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Original Scientific Paper

THE EFFECT OF A SINGLE ORAL DOSE OF L-ARGININE ON QUADRICEPS STRENGTH IN SMOKERS AND NON-SMOKERS: A NON-RANDOMIZED CLINICAL TRIAL

Goranka Radmilović[1], Sanja Popović-Grle[2] and Valentina Matijević[3]

[1]Daruvarske toplice Special Hospital for Medical Rehabilitation, Daruvar, Croatia, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia;

[2]Jordanovac Department for Lung Diseases, Zagreb University Hospital Center, Zagreb, Croatia;

[3]Department of Rheumatology, Physical Medicine and Rehabilitation, Sestre milosrdnice University Hospital Center, Zagreb, Croatia; Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

SUMMARY – Smoking is a major risk factor for the development of chronic obstructive pulmonary disease (COPD), which is thought to be caused by smoking in even 8 out of 10 cases. One of the first clinical signs in patients with COPD is reduced physical ability, which is usually attributed to reduced lung function, although a significant role is played by a disorder of the musculoskeletal system. The aim of the study was to examine differences in fitness and locomotor status between smokers and non-smokers, as well as the effect of oral administration of L-arginine on the strength of the quadriceps depending on smoking status. The study included 164 subjects, 84 non-smokers and 81 smokers not diagnosed with COPD. All subjects completed CAT and IPAQ questionnaires, and performed spirometry, 6-minute walking test and quadriceps strength testing without therapy and after oral administration of 500 mg L-arginine. The results showed that the increase in quadriceps strength after oral administration of L-arginine was not dependent on smoking status but was more pronounced in smokers who started smoking at an earlier age and who smoked more cigarettes, as well as a generally higher physical activity of non-smokers. These results could become relevant for recognizing the development of skeletal musculature hypotonus and hypotrophy in smokers who are prone to develop COPD.

Key words: *Chronic obstructive pulmonary disease; Smoking; Quadriceps; Arginine*

Introduction

Smoking, as well as long-term exposure to tobacco smoke, is a significant risk factor for the development of chronic obstructive pulmonary disease (COPD). Although non-smokers also suffer from COPD, smoking is thought to be the cause of as many as 8 out of 10 cases of COPD[1]. It was thought that COPD would become the third leading cause of death in the world by 2020 but it happened already in 2019, and it is estimated that this chronic disease is responsible for approximately 6% of total deaths[2]. One of the first clinical signs in COPD patients is decreased physical ability which is usually attributed to decreased lung function. However, in addition to reduced lung function, an important factor in reducing physical

Correspondence to: *Goranka Radmilović, MD*, Daruvarske toplice Special Hospital for Medical Rehabilitation, Julijev park 1, HR-43500 Daruvar, Croatia
E-mail: grgoga@gmail.com

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ability is a disorder of the musculoskeletal system. Chronically reduced activity in these patients leads to the loss of muscle mass but this is unlikely to be the only explanation for peripheral muscular dysfunction[3]. A study conducted in Finland that included 3355 respondents over a period of 31 years found a strong association between smoking and physical activity from childhood to adulthood, suggesting that in constantly active individuals the probability of being in the category of smokers at the highest risk was reduced[4]. Impaired skeletal muscle function in COPD patients has been recognized to lead to a decreased ability to exercise, loss of muscle mass, cachexia, and ultimately to reduce the quality of life, increased physical disability rate, and mortality[5-9]. Lower levels of physical activity in patients with COPD are associated with poorer lung outcome and reduced quality of life[10], and also represent the strongest predictive mortality factor in these patients[11].

Spirometry is the gold standard and the most commonly used method for early detection of COPD, but the first and often unrecognized symptoms of the disease occur earlier than a pulmonary function test can prove impaired lung function. The most likely connection between COPD and extra-pulmonary manifestations such as bone and muscle loss, as well as cardiovascular and metabolic diseases, lies in the role of inflammation mediators within the systemic inflammatory disease caused by smoking[12]. Cigarette smoke and systemic inflammatory mediators enhance proteolysis and inhibit protein synthesis leading to muscle loss and reduced skeletal muscle contractile endurance in smokers, which may result in reduced oxygen delivery to mitochondria and reduced ability to produce adenosine 5'-triphosphate due to the interaction of carbon monoxide with hemoglobin and myoglobin[13,14]. In smokers who have not developed COPD symptoms yet, a change in muscles has been observed in terms of replacing type I fibers (oxidative, slow, fatigue-resistant) with type II fibers (glycolytic, rapid) which are more sensitive to inflammation and hypoxia, and they suffer atrophy more easily, while in non-smoking patients with COPD, decreased muscle strength was not observed compared with healthy subjects[13].

