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Influence of Creatine Supplementation on the Functional Capacity of Patients with Heart Failure

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Abstract

Background: **Heart failure (HF) is a complex syndrome characterized by intolerance to exertion and reduced functional capacity.**

Objective: **To assess the functional capacity of patients with HF and supplemented with creatine.**

Methods: **Prospective, randomized, double-blind study. Thirty-three male patients over the age of 18 years with functional class II to IV HF were randomized into two groups as follows: the experimental group (CRE, n = 17), supplemented with 5 g/day of creatine for six months; and the placebo group (PLA, n = 16), receiving 5 g/day of maltodextrin for that same period. Both groups underwent functional capacity assessment by use of cardiopulmonary exercise test and 6-minute walk test (6MWT) before and after the intervention. The Ancova statistical model and Pearson correlation were used to assess the groups and the treatment.**

Results: **Of the variables assessed on the cardiopulmonary exercise test, peak oxygen consumption (peak VO_2), anaerobic threshold (AT), and oxygen pulse (O_2 pulse) showed no significant differences between the groups ($p>0.05$). On the 6MWT, no significant difference was observed in the covered distance.**

Conclusion: **Creatine supplementation in patients with HF did not significantly improve functional capacity. (Arq Bras Cardiol 2012;99(1):623-629)**

Keywords: **Heart Failure; Creatine; Supplementary Feeding; Exercise Test.**

Introduction

Heart failure (HF) is a cardiovascular syndrome characterized by pulmonary and/or systemic venous congestion associated with a reduced cardiac output[1]. Dyspnea, fatigue and edema are its typical symptoms, being associated with a reduction in the quality of life, an increase in morbidity and mortality, and a worsening in the functional capacity of patients[2,3].

Intolerance to exertion is a major characteristic of those patients, who have abnormal skeletal muscle metabolic responses, such as deficient oxygen (O_2) uptake and early onset of the anaerobic metabolism[4], in addition to endothelial dysfunction, abnormality in peripheral vasodilation and changes in the ventilatory response[5]. Thus, the reduction in functional capacity in patients with HF depends on central and peripheral changes, and has the interaction of the respiratory, hemodynamic, metabolic and muscle components[5,6].

Creatine, a nitrogenous amine, is an important energy source for muscle contraction, most of it (95%) being stored in the skeletal muscle, while the rest is stored especially in the cardiac muscle and brain[7]. The reduced availability of creatine has been associated with HF, increased prevalence of ventricular arrhythmias and ischemia[8,9]. Some researchers have suggested the use of creatine, either oral or intravenous, aiming at improving the cardiac function of individuals with HF[10,11].

Although several positive effects of creatine supplementation have been described in healthy individuals, studies using creatine in patients with HF are reduced. Thus, this study aimed at assessing the functional capacity of patients with HF after oral supplementation with creatine.

Methods

Type and place of study

This is a prospective, randomized, double-blind study carried out from April 2009 to January 2010 at the Hospital das Clínicas of the Universidade Federal de Goiás (HC-UFG).

Inclusion and exclusion criteria

The inclusion criteria were as follows: diagnosis of New York Heart Association functional class II to IV HF; male sex; and age over 18 years.

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The exclusion criteria were as follows: clinical instability, such as non-controlled atrial or ventricular arrhythmia and myocardial infarction, in the three months prior to the study; heart disease requiring surgical correction; alcoholism; creatinine concentration > 2.5 mg/dL; body mass index > 40 kg/m²; renal failure; change in the medication used for treating HF; orthopedic limitation that could hinder the execution of the tests; and difficulty complying with the protocol.

Procedures and data collection

Patients were screened from a data bank of the HF Outpatient Clinic of the HC-UFG. The 33 participants were randomized into the following two groups: the experimental group (CRE, n=17), supplemented with creatine (5 g/day) for six months; and the placebo group (PLA, n = 16), receiving maltodextrin (5 g/day) for the same period. Those products were presented as a white tasteless powder to be ingested orally, dissolved into fruit juice, and were directly obtained from the manufacturer (DYNAMICLab®).

