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ORIGINAL ARTICLE

The role of nutritional supplementation with essential amino acids in patients with chronic heart failure

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Abstract Essential amino acid supplementation (EAS) may counteract hypercatabolic states, such as chronic heart failure (CHF). This pilot study investigated whether EAS could improve quality of life (QoL), cardiac function and exercise tolerance in patients (pts) with stable CHF on optimal medical treatment (OMT). We enrolled 27 pts (21 males) with ejection fraction (EF) <35% and on OMT with no changes within the previous 6 months. EAS, composed of leu (1,250 mg), lys (650 mg), ile (625 mg), val (625 mg), thr (350 mg), cys (150 mg), his (150 mg), phe (100 mg), met (50 mg), t4 (30 mg), trp (20 mg), B1 (0.15 mg) and B6 (0.15 mg) vitamins, was given twice a day for 3 months. At baseline and after 3 months, we evaluated symptoms with NYHA classification, LVD36 questionnaire and QoL scale; cardiac function by echocardiography and exercise tolerance (modified Bruce protocol); pro-BNP, renal function, glucose and troponin. We observed a significant reduction of end-systolic and diastolic volumes (ESV 121.6 ± 63.08 vs. 106.82 ± 50.1 mL, $p = 0.018$; EDV 169.1 ± 75.3 vs. 150 ± 67.5 mL, $p < 0.02$), an increase of EF (29.8 ± 5.7 vs. 35.4 ± 5.8%, $p < 0.001$) and of cardiac output (5.58 ± 1.57 vs. 6.07 ± 1.66 L/min; $p = 0.015$). We assisted a no significant trend toward reduction in mitral regurgitation ($p = 0.3$). EAS improved QoL (NYHA $p < 0.001$; LVD36 14.1 ± 7.2 vs. 12.2 ± 6.9, $p = 0.015$; QoL scale 62.4 ± 12.5 vs. 74 ± 9.7%, $p < 0.001$); exercise tolerance (stage 3.24 ± 1.3 vs. 3.57 ± 1.3, $p = 0.016$; METS 6.6 ± 3.4 vs. 7.1 ± 3.3, $p = 0.18$; Minutes 8.1 ± 4.29 vs. 8.7 ± 3.94, $p = 0.055$). No changes in glucose, creatinine, cholesterol, troponin and a no significant trend toward reduction of pro-BNP was observed (1,077.4 ± 530.3 vs. 851.6 ± 315.1 ng/l, $p = 0.3$). No pts showed adverse effects. After 3 months, EAS significantly improves cardiac function, QoL and exercise tolerance in stable CHF pts.

Keywords Essential amino acids supplementation · Chronic heart failure · Hypercatabolism · Cachexia

Introduction

Muscle protein degradation, resulting in amino acid release, occurs predominantly during hypercatabolic states that are common feature of both chronic and acute diseases, such as heart failure, coronary artery disease, diabetes mellitus, liver cirrhosis and trauma, and physiologic conditions, such as senescence. Hypercatabolic states result in muscular wasting and cachexia [1].

Chronic heart failure (CHF) is a disabling condition that affects 4.8 million people in the United States [2, 3]. CHF is the major cardiovascular disease with rising incidence and prevalence in past decades [4]. The increasing age of the population, greater awareness of the disease and improved diagnostic technique for detecting CHF may have contributed to the steady rise in reported incidence. Another reason for the increasing incidence of CHF is improved treatment and survival of patients with ischemic heart disease, the most common etiology of CHF [5]. CHF is characterized by a high rate of hospital readmission and death, significant functional compromise, reduced health-related quality of life and increased caregiver burden.

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A considerable number of patients with reduced systolic function due to primary or ischemic cardiomyopathy have viable and no contractile myocardium. This may be related to numerous and perhaps overlapping factors, such as chronic ischemia (stunning/hibernation), neurohormonal abnormalities, oxidative stress, metabolic imbalances, and/or nutritional depletion. However, the viable but not contractile myocardium maintains a contractile reserve that can be unmasked by inotropic stimulation, such as the infusion of low-dose dobutamine [6, 7].

Change in myocardial substrate utilization has adverse effects on metabolism of the viable, but not on contractile myocardium. Shifting the energy substrate preference away from fatty acids toward glucose and lactate may ameliorate many of the biochemical and hemodynamic abnormalities seen in these cases. Recent data suggest that amino acids influence protein synthesis through regulatory signals in untranslated regions of messenger RNA (mRNA) which results in enhanced mRNA stability. Moreover, CHF is associated with insulin resistance with profound changes in cardiac metabolism including reduced glucose oxidation rates and impaired transcription of the major cardiac glucose transporter GLUT 4 [8, 9].

