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Original Article

Angiotensin-II blockage, muscle strength, and exercise capacity in physically independent older adults

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Abstract. [Purpose] This study aimed to assess the exercise capacity and muscle strength in elderly people using drugs for angiotensin-II blockage. [Subjects and Methods] Four hundred and seven older adults were recruited for this study. Data about comorbidities and medication use were recorded and the individuals were divided into three groups: control group- elderly people with normal exercise capacity (n=235); angiotensin-converting enzyme inhibitor group − individuals using angiotensin-converting enzyme inhibitors (n=140); and angiotensin-II receptor blocker group- patients using angiotensin-II receptor blockers (n= 32). Exercise capacity was evaluated by a 6-minute walking test and muscle strength was measured using a handgrip dynamometer. [Results] Patients from the angiotensin-converting enzyme inhibitor group (mean: 99 ± 12%) and the angiotensin-II receptor blocker group (mean: 101 ± 14%) showed higher predicted values in the 6-minute walking test than the control group patients (mean: 96 ± 10%). Patients from the angiotensin-converting enzyme inhibitor group (mean: 105 ± 19%) and the angiotensin-II receptor blocker group (mean: 105.1 ± 18.73%) showed higher predicted values of muscle strength than control group patients (mean: 98.15 ± 18.77%). [Conclusion] Older adults using angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers have better functional exercise capacity and muscle strength.
Key words: Ageing, Muscle strength, Exercise capacity

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INTRODUCTION

Ageing represents one of the biggest challenges to public health worldwide. According to the World Health Organization (WHO), currently, there are 650 million elderly (over 60 years of age). Of these, nearly 66% live in developing countries and this percentage may reach 75% in 2025[1)]. This marked increase in life expectancy increases the morbidity from chronic diseases[2)], depression[3)], and worsens physical performance and quality of life[4)]. Besides, ageing may affect physical performance of older adults, evoking negative impacts on their behavior and consequent changes in lifestyle, causing them to become dependent[5)]. Several studies have reported that the loss of functional capacity in elderly people is usually related to the presence and complexity of comorbidities[6)]. Although several mechanisms may be related to this impairment of physical function in this population, the gradual loss of muscle mass and strength is often associated with the onset and establishment of disabilities[7)]. The relation between angiotensin converting enzyme (ACE) gene polymorphism and differences in physical

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performance phenotypes have been explored during the last few years, being described as a positive association between polymorphism insertion/deletion (I/D) of the ACE gene and exercise performance[8]. According to the literature, individuals with ACE insertion (I allele) present lower ACE plasma levels[9] and an increase in slow-twitch rather than fast-twitch muscle fibers[10, 11] which, in turn, confers better cardiovascular and skeletal muscle strength after training[11, 12] with a positive effect in endurance sporting events[13, 14]. There are few reports about the effectiveness of pharmacological interventions that can prevent the decline in functional capacity in older adults. However, a cross-sectional study in healthy elderly individuals showed a positive correlation between the use of angiotensin-converting enzyme inhibitors (ACEIs) and skeletal muscle mass in these hypertensive patients[15]. It was also noticed that the increase in physical performance observed after treatment with perindopril is similar to that after a six-month training program[16]. In addition to ACEI, angiotensin receptor blockers (ARBs) may also modulate the effects of angiotensin II, as they block the angiotensin-1 (T-1) receptor, regardless of the amount of angiotensin II circulating levels[17].

Although some reports claim that the use of ACEIs can prevent the decline in ageing-related muscle strength, further studies are necessary to confirm this hypothesis, especially because many studies have evaluated this effect in patients with congestive heart failure (CHF) only and not in the elder population in general. Thus, this study aimed to evaluate if older adults treated with ACEIs or ARBs may have a better functional exercise capacity and muscle strength.

SUBJECTS AND METHODS

All subjects enrolled in this study agreed and signed a written formal consent. The study was approved by the Ethics Committee of the University of Northern Parana (PP070/09). This cross-sectional study followed the criteria established by Strobe[18]. The convenience sample consisted of older adults (age over 60 years), according to the recommendations of the World Health Organization (WHO) for developing countries[19] who participated in an interdisciplinary project-the EELO Project-Study on Ageing and Longevity. The EELO Project is a thematic project developed at the University of Northern Parana (UNOPAR), which aims to evaluate the socio-demographic factors and indicators of health conditions of older adults in Londrina, a city in Northern Paraná, Brazil. Further information can be found at http://www2.unopar.br/sites/eelo/. This study was developed in Londrina as the elder population of the city represents 12% of the total population-a percentage similar to that reported for other developed countries[20, 21]. The total sample of the EELO project consisted of 508 individuals, corresponding to the 43,610 citizens over 60 years old living in Londrina. Of those, 101 individuals did not match the inclusion criteria, and therefore were excluded from the study. Therefore, the convenience sample of the present study consisted of 407 physically independent elderly people capable of performing basic and instrumental activities of daily life.