Lung disease can trigger oxidative stress in peripheral muscles and previous experimental studies on animals have shown that inflammation and hypoxemia increase the production of reactive oxygen and nitrogen species (RONS) that react with acyl parts in the membrane of phospholipids, lipid peroxidation leads to changes in the structural and functional properties of the membrane, while protein oxidation or nitration by RONS can alter structure leading to reduced protein function[3]. RONS can also cause DNA damage and alterations such as deletions or mutations. The most relevant radicals in a living organism are superoxide anion (O2-) and nitric oxide (NO). The first is formed by univalent reduction of molecular oxygen in the triplet state, and the latter is synthesized from the amino acid L-arginine by NO synthetase (NOS), which includes neuronal (nNOS), endothelial (eNOS) and inducible (iNOS) isoforms. Both radicals can be converted to other reactive oxygen species (ROS) or reactive nitrogen species (RNS)[3,15,16]. These reactive species are important in a variety of specific physiological functions, and their accumulation can lead to oxidative stress and damage to the cellular component[17].

L-arginine is a conditionally essential amino acid that has several metabolic functions and is a substrate in the synthesis of creatine and NO[18]. Arginine and citrulline supplementation in healthy subjects showed an increase in plasma arginine 1 hour after ingestion with a half-life (t1/2) of 1.5-2 hours, although as much as 40% does not enter systemic circulation but is degraded in the small intestine under the action of the enzyme arginase[19,20]. L-arginine is endogenously synthesized *via* the intestinal-renal pathway from citrulline which is released from small intestine and is used in the kidney to produce arginine. Apart from the kidneys, citrulline is easily converted to arginine in almost all cell types including endothelial cells, adipocytes, enterocytes, macrophages, neurons, and myocytes[21]. Once arginine enters the cell, it is broken down in several ways by arginase, NOS, arginine glycine amidotransferase and arginine decarboxylase to produce NO, urea, ornithine, creatinine, polyamine and agmatine, which are of great biological importance. Plasma concentrations of arginine are significantly reduced in response to infection or inflammation[21,22]. Arginine-regulated intracellular protein turnover favors an increase in muscle mass and a decrease in adipose tissue mass[23,24]. It is known that 40%-45% of an adult's body weight is made up of skeletal muscle. There is evidence that oral administration of arginine improves endurance during exercise, improves muscle strength, reduces inflammation, maintains muscle

integrity, prevents endothelial dysfunction in young adults, and prevents cardiovascular dysfunction[21,25,26]. Arginine supplementation has shown an effect on various physiological and metabolic pathways that could improve performance in athletes and its most important benefit has been the synthesis of NO and the effect on increasing blood flow, improving muscle contraction, gas exchange, oxygen kinetics and mitochondrial biogenesis[26,27]. Arginine also stimulates the release of growth hormone which promotes cell growth and contributes to increased muscle mass and hypertrophy, contributes to a reduction in lactate, ammonia and fatty acids, as well as improving carbohydrate oxidation and oxygen efficiency after exercise[26]. Studies involving untrained or moderately trained healthy subjects have shown that NO supplementation with donors such as L-arginine and L-citrulline can improve tolerance to aerobic and anaerobic exercise while highly trained subjects did not show positive effect[28]. In patients with moderate to severe COPD, quadriceps strength along with age, body mass index (BMI) and forced expiratory volume in the first second (FEV1) was found to provide additional information in predicting mortality, and the measure of voluntary quadriceps contractions may also be an indicator of skeletal muscle dysfunction[29].

The aim of this study was to examine the effect of oral administration of L-arginine on the quadriceps muscle strength in healthy smokers and non-smokers, as well as to examine the same effect in healthy smokers with respect to the age of smoking onset and pack/years of smoked cigarettes.