Replenishing the tricarboxylic acid cycle components via amino acids rather than via fatty acids would increase adenosine triphosphate (ATP) production, with positive effects on cellular metabolism. However, many of the amino acids needed for the tricarboxylic acid cycle are essential amino acids that cannot be synthesized from other precursors and consequently need to be supplied by diet. In humans, these amino acids include histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Single amino acid oral supplementations are rapidly absorbed and available in the blood and are not digested by pancreatic enzymes; they are transported into cells without consuming energy [10].

Recently, it has been demonstrated that amino acid supplementation may be effective in counteracting the metabolic and morphologic consequences of an hypercatabolic state.

Scognamiglio et al. [11] showed that amino acid supplements improved metabolic control and decrease left ventricular dilatation and dysfunction in patients with type 2 diabetes with mild to moderate left ventricular dysfunction. Moreover, Aquilani et al. [12] demonstrated that amino acid supplements appear to increase exercise capacity by improving circulation function, muscle oxygen consumption and aerobic production of energy.

This was a pilot study and our aim was to determine whether essential amino acid supplementation associated with conventional therapy could exert a beneficial effect on left ventricular remodeling and function, on quality of life and on exercise tolerance in patients with moderate to severe chronic heart failure.

Patients and methods

We enrolled 27 consecutive patients (21 males, 66.1 ± 14.8 years) with stable chronic heart failure (NYHA 2b–3), who had resting moderate to severe left ventricular dysfunction (left ventricular ejection fraction <35%) within the previous 6 months and on optimal and stable medical therapy within the previous 3 months.

The inclusion criteria were prior diagnosis of heart failure of ischemic or non-ischemic etiology, left ventricular ejection fraction (LVEF) <35% as measured by two-dimensional echocardiography within previous 6 months, adult aged >18 years and women must not be pregnant. The exclusion criteria were planned revascularization, resynchronization or changes in medical therapy (except diuretics) during the study period.

Essential amino acids, composed of leucine (1,250 mg), lysine (650 mg), isoleucine (625 mg), valine (625 mg), threonine (350 mg), cystine (150 mg), histidine (150 mg), phenylalanine (100 mg), methionine (50 mg), thyrosine (30 mg), tryptophan (20 mg), B1 (0.15 mg) and B6 (0.15 mg) vitamins, were given twice a day for 3 months.

Primary endpoint was to investigate whether oral essential amino acid supplementation continued for 3 months could improve quality of life, cardiac function and exercise tolerance in patients with moderate to severe chronic heart failure. Secondary endpoint was to evaluate the impact of this supplementation on brain-natriuretic peptide (BNP).

Protocol

After enrollment, patients had a baseline evaluation, consisting of complete physical examination, quality of life assessment (NYHA classification, LVD36 questionnaire and quality of life scale), a comprehensive basic metabolic profile, complete lipid profile, a measurement of glycosilated hemoglobin (HbA1c), brain-natriuretic peptide (BNP) and troponin I.

Patients underwent an echocardiographic evaluation. The echocardiographic examinations were performed with Philip Sonos 7500 machine, equipped by a 3.5 MHz transducer and were read by a single observers blinded to the patient's identity and experimental condition. All Doppler echocardiographic recordings were obtained during normal respiration.

Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), intraventricular septal and left ventricular posterior wall thickness at

end-diastole were measured from parasternal M mode echocardiography of the left ventricle. Left ventricular end-diastolic and end-systolic volumes were calculated using modified Simpson's rule (biplane) and the standard formula was applied to give the left ventricular ejection fraction (LVEF) (LVEF = end-diastolic volume (EDV) – end-systolic volume (ESV)/EDV). Left ventricular (LV) volumes were calculated in 2 and 4 chambers. LVEDV and LVESV indices were obtained by correcting for body surface area.

Pulse wave Doppler studies were done using apical views. Recordings of mitral flow velocities were made from an apical four-chamber view with sample volume positioned adjacent to the tip of either mitral or tricuspid leaflets in diastole. Care was taken to obtain the smallest possible angle between the direction of transvalvar flow and the ultrasound beam. Peak velocity of early filling (E) and peak velocity of atrial filling (A) were calculated for transmitral flow, and deceleration time (DT) of early filling was measured from the transmitral Doppler spectrum. DT was calculated as the time between peak E wave and the upper deceleration slope extrapolated to the baseline.

