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Oral L-arginine supplementation improves endothelial function and ameliorates insulin sensitivity and inflammation in cardiopathic nondiabetic patients after an aortocoronary bypass

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Abstract

It is known that L-arginine treatment can ameliorate endothelial dysfunction and insulin sensitivity in type 2 diabetes mellitus patients, but little is known on L-arginine effects on these variables in nondiabetic patients with stable cardiovascular disease (coronary artery disease). We evaluated the effects of long-term oral L-arginine treatment on endothelial dysfunction, inflammation, adipokine levels, glucose tolerance, and insulin sensitivity in these patients. Sixty-four patients with cardiovascular disease previously submitted to an aortocoronary bypass and not known for type 2 diabetes mellitus had an oral glucose load to define their glucose tolerance. Thirty-two patients with nondiabetic response were eligible to receive, in a double-blind randomized parallel order, L-arginine (6.4 g/d) or placebo for 6 months. An evaluation of insulin sensitivity index during the oral glucose load, markers of systemic nitric oxide bioavailability and inflammation, and blood flow was performed before and at the end of the treatment in both groups. Compared with placebo, L-arginine decreased asymmetric dimethylarginine levels ($P < .01$), indices of endothelial dysfunction, and increased cyclic guanosine monophosphate ($P < .01$), L-arginine to asymmetric dimethylarginine ratio ($P < .0001$), and reactive hyperemia ($P < .05$). Finally, L-arginine increased insulin sensitivity index ($P < .05$) and adiponectin ($P < .01$) and decreased interleukin-6 and monocyte chemoattractant protein–1 levels. In conclusion, insulin resistance, endothelial dysfunction, and inflammation are important cardiovascular risk factors in coronary artery disease patients; and L-arginine seems to have anti-inflammatory and metabolic advantages in these patients.

1. Introduction

Insulin resistance and endothelial dysfunction are present very early and concur together to the evolution toward type 2 diabetes mellitus and cardiovascular disease. In fact, many studies have shown that hyperinsulinemia and insulin resistance increase neointimal index measured 6 months after coronary stenting [1]; and blunted nitric oxide (NO) endothelium-dependent vasodilation has been found to predict cardiovascular events independently of common risk factors [2].

Nitric oxide is involved in a wide variety of regulatory mechanisms of the cardiovascular system, including vascular tone, vascular structure, and cell-cell interactions in blood vessels [3]. Previous clinical studies have found that L-arginine induced beneficial effects over endothelial function and insulin sensitivity both in healthy individuals and

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in type 2 diabetes mellitus patients [4,5]. Four weeks of oral L-arginine supplementation (2 g, 3 times per day) increased maximum forearm blood flow (FBF), raised plasma L-arginine and cyclic guanosine monophosphate (c-GMP) concentrations, and increased the L-arginine to asymmetric dimethylarginine (ADMA) ratio in hypertensive patients with microvascular angina [6]. Moreover, other studies have found that, by increasing the bioavailability of NO through an oral administration of L-arginine, it is possible to decrease ADMA levels and improve endothelial dysfunction in patients affected by hypertension [3,7], explaining, at least in part, the beneficial effects of L-arginine on endothelial function. In fact, it is well known that ADMA inhibits vascular NO production, changing vascular tone and systemic vascular resistance [8]; and recently, it has been concluded that ADMA can be considered a novel cardiovascular risk factor [9].

Recently, leptin and adiponectin, whose concentrations have been found to be altered in insulin-resistant states, have been involved in the atherogenic process. Several clinical studies have shown that elevated leptin levels predict acute cardiovascular events, restenosis after coronary angioplasty, and cerebral stroke independently of traditional risk factors [1]. Conversely, reduction or lack of adiponectin resulted in accelerated atherosclerotic progression [10].

Until now, few data have been available on the effects of L-arginine supplementation in ameliorating endothelial dysfunction and proinflammation markers and in improving insulin sensitivity in nondiabetic patients with stable cardiovascular disease (coronary artery disease [CAD]) after a successful coronary artery bypass grafting (CABG). Accordingly, we tested the hypothesis of beneficial effects of long-term L-arginine treatment in these patients.

2. Research design and methods

2.1. Patients and study design

The study protocol was designed to study patients with CAD after a successful CABG and in the absence of type 2 diabetes mellitus, diagnosed by (1) anamnestic questionnaire, (2) fasting plasma glucose less than 126 mg/dL, (3) measurement of plasma glucose 2 hours after an oral glucose load less than 200 mg/dL, and (4) absence of angina episodes at rest or after exercise.

