Effects of Oral Amino Acid Supplements on Cardiac Function and Remodeling in Patients with Type 2 Diabetes with Mild-to-Moderate Left Ventricular Dysfunction

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The aim of this study was to evaluate the effects of an oral special mixture of amino acid (AA) supplements alongside angiotensin-converting enzyme (ACE) inhibitor therapy on left ventricular (LV) function and symptoms in patients with type 2 diabetes mellitus with mild-to-moderate LV dysfunction. It is established that the remodeling process is associated with late onset of heart failure and decreased survival. ACE inhibitor therapy reduces progressive increases in LV dimensions and significantly improves the clinical course of a broad spectrum of patients with LV dysfunction. Moreover, AA supplements prevent myocardial dysfunction caused by exercise in patients with type 2 diabetes. In addition to ACE inhibitor therapy, patients with diabetes were randomly assigned to receive AA supplements or placebo. LV function and dimensions were assessed with quantitative echocardiographic tests at intake into the study and after 6 months of follow-up. In patients with type 2 diabetes, LV end-diastolic index was reduced significantly during the 6-month period of AA consumption (89 ± 9 mL/m^2 vs 76 ± 8 mL/m^2; p <0.01), and LV ejection fraction (LVEF) improved (0.46 ± 0.07 vs 0.52 ± 0.05; p <0.001). No significant changes in LVEF or LV end-diastolic index occurred in the placebo group. These findings suggest that AA supplementation, together with ACE-inhibitor therapy, may have a beneficial effect on the LV remodeling process in patients with type 2 diabetes with mild-to-moderate LV dysfunction. **© 2008 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2008;101[suppl]:111E–115E)**

Left ventricular (LV) dysfunction is associated with significant increases in LV chamber volumes and muscle mass. These changes in myocardial structure and function help maintain cardiac performance under conditions of chronic overload and impaired pump capacity.[1,2] However, this remodeling process is associated with the late onset of progressive LV dysfunction and decreased survival.[2–6] The activation of the renin-angiotensin system is involved in the progression of LV dysfunction. Angiotensin-converting enzyme (ACE) inhibitor therapy reduces progressive increases in LV dimensions,[7] and significantly improves the clinical course of a broad spectrum of patients with LV dysfunction.[8–12] In patients with type 2 diabetes mellitus, a specific cardiomyopathy leads to more frequent congestive heart failure (HF) with or without coronary artery disease (CAD). Several mechanisms have been proposed as factors contributing to myocardial dysfunction[13–18]: small vessel disease, endothelial dysfunction, abnormalities in β-adrenergic pathway, changes in contractile proteins, and alterations in the intermediary metabolism.

AA metabolism plays a relevant role in cardiac homeostasis. In diabetes, cardiac amino acid (AA) metabolism is impaired. Indeed, inhibition of cardiac protein synthesis occurs. It is caused both by a decrease in ribonucleic acid (RNA) concentration and by a decrease in the efficiency of the protein synthesis itself. Moreover, in the diabetic heart, AA catabolism is increased.[19–21] In patients with type 2 diabetes, the increased amount of AAs needed to produce muscle proteins after exercise is largely derived from protein breakdown,[22] and there is a net release of these compounds from the heart even in the presence of mildly elevated plasma glucose.[21]

Recently, it has been demonstrated that ingestion of AAs may provide a practical means of stimulating protein synthesis.[23–25] Furthermore, 12 weeks of increased AA supply prevents myocardial dysfunction induced by exercise in patients with type 2 diabetes with normal resting LV function.[26]

Our aim therefore was to determine whether an extended period of AA supplements associated with conventional therapy could exert a beneficial effect on LV remodeling

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Table 1
Characteristics of the study population