Patients and Methods

The study was designed as a cross-sectional study and was conducted on patients who underwent medical rehabilitation or medically programmed rest in Daruvarske toplice Special Hospital for Medical Rehabilitation. The sample included smokers and non-smokers aged 40 to 65 years. All patients underwent spirometry and patients whose Tiffeneau-Pinelli index (the ratio of FEV1 and forced vital capacity [FVC]) was less than 70%, i.e., those with a diagnosis of COPD were excluded from the study. Patients suffering from inflammatory rheumatic diseases, malignant diseases, acute and severe heart or lung diseases (myocardial infarction within a month, any degree of heart failure, and chronic respiratory failure of any cause), unregulated hypertension, those who had undergone major surgery a year before, as well as patients with implanted hip, knee or ankle prosthesis, were also excluded from the sample.

Taking into account the set level of statistical significance (0.05), the desired statistical power (0.80) and the moderate impact factor (effect size d=0.5), the minimum sample size for the Wilcoxon rank sum test was 134 subjects divided into two groups. The required sample size was calculated using G*Power software (Heinrich Heine University, Düsseldorf, Germany). The study included 164 patients, 83 non-smokers and 81 smokers.

All respondents voluntarily agreed to participate in the research and signed an informed consent form before joining the research. The respondents were included in the study after arriving at Daruvarske toplice Special Hospital for Medical Rehabilitation and participated in the research for two days.

Body weight, body height, BMI, waist circumference, pulse (cp), oxygen saturation (SpO2), blood pressure were measured in all study subjects. All respondents underwent spirometry testing on a Flowscreen pro Jaeger device and the value of the Tiffeneau-Pinelli index was recorded.

The respondents' cardiorespiratory and muscular ability were tested using a 6-minute walk test and ride on a Lifecycle 97C bicycle ergometer. The value of the walked distance in meters was measured during a 6-minute walk test performed in a hall with a straight walk of 20 meters. Testing on the bicycle ergometer was performed for 5 minutes under a given load, 100 W in men and 75 W in women. At the end of the ergometry test, the value of the maximum oxygen uptake (VO2max, mL/kg/min) was measured. Each respondent assessed the intensity of shortness of breath on the Borg shortness breath scale (1-10)[30] before and after the 6-minute walk test and bicycle ergometer.

The quadriceps muscle strength was tested twice on a Biodex isokinetic device (Biodex System 3 Pro), without L-arginine and 90 minutes after the respondent took 500 mg of L-arginine *per os* on empty stomach, with the aim of monitoring the possible increase in quadriceps muscle strength. Each respondent performed that strength test at a 60 degree angle with an angular velocity of 75 degrees/second and each of them had a trial series of 5 repetitions while the test itself was conducted through 2 series of 5 repetitions with a rest period of 10 seconds. In order to avoid the possibility of better knowledge of testing

on Biodex and consequently better results, some of the respondents were tested for the first time without L-arginine and some with it. This randomization was performed by selecting one of the two offered papers marked with numbers 1 and 2 which the respondents did not see during selection.

All respondents completed the COPD Assessment Test (CAT) questionnaire to assess COPD[31], which is a standardized test of self-assessment of the holistic impact of COPD on person's health. The International Physical Activity Questionnaire (IPAQ)[32] was also completed for each respondent, on the basis of which weekly calorie consumption was calculated and the intensity of physical activity was validated as low, moderate, or high. The age at smoking onset and pack/years (number of cigarettes smoked *per* day/20 x number of smoking years) were recorded in all smokers.

Ethics

All procedures conducted in this study were in accordance with ethical standards set by the institutional Daruvarske toplice Ethics Committee and regional Josip Juraj Strossmayer University of Osijek, Faculty of Medicine Ethics Committee on Human Experimentation, which approved this multidisciplinary research as ethically acceptable according to the 1975 Helsinki Declaration, as revised in 1983.

Statistics

Statistical analysis was performed using the SAS System software package (SAS Institute Inc., North Carolina, USA). Numerical data were expressed as arithmetic mean and standard deviation (SD) if they followed normal distribution, and as median and interquartile range (IQR) in case of distribution that was not normal. The normality of distribution of numerical variables was tested by the Shapiro-Wilk test. The relationships between two numerical variables were tested using Spearman's correlation coefficient. Absolute values of the Spearman coefficient above 0.70 were considered as indicating strong correlation between variables, values between 0.30 and 0.70 indicating moderate correlation between variables, and values less than 0.30 indicating weak or no correlation between variables. Differences of normally distributed numerical variables between two independent groups were tested by Student's t-test, and in case of deviation from normal distribution, the Wilcoxon rank sum test was applied. The Kruskal-Wallis test was used to compare more than two independent groups. Differences between dependent measurements were tested by the Wilcoxon signed rank test. Categorical data were expressed as absolute and relative frequencies. Fisher exact test was used to analyze differences between categorical variables.