Both groups underwent functional capacity assessment by use of cardiopulmonary exercise test (CPET) and six-minute walk test (6MWT) before beginning supplementation and after finishing supplementation, at the end of the sixth month of study. The ejection fraction (EF) was assessed by use of echocardiography, data being collected from the patients' medical records, considering the tests performed in the preceding three months as long as the patient was stable during the period between test performance and inclusion in the study. The left ventricular EF (LVEF) value ≤ 50% was used as cutoff point, in accordance with the consensus on HF. Because that was an inclusion criterion and not an objective of the study, it was not repeated after treatment.

Six-minute walk test

The 6MWT was performed according to the criteria established by the American Thoracic Society[12]. Prior to beginning and after finishing the test, the following parameters were measured: blood pressure (BP); heart rate (HR); peripheral oxygen saturation; and modified Borg scale for dyspnea, with the patient in standing position. The following instruments were used: Omron HEM-711semi-automated sphygmomanometer; Onyx® 9500 oximeter (Nonin Medical, USA); chronometer Kenko®, model KK-2808; and the modified Borg scale.

Time (six minutes) was kept with a chronometer and, every two minutes, the HR, oxygen saturation, and subjective perception of exertion (Borg scale) were recorded. The 6MWT was performed twice at a 30-minute interval, and all patients of the sample could complete the 6MWT with neither stopping nor interrupting the test. In addition to those parameters, at the end of the test, the distance covered (number of laps x 60) was calculated and notes regarding pain and fatigue were made.

Cardiopulmonary exercise test

The tests were performed at the laboratory of Ergometry/Cardiopulmonary exercise test of the HC-UFG. The following devices were used for performing the test: Centurion 300® treadmill; Cortex/Metalyzer 3B gas analyzer (Micromed®); computerized system for ergometry (Micromed®) with the Ergo PC Elite 3.3 software and the metasoft 3.7 software; digital electrocardiogram (Micromed®); and mercury sphygmomanometer and stethoscope.

The equipment was calibrated prior to each test. The ergospirometer was calibrated by use of the following certified gas mixture (standard calibration mixture): 16 cmol/mol of O_2 and 4.0 cmol/mol of carbon dioxide (CO_2), balanced with nitrogen (N_2).

The CPET was performed at a mean temperature of 25 ºC and relative air humidity of 60% to 70%. Patients were on their usual medications. The symptom-limited protocol was used to all patients.

The gas exchange and ventilatory variables were computed every three seconds and measured by the metabolic analyzer. Heart rate was measured by use of electrocardiography every second. Oxygen consumption (VO_2) was measured every three seconds, on an open circuit by reading the expired O_2 and CO_2 fractions in a metabolic system. Peak VO_2, anaerobic threshold (AT) and O_2 pulse were assessed. The AT was determined as the point of inflection in the VO_2 x VCO_2 curve, by using the V-slope method. The CPET was symptom-limited, being interrupted by fatigue, exhaustion, arrhythmias or BP drop.

Statistical analysis

A descriptive analysis was performed using measures of frequency for qualitative data and measures of position and variability for quantitative data. When comparing the means of the several measures between both groups (PLA and CRE), the Student *t* test was used for the variables with Gaussian distribution and, in the cases with no normality, the non-parametric Mann-Whitney test was used in both groups. The chi-square test was applied to assess the association between the group and the NYHA functional class before treatment. For the purpose of analysis, a 5% significance level was adopted.

A linear model of analysis of covariance (Ancova), in which the measures in the pre-test were included as covariables, was used to assess the existence of a significant difference in the post-test measures between both groups (CRE and PLA). That procedure allowed the construction of 95% confidence intervals (95% CI). According to Kutner et al.[13], Ancova is a technique that combines characteristics of analysis of variance and regression. The basic idea is to enlarge the model of the analysis of variance with the introduction of one or more auxiliary quantitative variables, aiming at making the analysis more accurate. The correlation between variables was assessed by the Pearson correlation coefficient ($p < 0.05$). The significance level of 5% was adopted.

