

# Effect of Supplemental Oral L-Arginine on Exercise Capacity in Patients With Stable Angina Pectoris

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The concept that endothelial L-arginine and/or a nitric oxide system is involved in the pathogenesis of cardiovascular diseases is based on clinical findings which showed that endothelium-dependent relaxation is impaired or lost in systemic hypertension,<sup>1</sup> hypercholesterolemia,<sup>2,3</sup> atherosclerosis,<sup>4</sup> microvascular angina,<sup>5</sup> and in angiographically normal coronary arteries of patients with coronary artery disease.<sup>6</sup> In atherosclerosis, impairment of endothelium-dependent vasodilation in the coronary circulation occurs at an early stage<sup>4</sup> and deteriorates with progress of the disease, leading to complete loss of flow-mediated relaxation.<sup>4,7</sup> An attempt to restore endothelium-dependent vascular responses with L-arginine was successful in the coronary<sup>8</sup> and peripheral<sup>2</sup> circulation of hyperlipidemic patients, in the coronary circulation of cardiac transplant recipients,<sup>9</sup> and in patients with microvascular angina pectoris.<sup>10</sup> If infusion of L-arginine is able to eliminate the endothelial defect,<sup>2,8-10</sup> it is intriguing to speculate that L-arginine supplementation might improve endothelium-dependent vasodilator responses in patients with stable angina, and thereby increase exercise capacity. The present study investigates the effect of oral supplementation with L-arginine on exercise capacity in patients with healed myocardial infarction and stable angina.

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Patients were recruited at the Outpatient Cardiology Clinic of the Grochowski Hospital between June 1994 and November 1995. Study inclusion required the diagnosis of coronary artery disease based on a history of transmural myocardial infarction documented by the occurrence of typical retrosternal pain lasting >30 minutes, characteristic evolution of the electrocardiogram, and increase of enzymes. Patients were also receiving long-term oral cardiovascular medications (Table I). Patients were excluded if they had unstable angina, myocardial infarction within the preceding 2 months, symptoms of heart failure, atrial fibrillation, impaired renal or hepatic function, diabetes mellitus, or other systemic illnesses. Of the 251 patients reviewed, 85 fulfilled the above criteria and were eligible for further selection to the study group.

At 2 baseline exercise tests during the run-in phase, the patients had to reach exhaustion accom-

panied by ST-segment depression  $\geq 0.1$  mV 60 ms after the J-point within 3 to 9 minutes after the beginning of the test, detected in  $\geq 2$  of 3 consecutive precordial leads or in  $\geq 2$  of 3 unipolar limb leads. Total exercise time (to 0.1 mV ST-segment depression) of the 2 tests (>3 days apart from each other) was not to vary by >20%. Twenty-two patients (20 men, 2 women, mean age  $57 \pm 9$ , SD) who met the above selection criteria and gave informed consent, comprised the study group.

The study was conducted in a randomized, double-blind, placebo-controlled fashion, consisting of 3-day treatment periods. The patients were randomly assigned to oral doses of L-arginine (Lamberts UK, Tunbridge Wells, Kent, United Kingdom), two 1-g capsules 3 times a day for 3 days ( $n = 12$ ) or placebo (sacharum lactis 2 capsules 3 times a day,  $n = 10$ ) of identical appearance. Patients were instructed to take 2 capsules at 9 A.M. and at 2 and 10 P.M. Cardiovascular maintenance medication was kept constant throughout the study.

After randomization, the initial exercise test was performed before L-arginine and/or placebo and the second test after 3 days of treatment. All exercise tests were performed between 9 and 10 A.M. at least 2 hours after a light breakfast. Venous blood samples for determination of serum arginine, citrulline, and ornithine were taken immediately before the first and second exercise tests. Plasma concentrations of these amino acids were determined by high-performance liquid chromatography with an amino acid analyzer (Beckman Instruments, Inc., Palo Alto, California) at a commercial laboratory. Protocol of the study was approved by the local Ethics Committee.

Exercise tests were performed on a Marquette CASE 12 (Milwaukee, Wisconsin) treadmill exercise system according to the modified Bruce protocol. The end points were exhaustion, anginal pain, or myocardial ischemia on the electrocardiogram. A 12-lead electrocardiogram was recorded during and up to 4 minutes after exercise. Blood pressure was recorded before and at each level of the test. Total exercise time(s) to maximal ST-segment depression, sum of maximal ST-segment depression from all leads (millimeters), and maximal work load (METs) were measured.