The included subjects were divided into three experimental groups (according to the medication used): the control group (CG): physically independent elderly people with exercise capacity and muscle strength exceeding 80% of the predicted value; the ACEI group: patients who used ACEIs for at least six months; and the ARB group: patients who used ARBs for at least six months. Older adults using other antihypertensive drugs that may influence muscle strength or exercise capacity (e.g., calcium channel blockers) or individuals performing less than 80% of the predicted value of the tests were excluded from this study. The presence of comorbidities and medication consumption were investigated through structured questionnaires. Questions concerning height and weight were also included in order to determine the anthropometric characteristics. Functional exercise capacity was measured using a 6-minute walking test (6MWT). This test was performed in accordance with the guidelines established by the American Thoracic Society (ATS)[22] and the reference values used were those described by Troosters[23]. Data were expressed as walking distance (in meters) and as the percentage of the predicted value.

Blood pressure, heart rate (HR), respiratory rate, symptoms of dyspnea and fatigue as well as oxygen saturation were measured before, immediately after, and 2 minutes after test recovery. Two tests were performed with at least a 30-minute rest period between them. A dynamometer was used to assess muscle strength that was calibrated according to the methodology described by Vianna[24]. The individuals were placed in the standing position and after hand size adjustment, the device was held comfortably aligned with the forearm, running parallel to the longitudinal axis of the body. The proximal inter-phalangeal joint of the hand was adjusted under the support bar, which was then pressed between the fingers and thenar region. During handgrip, the arm remained still with flexion of the interphalangeal and metacarpophalangeal joints only. Considering standardization, the movement of the elbow or wrist during the act of handling was not allowed. Handgrip strength was measured in both the hands and the best result was considered. The values obtained were compared to the reference values described by Mathiowetz et al[25]. Data were analyzed using the GraphPad Prism 5.0 statistical program (GraphPad Software Inc., San Diego, CA, USA) and the significance level was set at $p<0.05$.

The normality of data distribution was verified using the Shapiro-Wilk test. Since data were regularly distributed, parametric tests were used and descriptive data were expressed as mean and standard deviation.

One-way analysis of variance (ANOVA) was used to compare the groups regarding muscle strength and functional exercise capacity.

RESULTS

No differences concerning sex ($p=0.99$), age ($p=0.46$), height ($p=0.11$), weight ($p=0.06$), and body mass index ($p=0.07$) were observed among the experimental groups. Therefore, it may be assumed that the groups were similar regarding anthropometric data; results are shown in Table 1. A longer walking distance performed by men from the ACEIG was observed when compared to that from those in the CG. However, the individuals from the ARBG were similar to individuals from the ACEIG and the CG, according to one-way ANOVA (p=0.04, Table 2).

Similar data were observed concerning women (p=0.04, Table 3). However, when the percentage of predicted value was considered, it was observed that individuals from both the ACEIG and the ARBG had better performance than individuals from the CG (Table 4). Regarding muscle strength, men from the ACEIG had higher values when compared to those of men from the CG. However, the individuals from the ARBG were similar to individuals from the ACEIG and the CG, according to one-way ANOVA (p=0.04, Table 2). Similar data were observed concerning women (p=0.04, Table 3). By contrast, when the percentage of the predicted value was considered, it was observed that individuals from both the ACEIG and the ARBG had better performance than individuals from the CG (Table 4).

Table 1. Anthropometric data of subjects in the experimental groups

Anthropometric data		CG (n=235)	ACEIG (n=140)	ARBG (n=32)
Gender	M	80 (34.04%)	48 (34.29%)	11 (34.38%)
	F	155 (65.96%)	92 (65.71%)	21 (65.62%)
Age (yrs)		69.0 ± 6.3	69.5 ± 6.4	70.3 ± 5.6
Height (cm)		156.8 ± 8.6	157.5 ± 10.0	153.8 ± 5.8
Weight (kg)		68.2 ± 11.7	71.4 ± 12.4	69.6 ± 12.5
BMI (kg/m)		27.6 ± 4.1	28.5 ± 3.9	28.6 ± 3.8

M: Male, F: Female, BMI: Body Mass Index, CG: Control Group, ACEIG: Angiotensin Converting Enzyme Inhibitor Group, ARBG: Angiotensin-II Receptor Blockers Group
Values are expressed as mean and standard deviation (Mean ± SD)

Table 2. Comparison of the walking distance (by the 6-minute-walking test [6MWT]) and muscle strength in men from the CG, ACEIG, ARBG

Variables	CG	ACEIG	ARBG
6MWT (m)	499.9 ± 76.4	538.1 ± 73.3*	516.8 ± 84.5
Muscle strength (kgf)	33.7 ± 5.9	36.9 ± 7.1*	32.2 ± 5.9