Sixty-four patients were invited to participate in a screening for the detection of glucose tolerance using a standard oral glucose load with 75 g glucose 3 months after a successful intervention of CABG. All the subjects filled a structured health questionnaire and kept a diary of food intake for 3 days before measurement of NO and c-GMP to control for differences in food intake, measured using Nutritionist Pro 2.5 (Axxya Systems, Stafford, TX). No differences were observed in daily energy intake between groups for either total amount of calories consumed or the proportion of calories as carbohydrate, lipid, or protein. Furthermore, because animal and vegetable nitrogen daily intakes were identical in both groups of subjects, it is unlikely that variations in any of these variables would influence the measurement of nitrite and nitrate (NOx) levels.

All participants had an oral glucose load to test for glucose tolerance; and the results obtained 2 hours after the oral glucose load showed that 43.8% (28/64) of them showed a normal glucose response, 36.0% (23/64) of them showed an impaired glucose tolerance, and 20.2% (13/64) of them showed a diabetic glucose answer.

Subjects who were diagnosed as not being diabetic in the screened study group were consecutively invited to the center to enter in a double-blind parallel L-arginine vs placebo study, and a total of 32 patients accepted to participate. Patients were randomly assigned to receive L-arginine 6.4 g (kind gift from FarmaDamor, Napoli, Italy; 3.2 g 2 times a day after breakfast and lunch) (L-arginine group; 16 patients, 15 male and 1 female) or identical placebo solutions (placebo group; 16 patients, 15 male and 1 female) for 6 months. Two patients in the placebo group withdrew the consent before the end of trial examinations. Therefore, statistical analysis is performed in 16 patients treated with L-arginine and 14 patients treated with placebo. The sample size of patients for each group was estimated taking advantage of previous studies in which reactive hyperemia of FBF marker of endothelial vasodilation [11-13] was evaluated after long-term oral administration of L-arginine (6 g daily, 6 months). Therefore, we have designed the study to be large enough to be able to detect, with a $\beta = 80\%$ and $\alpha = 5\%$, an increase in reactive hyperemia of FBF from 5% with placebo to 30% with L-arginine treatment; and we evaluated that the final sample for each group was at least 14 patients. All patients were treated with a standard medication for ischemic heart disease, hypertension, and hypercholesterolemia including platelet aggregation inhibitors, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statin treatments that remained unchanged throughout the study period without differences between the 2 groups (Table 1).

At baseline, all patients were free from symptoms or signs of infection, heart failure, and angina or evidence of depressed left ventricular function (ejection fraction <50%) and valvular heart disease as shown by means of echocardiography. Visits were performed every 2 months also to encourage all patients to follow a standard isocaloric diet and to maintain an adequate physical activity program that was similar in the 2 treatment groups. All patients were submitted to experimental evaluations before and 6 months after treatment with L-arginine/placebo. No gastrointestinal distress and no adverse events were recalled during the whole study period. The Institutional Ethical Committee approved the study, and all participants gave written informed consent to participate. The study was registered at ClinicalTrials.gov with a registration number NCT00408577.

After an overnight fast, vital signs and anthropometric evaluations were taken after at least 30 minutes of rest in the

Table 1
Clinical characteristics of nondiabetic patients with cardiovascular disease previously submitted to an aortocoronary bypass before and 6 months after L-arginine/placebo therapy

