Oral Amino Acid Supplements Improve Exercise Capacities in Elderly Patients with Chronic Heart Failure

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We investigated whether 30 days of oral supplementation with a special mixture of amino acids (AAs), together with conventional therapy, could improve exercise capacity in elderly outpatients with chronic heart failure (CHF). A group of 95 outpatients (12 women and 83 men; New York Heart Association class II–III) aged 65–74 years were studied. This was a randomized, double-blind, placebo-controlled study. The patients performed a basal exercise test and were then randomly assigned to a special oral nutritional mixture of AAs 4 g twice daily (n = 43) or placebo (n = 42). After 30 days we repeated the exercise test. In both tests we measured the following: oxygen consumption (VO_2), CO_2 production (VCO_2), minute ventilation (VE), oxygen cost of ventilation (VO_2/VE), CO_2 elimination per liter of ventilation (VCO_2/VE), respiratory exchange ratio (RER; calculated as VCO_2/VO_2), oxygen pulse (VO_2/heart rate [HR]) and anaerobic metabolism during exercise (ANA-VO_2). At day 30, exercise capacity in the AA group had improved (+11 ± 8 W, p <0.01; +67.5 ± 44 seconds, p <0.02). This improvement was associated with both reduced circulatory dysfunction and increased peripheral oxygen availability. Indeed, peak VO_2 increased by 1.2 ± 1.1 mL/kg per min (+12.7% ± 13%; p<0.02) and VO_2/HR improved by 1.5 ± 1.4 mL O_2 per heartbeat (p <0.05). ANA-VO_2 was reduced by >50% in patients on AAs (from 20.2 ± 10 mL/kg at day 0 to 10.9 ± 5 mL/kg at day 30; p <0.02). These variables did not significantly change for patients who received placebo. In conclusion, the study showed that oral AA supplementation, in conjunction with standard pharmacologic therapy, appears to increase exercise capacity by improving circulatory function, muscle oxygen consumption, and aerobic production of energy in elderly outpatients with CHF. **© 2008 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2008;101[suppl]:104E–110E)**

Patients with chronic heart failure (CHF) often have reduced exercise capacity because of early onset of fatigue and/or dyspnea. In elderly subjects with CHF, physical capacity may be even more reduced because of the limitations of physical activity associated with aging. Consequently, elderly patients with CHF risk losing their physical independence in performing activities of daily living. Therefore, even small improvements in exercise tolerance may be very important, not only for acquiring or maintaining autonomy but also, more generally, for delaying functional decline by improving body composition, diminishing falls, reducing depression, and maintaining cognition. Exercise tolerance in CHF has, in fact, been shown to improve after pharmacologic therapy, including angiotensin-converting enzyme inhibitors and β-blockers drugs and/or physical training.[1–8] However, research on improving exercise capacity in CHF by physical training in elderly patients with CHF is just beginning[9,10] and may in any case be impractical for certain individuals, such as those with musculoskeletal problems, a very frequent disorder in older persons. Furthermore, not all elderly patients with CHF can be prescribed β-blockers.

In addition to physical training and pharmacologic therapy for exercise intolerance, an additional safe and effective treatment option would be of great practical importance for elderly patients with CHF. We believe that nutritional supplementation with amino acids (AAs) could be such an option for the following reasons: First, AAs can enter the cellular energy-producing aerobic pathway as substrates.[11] Second, branched-chain amino acids (leucine, isoleucine, and valine) are normally used in peripheral skel-

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etal muscles, and their use increases during exercise.[12] Thirdly, the skeletal muscles of patients with CHF have high AA metabolism even at rest.[13] Fourth, AA supplements affected myocardial performance positively.[14,15] Lastly, oral AA supplements can improve ambulatory capacity and maximal isometric muscle strength in healthy elderly subjects.[16]

We therefore investigated whether 30 days of oral supplementation with a special mixture of AAs could improve exercise capacity in elderly outpatients with CHF. Our investigation also focused on postexercise recovery because shorter recovery times could contribute to physical independence of patients with CHF.[17]