For the assessment of left ventricular longitudinal function velocities were measured at the lateral sites of the mitral annulus. Right ventricular longitudinal function was assessed by measuring velocities at the lateral site of the tricuspid annulus. The off-line analysis included measurements of peak systolic velocities (S_m), and early diastolic (E_m) and late diastolic (A_m) annular velocities, the E/A ratio. All measurements were done as the mean of two or three consecutive cardiac cycles.

At the end, E/E_m was calculated.

Moreover, patients underwent an exercise test with modified Bruce protocol. Participants were encouraged to exercise to exhaustion. Patients do not stop assumption of beta-blockers. A standard 12-lead electrocardiograph recorded heart rate each minute. To evaluate the exercise tolerance were considered the reason of exercise interruption and were measured minutes of exercise, metabolic equivalent (METS), blood pressure every 3 min and oxygen saturation (SO_2, %) at rest, at top of exercise and during recovery.

After 3 months of treatment, patients repeated the antropometric and metabolic evaluations, exercise test and echocardiography examination.

Statistical analysis

The normality of distribution of continuous variables was tested with Kolmogorov–Smirnov test. Continuous variables are represented as mean ± standard deviation (SD) or as a medians (Q1 to Q3) ± interquartile range. *T* test and Mann–Whitney test were used to determine the differences between normal and non-normally distributed continuous variables, respectively. Categorical variables were reported as absolute values or percentages and were analyzed by Chi-Square (χ^2) or Fisher exact test. Data were analyzed with SPSS 13.0 for Windows. The value of $p < 0.05$ was considered significant.

Results

A total of 27 patients were enrolled in this study. The clinical characteristics of patients are shown in Table 1. Table 2 represented echocardiographic data of this study. After 3 months of amino acid supplementation, we

Table 1 Clinical characteristics of patients treated with amino acid supplementation ($n = 27$)

Sex M/F	21/5
Age (years)	66.1 ± 14.8
BMI (kg/m^2)	24.9 ± 4.3
Hypertension (*n*, %)	20 (74.1%)
Hypercolesterolemia (*n*, %)	13 (48.1%)
Diabetes mellitus (*n*, %)	6 (22.2%)
Familiar with CAD (*n*, %)	9 (33.3%)
Smoker (*n*, %)	3 (11.1%)
Previous AMI (*n*, %)	14 (5.9%)
AMI follow up (*n*, %)	0
Previous revascularization (*n*, %)	14 (51.9%)
Revascularization follow up (*n*, %)	0
Previous acute heart failure (*n*, %)	14 (51.9%)
Acute heart failure follow up (*n*, %)	0
ICD (*n*, %)	18 (66.7%)
Pacemaker (*n*, %)	5 (18.5%)
Cause of CHF	
Ischemic CHF	15 (55.6%)
Idiopathic CHF	12 (44.4%)
Drugs (*n*, %)	
ACE inhibitors	17 (63%)
ARB	12 (44.4%)
Diuretics	23 (85.2%)
Calcium-channel blockers	6 (22.2%)
Beta-blockers	25 (92.6%)
Antialdosteronic agent	14 (51.9%)
Digossin	12 (44.4%)
Nitrate	19 (70.4%)
Anticoagulant agent	13 (48.1%)
Pufa	7 (25.9%)
Statins	17 (63%)

BMI body mass index, *CAD* coronary artery disease, *CHF* cardiac heart failure, *AMI* acute myocardial infarction, *ICD* implantable cardioverter defibrillator, *CHF* chronic heart failure, *ACE* angiotensin converting enzyme, *ARB* angiotensin II receptor blockers

