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Improvement of Cardiac Performance by Intravenous Infusion of L-Arginine in Patients With Moderate Congestive Heart Failure

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Objectives. **The aim of this study was to evaluate the hemodynamic effect of L-arginine infusion in patients with congestive heart failure.**

Background. **Endothelium-dependent vasodilation is impaired in patients with congestive heart failure. Nitric oxide, which was identified as endothelium-derived relaxing factor, is generated by nitric oxide synthase from L-arginine. Our hypothesis was that administration of L-arginine in patients with congestive heart failure may increase nitric oxide production and have a beneficial hemodynamic effect.**

Methods. **Twelve patients with congestive heart failure (New York Heart Association class II or III) due to coronary artery disease (left ventricular ejection fraction <35%) were given 20 g of L-arginine by intravenous infusion over 1 h at a constant rate. Stroke volume, cardiac output and left ventricular ejection fraction were determined with Doppler echocardiography at baseline and at 30 and 60 min and 1 h after the end of infusion. Blood and urinary levels of nitrite/nitrate (NO_2/NO_3), stable metabolites of nitric oxide, were measured and clearance was calculated.**

Results. **One hour of infusion of L-arginine resulted in a significant increase in stroke volume (from 68 ± 18 ml to 76 ± 23 ml [mean ± SD], $p = 0.014$) and cardiac output (from 4.07 ± 1.22 liters/min to 4.7 ± 1.42 liters/min, $p = 0.006$) without a change in heart rate. Mean arterial blood pressure decreased (from 102 ± 11 mm Hg to 89 ± 9.5 mm Hg, $p < 0.002$), and systemic vascular resistance decreased significantly. Within 1 h after cessation of L-arginine infusion, blood pressure, stroke volume, cardiac output and systemic vascular resistance were statistically not different from baseline values. Clearance of NO_2/NO_3 increased significantly during L-arginine administration (from 13.28 ± 0.42 ml/min to 29.97 ± 1.09 ml/min, $p < 0.001$).**

Conclusions. **Infusion of L-arginine in patients with congestive heart failure results in increased production of nitric oxide, peripheral vasodilation and increased cardiac output, suggesting a beneficial hemodynamic and possibly therapeutic profile.**

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Endothelial dysfunction may be responsible for impaired vasodilation of the peripheral vasculature in patients with congestive heart failure (1–4). The endothelium participates in the regulation of vascular tone by producing vasoactive substances (5,6). The endothelium-derived relaxing factor, which was identified as nitric oxide, is generated by nitric oxide synthase, which converts the amino acid L-arginine to nitric oxide through oxidation of the guanidinium nitrogen. Nitric oxide stimulates guanylate cyclase in vascular smooth muscle cells, resulting in relaxation and vasodilation (7). This stimulation results in elevation of cyclic guanosine monophosphate, which affects physiologic processes such as control of vascular tone, platelet inhibition and neurotransmission (7,8).

Administration of vasodilators, such as nitrates, hydralazine or angiotensin-converting enzyme inhibitors, results in marked hemodynamic improvement in patients with congestive heart failure (8–10). Long-term studies (11–13) have demonstrated improved exercise performance, functional class and survival when vasodilators are given to patients with congestive heart failure. Recently, several studies (1–4,14,15) using invasive methods have proved that endothelium-dependent vasodilation is impaired in patients with congestive heart failure. Administration of L-arginine to these patients may increase nitric oxide production with consequent beneficial hemodynamic effects and thus prove to be an effective new therapeutic approach (16).

The purpose of this study was to evaluate the immediate hemodynamic response to intravenous L-arginine administration in patients with heart failure with the use of noninvasive echocardiographic studies and to correlate the response with changes in blood and urinary nitrite/nitrate (NO_2/NO_3), which are stable metabolites of nitric oxide (17,18).

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Table 1. Clinical Profiles of Patients

Pt No.	Age (yr)/ Gender	LVEF (%)	NYHA Class	Risk Factors
1	70/M	33	II	D, S
2	57/F	22	II	C
3	56/M	27	III	S
4	54/M	24	III	D, H
5	56/M	14	II	C
6	57/M	24	II	C
7	78/M	30	III	S
8	67/M	30	III	S
9	62/M	13	II	C
10	63/M	14	II	D, S
11	71/M	22	III	D, H, S
12	61/M	27	II	C

C = hypercholesterolemia; D = diabetes mellitus; F = female; H = hypertension; LVEF = left ventricular ejection fraction by radionuclide angiography; M = male; NYHA Class = New York Heart Association heart failure class; Pt = patient; S = smoking.