Data were analyzed with the Statistical Package for the Social Sciences program, version 17.0 for Windows (SPSS, Inc. Chicago) and Statistical Analysis System (SAS), version 9.2.

Ethical considerations

This study was approved by the Ethics Committee on Human and Animal Research of the HC-UFG (protocol 095/2008). Patients were asked about their interest in participating in the study and were instructed about its objectives. Those who agreed to participate in the research provided voluntarily written informed consent.

Results

The characteristics of the patients, such as age, total body mass (TBM), height, body mass index (BMI) and ejection fraction (EF), were expressed as mean and standard deviation, and the functional classes, as percentages (Table 1). Mean age was 59.9 ± 10.0 years in the PLA group and 51.7 ± 10.5 years in the CRE group, and significant difference was observed between the groups ($p < 0.05$). According to BMI, the patients were classified as follows: eutrophic, 60%; overweight, 25%; and low weight, 15%.

Creatine supplementation was assessed by creatinine and urea laboratory tests before and after supplementation, and proved to be safe. The final adjusted urea mean value was 38.78 mg/dL with a 95% CI (34.32; 43.24) in the CRE group and 36.67 mg/dL (32.07; 41.27) in the PLA group, no significant difference being observed between the groups ($p > 0.05$). The final adjusted creatinine mean value was 1.31 mg/dL (1.21; 1.42) in the CRE group and 1.20 mg/dL (1.09; 1.31) in the PLA group, no significant difference being found between the groups ($p = 0.1499$).

The major cause of HF was Chagas' heart disease (55%), followed by hypertensive (27%), ischemic (15%) and alcoholic dilated (3%) cardiomyopathies. The classes of drugs most used in the treatment were as follows: diuretics (75.75%); angiotensin-converting-enzyme (ACE) inhibitors (78.78%); digitalis (54.54%); and beta-blockers (48.48%).

The mean EF in the PLA group was 35.1 ± 14.8, and, in the CRE group, 32.3 ± 13.6, with no significant difference between groups. Both groups had patients with reduced ventricular function.

Table 2 compares the functional capacity measures between the CRE and PLA groups after supplementation. The mean peak VO_2 values obtained on CPET were very close in the two groups (CRE group = 21.76; PLA group = 21.46, $p > 0.05$). The AT, O_2 pulse and peak VO_2 values did not differ statistically between groups. Regarding the variables analyzed on the 6MWT, the difference of the mean distance covered was 25.29 m greater in the CRE group, with no significant difference between the groups. The measures of perceived exertion by use of the Borg scale did not differ statistically between the groups after supplementation.

Figure 1 shows a linear, moderate ($r = 0.62$), positive and statistically different from zero ($p = 0.0082$) correlation between peak VO_2 and the distance covered, after the intervention in the CRE group, and the greater the distance covered, the greater peak VO_2.

Discussion

The sample assessed was homogeneous regarding its variables before supplementation (Table 1). The mean age was similar to that of national and international studies[14-17]. Only males were selected to participate in this study because of the influence of creatine consumption on TBM gain. This increment can be undesired in the female sex, causing loss to follow-up, hindering the conclusion of the study within the established deadline.

In this study, most patients were classified as eutrophic according to their BMI. Our results are in accordance with those reported by Veloso et al.[18]. However, Nakasato et al.[15] and Nogueira et al.[16] have reported most of the participants of HF studies as overweight.

In the study by Nakasato et al.[15], the patients were males, with mean age of 52.3 ± 1.6 years, mean weight of 75.4 kg ± 2.0, and BMI of 28.0 $kg.m^{-2}$ ± 0.6. Nogueira et al.[16] have assessed patients of both sexes [22 (47.8%) males and 24 (52.2%) females], with mean age of 52.26 ± 9.09 years, mean weight of 72.0 kg ± 11.27, and BMI of 27.36 $kg.m^{-2}$ ± 4.24. The eutrophic state of our patients can be explained by the fact that the studies used different classification criteria of the nutritional status according to the BMI, only for adults. In addition, our patients were on periodical clinical follow-up at a referral service (cardiology) and had been clinically stable in the preceding six months.

