensive group; HIIT: High-intensity interval training; HR: heart rate; LDL-C: low density lipoprotein cholesterol; MBP: mean blood pressure; MICT: moderate intensity continuous training; NG: normotensive group; NOx: nitric oxide metabolites; RHR: reserve heart rate; SBP: systolic blood pressure; TCEG: Tai Chi exercise group; VO2max: maximum oxygen consumption; WBVT: whole-body vibration training.

was an increase in plasma NO levels and an improvement in vascular structure and function after training.[25] On the other hand, three studies showed a decrease in BP, but unrelated to changes in NO or NOS production.[27,28,30] In these studies, the hypotensive effect was associated with an improvement in the balance between vasodilator and vasoconstrictor factors, with changes in prostanoids levels,[27,28] increased hydrogen sulfide-producing enzyme (cystathionine gamma-lyase) and reduced thromboxane,[28] or with decreased levels of total cholesterol and LDL.[30]

Discussion

In the present review it was verified that physical training was able to increase NO production and reduce BP in hypertensive and prehypertensive individuals. Most studies used an exercise intensity ranging from 60% to 100% of HR_{max}, 50% to 100% of VO_{2max}, 30% to 90% of HR_{max} reserve, and between 11 and 13 points on the scale of perceived exertion (Borg). Based on analysis of the relationship between these parameters, we can verify that exercises of intensities of 60-79% of HR_{max}, 50-74% of VO_{2max} or reserve of HR_{max} and Borg of 12-13 are considered of moderate intensity.[32,33]

Based on the literature, approximately 75% of hypertensive individuals when submitted to physical training, mainly of moderate intensity, have reduced BP levels.[34] The practice of physical exercise may be responsible for promoting several adaptations, such as attenuation of vascular and cardiac sympathetic activity, decrease in serum levels of vasoconstrictor factors and increase in endothelial dilating factors, resulting in a reduction of peripheral vascular resistance.[35,36]

The time, frequency and duration of training are also important factors to be considered. Despite the great discrepancy between the training protocols of the selected studies, ranging from 20 to 60 min per session, three to four days per week, and from six to 24 weeks, this did not affect the results on NO concentrations. In this context, the Brazilian Society of Cardiology (*Sociedade Brasileira de Cardiologia*) recommends that individuals diagnosed with AH initiate regular exercise programs, three to five times a week, in sessions of at least 30 min, with ideal duration between 40 and 50 minutes.[1] Furthermore, aerobic exercises are preferred, of light to moderate intensity, between 60% and 80% of HR_{max}, or between 50% and 70% of VO_{2max}, and complemented by resistance exercises.[1,4,37]

Dynamic or isotonic resistance training should be performed with caution, since there are still few randomized and controlled studies with this type of exercise in AH, and its isolated effect on resting BP is not yet well established.[38,39] In this case, it is recommended an overload of up to 50-60% of one-repetition maximum (1RM) from two to three times a week, one to three series, 8 to 15 repetitions up to moderate fatigue, and passive breaks of 90 to 120 seconds.[1] In this sense, the study by Tomeleri et al.,[20] evaluated the effect of resisted exercise – series of 10 to 15 repetitions according to 1RM, twice a week – in pre- and hypertensive women. Although they did not specify the length of breaks and the percentage of RM, the parameters used in this study were consistent with the recommendations of the Hypertension Guideline[1] and indicated an increase in plasma NO levels with resistance training.

Three articles included in the present review showed improvement in NO levels and consequent decrease in BP due to increased vascular mechanical stress imposed by high-intensity interval training (HIIT) in hypertensive patients.[16,18,19] HIIT consists of alternating short periods of high-intensity aerobic exercise (85-100% VO_{2max}) with active periods of moderate to low intensity exercise. Hence, blood flow varies between high and low intensities, representing a greater challenge to the heart, improving cardiorespiratory fitness.[19] The authors justify that in this type of training, the increase in shear stress induces an increase in the apelin pathway, which is positively correlated to the increase in NO production, generating a vasodilatation with a consequent reduction in BP.[19] Nevertheless, this type of training is still best suited to healthy adult individuals, as described by the Update of the Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology.[40]