CG: Control Group, ACEIG: Angiotensin Converting Enzyme Inhibitor Group, ARBG: Angiotensin-II Receptor Blockers Group
*Statistically different from control group, one-way ANOVA followed by Bonferroni test

Table 3. Comparison of the walking distance (by the 6-minute-walking test [6MWT]) and muscle strength in women from the CG, ACEIG, and ARBG

Variables	CG	ACEIG	ARBG
6MWT (m)	504.4 ± 73.9	529 ± 82.2*	525.1 ± 62.1
Muscle strength (kgf)	23.3 ± 4.5	24.7 ± 4.6*	23.5 ± 4.7

CG: Control Group, ACEIG: Angiotensin Converting Enzyme Inhibitor Group, ARBG: Angiotensin-II Receptor Blockers Group
*Statistically different from control group, one-way ANOVA followed by Bonferroni test

Table 4. Comparison of the walking distance (by the 6-minute-walking test [6MWT]) and muscle strength in individuals from the CG, ACEIG, and ARBG

Variables	CG	ACEIG	ARBG
6MWT (% predicted value)	95.6 ± 9.9	99.2 ± 12.1*	100.9 ± 13.6*
Muscle strength (% predicted value)	98.1 ± 17.7	104.8 ± 18.8*	105.1 ± 18.7*

CG: Control Group, ACEIG: Angiotensin Converting Enzyme Inhibitor Group, ARBG: Angiotensin-II Receptor Blockers Group
*Statistically different from control group, one-way ANOVA followed by Bonferroni test

DISCUSSION

In this study, we found that elder individuals who use ACEIs or ARBs have better exercise capacity compared to those elderly who do not use this medication. This result is in agreement with the results of the study by Onder et al.[26] who also observed a better physical performance in individuals using ACEIs. Additionally, we also observed an increase in the muscle strength in older adults treated with both ACEIs and ARBs, showing concordance with the results of the study by Di Bari, et al.[15], that describes a rise in muscle mass in elder patients treated with ACEIs. Moreover, Sumukadas et al.[16] reported that treatment with Perindopril may increase exercise capacity similar to that by a six-month physical training program. Vescovo et al.[27] reported significant increases in maximum oxygen uptake (VO_2max) and ventilatory threshold after six months of treatment with losartan. Additionally, Corder et al.[28] observed an increase in VO_2max and exercise duration after twelve weeks of treatment with Cilazapril in individuals with CHF. On the other hand, treatment with enalapril in patients with CHF evoked no changes in exercise capacity and VO_2max, although a significant increase in the density of skeletal muscle fibers was observed[29].

The exact mechanism by which pharmacological blockade of angiotensin-II influences the physical performance is still unclear. However, several hypotheses could be postulated according to Onder, et al[26]. Initially, it can be assumed that the blockade of angiotensin-II could trigger metabolic and mechanical changes in the skeletal muscle. In this context, ACEIs increase insulin sensitivity, glycogen stockage, and glucose uptake by skeletal muscles, improving muscle metabolic efficiency[30]. In addition, decreased degradation of bradykinin by blocking the ACE could improve the blood flow to the skeletal muscles through vasodilatation and an increase in capillary permeability, thus increasing the uptake of glucose and amino acids also, contributing to a higher metabolic efficiency[31]. Besides, ACEIs can reduce the inflammatory response produced by angiotensin-II[32], which increases the production of interleukin 6 (IL-6) and alpha tumor necrosis factor (TNFα) in vascular smooth muscle cells[33]. This reduction in inflammatory status is also related to the prevention of loss of muscle mass. The ACEIs may exhibit this effect since they indirectly potentiate the action of bradykinin, which, in turn, releases nitric oxide, a potent suppressant agent of the inflammatory response[34].

From these results, it can be suggested that the beneficial effect observed by treatment with ACEIs may be at least partially mediated by bradykinin, since the ACEIs limit the degradation of bradykinin, which plays an important role in modulating endothelium relaxing factors[31]. The reduction of bradykinin as a result of ACE inhibition may increase the blood supply to the skeletal muscles by causing vasodilation and increased capillary density, favoring the uptake of glucose and amino acids, leading to a higher metabolic efficiency[35]. These data may suggest that this beneficial effect on the physical performance is due to ACE inhibition and not only due to the pharmacological effects of angiotensin II. As limitations of this study, it is important to analyze whether this effect was dose or time dependent. Inflammatory biomarker levels (such as IL-6 and TNFα) were not assessed in this study. Furthermore, it should be highlighted that cohort as well as clinical randomized trials should be conducted to confirm this hypothesis.

Considering the beneficial effect of these drug types on physical performance, it can be suggested that such drugs may contribute to a smaller decline in physical capacity related to the ageing process. It can be concluded that older adults who use ACEIs or ARBs may have a better functional exercise capacity and muscle strength compared to those in controls. Thus, elderly who use this medication may present a lower decline of functional capacity related to the ageing process.

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