Materials and Methods

A group of 95 outpatients (12 women and 83 men) all aged >65 years participated in this randomized, double-blind, placebo-controlled study. They were diagnosed with CHF of New York Heart Association (NYHA) functional class II (n = 54) or III (n = 41). The diagnosis of CHF was based on a history of exertional dyspnea or pulmonary edema and a reduced left ventricular ejection fraction (LVEF) (<0.45). The underlying cause of CHF was ischemia in 70% and idiopathic dilated cardiomyopathy in 30% of the group. The patients were accustomed to exercise testing before the study because they had been coming to our laboratory over a period of time. These 95 patients were selected because they were normally nourished (body mass index >25 and arm muscle area >10th percentile for age and sex) and had reduced exercise tolerance (peak oxygen consumption [VO_2 peak] <15 mL/kg per min in a bicycle ramp exercise test). At the time of the study, the patients were clinically stable and were receiving medical therapy that was maintained stable both before and after the study.

Patients were not engaged in any structured physical exercise but were independent in their daily physical activities. After a medical evaluation as part of their long-term follow-up, patients were randomly assigned to an oral nutritional mixture providing 4 g per packet of a special mixture of AAs (Big One; Professional Dietetics, Milan, Italy) (see Table 1) (AA group; n = 50) or isocaloric placebo (placebo group; n = 45). The placebo packets were indistinguishable from the AA packets but contained 4 g of carbohydrates instead of 4 g of essential AAs. The AA group was asked to take 2 packets of AAs per day for a total of 8 g of AAs. Both groups were asked to consume their respective supplements for 30 days. After randomization, the patients underwent a bicycle exercise test and respiratory gas analysis to monitor metabolic variables. The test was repeated using the same protocol after 30 days of nutritional supplements or placebo. All patients gave their written informed consent to participate in the study, and the institutional committee approved the study protocol.

Bicycle exercise test: All exercise tests were performed in the morning after overnight fasting for 12–16 hours. We adopted a ramp test in which the workload increased 10 W/min with pedaling at 40–50 rpm. The patients were connected to a system for respiratory gas analysis, which was conducted in a resting state while sitting on the bicycle before and during exercise. Patients were asked to exercise until exhausted. At this point, the load was removed; the patients stopped pedaling but remained connected to the gas analysis system for the study of the recovery of metabolic variables (12 minutes).

Measurements of metabolic variables: VO_2, CO_2 production (VCO_2), minute ventilation (VE), oxygen cost of ventilation (VO_2/VE), CO_2 elimination per liter of ventilation (VCO_2/VE) and respiratory exchange ratio (RER; calculated as VCO_2/VO_2) were measured on a breath-by-breath basis, averaged and printed each minute. We also calculated the oxygen pulse (VO_2/heart rate [HR]), which is considered an index of peripheral oxygen availability. Given that VO_2/HR = stroke volume (SV) × arteriovenous difference in oxygen (A-V), an increase in the oxygen pulse is reflected in an increase in SV and/or A-V. VO_2 peak was defined as the highest value of VO_2 obtained at the end of the test and was considered an index of the severity of the circulatory dysfunction. Having monitored the metabolic variables during the postexercise recovery period, we calculated the anaerobic metabolism during exercise (ANA-VO_2) as follows: ANA-VO_2 (mL/kg) = □(VO_{2R} − VO_{2Bas}), where VO_{2R} is the excess of VO_2 during the recovery period in relation to VO_2 at baseline (VO_{2Bas}). In addition, we calculated the time in seconds to achieve 33% and 50% reductions in the peaks of VO_2, HR, VO_2/HR, and VE for each patient. A standard 12-lead electrocardiograph recorded heart rate each minute. Blood pressure was measured with a sphygmomanometer every 3 minutes.

Statistical analysis: Data are expressed as mean ± SD. Possible differences in anthropometric, biochemical, functional, and hormonal characteristics, and LVEF between the treatment and placebo groups were analyzed by unpaired *t*-tests. Differences in functional classes (NYHA) and medications between the 2 groups were determined by the χ^2 test. The differences in metabolic variables between the 2 groups of patients recorded at rest (baseline), during exercise, and during recovery, both at entry to the study (day 0) and after 30 days (day 30), were tested by analysis of variance (ANOVA). Statistical significance was set at $p < 0.05$.