The shear stress caused by the increased unidirectional blood flow during physical exercise is the main mechanism of improvement of endothelial function.[33,41] This mechanical stress produced by the friction between red blood cells and endothelial cells activates endothelial NOS, increasing the production of NO. NO diffuses into the underlying vascular smooth muscle and activates the enzyme guanylate cyclase. This, in turn, induces the cGMP production that activates the metabolic pathways of cGMP-dependent protein kinase G (PKG), causing vascular relaxation.[42] Thus, shear stress is considered a powerful stimulus for the release of vasodilator factors produced by the vascular endothelium.[41]

In addition to its potent vasodilating action, NO can induce other important vascular, renal and cardiac effects, including inhibition of platelet aggregation, modulation of glomerular filtration rate, and an effect on vascular and cardiac remodeling.[43] On the other hand, the endogenous reduction of NO synthesis is related to several pathophysiological disorders or associated conditions, such as reduction of endothelium-dependent vasodilation in patients with hypertension, hypercholesterolemia, diabetes or arteriosclerosis.[44]

Studies have shown that the responses in BP control are related to humoral mechanisms, especially with involvement of NO. In fact, in the studies by Firoenza et al.,[18] Pan et al.,[24] Nyberg et al.,[27] and Hansen et al.,[28] it was observed that hypertensive individuals had lower levels of muscle eNOS and plasma NO compared to normotensive individuals. In addition, Pan et al.[24] and Tomeleri et al.[20] demonstrated a negative correlation between NO and BP values. Also, there is evidence that one cause of AH is the presence of products analogous to endothelial L-arginine, which hampers its action on eNOS, resulting in a substantial decrease in NO production.[45] Furthermore, the increase in BP is not only caused by elimination of the vasodilating action of NO, but also by elimination of its influence in central regions of the autonomic cardiovascular control, especially of the sympathetic nervous system.[45]

Therefore, characteristics of physical exercise, i.e., its intensity, duration, frequency, and the muscle groups involved (larger or smaller muscle groups), can be determinant in the greater production of NO and in the control of BP in hypertensive patients.[46,47] The increase in NO bioavailability promotes relaxation of smooth muscle cells in the blood vessel wall, leading to an increase in its diameter and a decrease of vascular resistance and systemic BP.[6] Besides, the decrease in sympathetic activity induced by physical exercise also suggests that the increase in NO production promotes a buffering action to the low-frequency oscillations in BP, acting in opposition to the vascular sympathetic modulation.[48-50]

In 2018, Pagan et al.[51] published an editorial addressing the role of exercise in endothelial function, with emphasis on NO, and discussed the studies with animal models that obtained improvement of this function associated with increased levels of NO,[52,53] also in hypertensive animals.[54] The authors emphasized the need to establish better training intensity, type, and duration for this objective. In the present integrative review, a diversity of training parameters in humans was found, as also pointed out by Pagan et al.[51] Therefore, among the limitations of this review, we can point out the lack of information and standardization of tests and training protocols, which made it difficult to interpret the effectiveness of exercise intervention on NO bioavailability.

Therefore, we concluded that the regular practice of physical exercises in pre-hypertensive and hypertensive individuals can increase the bioavailability of NO and, consequently, cause a hypotensive effect. Thus, we can establish a relationship between NO levels and BP control in hypertensive individuals, that is, the greater the NO production, the lower the BP values. However, it is important to note that the higher bioavailability of NO depends on the type – different by controlled, and of moderate intensity – of physical exercise and the muscle mass involved.

Author contributions

Conception and design of the research: Facioli TP, Durand MT. Acquisition of data: Facioli TP, Buranello MC. Analysis and interpretation of the data: Facioli TP, Buranello MC, Durand MT. Writing of the manuscript: Facioli TP, Buranello MC, Durand MT, Regueiro EMG, Vanelli RPB. Critical revision of the manuscript for intellectual content: Durand MT, Regueiro EMG, Vanelli RPB.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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