	L-Arginine		Placebo		*t* test at baseline	Treatment effect
	Before	End of treatment	Before	End of treatment		
Age (y)	65 ± 10		64 ± 11			
Sex (M/F)	15/1		13/1			
Body weight (kg)	79.2 ± 3.6	79.7 ± 3.6	73.2 ± 3.4	74.2 ± 3.3	$P < .16$	$P < .69$
Fat mass (kg)	20.7 ± 1.5	21.7 ± 1.6	17.1 ± 1.4	18.1 ± 1.4	$P < .52$	$P < .99$
Fat-free mass (kg)	59.1 ± 2.4	58.0 ± 2.2	56.1 ± 2.3	56.1 ± 2.3	$P < .83$	$P < .83$
Waist (cm)	98.3 ± 2.6	96.9 ± 2.6	93.3 ± 3.0	94.3 ± 2.4	$P < .95$	$P < .67$
Systolic blood pressure (mm Hg)	129 ± 4	125 ± 3	122 ± 3	124 ± 4	$P < .75$	$P < .36$
Diastolic blood pressure (mm Hg)	79 ± 2	75 ± 2	73 ± 2	77 ± 2	$P < .93$	$P < .05$
Ejection fraction (%)	56.9 ± 1.0	58.3 ± 2.0	55.4 ± 2.3	57.0 ± 1.4	$P < .38$	$P < .95$
Basal blood flow (mL/100 mL/min)	3.02 ± 0.94	3.00 ± 0.94	2.91 ± 0.96	2.52 ± 1.13	$P < .44$	$P < .47$
Medications						
Platelet aggregation inhibitors	16 (100%)		14 (100%)			
Statins (simvastatin 20 mg/d)	16 (100%)		14 (100%)			
β-Blockers (atenolol 50 mg/d or carvedilol 12.5 mg/d)	11 (79%)		13 (81%)			
ACE inhibitors (ramipril 5 mg/d)	7 (50%)		8 (50%)			

Mean ± SD.

supine position. Fat mass and fat-free mass distribution was evaluated by bioimpedenziometry using TANITA body fat analyzer (Tanita, Tokyo, Japan) in all patients before and at the end of the study. Evaluation of basal FBF and reactive hyperemia of FBF was performed using venous occlusion plethysmographic technique. After at least 30 minutes from the end of the FBF measurement, fasting hormonal, lipids, endothelial, inflammation markers, and adipokines levels were withdrawn; an oral glucose load was performed; and samples at 0, 30, 60, 90, and 120 minutes after the glucose load were withdrawn for the measurements of glucose and insulin levels. An insulin sensitivity index (SI) was calculated as $0.222 - 0.00333 \times \text{body mass index} - 0.0000779 \times \text{Ins}_{120} - 0.000422 \times \text{age}$, as suggested by Stumvoll et al [14]. A standard transthoracic echocardiography was performed in all patients at baseline and repeated at the end of the study period. Doppler echocardiography was performed using a 5-MHz multiplane probe connected with commercially available equipment (HP 1500 or 5500; Hewlett-Packard, Andover, MA).

2.2. Assays

Glucose; total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol; triglycerides; and free fatty acid (FFA) levels were measured with spectrophotometric methods adapted to Cobas MIRA using commercial kits (ABX, Montpellier, France). Insulin levels were assayed with a microparticle enzyme immunoassay (IMX, Abbott Laboratories, Rome, Italy). The NOx levels were evaluated through the measurement of metabolic end products, that is, nitrite and nitrate, using enzymatic catalysis coupled with Griess reaction. The c-GMP levels were measured with radioimmunoassay kit (NEN Life Science Products, Boston, MA) [15]. Human adiponectin and leptin levels were assayed with enzyme-linked immunosorbent assay (ELISA) kits (LINCO Research, St Charles, MO). Human interleukin-6 (IL-6), tumor necrosis factor–α, and monocyte chemoattractant protein–1 (MCP-1) levels were assayed with ELISA kits (Bender Med Systems, Vienna, Austria). Chemiluminescent protein array system was used for the quantitative measurement of matrix metalloproteinase 9. Human atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were assayed with ELISA kits (Europe, Korlsruhe, Germany). Asymmetric dimethylarginine, symmetric dimethylarginine (SDMA), and L-arginine were assayed by high-performance liquid chromatography [16].

2.3. Statistical analysis

All values are expressed as mean ± SD at each time interval. Incremental areas under the curve (ΔAUCs) of glucose and insulin concentrations during the oral glucose load were calculated by the trapezoidal rule. All data were tested for normal distribution with the Kolmogorov-Smirnov test. Comparison between the 2 groups at baseline was performed by using the *t* test. The treatment effects were determined using an analysis of covariance adjusted for age, sex, and body mass index. An adjusted *P* value of less than .05 was taken to indicate a significant difference. Pearson correlations were conducted on change scores (Δincrement level during L-arginine/placebo treatment − level at baseline). All analyses were performed using SPSS version 15.0 software (SPSS, Chicago, IL).

