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Research Article

Effects of Bioarginina® C Supplementation on Physical Performance During Cardiac Rehabilitation in Patients with Heart Failure

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Introduction

L-arginine, an amino acid that acts as a nitric oxide (NO) precursor, has been studied for its potential benefits in heart failure (HF). The endothelium regulates vascular tone through the production of NO, formed from L-arginine and oxygen by the enzyme NO synthase (NOS), generating vasodilation and redistribution of muscle flow. Therefore, alterations in NO metabolism can cause the progression of heart failure and imbalance in the NO pathway implies worse clinical outcomes [1,2].

A study involving 50 patients with ischemic heart failure demonstrated that daily supplementation of 3 grams of L-arginine over 10 weeks significantly improved cardiac function. Notable enhancements were observed in ejection fraction, left ventricular function, and quality of life scores measured by the Minnesota Living with Heart Failure Questionnaire. The results indicated improvements in diastolic dysfunction and overall cardiac recovery compared to a placebo group [3]. Another study explored the effects of intravenous L-arginine in patients with congestive heart failure. The infusion led to increased NO production, resulting in improved stroke volume and cardiac output without altering heart rate. L-arginine's primary mechanism involves its conversion to nitric oxide, which plays several roles: it enhances blood flow by relaxing blood vessels, It increases stroke volume and overall heart function and may help lower systemic vascular resistance [3-6]. This suggests that L-arginine can enhance hemodynamic performance by promoting vasodilation [4]. One of the main symptoms of HF is reduced ability to exercise, therefore physical training is recommended to improve physical capacity, quality of life and prognosis (reduction in hospitalizations for heart failure) [7,8]. Exercise is advisable because it can cause changes in arginine metabolism with an increase in NO production.

Furthermore, reduced exercise capacity in HF may be caused by reduced exercise-induced hyperemic blood flow response arising from the endothelium dysfunction in heart failure [7,8].

There is no evidence regarding changes in plasma concentrations of arginine derivatives during physical exercise in patients with heart failure [2]. There is evidence, however, that nutritional support with L- arginine and liposomal vitamin C, improve the perceived tolerance to effort [8]. There is also evidence supporting a benefit in the Cardiac Rehabilitation (CR) of patients with ischaemic heart disease and post covid syndrome [9].

We hypothesized that L- arginine and liposomal vitamin C supplementation during a program of CR in patients with reduced ejection fraction (HFrEF) enhances its response.

Aim of the study

To evaluate the effects of the use of combination of oral L-arginine + liposomal vitamin C (Bioarginina®C, 1.66 g 2 bottles/day) on perceived exertion measured Borg modified scale (BMS) and the functional capacity measured with the six-minute walking test (6MWT) of subjects with heart failure during CR.

Methods

The routine data of patients with HF with post-ischaemic HFrEF, admitted to Rehabilitation of S. Gennaro Hospital (Naples) were analysed. 73 patients (55 M and 18 F), with mean age 64 ± 9 years, (Group A) undergoing integration with two bottles of L arginine and liposomal vitamin C were examined above for 90 days during the CR cycle. As a control population, the results obtained with standard treatment in 36 patients with post-ischaemic HFrEF (24 M and 12 F) (mean age 63 ± 8 years) (Group B) after CR cycle, were examined. The entire study lasted 3 months. In all patients at baseline and after 3 months, routine blood sample and M and B mode echocardiogram were performed. The ability to perform normal daily activities was analyzed with the six minute walk test (6MWT) which measures the distance that a subject can run on a flat surface, walking as fast as possible in six minutes, including any interruptions that patient deems necessary [11].