Methods

Patients (Table 1). Twelve patients with congestive heart failure without clinical or echocardiographic evidence of primary valvular heart disease participated in the study. The nature and potential risks and benefits of the study were explained, and all patients agreed to participate in the study and signed an informed consent form approved by the Investigational Review Board of the Tel Aviv Medical Center and Israeli Ministry of Health. All patients had congestive heart failure due to ischemic heart disease and previous myocardial infarction. The group comprised 11 men and 1 woman with an age range of 55 to 78 years. All patients had New York Heart Association functional class II or III heart failure and were admitted to the coronary care unit for the study. Left ventricular ejection fraction by radionuclide angiography was <35% (range 13% to 33%) in all patients. All patients had sinus rhythm, and none had active anginal syndrome, recent myocardial infarction, coronary artery bypass surgery or any systemic chronic disease. Doppler echocardiography, performed before the study to ensure adequate visualization, showed mild functional mitral regurgitation in 3 of the 12 patients.

All patients were treated with digitalis and furosemide, which were withheld on the day of the study. Nine patients were receiving angiotensin-converting enzyme inhibitors, and none of the 12 had been given any vasodilators for 24 h before the study. The study was performed after overnight fasting.

Noninvasive hemodynamic studies. An Acuson ultrasound imaging system (128/5XP, USA) was used for both imaging and Doppler flow studies. Two-dimensional echocardiographic images were obtained with 2.5- or 3.5-MHz transducers, depending on which provided optimal visualization of the endocardium. For volume estimation the apical four-chamber view was used as described by Schnittger et al. (19) and Gordon et al. (20) and previously used by us (21,22). Maximal effort was made to ensure maximal length and width of the left ventricle. The interval between the end of the baseline study and the intervention study was 30 and 60 min. A separate control study was performed at 120 min, 60 min after the end of the intervention. Images were accepted for analysis if ≥75% of the endocardium was seen.

Tracing was performed with a built-in computer program for single-plane area-length volume calculations and Simpson's rule computation from tracings of the ventricular outlines. Left ventricular volumes were measured at end-diastole (i.e., largest dimension or onset of the QRS complex) and at end-systole (i.e., smallest dimension or one frame before opening of the mitral valve). Left ventricular ejection fraction was calculated from end-diastolic volume (EDV) and end-systolic volume (ESV) by the standard formula: LVEF = (EDV − ESV)/EDV.

Forward aortic flow by pulsed Doppler echocardiography. For the recording of left ventricular outflow at the level of the aortic annulus, the transducer was placed at the apical position and rotated toward the long-axis or hemiaxial view. The sample volume was placed in the middle of the left ventricular outflow tract immediately proximal to the leaflet of the aortic valve, as described by Lewis et al. (23).

Forward stroke volume was determined as the product of the time-velocity integral (average of five cardiac cycles) and the cross-sectional area of the aortic annulus. Curves of highest peak velocities were selected. The average of the time-velocity integral was obtained by tracing the contour of the darkest portion of the outflow tract curve. The cross-sectional area of the aortic annulus was calculated as πr^2, where r represents half of the annular diameter measured from the parasternal long-axis view immediately proximal to the points of insertion of the aortic leaflets after maximal systolic outflow separation. All Doppler and echocardiographic analyses were performed by two operators who did not know at which stage of the study the recording was obtained. Systemic vascular resistance (SVR) was calculated by using standard formula and the following variables: forward stroke volume (FSV), heart rate, derived cardiac output (CO), mean blood pressure (MBP) and central venous pressure estimated from jugular venous pressure (JVP). The formula used was: SVR = (MBP − JVP) × 80/CO in dynes·s·cm^{-5}.

Study protocol. *Drug administration.* After the basal Doppler echocardiographic study, blood sampling and a 2-h urine collection were performed. A continuous 1-h infusion 100 ml of 5% glucose mixed with 100 ml of 20% solution of L-arginine hydrochloride was performed through the peripheral vein; a total of 20 g of L-arginine was administered at a constant rate. The study was conducted in a quiet, temperature-controlled room with the patients resting in the supine position. Heart rate and blood pressure were recorded every 10 min during the study.