3. Results

3.1. Clinical and laboratory characteristics of the study population at baseline and after L-arginine/placebo

As presented in Tables 1 and 2, body weight, fat distribution, waist circumference, systolic blood pressure,

Table 2
Metabolic characteristics of nondiabetic patients with cardiovascular disease previously submitted to an aortocoronary bypass before and 6 months after L-arginine/placebo therapy

	L-Arginine		Placebo		*t* test at baseline	Treatment effect
	Baseline	End of treatment	Baseline	End of treatment		
Fasting insulin (U/L)	11.5 ± 1.5	10.5 ± 1.1	10.6 ± 1.4	10.5 ± 1.4	$P < .68$	$P < .76$
Fasting glucose (mg/dL)	103.9 ± 13.9	96.6 ± 13.8	95.3 ± 14.4	97.3 ± 13.3	$P < .22$	$P < .05$
ΔAUC insulin (μU/mL, 0–120 min)	7184 ± 4026	5890 ± 3061	8087 ± 5123	6728 ± 5070	$P < .05$	$P < .96$
IFG (%)	10/16 (63)	5/16 (31)	7/14 (50)	8/14 (57)		
IGT (%)	7/16 (47)	2/16 (13)	6/14 (43)	7/14 (50)		
Fasting triglycerides (mg/dL)	115.2 ± 16.3	101.8 ± 12.3	99.3 ± 8.9	89.3 ± 13.2	$P < .38$	$P < .90$
Fasting FFA (mmoL)	0.61 ± 0.04	0.44 ± 0.05	0.63 ± 0.08	0.56 ± 0.06	$P < .46$	$P < .25$
Fasting cholesterol (mg/dL)	158.4 ± 10.1	152.6 ± 7.5	153.0 ± 8.2	146.1 ± 8.7	$P < .47$	$P < .95$
Fasting HDL cholesterol (mg/dL)	39.0 ± 1.6	40.5 ± 2.1	37.3 ± 2.7	42.0 ± 3.2	$P < .21$	$P < .52$
Fasting LDL cholesterol (mg/dL)	96.4 ± 9.1	91.7 ± 6.1	95.8 ± 8.5	86.2 ± 7.3	$P < .20$	$P < .64$
GFR (mL/[min 1.73 m^{-2}])	105.7±22.3	105.9±17.9	105.2±17.3	105.6±20.9	$P < .70$	$P < .70$
Fasting NOx (μmol/L)	19.2 ± 2.7	15.6 ± 2.2	13.1 ± 1.3	12.9 ± 2.2	$P < .96$	$P < .97$
L-Arginine (μmol/L)	81.7 ± 0.6	126.1 ± 1.7	79.5 ± 0.7	81.1 ± 0.7	$P < .001$	$P < .0001$
ADMA (μmol/L)	0.55 ± 0.18	0.40 ± 0.16	0.48 ± 0.17	0.58 ± 0.11	$P < .59$	$P < .01$
SDMA (μmol/L)	0.62 ± 0.20	0.64 ± 0.23	0.64 ± 0.16	0.66 ± 0.28	$P < .46$	$P < .50$
Leptin (pg/mL)	12.1 ± 4.0	10.4 ± 3.6	11.9 ± 4.7	12.0 ± 5.0	$P < .36$	$P < .36$
TNF-α (pg/mL)	16.7±5.3	13.2±7.3	21.6 ± 10.3	15.3 ± 10.7	$P < .03$	$P < .52$
MMP9 (pg/mL)	603 ± 445	442 ± 259	437 ± 232	486 ± 313	$P < .51$	$P < .22$
ANP (pg/mL)	57.1 ± 21.9	52.1 ± 28.5	55.3 ± 34.1	54.8 ± 32.9	$P < .77$	$P < .81$
BNP (pg/mL)	32.4 ± 12.8	28.6 ± 14.5	29.9 ± 17.9	27.7 ± 12.9	$P < .43$	$P < .84$

Mean ± SD. IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance; GFR: glomerular filtration rate; TNF-α, tumor necrosis factor–α; MMP9, matrix metalloproteinase 9.

FFA, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides levels and glomerular filtration rate did not change after both L-arginine and placebo treatments. Conversely, diastolic blood pressure decreased only after L-arginine therapy. The measurements of plasma levels of L-arginine showed a significant increment only in the L-arginine group, whereas no changes were found in the placebo group, as expected. All patients showed a preserved ejection fraction measured at baseline that did not change after L-arginine/placebo treatments, and this finding was also confirmed by measuring circulating indices of myocardial performance as ANP and BNP levels.