Results

The study included 164 respondents of whom 81 (49.4%) were smokers while the rest were non-smokers. The t-test for independent samples revealed a statistically significant difference in the mean body height of smokers and non-smokers (p=0.035), whereas it was not recorded in age, body weight, BMI, and waist circumference. Women were significantly more represented in the smoking sample. Demographic characteristics of the respondents with regard to smoking status are shown in Table 1.

There was no statistically significant difference in the mean pulse (t-test for independent samples; p=0.390), SpO2 saturation (Wilcoxon rank sum test; p=0.815), diastolic (Wilcoxon rank sum test; p=0.899) and systolic pressure (Wilcoxon rank sum test; p=0.673) between smokers and non-smokers.

The IPAQ results indicated a statistically significant difference in physical activity between smokers and non-smokers (p=0.003). Analysis of burned calories (kcal) on physical activity in the past seven days also indicated a generally higher physical activity of non-smokers compared to smokers (p<0.001). Differences in the intensity of physical activity of the respondents and the weekly calorie consumption between smokers and non-smokers are shown in Table 2.

Results of the 6-minute walking test did not differ significantly between smokers and non-smokers (t-test for independent samples; p=0.222). The mean score was 680.1±73.6 meters for non-smokers and 666.5±68.8 meters for smokers. After the 6-minute walking test there was no statistically significant difference in shortness of breath measured on the Borg scale between smokers and non-smokers (Wilcoxon rank sum test; p=0.188).

The mean value of VO2 max was statistically significantly higher in non-smokers (38.0±4.9) compared to smokers (34.2±5.8) (t-test for independent samples; p<0.001). Change in the intensity of shortness of breath after bicycle ergometer measured

on the Borg scale was statistically significantly higher in smokers compared to non-smokers (Wilcoxon rank sum test; p<0.001).

The distribution of FEV1/FVC ratio did not differ statistically significantly between smokers and non-smokers, unlike the CAT index values which were generally higher in the group of smokers (Table 3).
The median (IQR) of initial quadriceps strength measurements was 156 (127-181) and the median (IQR) of quadriceps strength after arginine therapy was 166 (142-193). After L-arginine therapy, there was a general increase in quadriceps strength (Wilcoxon rank sum test; p<0.001) and the increase in strength was equal in smokers (median 7.0; IQR 13.9) and non-smokers (median 7.1; IQR 11.7) (Wilcoxon rank sum test; p=0.371).

The median number of smoked cigarettes (pack/years) was 25.0 (IQR 20) and median of age at the smoking onset was 18.0 (IQR 4.0). According to the results of Spearman's correlation test, the mean number of smoked cigarettes (pack/years) was statistically significantly associated with changes in quadriceps strength after arginine therapy (p=0.031; Spearman's coefficient r=0.248), as well as with the CAT test values (p=0.029; Spearman's coefficient r=0.242).

Age at the onset of smoking was statistically significantly associated with change in quadriceps strength after arginine therapy (Spearman's correlation test; p<0.001; r=-0.602).

The effect of age at the onset of smoking and number of smoked cigarettes (pack/years) on the increase in quadriceps strength after arginine therapy was estimated using a log-linear regression model, which explained a significant part of variability in the increase in quadriceps strength after arginine therapy (corrected R2=0.410) (Table 4). Of all the variables in the study, age at the onset of smoking was the most important variable in explaining the effect of arginine. For a unit increase in the mean number of smoked cigarettes (pack/years), the expected increase in quadriceps strength enhancement after arginine therapy is 1.5%, whereas for a unit increase in the age at smoking onset, the expected decrease in quadriceps strength enhancement upon arginine therapy is -23.5%.

Table 1. Demographic characteristics of study respondents

Variable	Smokers		Non-smokers		p-value
	n	Median (IQR)	n	Median (IQR)	
Age (years)	81	53 (49-56)	83	54 (50-58)	0.138†
Sex					0.011‡
Women	17		6		
Men	64		77		
Weight (kg)	81	92 (78-103)	83	89 (80-98)	0.674§
Height (cm)	81	178 (172-182)	83	180 (174-184)	0.035§
Body mass index	81	29 (26-32)	83	28 (26-29)	0.091§
Waist circumference (cm)	81	96 (89-107)	83	97 (90-102)	0.945§

IQR = interquartile range; †Wilcoxon rank sum test; ‡χ^2-test; §t-test for independent samples