Regarding the causes of the disease, our results differ from those of other national studies, in which ischemic HF is the major cause[14,16]. This might be due to the fact that the state of Goiás is considered an endemic area of Chagas' disease[19].

Considering the measures obtained from the gases expired, peak VO_2 and AT are the major indicators of cardiorespiratory functional fitness[20]. Those ventilatory variables, along with O_2 pulse, plays a role in quantifying the individual's limitation, in the prognosis and in indicating heart transplantation[21-23].

Peak VO_2 values lower than 14 mL/kg/min characterize an important functional limitation, and help in indicating heart transplantation[24]. Of the patients assessed in this study, none had indication for transplantation. When comparing the values after supplementation related to AT, the mean values found in the CRE group classify it as having a moderate functional impairment[25].

The O_2 pulse is the most important variable to identify systolic volume changes, with a cutoff point of O_2 pulse > 11 mL/beat for men up to 40 years, and > 10 mL/beat for men aged 60 to 80 years[26]. The O_2 pulse values found in the present study were greater than those of other studies[27,28], suggesting a better physical fitness of this study's patients.

To assess functional capacity, the following have been widely used: the 6MWT[29], because data are easily obtained; and the correlation with peak VO_2 obtained on CPET[30]. In the present study, although the distance covered showed no significant difference between the groups, the mean value found after supplementation in the CRE group (547.37 m) was greater than those reported by Rubim et al.[31].

The Borg scale provides objective data about the fatigue intensity during the test. Thus, even if patients do not increase by much the distance covered, thy can show a lower fatigue intensity, reflecting their physical condition and/or clinical status[32]. The CRE group patients showed an increase in the mean distance covered as compared with the values prior to supplementation, but were also more tired after walking for six minutes.

The ergogenic effects of creatine supplementation in healthy individuals for short-duration and high-intensity activities, which essentially depend on energy production (ATP-CP) via anaerobic glycolysis, have been well described in the literature[33]. The same, however, has not occurred for activities that recruit the aerobic metabolism as a priority.

Table 1 – Characteristics of the patients according to group of treatment

Variable	Group	N	Mean ± SD	p - value
	Placebo	16	59.9 ± 10.0	
Age*				**0.0439**
(years)	Creatine	17	51.7 ± 10.5	
	Placebo	16	68.5 ± 10.3	
TBM*				0.3641
(kg)	Creatine	17	66.0 ± 5.6	
	Placebo	16	169.0 ± 6.0	
Height*				0.7149
(cm)	Creatine	17	168.0 ± 7.0	
	Placebo	16	24.3 ± 3.5	
BMI†				0.4824
($kg.m^{-2}$)	Creatine	17	23.6 ± 2.8	
	Placebo	15 (94%)		
Functional class II and III‡			-	0.6572
(NYHA)	Creatine	15 (88%)		
	Placebo	1 (6%)		
Functional class IV‡			-	0.6572
(NYHA)	Creatine	2 (12%)		
	Placebo	16	35.1 ± 14.8	
Ejection fraction – EF†				0.9569
(%)	Creatine	17	32.3 ± 13.6	

TBM: total body mass; BMI: body mass index; NYHA: New York Heart Association; significance level (p) of 5%.
** - Student t test; † - non-parametric Mann-Whitney test; ‡ - chi-square test.*

Table 2 – Functional capacity of the creatine and placebo groups after supplementation