3.2. Endothelial and inflammatory markers at baseline and after L-arginine/placebo

After 6 months of placebo therapy, reactive hyperemia, c-GMP, ADMA, and arginine to ADMA ratio did not change, whereas these variables were significantly modified after L-arginine therapy as shown in Table 2 and in Fig. 1. In fact, reactive hyperemia increased by 31% and c-GMP levels increased by 54%, whereas ADMA levels decreased by 27%. In addition, the arginine to ADMA ratio increased by 116%. Basal FBF, NOx, and SDMA remained unchanged in both treatments.

Whereas IL-6, MCP-1, and adiponectin levels did not change after placebo, L-arginine caused a significant decrease of IL-6 levels by 47% and of MCP-1 levels by 19%, whereas adiponectin levels increased by 37% (Fig. 1).

3.3. Insulin sensitivity and glucose tolerance at baseline and after L-arginine/placebo

In Fig. 2 are reported glycemic and insulinemic profiles and the ΔAUCs of glucose during the oral glucose load. L-Arginine improved the glucose levels at the end of the test in 14 of 16 patients against 7 of 14 patients with placebo ($\chi^2 = 8.99$, $P < .01$); and also, the ΔAUC of glucose during the glucose load and insulin sensitivity significantly improved after L-arginine (treatment effect, $P < .05$; Fig. 2).

3.4. Pearson correlations

The Δincrement in SI was positively correlated with the Δincrement in c-GMP ($r = 0.38$, $P < .04$, data not shown), in the arginine to ADMA ratio ($r = 0.58$, $P < .003$, data not shown), and in reactive hyperemia ($r = 0.37$, $P < .05$, data not shown). In addition, the Δincrement in reactive hyperemia was positively correlated with the changes in c-GMP index ($r = 0.65$, $P < .0001$, data not shown).

4. Discussion

To our knowledge, this is the first study evaluating the effects of an oral L-arginine supplementation added on the top of usual treatment in cardiopathic nondiabetic patients after CABG. In particular, the present study demonstrated that L-arginine supplementation was able to improve both endothelial dysfunction and insulin sensitivity.