Data are presented as mean  $\pm$  SD. Student's *t* test was used for analysis of data. Statistical significance was defined as  $p < 0.05$ .

There were no significant differences in gender, age, and concomitant medication between the patients allocated to placebo or L-arginine (Table I). As shown in Figure 1, administration of placebo slightly lengthened mean exercise time (seconds) to maximal ST-segment depression (from  $501 \pm 101$  to  $555 \pm$

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TABLE 1 Characteristics of Patients Allocated to Placebo or L-Arginine		
	Placebo	L-Arginine
Men/women	9/1	11/1
Age (yr)		
Mean $\pm$ SD	58 $\pm$ 9	57 $\pm$ 11
Range	48–70	34–69
Blood pressure (mm Hg, mean $\pm$ SD)		
Systolic	119 $\pm$ 23	124 $\pm$ 21
Diastolic	88 $\pm$ 8	84 $\pm$ 7
Myocardial infarction in the past (no.)		
Anterior	4	4
Other	6	8
Total cholesterol (mg/dl, mean $\pm$ SD)	204 $\pm$ 16	210 $\pm$ 17
Concomitant medication (no.)		
Aspirin	10	12
$\beta$ blocker	10	12
Oral nitrate	8	11
Calcium antagonist	5	5
Converting enzyme inhibitor	4	6
Anticoagulant	1	2

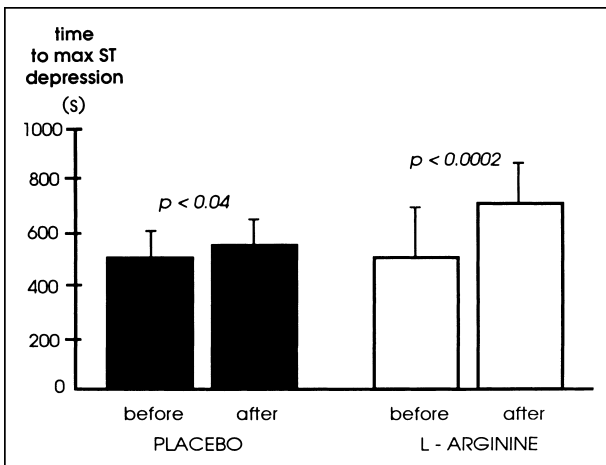


FIGURE 1. Time to maximum ST-segment depression (mean  $\pm$  SD) during exercise test before and after placebo or L-arginine.

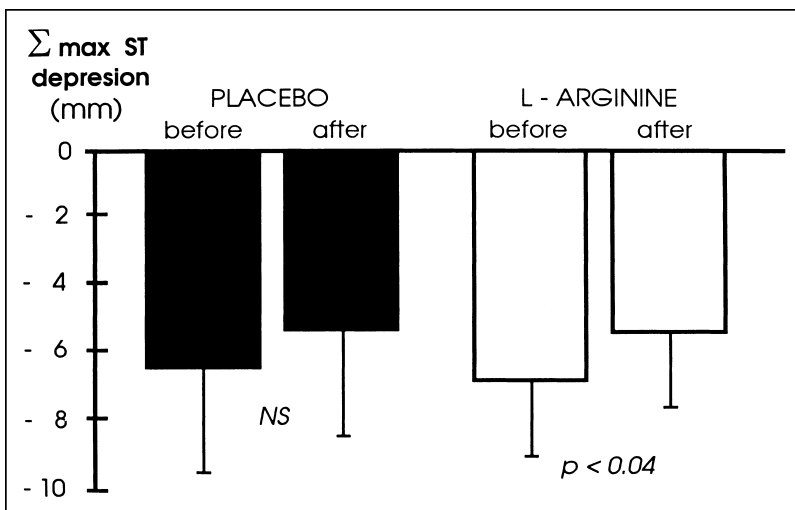


FIGURE 2. Sum of maximum ST-segment depression (mean  $\pm$  SD) during exercise test before and after placebo or L-arginine.

106,  $p < 0.04$ ), whereas in L-arginine treated patients the prolongation of this time period was distinctly pronounced (from  $531 \pm 195$  to  $700 \pm 173$  seconds,  $p < 0.0002$ ). The difference between an increase of mean exercise time to maximal ST-segment depression between the L-arginine group and the placebo group was significant ( $p < 0.02$ ).