Results

Subjects: At the start of the study (day 0), the 2 groups of elderly patients with CHF (placebo and AA groups) were similar for demographic, clinical, functional, and hormonal characteristics (Table 2). After 30 days of placebo or AA supplements (day 30), these characteristics remained statis-

Table 1
Nutritional composition of a single packet containing 4 g of an amino acid (AA) mixture*

Total AAs†	4 g
L-Leucine	1250 mg
L-Lysine	650 mg
L-Isoleucine	625 mg
L-Valine	625 mg
L-Threonine	350 mg
L-Cysteine	150 mg
L-Histidine	150 mg
L-Phenylalanine	100 mg
L-Methionine	50 mg
L-Tyrosine	30 mg
L-Tryptophan	20 mg

* Big One; Professional Dietetics, Milan, Italy.
† 35.3 kcal (149.9 kJ).

Table 2
Clinical, biochemical, functional, and hormonal characteristics of the patients given a special amino acid (AA) mixture* versus the placebo group

Parameters	Placebo Group (n = 45)	AA Group (n = 60)	p†
Men/women	37/8	46/4	
Mean age (yr)	72 ± 3	74 ± 5	NS
Mean Weight (kg)	78 ± 8	75 ± 10	NS
Mean body mass index	27 ± 2	26 ± 2	NS
NYHA functional class II/III	25/20	30/20	—
Medications (% of patients):			
ACE inhibitors	100%	100%	NS
Diuretics	100%	100%	NS
Digoxin	35%	40%	NS
Ca^{2+} antagonists	0	5%	—
Nitrates	20%	35%	p <0.05
β-blockers	35%	40%	NS
Sartans	25%	20%	NS
Statins	20%	15%	NS
LVEF	0.32 ± 0.06	0.34 ± 0.09	NS
Hemoglobin (g/dL)	14.5 ± 1.1	14.9 ± 1	NS
Serum sodium level (mEq/L)	140 ± 2.4	139 ± 2.3	NS
Noradrenaline (pg/mL)	448 ± 25	420 ± 30	NS

ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NS = not significant; NYHA = New York Heart Association.
* Big One; Professional Dietetics, Milan, Italy.
† Statistically significant by unpaired *t* test.

tically unchanged. However a trend toward improved NYHA class (p = 0.06) was noted in patients who had received AAs. Indeed, in this group 38% of the patients (n = 17) improved from class III to class II while in the placebo group 22% of the patients (n = 11) worsened from class II to class III (p <0.01 between the 2 groups). No patient complained of any discomfort resulting from the AA supplements.

Exercise study: Table 3 describes the metabolic, ventilatory, and circulatory variables and the power output of the 2 groups, both at entry into the study (day 0) and after 30 days of supplements (day 30). At day 0, the AA group had a lower exercise capacity than the placebo group (power output, 70 ± 21 W vs 83 ± 23 W, p <0.03; duration, 435 ± 119 seconds vs 520± 134 seconds, p <0.02), but similar VO_2 peak, oxygen cost for ventilation, pulmonary CO_2 washout, heart rate, peripheral tissue oxygen availability (VO_2/HR), and net oxygen cost for work (□VO_2/W). At day 30, exercise capacity in the AA group had improved (+11 ± 8 W, p <0.01 vs baseline; duration time, +67.5 ± 44 seconds, p <0.02). This improvement was associated with both reduced circulatory dysfunction and increased peripheral oxygen availability. In fact, peak VO_2 increased by 1.2 ± 1.1 mL/kg per min (+12.7% ± 13%, p <0.02; Figure 1) and VO_2/HR improved by 1.5 ± 1.4 mL O_2/heartbeat (p <0.05). Moreover we found a trend toward an increase in basal VO_2/HR at day 30 compared with day 0 (p = 0.06). All the other parameters remained similar to those recorded at day 0. At day 30, no significant changes in variables were observed in the placebo group.