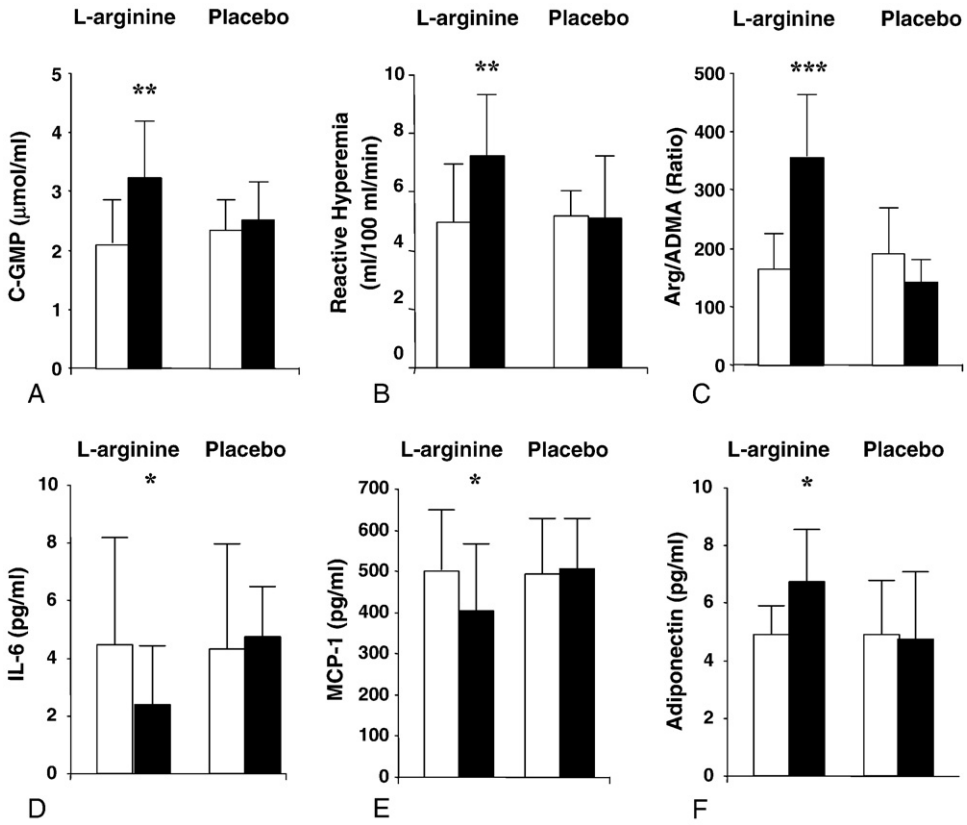

Fig. 1. Cyclic GMP levels (A), reactive hyperemia (B), L-arginine to ADMA ratio (C), IL-6 (D), MCP-1 (E), and adiponectin (F) levels in 30 nondiabetic patients with cardiovascular disease previously submitted to CABG before (white boxes) and 6 months after (black boxes) L-arginine/placebo therapy. Data are presented as mean ± SD. **c-GMP: treatment effect, *P* less than .01; reactive hyperemia: treatment effect, *P* less than.01. ***Arginine to ADMA ratio: treatment effect, *P* less than .001. *MCP-1: treatment effect, *P* less than .05; IL-6: treatment effect, *P* less than .05; and adiponectin: treatment effect, *P* less than .05.

To support a role of L-arginine on endothelial function, L-arginine supplementation was able to determine a significant increment of reactive hyperemia, marker of endothelial-mediated vasodilation, and c-GMP levels, second messenger of NO. Furthermore, after 6 months of L-arginine supplementation, we demonstrated decreased ADMA and increased L-arginine to ADMA levels, recently proposed as one of the most accurate measure of endothelial NO synthase substrate availability [17]. Moreover, in a recent cohort study in elderly subjects, L-arginine to ADMA ratio was positively related to endothelium-dependent vasodilation in the forearm resistance arteries [18]. Our finding of a positive correlation between the Δincrement in c-GMP and the Δincrement in reactive hyperemia suggests a role of L-arginine in enhancing the production/activity of NO, and it is confirmatory of previous data in type 2 diabetes mellitus patients [19].

L-Arginine also decreased important markers of inflammation such as IL-6 and MCP-1 levels. This is an interesting result if we consider the fundamental role of MCP-1 in the interaction process that lets monocytes migrate into the subendothelial layer of the intima where they differentiate into macrophages [20], thus representing a possible way for L-arginine to beneficially interfere with cardiovascular risks. Another beneficial mechanism of L-arginine is mediated by an increase in adiponectin levels, as previously reported [5]. The direct effect of adiponectin on atherosclerosis was recently investigated by Kumada et al [21] who showed that adiponectin specifically increased tissue inhibitor of metalloproteinase-1, reducing vascular inflammation and, in turn, delaying the development of atherosclerosis.

The result that almost 20% of patients after CABG with no history or previous diagnosis of type 2 diabetes mellitus manifested a diabetic response after an oral glucose load is in line with previous reports of an increased incidence of glucose intolerance in subjects with CAD [22]. In this light, a stimulating result of the present study is that 6 months of L-arginine supplementation at a dose of 6.4 g/d improved glucose tolerance in a group of patients submitted to CABG. In the L-arginine group, improvement in glucose tolerance was associated with a significant increment of SI. The present findings of a positive correlation between Δincrement of reactive hyperemia and the Δincrement of SI are confirmatory of a strict relation between endothelial dysfunction and insulin resistance and support a beneficial effect of L-arginine. Previous studies have found that short- and long-term oral L-arginine supplementation improved insulin sensitivity, endothelial function, and markers of