As shown in Figure 2, after placebo, the mean value of the maximal ST-segment depression, calculated as the sum of maximal ST-segment depression from all leads (millimeters), changed from  $-6.5 \pm 3$  to  $-5.4 \pm 3$  (NS). After L-arginine, the mean value of maximal ST-segment depression was also less negative but the difference was significant ( $-6.8 \pm 2$  vs  $-5.5 \pm 2$ ,  $p < 0.04$ ).

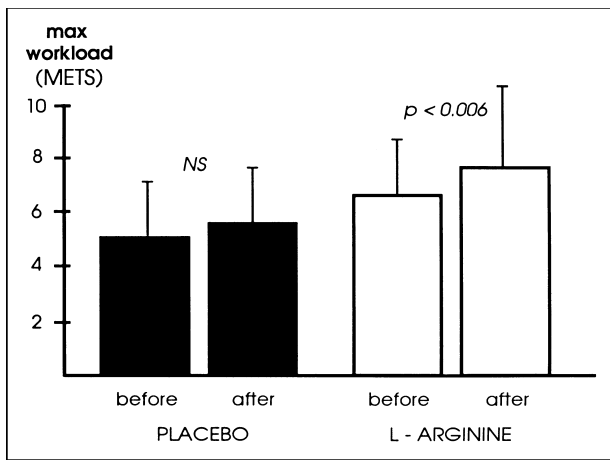
As shown in Figure 3, maximum workload (METs) before and after placebo did not change significantly ( $5.0 \pm 2$  vs  $5.7 \pm 2$ , NS), whereas in L-arginine treated patients the maximum workload increased significantly from  $6.4 \pm 2$  to  $7.4 \pm 3$ ,  $p < 0.006$ .

L-arginine was well tolerated and no adverse effects of the drug were observed. Of the 3 amino acids measured, only the plasma level of ornithine increased significantly after L-arginine supplementation from  $119 \pm 29$  to  $164 \pm 57$  nmol/ml ( $p < 0.0009$ ). Plasma levels of arginine and citrulline before and after L-arginine supplementation were not significantly different ( $99 \pm 60$  vs  $106 \pm 33$  and  $37 \pm 23$  vs  $32 \pm 26$  nmol/ml, respectively). There were no differences in either amino acid level before and after placebo.

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This is the first controlled study that shows that supplemental oral L-arginine improves exercise capacity in patients with stable angina. Regardless of the symptoms signaling a limit of exercise tolerance (exhaustion, anginal pain, and/or ischemic changes on the electrocardiogram), the common mechanism leading to these manifestations is an imbalance of myocardial oxygen supply and demand, resulting predominantly from disturbed regulation of coronary blood flow. The finding of increased exercise capacity after L-arginine suggests that the mismatch between myocardial oxygen supply and demand has been altered in favor of vasodilator influences that facilitate oxygen supply and reduce oxygen demand.

Recently, it has been demonstrated that intravenous infusion of L-arginine in the patients with congestive heart failure leads to peripheral vasodilation and improves cardiac output with simultaneous increase of nitric oxide production.<sup>11</sup> Moreover, in a double-blind crossover investigation, oral L-arginine improved functional status of patients with heart failure.<sup>12</sup> It has been suggested, therefore, that improvement of endothelial function



**FIGURE 3.** Maximum workload (mean  $\pm$  SD) during exercise test before and after placebo or L-arginine.

with L-arginine in patients with heart failure may improve coronary and/or peripheral vasodilation, and in consequence, increase exercise tolerance. In view of our results, this suggestion may also apply to patients with stable angina.

Apart from the direct relaxing action of nitric oxide on vascular smooth muscle, vasodilation by nitric oxide may involve an inhibitory effect on  $\alpha$ -receptor mediated sympathetic vasoconstriction.<sup>13</sup> As shown in patients with exertional angina pectoris, dynamic exercise induces narrowing of the already stenotic areas of the coronary arteries, which most probably results from  $\alpha$ -adrenergic stimulation and contributes to producing myocardial ischemia during exercise.<sup>14</sup> If supplemental oral L-arginine increased synthesis of nitric oxide, and/or inhibited its inactivation, attenuation of sympathetic vasoconstriction might have also contributed to beneficial effects of L-arginine on exercise capacity in our patients.

**In summary, the results of this study suggest that oral L-arginine supplementation has a benefi-**

**cial effect on exercise capacity in patients with stable angina.**

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