The perception of the tolerance to the effort was measured by Borg modified 0–10 Rate of Perceived Exertion (BRPE) scale [12,13]. Thirty minutes after each 6MWT, the nurse asked the patient to rate his/her level of effort at performing the exercise on the BRPE scale. BRPE is a personalized exertion grading since it gives a good estimate of heart rate during physical activity. 6minute walk test was performed and after that patient BRPE level was graded based on Modified Borg scale grading 1-10 with 1 as “nothing”, 2 as “very easy” 3 as “Easy “, 4 as “comfortable”,5 as “somewhat difficult”, 6 as “difficult”, 7 as “hard”, 8 as “very hard”, 9 as “extremely hard”, 10 as “maximal exhaustion”. The BRPE was used to measure the physical activity intensity level.

The health-related quality of life (HRQoL) was assessed by the EuroQol-5 and Dimension (EQ-5D) visual analog scale (VAS) score [14]. The EQ-5D instrument measures health status in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated according to the following levels: a) no problems; b) some problems; c) extreme problems. The EQ-5D VAS is a quantitative measure of patients’ perceived health. Patients estimated their overall health status on a 20-cm VAS with the endpoints being “best imaginable health state” (score = 100) and “worst imaginable health state” (score = 0). EQ5D and EQ5D-VAS were evaluated in all patients during follow up.

Quality of life was also assessed with Minnesota living with heart failure questionnaire (MLHFQ). The MLHFQ is a self-administered, 21-item disease specific instrument for patients with heart failure [15] MLHFQ is an instrument which has been widely used to assess quality of life among heart failure patients. Each item is scored in a 6-point Likert Scale (0 to 5), thus the total score could range from 0 to 105, with higher scores indicating more significant impairment in health-related quality of life. The MLHFQ has two domains; physical domain (eight items, score range from 0 to 40) and emotional domain (five items, score range from 0 to 25).

Statistical Analysis

Normally distributed variables are presented as mean ± standard deviation (SD) and were compared by Student’s t-test for paired data for differences in the same group and with the Student’s T test for unpaired data for differences between the two groups. Categorical variables are summarized in terms of number and percentages and were compared by using Chi-square test. A p-value ≤ 0.05 was considered statistically significant.

Results

The basal characteristics of patients are shown in (Tables 1). At 3 months, improvement in 6MWT values was observed in both groups in Group A: 248 ± 132 m vs 307 ± 124 m ($p < 0.0001$) - Group B: 231 ± 126 m vs 241 ± 140 m ($p < 0.021$). However in group A, these was more significant. In the Borg score was a significant improvement in A group but not in B group. After the CR cycle, the increase in the 6MWT distance in group B was not accompanied by a statistically significant reduction in the Borg score, denoting a persistent muscle load. 6MWT values and BRPE values are shown in (Table 2).

	A group 73 pts	B group 36 pts	P value
Age (yrs)	63 ± 9	61 ± 6	0,35
M/F	55/18	24/13	---
BMI	26±3	25±3	0,11
Hypertension	67 (91)	24 (64)	0,002
Hypercholesterolemia	58 (79)	29 (78)	0,89
Current smoker	5 (6)	7 (19)	0,04
Diabetes	38 (67)	13 (36)	0,11
GFR<60 ml/min	31 (42)	19 (52)	0,16
History PCI	59 (80)	30 (83)	0,75
History of prior MI	65 (89)	31 (86)	0,65
ICD	21 (28)	9 (25)	0,67
CRT	16 (21)	4 (11)	0,17
ACEi	31 (42)	11(30)	0,22
ARBs	3 (4)	6 (16)	0,02
ARNI	39 (53)	19 (53)	0,94
MRA	66 (90)	27 (75)	0,03
SGLT1 i	58 (79)	25 (69)	0,24
Diuretics	61 (83)	22 (61)	0,009
Beta Blockers	70 (95)	31 (86)	0,06
Statins	66 (90)	28 (77)	0,07
Ezetimibe	54 (73)	19 (53)	0,02
PCSK9i	9 (12)	2 (5)	0,0001

ICD = Implantable cardioverter–defibrillator

CRT = Cardiac resynchronization therapy.