Variable	Groups	Initial mean – 95%CI	Final adjusted mean – 95%CI	Difference between the final adjusted means – 95%CI	p – value
Peak VO_2 (mL/kg/min)	CRE	19.45 (16.46;22.45)	21.76 (19.13; 24.39)		
				0.30 (-3.47; 4.08)	0.8708
	PLA	19.46 (16.42;22.51)	21.46 (18.75; 24.17)		
AT (mL/kg/min)	CRE	10.84 (9.24;12.43)	11.80 (10.23; 13.37)		
				1.73 (-0.54; 4.00)	0.1293
	PLA	11.68 (9.63;13.73)	10.07 (8.45; 11.69)		
O_2 pulse (mL/beat)	CRE	12.22 (10.35;14.09)	13.99 (11.41; 16.56)		
				1.85 (-1.93; 5.63)	0.326
	PLA	14.71 (12.25;17.17)	12.14 (9.48; 14.79)		
Total distance covered in 6 min (m)	CRE	517.35 (457.95;576.75)	547.37 (516.29; 578.44)		
				25.29 (-19.33; 69.92)	0.2563
	PLA	519.00 (453.24;584.76)	522.08 (490.05; 554.11)		
BORG (beginning)	CRE	0.41 (-0.04;0.86)	0.12 (-0.03; 0.27)		
				0.05 (-0.16; 0.27)	0.6171
	PLA	0.13 (-0.06;0.31)	0.06 (-0.09; 0.22)		
BORG (6th min)	CRE	4.41 (3.16;5.66)	3.52 (2.61; 4.43)		
				0.79 (-0.54; 2.13)	0.2349
	PLA	3.06 (2.08;4.04)	2.73 (1.79; 3.66)		

Statistical model used: ANCOVA; significance level (p) of 5%; peak VO_2: peak oxygen volume; AT: anaerobic threshold; numbers between parentheses represent max. and min. values of the confidence interval; the P-values shown refer to the final adjusted mean.