Recovery study: Table 4 shows the parameters of postexercise recovery in both groups of patients at day 0 and at day 30. Figure 2 illustrates the time course of the variables recovery. At day 0, the peak exercise VO_2 declined toward the baseline pre-exercise VO_2 of 8.21 ± 1.6 minutes in placebo patients, which was not different from the 8.8 ± 2.4 minutes recorded in the AA group (p = NS). This similarity in the 2 groups was also observed when theVO_2 recovery time was considered for the same percentage of the decline of the peak VO_2 (33% and 50% respectively). Moreover, at each isodecline of peak VO_2, the recovery of ventilatory and circulatory functions was similar in the 2 groups of patients. At day 30, patients who had received AA supplements improved in certain recovery parameters, whereas the placebo group showed no change at all. Indeed, in the AA group, the decline time of peak VO_2 shortened to 6 ± 1 minute (p <0.02 vs day 0). This recovery improvement was also observed in the 33% decline in peak VO_2 (95 ± 40 seconds in the AA group vs 185 ± 28 seconds in the placebo recipients; p <0.001) and in the 50% decline in VO_2 (161 ± 52 seconds in the AA group vs 327±65 seconds in the placebo group, p <0.001). In both groups of patients, the recovery time course of both VE and VO_2/HR paralleled the recovery time course of VO_2.

With regard to anaerobic metabolism, at day 0 ANA-VO_2 was similar in both groups (Figure 2), but at day 30 ANA-VO_2 had more than halved in patients on AAs (from 20.2 ± 10 mL/kg at day 0 to 10.9 ± 5 mL/kg at day 30; p <0.02). No significant change in ANA-VO_2 was observed in patients who had received placebo (Figure 2).

Discussion

This investigation showed that oral supplementation with a special mixture of AAs associated with standard pharmaco-

Table 3
Metabolic, ventilatory, and cardiocirculatory variables at baseline (BAS) and at peak exercise (Ex) found in the placebo group and in patients given a special mixture of amino acids (AAs)* before (T_0) and after (T_1)† 30 days of nutritional supplements

Variables	Placebo group				AAs group			
	BAS T_0	Ex T_0	BAS T_1	Ex T_1	BAS T_0	Ex T_0	BAS T_1	Ex T_1
VO_2 (mL/min/kg)	4.3 ± 0.5	11.6 ± 3.1	4.0 ± 0.7	11.7 ± 3.4	4.5 ± 1.0	12 ± 2.6	4.1 ± 1.0	12.1 ± 3.1
RER	0.87 ± 0.03	1.12 ± 0.1	0.96 ± 0.1	1.11 ± 0.2	0.86 ± 0.02	1.10 ± 0.2	0.95 ± 0.02	1.11 ± 0.07
VE (L/min)	15.3 ± 4.1	43.1 ± 15	14.7 ± 3.2	43.6 ± 14	13.4 ± 4.5	40.2 ± 11.1	15.3 ± 3.6	43.2 ± 10.9
VCO_2 (mL/min/kg)	3.8 ± 0.4	13.2 ± 3.9	3.8 ± 0.4	12.8 ± 3.7	3.9 ± 0.3	12.5 ± 2.8	3.9 ± 0.3	13.6 ± 3.1
VO_2/VE (mL/L/min)	20.1 ± 2.6	21.3 ± 3.6	20.9 ± 3.1	21.3 ± 3.5	19.0 ± 5.1	22.3 ± 3.6	18.1 ± 5.8	21.3 ± 4.7
VCO_2/VE (mL/L/min)	18.7 ± 2.3	24.1 ± 3.9	20.8 ± 2.9	22.5 ± 4.5	21.2 ± 2.8	23.1 ± 3.4	19.4 ± 3.3	23.7 ± 4.7
HR (beats/min)	91.0 ± 14.1	129.0 ± 27.0	86.0 ± 20.0	123.0 ± 32.0	88.0 ± 11.0	130.0 ± 25.0	87.0 ± 12.0	124.0 ± 17.0
VO_2/HR (mL/min/beat)	3.9 ± 1.2	7.2 ± 1.7	3.7 ± 1.0	7.3 ± 1.7	3.8 ± 1.0	6.9 ± 1.3	3.6 ± 1.1	7.7 ± 1.4
Watts	—	83.0 ± 23.0	—	87.0 ± 22.0	—	70.0 ± 21.0‡	—	86.0 ± 21.0§