Table 2 Echocardiographic data before and after amino acid administration

Echocardiographic data	Before	After	*p* value
Left atrium (mL)	90.52 ± 41.5	92.8 ± 41.5	0.45
End-diastolic diameter (mm)	62.2 ± 7.8	61.1 ± 9.5	0.35
End-systolic diameter (mm)	49.2 ± 10.1	48.2 ± 9.5	0.31
Ventricular septal (mm)	10.2 ± 2.1	10 ± 1.7	0.71
Posterior wall (mm)	10.1 ± 1.5	9.8 ± 1.4	0.22
Ejection fraction (%) two chamber	29.6 ± 5.9	34.05 ± 4.9	0.001
End-diastolic volume (mL)	169.1 ± 75.3	150 ± 67.5	0.02
End-systolic volume (mL)	121.6 ± 63.08	106.82 ± 50.1	0.018
Ejection fraction (%) four chamber	29.8 ± 5.7	35.4 ± 5.8	0.001
End-diastolic volume (mL)	178.7 ± 59.5	167.5 ± 56.3	0.08
End-systolic volume (mL)	128.1 ± 53.1	109.3 ± 49.4	0.001
Cardiac output (l/min)	5.58 ± 1.47	6.07 ± 1.66	0.015
Longitudinal diameter (mm)	77.9 ± 8.8	77.1 ± 8.8	0.23
Transversal diameter (mm)	59.05 ± 9.9	57.6 ± 9.4	0.34
Ventricular sphericization	1.55 ± 0.29	1.55 ± 0.26	1
Mitral regurgitation			
+	9	9	
++	7	10	
+++	7	4	0.3
++++	3	3	
eroA (mm^2)	20.07 ± 7.4	17.7 ± 5.3	0.3
Vena contracta (cm)	0.6 ± 1.4	0.6 ± 1.5	0.8
TDI S_m (m/sec)	0.071 ± 0.013	0.078 ± 0.012	0.002
TDI E_m (m/sec)	0.097 ± 0.04	0.104 ± 0.038	0.046
TDI A_m (m/sec)	0.095 ± 0.03	0.101 ± 0.03	0.3
E wave (m/sec)	0.93 ± 0.4	0.8 ± 0.2	0.2
A wave (m/sec)	0.9 ± 0.3	0.8 ± 0.3	0.2
Deceleration time (msec)	232.2 ± 72.5	217.23 ± 73.7	0.23
E/E_m	9.5 ± 3.8	7.9 ± 2.3	0.029
E/A	1.17 ± 0.75	1.06 ± 0.7	0.4
TAPSE (cm)	1.98 ± 0.3	1,93 ± 0.3	0.52
Tricuspidal TDI (m/sec)	1.14 ± 0.2	1.1 ± 0.25	0.58
sPAP (mmHg)	34.1 ± 7.8	33.4 ± 6.9	0.54

TDI tissue Doppler imaging, *TAPSE* tricuspid annular plane systolic excursion, *sPAP* systolic pulmonary artery pressure

observed a significant reduction of end-systolic and diastolic volumes (ESV 121.6 ± 63.08 vs. 106.82 ± 50.1 mL, $p = 0.018$; EDV 169.1 ± 75.3 vs. 150 ± 67.5 mL, $p < 0{,}02$) and an increase of LVEF (29.8 ± 5.7 vs. 35.4 ± 5.8%, $p < 0.001$). Moreover, we observed a significant improvement of cardiac output (5.58 ± 1.57 vs. 6.07 ± 1.66 L/min; $p = 0{,}015$). We found out a significant increase of peak systolic (S_m 0.071 ± 0.013 vs. 0.078 ± 0.012 m/s, $p = 0.002$), and of early diastolic annular velocities (E_m 0.097 ± 0.04 vs. 0.104 ± 0.038 m/s, $p = 0.046$); whereas the late diastolic annular velocities was not significant (A_m 0.095 ± 0.03 vs. 0.101 ± 0.03 m/s, $p = 0.3$). E/E_m ratio significantly reduced (9.5 ± 3.8 vs. 7.9 ± 2.3, $p = 0.029$). Moreover, we assisted a no significant reduction in mitral regurgitation ($p = 0.3$). If we considered only moderate and severe mitral regurgitation (3+/4+), we observed an important reduction of the regurgitation ($p = 0.08$).

As shown in Table 3, essential amino acid supplementation improved quality of life (NYHA $p < 0.001$; LVD36 14.1 ± 7.2 vs. 12.2 ± 6.9, $p = 0.015$; QoL 62.4 ± 12.5 vs. 74 ± 9.7%, $p < 0.001$). Patients acquired a better exercise tolerance (BRUCE stage 3.24 ± 1.3 vs. 3.57 ± 1.3, $p = 0.016$; METS 6.6 ± 3.4 vs. 7.1 ± 3.3, $p = 0.18$; Minutes 8.1 ± 4.29 vs. 8.7 ± 3.94, $p = 0.055$) (Table 4).

There were no changes in glucose, creatinine, cholesterol and troponin I. A no significant trend toward reduction of pro-BNP was observed (1,077.4 ± 530.3 vs. 851.6 ± 315.1 ng/l, $p = 0.3$). No patients died or experienced major cardiac complications during the study period.