ACE i = Angiotensin-converting enzyme

ARBs = angiotensin receptor blockers

MRA = Mineralcorticoid receptor antagostists

SGLT1i = Sodium-glucose cotransporter 1 inhibitors

PCSK9i = Proprotein Convertase Subtilisin/Kexin-type 9 inhibitors

Table 1: Baseline Characteristics

	A group baseline	A group after 3 months	P value	B group baseline	B group after 3 months	P value
six-minute walk test (6MWT)	248 ± 132 m	307 ± 124 m	p <0.0001	231 ± 126 m	241 ± 140 m	p <0.021
Borg modified 0–10 Rate of Perceived Exertion (BRPE)	3,5 ± 3,1	2,8 ± 3,1	p <0.031	3,1 ± 2,8	2,9 ± 2,4	0,41

Table 2: Results of 6MWT and BRPE scale

Regarding the echocardiographic evaluation between the two groups, a statistically significant difference between two groups was observed after CR cycle only in Left ventricular diastolic dimension and Left ventricular ejection fraction values. There were no significant differences in the other echocardiographic parameters (Table 3). In laboratory results, no statistically significant differences were observed in liver and kidney function and haemoglobin values (Table 4).

	A group baseline	**B group baseline**	**P value**	**A group after 3 months**	**B group after 3 months**	**P value**
Left ventricular diastolic dimension (mm)	53 ± 8	54 ± 7	0,81	49 ± 7	53 ± 7	0,049
Left atrial size	50 ± 10	51 ± 7	0,92	49± 10	50 ± 12	0,75
Left ventricular ejection fraction (%)	36 ± 6	35 ± 7	0,68	39 ± 5	36 ± 5	0,045
Right ventricular basal diameter (mm)	27±2	26±3	0,66	26±3	27±3	0,49
Pulmonary artery systolic pressure (mmHg)	34 ± 7	35 ± 8	0,72	33 ± 9	35 ± 11	0,52

Table 3: Echocardiographic findings.

	A group baseline	B group baseline	P value	A group after 3 months	B group after 3 months	P value
Glucose (mg/dL)	99±38	96± 35	0,75	95 ± 27	98 ± 32	0,55
Creatinine (mg/dL)	0,74 ± 0,2	0,80± 0,2	0,06	0,85 ± 0,2	0,89 ±0,2	0,07
BUN (mg/dL)	54 ± 14	49 ±14	0,2	51 ± 15	50±12	0,32
Sodium (mEq/L)	139± 5,8	140 ± 4,3	0,09	139 ± 5,1	138 ± 5,6	0,069
Potassium (mEq/L)	3,7 ± 0,9	3,8 ± 0,8	0,61	4,0 ± 0,9	3,8 ± 0,9	0,48
Hemoglobin (g/dL)	13,8± 1,9	12,9 ± 1,7	0,06	13,8 ± 1,8	13,6 ± 2,0	0,07
AST (U/L)	33 ± 12	32 ± 15	0,39	32 ± 11	37 ± 12	0,1
ALT (U/L)	32 ± 22	33 ± 24	0,12	31 ± 15	34 ± 18	0,44

Table 4: A Laboratory Results

Data regarding quality of life (without statistically significant differences at baseline) after 3 months demonstrate significant differences regarding dimensions of mobility, self-care, usual activities, pain/discomfort but not for anxiety/depression. EQ5D and EQ5D-VAS values are shown in (Table 5). Also for the MLHFQ results, better results were observed for physical performance but not for emotional performance. (Table 6) shows results of MLHFQ.

