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EDITORIAL

Exercise training in the management of patients with resistant hypertension

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Abstract

Hypertension is a very prevalent risk factor for cardiovascular disease. The prevalence of resistant hypertension, *i.e.*, uncontrolled hypertension with 3 or more antihypertensive agents including 1 diuretic, is between 5% and 30% in the hypertensive population. The causes of resistant hypertension are multifactorial and include behavioral and biological factors, such as non-adherence to pharmacological treatment. All current treatment guidelines highlight the positive role of physical exercise as a non-pharmacological tool in the treatment of hypertension. This paper draws attention to the possible role of physical exercise as an adjunct non-pharmacological tool in the management of resistant hypertension. A few studies have investigated it, employing different methodologies, and taken together they have shown promising results. In summary, the available evidence suggests that aerobic physical exercise could be a valuable addition to the optimal pharmacological treatment of patients with resistant hypertension.

Key words: Exercise training; Resistant hypertension; Blood pressure; Non-pharmacological; Cardiovascular disease

Core tip: Taken together, the available evidence indicates that, unless there is a contraindication to performing physical exercise, patients with resistant hypertension should be encouraged to engage in regular aerobic physical exercise in addition to the optimal pharmacological treatment.

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RESISTANT HYPERTENSION

Arterial hypertension (defined as blood pressure > 140/90 mmHg) is the most important risk factor for cardiovascular events and end-stage renal disease[1]. In the general population, arterial hypertension has a prevalence of 30%-45%[1]. The control of blood

pressure is essential to avoid cardiovascular events in primary and secondary prevention[1]. In an important percentage of subjects, arterial hypertension is not controlled (< 140 and 90 mmHg) with a strategy to correct lifestyle behavior and three antihypertensive drugs in high doses, including a diuretic[1,2], and is defined as resistant hypertension. Some authors suggest that resistant hypertension should be diagnosed in those who meet the criteria of blood pressure control with the use of four antihypertensive drugs[2]. Several studies found that the prevalence of resistant hypertension in the hypertensive population is between 5% and 30%[1]. So, it is essential that the diagnosis of resistant hypertension is well defined in order to exclude false resistant hypertension[3]. Normally, arterial hypertension is defined by office blood pressure obtained by an electronic oscillometric device, called casual blood pressure. Ambulatory blood pressure is another way to measure blood pressure. Ambulatory blood pressure is superior to casual blood pressure in the diagnosis[1] and the cardiovascular events prognosis[4,5].

Blood pressure shows circadian rhythm; it is higher in the morning after waking (morning surge), declines during the day and in a more pronounced way during the night with sleeping (nighttime dipping)[6]. In relation to cardiovascular events prognosis, several studies have shown that nighttime blood pressure is superior to daytime blood pressure[4,7]. In patients with resistant hypertension, the absence of nighttime dipping is more prevalent than in patients with nonresistant hypertension and it is associated with higher cardiovascular events[6]. Ambulatory blood pressure also makes the exclusion of the alert reaction (difference between casual blood pressure and day blood pressure determined by ambulatory blood pressure) possible, which is one of the causes of false resistant hypertension or pseudo resistant hypertension[3]. In pseudo resistant hypertension, blood pressure is not controlled in office behavior but has normal values in ambulatory blood pressure. Nonadherence to the prescribed treatment is another cause of false resistant hypertension[5].

Resistant hypertension is associated with higher organ damage and cardiovascular events and a worse renal prognosis[1]. Resistant hypertension can be caused by obesity, excessive alcohol ingestion, high salt intake and obstructive sleep apnea[5]. Secondary hypertension can be the cause of resistant hypertension[8]. Secondary causes of hypertension include hyperaldosteronism, obstructive sleep apnea, renal artery stenosis and pheochromocytoma[9]. Hyperaldosteronism is the most common secondary cause of hypertension; nonetheless, many newly diagnosed hypertensive patients[10] and resistant hypertension patients[11] can have undetected primary aldosteronism. So, in studies looking for the impact of lifestyle changes on blood pressure of patients with resistant hypertension, it is recommended to assess at least the plasma aldosterone-renin ratio even if the serum potassium level is normal[9]. The treatment of arterial hypertension implies changes in lifestyle attitudes, namely regarding exercise habits[8]. Recently, a prospective, blinded, randomized, sham-controlled trial assessing the effect of renal denervation or a sham procedure on ambulatory blood pressure monitoring measurements 6 mo post-randomization failed to demonstrate a benefit of renal artery denervation on reduction in ambulatory blood pressure[12]. However, recently several predictors of blood pressure response in the SYMPLICITY HTN-3 trial were identified, which could at least partially explain the results of the trial[13]; among the predictors are the total number of ablation attempts, baseline office SBP $\geqslant$ 180 mmHg, prescription of an aldosterone antagonist at baseline, and age < 65 years in age[13]. This information is significant for designing future studies in this field.