Table 3 Evaluation of symptoms with New York Heart Association (NYHA) classification, LVD36 questionnaire and quality of life scale (QOL)

Symptoms	Before	After	*p* value
NYHA			
1	1	4	
2a	10	18	0.001
2b	9	5	
3	7	0	
4	0	0	
LVD 36	14.1 ± 7.2	12.2 ± 6.9	0.015
QOL (%)	62.4 ± 12.5	74 ± 9.7	0.001

NHYA New York Heart Association, *LVD* 36 left ventricular dysfunction questionnaire, *QoL* quality of life

Discussion

Chronic diseases, such as diabetes, heart failure and senescence share the common denominator of hypercatabolic syndrome with insulin resistance. Hypercatabolic syndrome is characterized by increased hormonal catabolic stimuli that causes muscle protein breakdown and consequent cell release of amino acids, muscular wasting and altered energy production.

The impact of heart failure is tremendous, whether measured in terms of morbidity, mortality or economic cost. Recently, Neubauer has pointed out that deprivation of cardiac energy plays a major role in the failing heart and that maintenance of cardiac metabolism and energy production by metabolic therapy is a promising new avenue into mechanical energy [13].

Although the mechanism by which the addition of amino acids to optimal medical treatment improves left ventricular function, symptoms and exercise tolerance in patients with chronic heart failure is not easily understood, some hypothesis can be put forward to explain our findings.

Basic laboratory and clinical evidence showed that oral administration of amino acids stimulated cytosolic muscle protein synthesis, mitochondrial biogenesis and glucose intracellular transport and use. These mechanisms may help to maintain skeletal and cardiac muscle structures and energy content; importantly, these amino acid activities used an insulin-independent pathway (mTOR kinase pathway) [14]. CHF is characterized by alterations in nitrogen metabolism. Exogenous L-arginine promotes endothelial NOS expression and NO production leading to improvement of the mitochondrial biogenesis and functions that are defective in several tissues, including fat, skeletal and cardiac muscle in aged subjects [15]. Most amino acids in our mixture feed into the Krebs cycle and may have become glutamate through α-ketoglutaric acid. Histidine could also contribute to glutamate via α-ketoglutaric acid. These observations support the relevant cardioprotective role of these amino acids by improving energy substrate metabolism and adenosine triphosphate (ATP) production mediated by a direct metabolic effect on the heart.

Increased protein intake with meals did not increase protein synthesis, because the meal must be digested and absorbed and, often, as in the case of chronic diseases, the exocrine pancreas and mesenteric circulation are impaired. Individual amino acid introduced by nutritional supplementation are not digested, but are rapidly absorbed with massive blood increases and easily transported into cells, where amino acids maintain myocyte structure and metabolism [16].

In previous works, amino acid supplements improved metabolic control and decrease left ventricular dilatation and dysfunction in patients with type 2 diabetes with mild to moderate left ventricular dysfunction [11] and increased

Table 4 Variable of exercise test (modified Bruce protocol)

Exercise test	Before	After	*p* value
Bruce stage	3.24 ± 1.3	3.57 ± 01.3	0.016
Mets	6.6 ± 3.4	7.1 ± 3.3	0.18
Minutes	8.1 ± 4.29	8.7 ± 3.94	0.055
Double product	15,376.6 ± 3,666.2	15,442.8 ± 2,627.7	0.9
Basal SO_2 %	98 ± 1.6	97.5 ± 1.4	0.34
SO_2 % at top of exercise	96.24 ± 2.09	97.24 ± 1.9	0.1
SO_2 % at recovery	97. ± 1.4	98 ± 1.5	0.9
Exercise interruption			
Angina	0	0	
ECG positive for ischemia	0	0	
Dyspnea	7	5	0.059
Muscular soreness	13	14	
Maximal test	1	2	

METS metabolic equivalent, *SO2* oxygen saturation, *ECG* electrocardiography

exercise capacity by improving circulation function, muscle oxygen consumption and aerobic production of energy [12].

Our results demonstrated that the use of amino acid supplementation in patients with moderate to severe left ventricular dysfunction (LVEF <35%), significantly reduced left ventricular dilatation and dysfunction increasing LVEF (29.8 ± 5.7 vs. $35.4 \pm 5.8\%$, $p < 0{,}001$); cardiac output and peak systolic and early diastolic annular velocities significantly improved. Moreover, we observed a trend toward the reduction of mitral regurgitation, although not significant, maybe because mitral insufficiency was not based only on ventricular remodeling. From clinical point of view, we assisted a considerable increase of quality of life and patients acquired better exercise tolerance.

Although the study did not allow us to prove that direct metabolic effects on the heart were the cause of improvement in myocardial performance, our experimental data suggest that amino acid supplementation may increase the availability of energy substrate and/or improve conversion of chemical energy into mechanical energy.

As a result, amino acid supplementation counteract catabolic stimuli present in chronic heart failure by stimulating muscle metabolism with consequent functional damage.

Conflict of interest None.

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