HR = heart rate; RER = respiratory exchange ratio; VCO_2 = pulmonary washout of carbon dioxide; VCO_2/VE = pulmonary washout of carbon dioxide per liter of pulmonary ventilation; VE = pulmonary ventilation; VO_2 = oxygen consumption; VO_2/VE = oxygen consumption per liter of pulmonary ventilation; VO_2/HR = oxygen pulse; Watts = power output.

* Big One; Professional Dietetics, Milan, Italy.

† Data are expressed as mean ± SD.

‡ $p < 0.03$ vs placebo group Ex T_0 (analysis of variance).

§ $p < 0.01$ vs AA group Ex T_0 (analysis of variance).

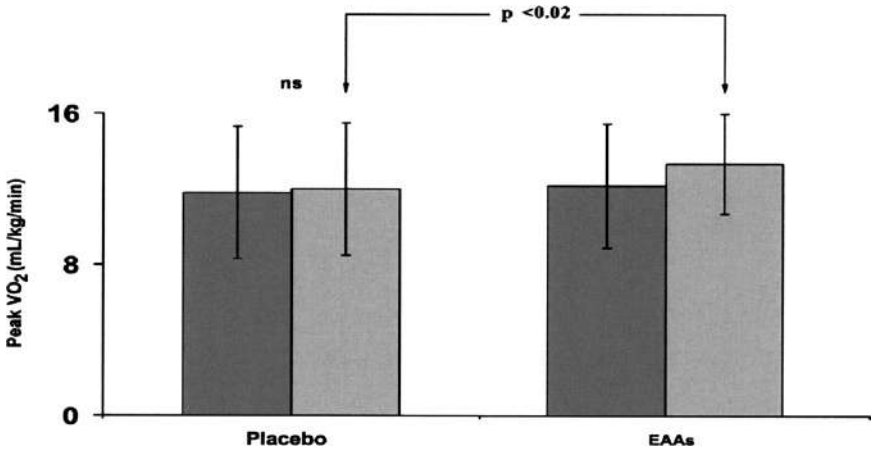

Figure 1. Comparison of peak oxygen consumption (VO_2) variation between the placebo group (*left*) and the amino acid group (*right*). In both groups the bars represent peak oxygen consumption (peak VO_2) level at day 0 (*black bars*) and day 30 (*gray bars*) ($p < 0.02$ for intergroup difference).

logic therapy effectively improves exercise capacity and shortens recovery time in elderly outpatients with CHF, thus increasing the patients' potential for more physical independence in their real life.

Exercise study: The improvement in exercise capacity consisted of increased mechanical work (measured in Watts), longer duration, and more intense oxidative metabolism (peak VO_2). The factors responsible for this improvement were as follows: (1) a real improvement in circulatory function; (2) a reasonable increase in muscle AA use; and (3) a possible increase in skeletal muscle mass. The improvement in circulatory function consisted of greater oxygen delivery and availability for skeletal muscle (VO_2/HR) and hence the observed increased oxygen consumption (VO_2). Given that $VO_2/HR = SV \times (A\text{-}V)O_2$, AA supplements may be able to increase SV and/or A-V during physical activity. The study showed that even at rest, VO_2/HR tended to be higher at day 30 than at day 0. Our data do not allow us to understand which of the 2 circulatory functions played the more important role or whether both of them were involved. Indeed, AAs are substrates that can potentially act by both central (SV) and peripheral (A-V) mechanisms. AAs can improve myocardial performance by promoting an anabolic effect on heart protein metabolism[18]; in patients with coronary artery disease this may protect the heart against myocardial ischemic injury by enhancing postischemic pressure recovery and improving postischemic systolic and diastolic myocardial function.[19] Moreover, in patients with type 2 diabetes, a supply of AAs, such as in this study, can reduce exercise-induced left ventricular dysfunction.[15] Leucine, one of the AAs in the mixture, may indirectly increase the A-V by increasing production of insulin, the anabolic hormone involved in peripheral vasodilatation.