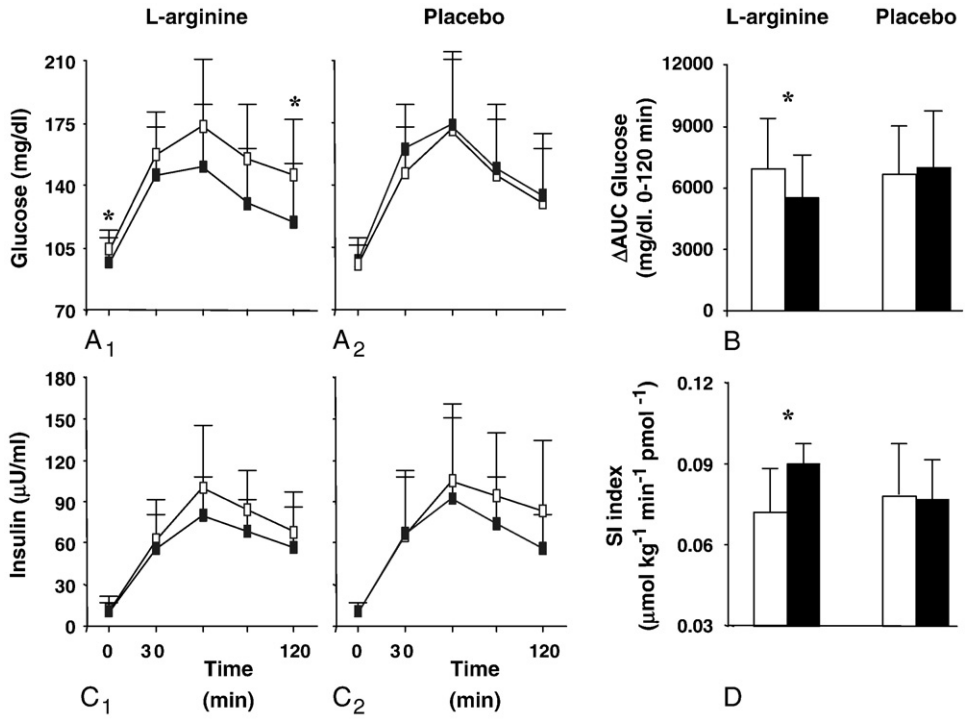

Fig. 2. Glucose (L-arginine [A_1] and placebo [A_2]) and insulin profiles (L-arginine [C_1] and placebo [C_2]), ΔAUC of glucose (B), and SI (D) during the glucose load (0-120 minutes) in 30 nondiabetic patients with cardiovascular disease previously submitted to CABG before (white boxes) and 6 months after (black boxes) L-arginine/placebo therapy. Data are presented as mean ± SD. *Fasting glucose levels: treatment effect, *P* less than .05; glucose levels at the end of the glucose load: treatment effect, *P* less than .05; ΔAUC of glucose during glucose load: treatment effect, *P* less than .05. *SI: treatment effect, *P* less than .05.

oxidative stress in type 2 diabetes mellitus patients [5,23]. Although in the present study L-arginine seems to produce beneficial effects on endothelial function, in a recent study by Wilson et al [24] in peripheral artery disease, L-arginine supplementation had no effect on vascular reactivity and, on the contrary, seemed to attenuate the expected placebo effect observed in studies of functional capacity. A possible explanation for this discrepancy could be the amount of L-arginine administered to the patients that was 50% lower in the study of Wilson et al as compared with our study. An interesting aspect of the present study is that no patient interrupted the treatment during the study period or manifested adverse events. These data are different from those found in an important study evaluating 6 months of dietary L-arginine addition on standard therapy in 153 postinfarction patients (Vascular Interaction with Age in Myocardial Infarction [VINTAGE MI] trial). In the latter study, a higher postinfarction mortality was found in patients receiving L-arginine supplementation [25] compared with those having placebo. However, in that study, neither difference in L-arginine plasma levels was observed between the 2 treatment groups; nor a dose-related difference in L-arginine plasma levels at 6 months was found. These data seem to imply, as suggested by Böger [26], that the increased mortality found in L-arginine group could hardly be imputed to an adverse contribution of L-arginine supplementation but preferably to other concomitant reasons. In our opinion, the most important difference between the VINTAGE MI trial and our study could be the different selection criteria used for patient recruitment into the study and the timing for the start of the L-arginine therapy. In fact, in the VINTAGE MI trial, patients were enrolled within 3 to 21 days after a first ST-elevation myocardial infarction, in a period of an unstable cardiovascular condition. Conversely, in our study, we enrolled patients 3 months after a successful intervention of CABG in stable cardiovascular conditions being treated with low doses of statins, β-blockers, and ACE inhibitors.

The limitation of the present study is the relatively small sample size; but we reached our goal of demonstrating a relevant increase in reactive hyperemia and a concomitant decrease of ADMA levels, determining positive effects on insulin sensitivity. However, before final conclusions on the effects of L-arginine on glucose tolerance and insulin sensitivity in patients after CABG are drawn, it is mandatory to perform further studies with a larger number of subjects.

In conclusion, long-term oral L-arginine therapy added to usual medical treatment of patients affected by stable CAD without known type 2 diabetes mellitus is able to improve endothelial function, decrease ADMA levels, and ameliorate insulin sensitivity and glucose tolerance.

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