Blood samples were obtained and a Doppler echocardiographic study was repeated at baseline, at 30 and 60 min during drug administration and at 60 min after cessation of the infusion. Urine was collected immediately before and at the end of L-arginine administration and 60 min later. In all urinary and blood samples, NO_2/NO_3, creatinine and sodium

Table 2. Hemodynamic and Echocardiographic Findings Before and After L-Arginine Infusion

	Baseline	Infusion		After Infusion (120 min)
		30 min	60 min	
SV (ml)*†	68 ± 18	74 ± 20‖	76 ± 23‖	73 ± 26
HR (beats/min)	60 ± 7	61.6 ± 9	61.2 ± 9	60.5 ± 8
CO (liters/min)‡	4.07 ± 1.22	4.54 ± 1.44‖	4.7 ± 1.42‖	4.4 ± 1.57
MBP (mm Hg)§	102 ± 11	90 ± 13‖	89 ± 9.5‖	101 ± 11
TPR (dynes·s·cm^{-5})§	1,926 ± 515	1,521 ± 420‖	1,452 ± 367‖	1,834 ± 637
EF (%)	33 ± 6	35 ± 4.5	36 ± 4.8	34 ± 4.4

*p value by analysis of variance with repeated measurements: †p = 0.17; ‡p = 0.014; §p < 0.0001. ‖Significant difference from baseline value by paired Student *t* test with Bonferroni correction. All values are expressed as mean value ± SD. CO = cardiac output; EF = left ventricular ejection fraction, calculated from two-dimensional echocardiography; HR = heart rate; MBP = mean blood pressure; SV = stroke volume; TPR = total peripheral resistance.

levels were determined. Creatinine clearance was calculated. Urinary and blood NO_2 and NO_3 were determined as previously described (18). After the reduction of NO_3 to NO_2 by a 90-min incubation in a tilting bath (37°C) using nitrate reductase from *Escherichia coli* (prepared by our laboratory) and beta-nicotinamide adenine dinucleotide phosphate (reduced form) (Sigma) as cofactor, the NO_2 was determined with Griess reagent.

Statistical analysis. The results are expressed as mean value ± SD. The data were computerized (SPSS/PC+) and analysis of variance with repeated measurements for the changes in the different variables was performed. Differences were considered statistically significant at $p < 0.05$. A paired Student *t* test with Bonferroni correction was used to compare two time data points of the same variable.

Results

Table 2 shows the changes in the hemodynamic variables studied. Intravenous administration of L-arginine resulted in significant changes (analysis of variance with repeated measurements) in stroke volume ($p = 0.017$), cardiac output ($p = 0.014$), mean blood pressure ($p < 0.0001$) and total peripheral resistance ($p < 0.0001$). Stroke volume increased from 68 ± 18 ml to 74 ± 20 ml at 30 min ($p = 0.012$) and 76 ± 23 ml at 60 min ($p = 0.014$) after the initiation of L-arginine infusion. There were no significant changes in heart rate. Cardiac output increased from 4.07 ± 1.22 liters/min to 4.54 ± 1.44 liters/min at 30 min ($p = 0.003$) and to 4.7 ± 1.42 liters/min at 60 min ($p = 0.006$). One hour after drug administration stroke volume and cardiac output were not significantly different from baseline.

The mean blood pressure decreased from 102 ± 11 mm Hg to 90 ± 13 mm Hg at 30 min ($p < 0.0001$) and 89 ± 9.5 mm Hg at 60 min ($p = 0.002$) and returned to the baseline value 1 h after drug administration. Peripheral vascular resistance decreased during L-arginine infusion from 1,926 ± 515 to 1,521 ± 420 dynes·s·cm^{-5} at 30 min ($p < 0.0001$) and 1,452 ± 367 dynes·s·cm^{-5} at 60 min ($p < 0.0001$). On cessation of L-arginine administration, peripheral vascular resistance increased to 1.834 ± 637 dynes · s · cm^{-5}. The increase in stroke volume and cardiac output was not associated with an increase in heart rate. Left ventricular ejection fraction calculated from echocardiographic left ventricular volumes, tended to increase during L-arginine infusion from 33 ± 6% to 36 ± 5% (p = NS).