EXERCISE TRAINING AND RESISTANT HYPERTENSION

The cardioprotective benefits of exercise training in those with cardiovascular diseases include the modification of traditional cardiovascular risk factors, the improvement of exercise tolerance, myocardial and peripheral perfusion, cardiac function, arterial stiffness, autonomic function, endothelial repair, as well as the mitigation of endothelial dysfunction and low-grade vascular wall inflammation, and, most importantly, the reduction of morbidity and mortality[14-25]. Indeed, it is widely accepted that exercise training is a polypill with several beneficial effects, including antihypertensive effects. Indeed, exercise is able to induce a decrease of 5-7 mmHg in systolic blood pressure in patients with hypertension[26]. Nonetheless, the antihypertensive effects of exercise in patients with cardiovascular disease are often underestimated because the analysis is frequently made without assessing the influence of the baseline blood pressure on the effects of exercise training. We showed[17,27] in previous studies that if cardiovascular disease patients with high and low blood pressure at baseline are considered together, an exercise training intervention has no effect on blood pressure. But, if the analysis is conducted dividing patients into two subgroups on the basis of baseline blood pressure (pre-hypertension/hypertension *vs* normotension), exercise training significantly decreases systolic blood pressure[17,27]. An interesting aspect of exercise for patients with hypertension is that they could benefit from the antihypertensive effect of aerobic exercise after just three exercise sessions. Additionally, the duration of the exercise sessions can be as short as 10 min and the intensity of exercise can be relatively low (40% to < 60% VO_2 peak)[26]. The exercise prescription recommendation of the American College of Sports Medicine for those with high blood pressure

is to perform 30 min of continuous or accumulated aerobic exercise of moderate intensity (40%-60% of VO_2 Reserve) per day, on most, preferably all, days of the week[28]. The aerobic exercise could be supplemented by resistance exercise[28].

The management of resistant hypertension includes lifestyle interventions that aim to reduce sodium intake and increase the levels of daily physical activity[29]. Nonetheless, there are few studies evaluating the effects of lifestyle interventions, including physical exercise in patients with resistant hypertension. The potential of aerobic physical exercise as an adjunct non-pharmacological therapeutic tool to manage resistant hypertension was recently addressed in three studies[30-32].

Dimeo *et al*[30] first showed that patients with a reduced responsiveness to medication do not necessarily have reduced responsiveness to non-pharmacological therapies, *i.e.,* aerobic physical exercise, to lower blood pressure. The authors conducted a randomized trial encompassing fifty patients with resistant hypertension on an exercise training program, consisting of walking on a treadmill 3 times per week for 8 to 12 wk. Initially, the duration of the sessions was 30 min (interval training until the fifth week) and then was gradually increased to 30, 32 and 36 min of continuous training. Dimeo *et al*[30] observed a 6 ± 12 and 3 ± 7 mmHg reduction in ambulatory systolic and diastolic daytime ambulatory blood pressure, respectively. More recently, Guimaraes *et al*[31] confirmed these positive results using a different exercise approach. They enrolled 32 patients in a heated water exercise program or to a control group. The heated water exercise program was performed three times per week for 12 wk and consisted of callisthenic exercises (*i.e.*, exercises performed in a rhythmic, systematic way using the body weight for resistance) against water resistance and walking inside a pool with controlled temperature (30℃-32℃). After 12 wk, the exercise program group showed a decrease in 24 h systolic (from 137 ± 23 to 120 ± 12 mmHg) and diastolic blood pressure (from 81 ± 13 to 72 ± 10 mmHg), daytime systolic (from 141 ± 24 to 120 ± 13 mmHg) and diastolic blood pressure (from 84 ± 14 to 73 ± 11 mmHg), and nighttime systolic (from 129 ± 22 to 114 ± 12 mmHg) and diastolic blood pressure (from 74 ± 11 to 66 ± 10 mmHg). This reduction in blood pressure is of great importance as higher ambulatory blood pressure predicts cardiovascular morbidity and mortality in resistant hypertensive patients[33].

Concern for safety must come first in all that prescribe or supervise exercise. Thus, patients with resistant hypertension should consult a physician prior to engagement in exercise training, particularly vigorous intensity exercise[34]. The progression of intensity of aerobic exercise should be gradual to enhance compliance; slow progression of frequency and intensity of resistance exercise is also encouraged to avoid injuries. Isometric exercise is not recommended. In patients with poorly controlled blood pressure, vigorous intensity exercise should be discouraged or postponed until appropriate drug treatment has been instituted and blood pressure lowered[34]. It seems prudent to keep systolic blood pressures at ⩽ 220 mmHg and/or diastolic blood pressures ⩽ 105 mmHg during exercise[35]. It is also important to know that in some patients, β-blockers and diuretics have an adverse impact on thermoregulatory function and could cause hypoglycemia[35,36]. Additionally, patients treated with calcium channel blockers, β-blockers and vasodilators should stop exercise gradually as they have an increased likelihood of hypotension post exercise[35,36]. Hence, it is important to monitor the room temperature during exercise, use the Borg scale as an adjunct to heart rate to monitor exercise intensity, and extend the cool down period.

FUTURE PERSPECTIVES

The above-mentioned results are promising and provide good perspectives for the future. Nonetheless, more studies enrolling a large number of patients are clearly needed to reinforce the role of physical exercise associated with antihypertensive medication in the control of blood pressure in patients with resistant hypertension. Future studies are also warranted to disclose the mechanisms responsible for the positive effects of exercise. Several mechanisms, none of them definitive, have been proposed to explain the benefits of exercise training in these patients, including the decrease of sympathetic and the increase of vagal nerve activity, the improvement of the sensitivity of the baroreceptor reflex, the improvement of endothelial function and arterial stiffness, the decrease in the concentration of rennin, angiotensin Ⅱ and aldosterone, and the reduction of renal sympathetic outflow. These aspects seem to merit close attention in future studies.

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