	Treated Group (n = 103)	Placebo Group (n = 104)	p Value
Age (yr)	58 ± 6	58 ± 8	NS
Male/female	70/35	71/36	NS
Duration of DM (yr)	12 ± 4	12 ± 5	NS
Total cholesterol (mg/dL)	222 ± 37	224 ± 42	NS
HDL cholesterol (mg/dL)	54 ± 14	54 ± 15	NS
LDL cholesterol (mg/dL)	139 ± 33	140 ± 35	NS
Triglycerides (mg/dL)	150 ± 82	152 ± 80	NS
BMI	28.6 ± 1.5	29 ± 1.8	NS
HbA_{1c} (%)	7.6 ± 1.6	7.5 ± 1.7	NS
HR (beats/min)	72 ± 8	70 ± 12	NS
SBP (mm Hg)	118 ± 9	120 ± 10	NS
DBP (mm Hg)	75 ± 5	77 ± 7	NS
LVEDVI $(mL/m)^2$	89 ± 9	90 ± 9	NS
LVESVI $(mL/m)^2$	48 ± 8	49 ± 8	NS
LVEF	46 ± 4	46 ± 4	NS
Enalapril (% of pts)	62	61	NS
Ramipril (% of pts)	38	39	
Arterial hypertension (%)	38 (36.8)	38 (36.5)	NS
Fasting plasma glucose (mg/dL)	155 ± 44	157 ± 46	NS
Fasting plasma insulin (μU/mL)	16 ± 9	16 ± 9.9	NS
NYHA class 0 (% of pts)	48	49	NS
NYHA class I (% of pts)	35	36	NS
NYHA class II (% of pts)	20	19	NS

BMI = body mass index; DBP = diastolic blood pressure; DM = diabetes mellitus; HbA_{1c} = glycoted hemoglobin; HDL = high-density lipoprotein; HR = heart rate; LDL = low-density lipoprotein; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; NS = not significant; NYHA = New York Heart Association; pts = patients; SBP = systolic blood pressure.

and function in patients with type 2 diabetes with mild-to-moderate chronic LV systolic dysfunction.

Material and Methods

Study patients: We recruited 212 consecutive patients with type 2 diabetes who had resting mild-to-moderate LV systolic dysfunction (LV ejection fraction [LVEF] between 0.40 and 0.50). Diabetes was treated with oral hypoglycemic drugs. Patients were active, with no limits in their ambulatory capacity. On admission, all patients received ACE inhibitor therapy irrespective of previous diagnosis of arterial hypertension: 134 patients (63%) received enalapril (at a mean dosage of 30.5 mg/day) and 78 (37%) received ramipril (6.5 mg/day). No patient was receiving β-blockers, calcium channel blockers, digitalis, diuretics, or other vasodilators.

To recruit patients with a homogenous pathophysiologic status, we used the following exclusion criteria: (1) diabetic proliferative retinopathy; (2) diabetic autonomic neuropathy assessed by lying-to-standing, deep breathing, and Valsalva maneuvers; (3) overt diabetic nephropathy (creatinine >1.4 mg/dL [1 mg/dL = 76.25 μmol/L]); (4) poorly controlled arterial hypertension (>130/80 mm Hg during therapy); and (5) inadequate echocardiogram to assess LV dimensions and function.

In each subject, the habitual daily amount of calories and the qualitative composition of the diet, verified by a dietitian, was 1,600 ± 370 kcal/day (1 kcal = 4.2 kJ), containing 55% of total caloric intake in carbohydrates, 30% in lipids, and 15% in proteins. The diet was verified to exclude differences in dietetic regimens. During placebo or AA treatment, each subject followed his or her habitual daily diet. Of the 212 enrolled patients, 207 completed the trial and 5 were withdrawn (because they wished to discontinue without any significant side effects). The study protocol was approved by the ethics Committee of the Medical School of the University of Padua, and patients gave informed consent before being tested. Key patient characteristics are listed in Table 1. Treatment of patients with cardiovascular medications did not change during the study

Study design: Patients were randomly assigned to receive AA supplements or an isocaloric placebo. Both patients and physicians were blinded regarding the medication. The formulation of AA supplements contained all essential and 2 nonessential AAs (tyrosine and cysteine), in a complex ratio that was planned to match metabolic requirements under high demand.[13,14] The AA mixture 8 g/day (Big One; Professional Dietetics, Milan, Italy) or placebo was ingested as a snack with tap water at 10:00 AM and 4:00 PM.

After the baseline examination with anthropometric and metabolic evaluation and echocardiographic assessment of LV function, patients were randomized into the study and assigned to receive AA treatment (n = 105) or placebo (n = 107). After 6 months of treatment, patients repeated the anthropometric and metabolic evaluations and echocardiographic assessment of LV function.