Table 2. Comparison of physical activity intensity between smokers and non-smokers

Variable	Smokers		Non-smokers		p-value
	n	Median (IQR)	n	Median (IQR)	
IPAQ intensity of physical activity					0.003‡
Low	7		0		
Moderate	73		78		
High	1		5		
Weekly kilocalorie consumption	81	1894 (1278-2654)	83	2335 (1878-2815)	<0.001§

IQR = interquartile range; IPAQ = International Physical Activity Questionnaire; ‡Fisher exact test; §Wilcoxon rank sum test

Table 3. Distribution of FEV1/FVC values and CAT index according to smoking status

Variable	Smokers		Non-smokers		p-value†
	n	Median (IQR)	n	Median (IQR)	
FEV1/FVC	81	100 (89-105)	83	101 (91-107)	0.451
CAT index	81	8 (5-11)	83	4 (2-6)	<0.001

IQR = interquartile range; †Wilcoxon rank sum test; FEV1/FVC = ratio of forced expiratory volume in the first second and forced vital capacity of the lungs; CAT index = COPD Assessment Test index

Table 4. Effect of age at smoking onset and pack/years on change in quadriceps strength after arginine therapy

Variable	Coeff	Exp (coeff)	SE	t-value	p-value
Constant	5.500	-	0.589	9.340	<.001
Age at smoking onset	-0.202	0.817	0.030	-6.740	<0.001
Pack/years	0.013	1.013	0.005	2.330	0.023

Note: Values of quadriceps strength change after arginine therapy were logarithmically transformed prior to analysis; Coeff = coefficient; Exp (coeff) = exposed value of the coefficient for easier interpretation of the results; SE = standard error; N=76 (patients with reduced values of quadriceps strength after arginine therapy were excluded); corrected R^2=0.410.

Discussion

The results of the current study showed a statistically significant difference in physical activity between smokers who had preserved lung function and non-smokers, indicating a generally higher physical activity in non-smokers. Studies have shown that physical inactivity in patients suffering from COPD is the strongest predictor of all causes of mortality, and including in physical activity could reduce the risk of death related to COPD by up to 30%-40%[11,33]. Ergolu and Yüksek conducted a study to analyze the effect of smoking habit on physical fitness of elderly male subjects and found that non-smoking subjects had a higher physical fitness level compared to smoking elderly male subjects in all tests[34]. A recent study by Albarrati *et al.* confirmed that daily physical activity in COPD was independent of traditional risk factors including age and spirometry and that the

breathlessness score was a better predictor of daily physical activity[35]. We can conclude that the results of the current study were consistent with the study results reported by Albarrati *et al.*[35], given that all our subjects had a FEV1/FVC ratio >0.70 but smokers had a higher CAT index values, significantly lower VO2 max, and shortness of breath after bicycle ergometer measured on Borg scale was significantly higher in smokers compared to non-smokers.

The CAT questionnaire is a standardized test of self-assessment of the holistic impact of COPD on human health. Since the questionnaire contains several questions about the frequency of respiratory problems such as shortness of breath, coughing and expectoration, which do not necessarily relate to diagnosis of COPD but are present in smokers more often, we thought that the application of the questionnaire will contribute to the research.

The subject of many studies is the impact of smoking on the musculoskeletal system. One study found that quadriceps was more fatigable during electrically induced contraction in young smokers without lung disease compared to non-smokers, but there was no difference in muscle strength or contractile properties, and no effect of cigarette smoking history on fatigability, which contradicted the hypothesis assuming the effect of smoking is either acute or reaches a ceiling rather than cumulative[36]. In another study, it was shown that cigarette smoking caused a mild but significant reduction in quadriceps strength by direct oxidative modifications of specific muscle proteins without inducing a significant increase in muscle inflammation[37], however, a limitation was a small number of subjects, only 29.