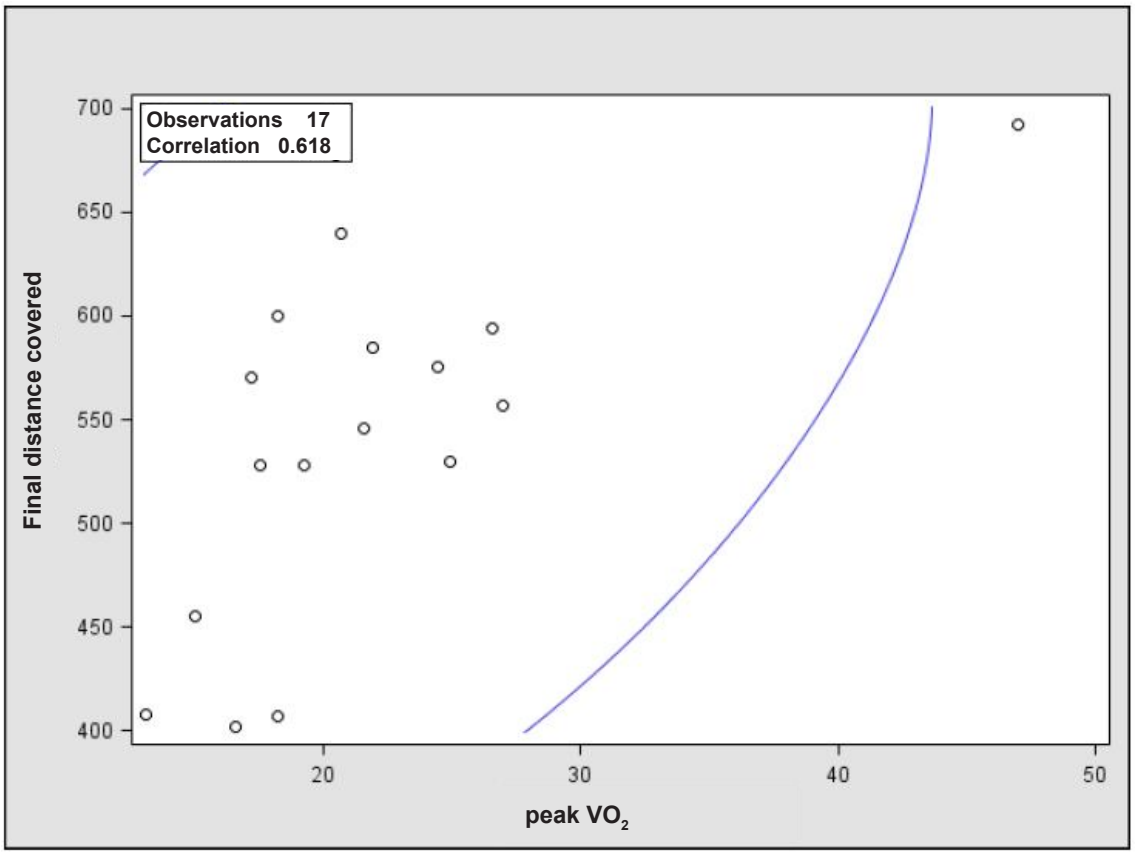

Figure 1 – *Correlation between the variables distance covered and peak VO_2, after the period of creatine supplementation (r = 0.62; p = 0.0082), with 95% confidence interval between the curves (blue lines).*

Gordon et al.[34] , in a study with 17 patients with HF supplemented with 20 g/d of creatine for ten days, have reported an increase in muscle strength and aerobic capacity, assessed by use of the exercise test on a cycle ergometer. Another study performed in a patient with chronic obstructive pulmonary disease supplemented with creatine has also shown the increase in lean mass, strength, and aerobic capacity, in addition to an improvement in the general health status (assessed by use of a questionnaire)[35]. Those studies have shown that, despite acting on the anaerobic metabolism (ATP-CP system), creatine favored the patients' aerobic capacity, increasing oxygen uptake in the cell.

Contrary to the results of previous studies, another study carried out with eight healthy, untrained individuals, supplemented with creatine, using a 20-second sprint cycle ergometer, even in the presence of an increased muscle CP content, has shown neither exercise performance improvement nor changes in the muscle anaerobic metabolism[36]. Stroud et al.[37], studying the effect of creatine supplementation (4 g for five days) on more prolonged exercises in healthy individuals, have assessed peak VO_2 during a 10-km walk on a treadmill and have found no significant difference.

Kuethe et al.[17], assessing 20 patients with functional class II and III HF (15 males) supplemented with creatine (20 g/day for six weeks), have reported mean values of peak VO_2 (14.8 ± 3.4) lower than those found in our study. However, the results of VO_2, AT, distance covered, and Borg scale were close to ours. Thus, those authors have also not observed an improvement in those variables and, consequently, in functional capacity. Although an increase in muscle strength was observed after creatine supplementation, significant difference was observed in neither aerobic and anaerobic capacities nor quality of life.

Studies have reported that creatine supplementation can be beneficial in long-term activities, with aerobic characteristics (approximately 80 minutes), as long as they are intense and have intervals. The hypothesis is that creatine supplementation can change the use of substrates, and improve performance during the prolonged submaximal exercise, such as that occurring during the cyclic stage of a short- and middle-distance triathlon competition. That ergogenic effect might be due to an increase in the resynthesis of creatine phosphate during the recovery interval and/or due to a kinetic improvement in oxygen uptake[38].

The present study showed the correlation of peak VO_2 with the distance covered, observing a positive correlation between the methods, as reported in the literature[3,39]. The use of both tests was aimed at comparing the CPET, a test considered standard, but of difficult access to most individuals, with the 6MWT, which is easily performed, accessible and providing similar responses regarding functional capacity assessment[40].

The functional capacity assessment of the sample studied showed better indices as compared with those of other studies. This is probably justified by the more systematic cardiological follow-up, access to and availability of medications, and the general instructions provided by an outpatient clinic specialized in HF.

The lack of systematic routine of aerobic and anaerobic physical exercise, associated with creatine supplementation, might have interfered with the results, because no positive effect was observed on the functional capacity of the patients supplemented with creatine. That association has been widely discussed in scientific studies, and ergogenic effects have been reported in healthy individuals. We aimed at observing that exclusive effect of supplementation for a longer period (six months) than already studied in patients with HF, who have a significant reduction in functional capacity. Its therapeutic use still yields conflicting results, evidencing incipient knowledge and need for further studies.

Conclusion

Creatine supplementation (5 g/day for six months) in males with HF did not significantly improve functional capacity assessed by use of CPET and 6MWT.

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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