Echocardiographic analysis: Echocardiographic examinations were performed with Hewlett-Packard Sonos 5500 echocardiographic equipment interfaced to a S3 transducer. Echocardiographic studies were coded and read by 2 independent observers blinded to the patient's identity and experimental condition. The analysis was performed using the digitized cine loop method (Pre Vue III System; Nova MicroSonics, Inc.). LV volumes were calculated by an ellipsoid biplane area-length method,[27] and LVEF was derived as end-diastolic volume (EDV) − end-systolic volume (ESV)/EDV. LV echocardiograms in the apical 4- and 2-chamber views, for a minimum of 2 to 4 cardiac cycles, were digitized at end-diastole (R-wave peak) and end-systole (time of smallest cavity area) by 2 independent observers. A discrepancy of >10 mL for LV volume required the analysis of the echocardiographic tracing by a third observer. Agreement was achieved by consensus.

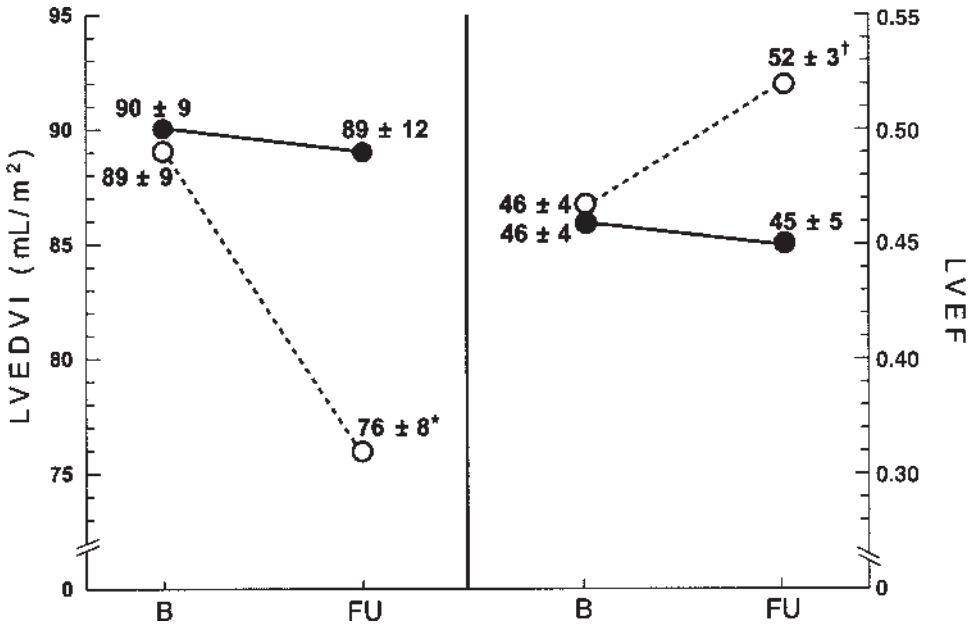

Figure 1. (*Left*) Left ventricular end-diastolic volume index (LVEDVI) at baseline (B) and at follow-up (FU) evaluation in patients receiving amino acid (AA) supplements (*white circles*) compared with controls given placebo (*black circles*). (*Right*) Changes in left ventricular ejection fraction (LVEF) at 6 months FU in patients treated with AAs; *p <0.01 vs baseline; †p <0.001 vs baseline.

Statistical analysis: Results are expressed as mean ± SD. Comparisons were made with the paired or unpaired Student's *t* test as appropriate. Multiple comparisons were performed by a 2-way repeated measures analysis of variance, followed by the Fisher protected least significant difference test. For all statistical analyses we used the SPSS package version 10.1 for Windows (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). All tests were 2-tailed with significance at p ≤0.05.

Results

A total of 207 patients completed the trial (103 in the treated group and 104 in the placebo group); 5 were withdrawn because they wished to discontinue without any side effects. The only symptom reported in a few patients of both study groups who concluded the study was dyspepsia, and this effect showed no significant difference between treated and untreated patients (1.1% vs 1.2%; p = Ns). No patient died or experienced major cardiac complications during the study period.

Metabolic parameters: Glycated hemoglobin (HbA_{1c}) levels decreased significantly in patients given AA supplements compared with baseline (7.6% ± 1.65 vs 7.0% ± 1.2%; p <0.05). Both fasting plasma glucose (155 ± 44 mg/dL vs 152 ± 39 mg/dL; p = NS) and insulin (16 ± 9 μU/mL vs 15 ± 9 μU/mL; p = NS) slightly declined, but the difference was not statistically significant. No significant changes occurred in levels of total cholesterol, high-density lipoprotein cholesterol, triglycerides, or urinary albumin excretion rate (data not shown).