	A group Baseline 73 pts n.(%)	B group Baseline 36 pts n.(%)	P-value	A group after 3 months 73 pts n.(%)	B group after 3 months 36 pts n.(%)	P-value
EQ-5D						
Pain/discomfort, no. (%)						
I have no pain/discomfort	41(56)	21 (58)	0,122	66 (90)	25(70)	< 0,0001
I have moderate pain/discomfort	13 (18)	7 (19)	0,83	6 (9)	7 (19)	0,0009
I am in extreme pain/discomfort	19 (26)	8 (23)	0,415	1 (1)	4(11)	0,015
Anxiety/depression, no. (%)						
I am not anxious or depressed	22 (29)	26(71)	0,083	53 (73)	27(75)	0,967
I am moderately anxious or depressed	50 (67)	9(25)	0,141	19 (26)	9 (25)	< 0,0001
I am extremely anxious or depressed	3 (4)	1(4)	0,766	1 (1)	0	0,486
Mobility, no. (%)						
I have no problems in walking about	45 (62)	20(56)	0,0035	67 (91)	28 (77)	0,0002
I have some problems in walking about	22 (29)	11 (31)	0,0246	6 (9)	7 (19)	0,0505
I am confined to bed	6 (9)	5 (13)	0,3036	0	1 (4)	0,129
Self-Care, no. (%)						
I have no problems with self-care	55 (75)	22(62)	< 0,0001	68 (94)	30 (84)	0,0004
I have some problems washing or dressing myself	16 (22)	10 (27)	0,0012	5 (6)	6 (16)	0,0668
I am unable to wash or dress myself	2 (3)	4 (11)	0,058	0	0	ns
Usual Activities (e.g. work, study, housework, family or leisure activities), no. (%)						
I have no problems with performing my usual activities	59 (81)	29(83)	0,0011	71 (97)	32 (87)	0,0048
I have some problems with performing my usual activities	11 (15)	5 (13)	0,0038	2 (3)	4 (11)	0,065
I am unable to perform my usual activities	3 (4)	1 (4)	0,7872	0	0	ns
EQ5D-VAS values	51±20	54±18	0,012	58±20	62±21	0,039

Table 5: Health-related quality of life

	A group baseline	A group after 3 months	P value	B group baseline	B group after 3 months	P value
MLHFQ total score	60 ± 24	47± 25	p <0.0001	62 ± 22	53± 20	p <0.01
MLHFQ physical domain	30± 5	27± 6	0,003	29±9	23± 5	0,042
MLHFQ emotional domain score	10±2	9±2	0,010	10±2	9±2	0,012

Table 6: Results of MLHFQ

Discussion

Our data suggest that functional capacity, significantly reduced in post-ischaemic HFrEF, may further improve after a CR cycle, with supplementation during a CR programme enhancing its response. In fact, after 3 months of CR programme, we were able to detect a statistically and clinically significant increase in 6MWT distance and a significant improvement in physical activity intensity level measured by BRPE (in A group compared to B group). This evidence would confirm previous observations regarding the effect of L-arginine (3-6). L-arginine enhances blood flow by relaxing blood vessels, It increases stroke volume and overall heart function and may help lower systemic vascular resistance and these effects are endothelium mediated. Vitamin C, with its antioxidant properties, may also have a beneficial effect on endothelial function. This effect, when combined with L-arginina, increases its effectiveness. is enhanced when combined with bioarginine. Unfortunately, the rapid oxidation of vitamin C may limit its use in combination. It would also be confirmed that liposomal vitamin C supplementation increase circulating L-arginine concentrations and have an antioxidant effect with additional benefit on endothelial function [8,10,16]. The results of our study with bioargine + liposomal vitamin C, seem to confirm these hypotheses, with improvements in left ventricular function, exercise capacity and tolerans, and ultimately quality of life; although, in A group, no improvements were observed in emotional state (anxiety and depression) compared to B group.

Conclusion

In conclusion, L-arginine shows promise as a supplementary treatment for improving cardiac function and quality of life in certain heart failure patients, particularly those with ischemic conditions. However, the variability in study outcomes highlights the need for further research to establish definitive guidelines regarding its use in heart failure management. We hypothesized that a supplementation combining L-Arginine (to improve endothelial function) and Vitamin C (to reduce oxidation) could have favorable effects on ventricular function and HRQoL in patients with post ischemic HFrEF. This study also, suggest that oral L-arginine + liposomal vitamin C supplementation could improve cardiac recovery and function.

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