Table 4
Time of postexercise recovery (R) to achieve 33% or 50% decline of the peak values of the metabolic and cardiocirculatory variables at baseline (T_0) and after 30 days of nutritional supplements*† (T_1)

Variables	Time to 33% Peak Decline (sec)				Time to 50% Peak Decline (sec)			
	Placebo		AAs		Placebo (50%)		AAs (50%)	
	R T_0	R T_1	R T_0	R T_1	R T_0	R T_1	R T_0	R T_1
VO_2	215 ± 95	185 ± 28	225 ± 68	95 ± 40‡	330 ± 65	327 ± 65	315 ± 79	161 ± 52‖
VE	205 ± 58	185 ± 40	182 ± 28	105 ± 24‡	326 ± 58	290 ± 46	300 ± 35	174 ± 30‖
VO_2/HR	386 ± 65	318 ± 90	358 ± 159	156 ± 78§	434 ± 65	358 ± 65	435 ± 65	346 ± 108
HR	354 ± 82	320 ± 96	345 ± 65	318 ± 85	NA	NA	NA	NA

HR = heart rate; NA = not achieved; VE = pulmonary ventilation; VO_2 = oxygen consumption; VO_2/HR = oxygen pulse.

* Big One; Professional Dietetics, Milan, Italy.

† Values are given as mean ± SD. Statistical analysis by analysis of variance test. At 33% decline, differences between groups were ‡ $p < 0.01$ versus placebo RT_1; § $p < 0.03$ versus placebo RT_1. Differences within groups were $p < 0.001$, AAs RT_1 versus AAs RT_0. At 50% decline, differences between groups were ‖ $p < 0.001$ versus placebo RT_1. Differences within groups were $p < 0.005$, AAs RT_1 versus AAs RT_0.

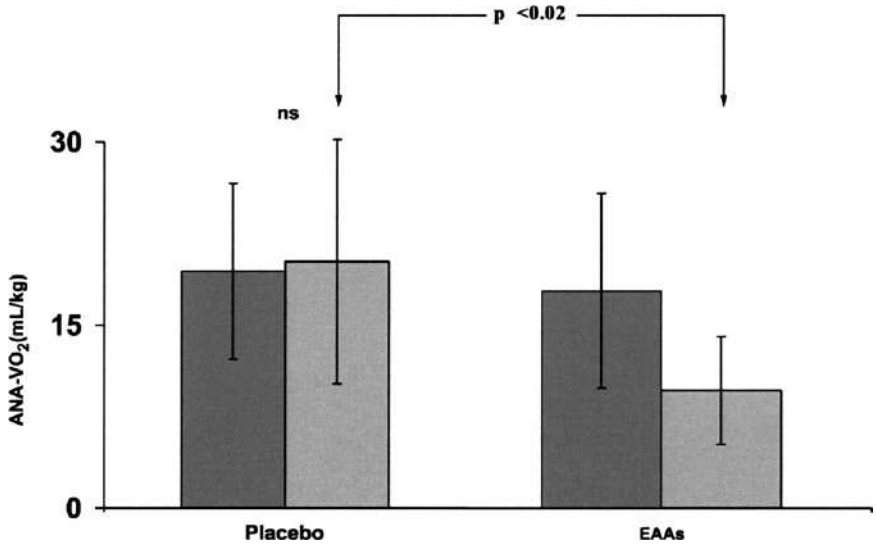

Figure 2. Comparison of anaerobic metabolism during exercise (ANA-VO_2) variation between the placebo group (*left*) and the amino acid group (*right*). In both groups the bars represent the ANA-VO_2 level at day 0 (*black bars*) and day 30 (*gray bars*) ($p < 0.02$ for intergroup difference).