Effects of AA supply on arterial pressure and heart rate: Compared with baseline, the addition of AA supplements to ACE inhibitor therapy did not significantly change either systolic (118 ± 9 mm Hg vs 120 ± 8 mm Hg; p = NS) or diastolic blood pressure (75 ± 5 mm Hg vs 74 ± 6 mm Hg; p = NS). Heart rate also did not change significantly during AA supplementation (72 ± 8 beats per minute vs 74 ± 9 beats per minute, p = NS) (data not shown).

Changes in LV size and function: As shown in Figure 1, reduced LV dilatation during the 6-month period of AA assumption was seen in patients with diabetes (89 ± 9 mL/m^2 vs 76 ± 8 mL/m^2; p <0.01), whereas baseline LV end-diastolic index did not differ significantly in the placebo group (90 ± 9 mL/m^2 vs 89 ± 12 mL/m^2; p = NS). Patients treated with AAs had significant increase in LVEF over the treatment period compared with baseline (0.46 ± 0.04 vs 0.52 ± 0.03; p <0.001). No difference in LVEF (4% ± 4% vs 45% ± 5%; p = NS) was seen in the placebo group by comparing baseline and washout values. Figure 1 shows changes in LVEF.

Discussion

The most important finding of our study is that AA supplements, together with ACE inhibitor therapy, decreased LV dilatation and improved LV function in patients with type 2 diabetes with mild-to moderate LV dysfunction.

The effects of ACE inhibitors are well known. Several large-scale clinical trials show that ACE inhibitor therapy can beneficially influence the clinical course of patients with LV systolic dysfunction.[8–12] Clinical benefits are related, at

least in part, to the effects of ACE inhibitors on the remodeling process through reduction of LV size.[7,28–30] However, our study showed that oral AA supplementation, given concomitantly with ACE inhibitors, improved cardiac performances.

Indeed, previous studies have shown that intravenous infusion of AAs, such as glutamine/glutamate and aspartate, improves cardiac performance in patients with CAD.[31,32] More recently, it has been demonstrated that muscle protein synthesis substantially increased after oral ingestion of AAs.[23] Moreover, in patients with type 2 diabetes, an increased AA supply improves metabolic control and prevents LV dysfunction induced by exercise,[24] an early marker of diabetic cardiomyopathy.[13] These results allow us to hypothesize that, even in well-nourished patients with type 2 diabetes, use of AA supplements, in addition to the usual dietary intake, should have positive effects on myocardial contractility.

Although the mechanisms by which the addition of AAs to ACE inhibitor therapy improves LV function and symptoms is not easily understood, some hypotheses can be put forward to explain our findings. Both diabetic HF and coronary HF are characterized by alterations in nitrogen metabolism.[33,34] Most AAs 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 AAs by improving energy substrate metabolism and adenosine triphosphate (ATP) production mediated by a direct metabolic effect on the heart.[35] Moreover, it has been shown that although plasma levels of glucose and insulin independently regulate the proportional contribution of exogenous glucose to myocardial glycolytic and Krebs cycle flux in vivo in a dose-dependent manner, nonglucose substrates continue to supply >40% of myocardial Krebs cycle flux.[36] Thus, although the study design 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 AA supplementation may increase the availability of energy substrate and/or improve the conversion of chemical energy into mechanical energy.

Interestingly, Neubauer[37] recently 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 for treatment of HF.[37]

Controversies still exist about the effects of AA intake on glycemic control in diabetic patients.[38,39] Here, we showed that oral administration of AAs improved metabolic control as assessed by glycated hemoglobin (HbA_{1c}). As a consequence, we cannot exclude the fact that better metabolic control may help to improve myocardial function. Finally, it has been reported that diabetes may alter the cardiac myosin isoform profile contributing to impaired cardiac function.[40] We could hypothesize that improved metabolic control, together with the increased protein synthesis[23] and energy substrate availability, could positively influence myocardial contractile function by reverting the shift from the low ATPase isoform, V_3, to the high ATPase cardiac isoform, V_1.

Conclusion

Our results demonstrate that the use of oral AA supplements in conjunction with ACE inhibitor therapy decreases LV dilatation and dysfunction, and improves metabolic control in patients with type 2 diabetes with mild-to-moderate LV dysfunction. Because this LV remodeling is related to further deterioration in LV performance and a less favorable clinical course,[2–5] it is likely that these effects of this dietetic approach could have clinical benefits.

Author Disclosures

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

Roldano Scognamiglio, 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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