In our study, there was no statistically significant difference in quadriceps strength between smokers and non-smokers, or after oral administration of L-arginine, although strength generally increased statistically significantly compared to the initial measurement. Our results showed a statistically significant association between the pack/years, onset of smoking, and changes in quadriceps strength after arginine therapy. A negative correlation was observed between the age at the onset of smoking and change in quadriceps strength, meaning that a younger age at the onset of smoking generally led to a greater change in quadriceps strength after arginine therapy. A positive correlation was observed between the pack/years and changes in quadriceps strength after arginine therapy, which means that a higher number of pack/years led to a greater change in quadriceps strength after arginine therapy, more precisely, each unit increase in pack/years was expected to increase quadriceps strength by 1.5% after arginine therapy. The latter two findings correlated with our assumptions that arginine would show a better effect on quadriceps strength in smokers who started smoking at a younger age and who smoked a larger number of cigarettes, with the premise that such a muscle is more severely damaged since it is more severely affected by oxidative stress caused by cigarette smoking. This assumption is based on previous studies and meta-analyses on the effects of arginine, which, although not uniform, show a beneficial effect of acute and chronic L-arginine supplementation on endothelial function and reduction of systemic blood pressure (both systolic and diastolic), which is more pronounced in borderline and hypertensive than in normotensive patients[16,38-40]. Short-term treatment with L-arginine improved endothelial function in healthy smokers, suggesting that it inhibits the prothrombotic and antifibrinolytic effects, and may partly decrease the proinflammatory effect of smoking in healthy individuals, possibly by improving NO bioavailability in human vasculature[41].

Studies involving untrained or moderately trained healthy subjects showed that NO donors could improve tolerance to aerobic and anaerobic exercise, so training status of the subject seems to be an important factor linked to the ergogenic effect of NO supplementation[28], while a study by Meirelles and Matsuura that included healthy trained men aged 27±3 years showed that acute supplementation of L-arginine affected neither strength performance nor NO production[42].

Conclusion

The results of our study suggested that the increase in quadriceps strength measured on an isokinetic device after oral administration of L-arginine was not dependent on smoking status but was more pronounced in smokers who started smoking at an earlier age and smoked more cigarettes. The study also found a generally higher physical activity in non-smokers compared to smokers, although spirometry values showed no impairment of lung function; therefore, the CAT questionnaire values were significantly higher in smokers compared to non-smokers, shortness of breath after bicycle ergometer measured on the Borg

scale was also higher, while VO2 max was significantly lower in smokers compared to non-smokers.

The results of this study could be relevant for recognizing the development of skeletal muscle hypotrophy and hypotonia in smokers who are, given to smoking status, a group at the highest risk of developing COPD as a multisystem disease. These results could also potentiate the identification of smokers who are a risk group for the development of COPD, so the preventive targeted physical therapy could be introduced as an important measure to prevent reduction in fitness status, muscle tone, trophic status, and maintenance of physical activity, which is the most significant predictive mortality factor in patients with COPD.

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Sažetak

UČINAK JEDNE DOZE ORALNO PRIMIJENJENOG L-ARGININA NA SNAGU KVADRICEPSA U PUŠAČA I NEPUŠAČA: NERANDOMIZIRANI KLINIČKI POKUS

G. Radmilović, S. Popović-Grle i *V. Matijević*

Pušenje je značajan rizični čimbenik za razvoj kronične opstruktivne plućne bolesti (KOPB) i smatra se da je pušenje uzročnik u čak 8 od 10 slučajeva KOPB-a. Jedan od prvih kliničkih znakova u bolesnika oboljelih od KOPB-a je smanjena tjelesna sposobnost koja se obično pripisuje smanjenoj plućnoj funkciji, iako značajnu ulogu zauzima i poremećaj mišićno-koštanog sustava. Cilj istraživanja bio je ispitati razlike u kondicijskom i lokomotornom statusu između pušača i nepušača, kao i utjecaj peroralne primjene L-arginina na snagu kvadricepsa ovisno o pušačkom stausu. U istraživanje je uključeno 164 ispitanika, 84 nepušača i 81 pušač koji nisu imali dijagnosticiran KOPB. Svi ispitanici su ispunili upitnike CAT i IPAQ, učinjena je spirometrija, 6-minutni test hoda, ergometrija na biciklu te testiranje snage kvadricepsa bez terapije i nakon peroralne primjene 500 mg L-arginina. Rezultati su pokazali kako povećanje snage kvadricepsa nakon peroralne primjene L-arginina nije ovisno o pušačkom statusu, ali je izraženije kod pušača koji su počeli pušiti u ranijoj dobi i koji puše više cigareta te općenito veću fizičku aktivnost nepušača. Ovi rezultati bi mogli postati važni za prepoznavanje razvoja hipotonusa i hipotrofije skeletne muskulature u pušača koji su skloni razviti KOPB.

Ključne riječi: *Kronična opstruktivna plućna bolest; Pušenje; Kvadriceps; Arginin*