Besides acting on cardiocirculatory functions, essential AAs may improve exercise capacity by enhancing the production of energy compounds (adenosine triphosphate, creatine phosphate) via their use in muscle aerobic pathway (Krebs' cycle). Indeed, normally, both cellular uptake and AA use not only occur at rest and even more so during exercise[12] but are also independent of plasma insulin level and peripheral insulin activity.[20,21] Energy produced by AA use can compensate, at least partially, for the energy shortage documented in CHF secondary to abnormalities in both lipid and glucose metabolism.[13]

We cannot exclude that an increase in muscle mass after 30 days of AA supplements could contribute to increased exercise capacity. An appropriate study is in progress to determine whether 30 days of supplements with 8 g/day of AAs alone effectively increases muscle mass.

In summary, whatever the mechanisms involved, exercise output intensity and duration did improve in elderly exercising outpatients with CHF who received 8 g/day of AAs. This, together with a trend toward an increased oxygen pulse at rest after 30 days of AA supplements might account for the symptomatic improvement (NYHA class reduction) documented in 38% of the patients in the AA group.

Recovery study: As slow recovery of VO_2 reflects a slow recovery of energy stores (adenosine triphosphate, creatine phosphate),[22] the impressive improvement of postexercise VO_2 recovery in patients with CHF receiving AAs might be ascribed to increased rate of energy resynthesis within skeletal muscle during the postrecovery period.

The increased rate of energy resynthesis may, in turn, be shown by the reduced anaerobic metabolism observed in patients after 30 days of AA supplements. Here, the recovery of VO_2 did not appear to be linked to improved pulmonary CO_2 washout or to a reduced cost of breathing,[23] because these variables were similar in the 2 groups of patients, both at baseline and after day-30 exercise. Further-

more, there was a faster recovery of oxygen pulse after exercise among those patients who had received the AA supplements. It is not unrealistic to assume that this improvement may be mainly a result of a faster recovery of SV as opposed to A-V, because, within 3 minutes after exercise, cardiac output is particularly important for oxygen consumption.[23] In any case, the improved recovery of oxygen pulse also improved the patient's cardiovascular reserve.

We are aware that our study has some limitations. Indeed, the effects of AA supplements were not investigated in patients with documented malnutrition. This issue merits appropriate future investigations, because it is potentially relevant for CHF. In fact, a possible beneficial effect of AAs on muscle-depleted normal-weight patients (sarcopenic state)[24] may prevent the passage from sarcopenia to cachexia in which body weight loss, secondary to general loss of fat tissue, lean tissue, and bone tissue, occurs.[25–29] Indeed, through their mechanisms of action, over time AAs may maintain muscle function and mass in patients with sarcopenia as well as avoid a loss of tissue by increasing insulin production/activity. In patients with CHF and cachexia, AAs may stabilize current nutritional status by reducing risk over time for further tissue deterioration and poorer prognosis.[30]

Another limitation of the study is that exercise duration was not determined 2–3 weeks after suspending the AA supplements. This is an important point, because if the improvement in exercise tolerance is maintained after withdrawal of AAs, this would indicate a permanent structural change in both cardiocirculatory function and muscle aerobic metabolism. The effects of essential AAs on muscle energy production have been presumed in this study and were not directly demonstrated, although the muscle metabolic destiny of AAs is well known thanks to a vast body of literature. Future studies should look at whether supplementation with AAs >8 g/day increases the number of patients with CHF who improve their NYHA class.

The number of patients who assumed nitrates was higher in the AA group than in the group given placebo. We cannot exclude that this numerical difference may have contributed to increased exercise capacity. These drugs, in fact, are known to improve exercise tolerance in patients with heart failure by determining vasodilation and possibly attenuating the process of ventricular remodeling. An appropriate study is thus needed to understand better whether nitrates do play an additive role in ameliorating exercise tolerance in patients with CHF given AA supplementation.

Conclusion

The study showed that oral AA supplements appears to increase exercise capacity by improving circulatory function, muscle oxygen consumption, and aerobic production of energy. Similarly, AA supplements improved postexercise recovery by quickening the recovery of circulatory function and muscle replenishment of energy once the exercise had stopped.

Author Disclosures

The authors who contributed to this article have disclosed the following industry relationships:

Roberto Aquilani, MD, has no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this supplement.

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