Nitrite/nitrate changes (Table 3). The changes in the urinary nitric oxide excretion and the nitric oxide clearance (by analysis of variance with repeated measurement) were statistically significant, $p = 0.042$ and $p < 0.0001$, respectively. Blood levels of NO_2/NO_3 did not change significantly throughout the study period. NO_2/NO_3 urinary excretion (nmol/mg creatinine) increased significantly to 1.48 ± 1.09 from the preinfusion value of 0.84 ± 0.42, $p < 0.01$). Sixty minutes after the end of L-arginine administration the mean value of NO_2/NO_3 excretion remained higher than the preinfusion value (p = NS). The NO_2/NO_3 clearance data showed a twofold increase ($p < 0.001$) during L-arginine infusion over the baseline value (29.97 ± 1.09 vs. 13.28 ± 0.42 ml/min). This

Table 3. Changes in NO_2/NO_3 After Intravenous L-Arginine Infusion

	Baseline	Infusion (60 min)	After Infusion (120 min)
Blood NO (nmol/mg creatinine)	53.7 ± 18.1	48.2 ± 15.4	52.2 ± 13.6
Urinary NO (NO_2 + NO_3) (μmol/liter)*†	0.84 ± 0.42	1.48 ± 1.09§	1.37 ± 1.31
NO_2 + NO_3 (ml/min) clearance‡	13.28 ± 0.42	29.97 ± 1.09§	17.73 ± 1.31

*p value by analysis of variance with repeated measurements: †p = 0.042; ‡p < 0.0001. §Significantly different from baseline value by paired Student *t* test with Bonferroni correction. All values are expressed as mean value ± SD. NO = nitric oxide; NO_2/NO_3 = nitrite/nitrate.

mean clearance value at 60 min after termination of L-arginine infusion was higher than the preinfusion value (p = NS).

Discussion

In the present study, noninvasive methods were used to estimate the hemodynamic response and left ventricular performance during administration of L-arginine, the substrate of nitric oxide, to patients with moderate congestive heart failure. Infusion of 20 g of L-arginine at a steady rate over 1 h resulted in increased stroke volume and cardiac output with a concomitant decrease in total peripheral resistance without acceleration in heart rate. Urinary excretion and clearance of NO_2/NO_3, both indicating an increased production of nitric oxide, were significantly elevated during L-arginine administration.

L-arginine, whether given intravenously or intraarterially, can reduce vascular tone (24–26). The mechanism by which it exerts its vasodilator effect is controversial (26). The main underlying mechanism seems to be the L-arginine–nitric oxide synthase–nitric oxide pathway. However, other possible mechanisms are volume expansion with increased atrial natriuretic peptide and insulin levels during L-arginine infusion and the hypertonicity of the L-arginine solution. Nitric oxide also seems to modulate sympathetic neurotransmission at the prejunctional level in the isolated perfused rat heart (27). Enhancement of the endothelial production of nitric oxide is the most likely underlying mechanism for the beneficial effect of L-arginine on the ischemic reperfused heart (28).

It is less plausible that the infusion of L-arginine in our patients caused an improved contractility of the ischemic myocardium by a direct intracellular metabolic effect. Stimulated nitric oxide synthase activity and a high nitric oxide level were found to cause hypocontractility in cardiac myocytes (29). Furthermore, improved contractility should have resulted in a significant increase in left ventricular ejection fraction, which was not observed in our study. The hemodynamic changes found in our study are similar to those observed with other known vasodilators given to patients with congestive heart failure.

The syndrome of congestive heart failure is characterized by left ventricular dysfunction and reduced exercise capacity (30). The syndrome evolves with time after the initial insult to the myocardium and is associated with activation of neurohumoral systems, fluid accumulation, limitation of peripheral circulation and end-organ failure, presenting the clinical syndrome of congestive heart failure (1,31). In recent years it has become apparent that symptoms and reduced exercise capacity do not necessarily relate to the severity of left ventricular dysfunction (32,33). Important myocardial and peripheral adaptive processes occur and patients may remain relatively asymptomatic for a prolonged period despite markedly depressed ejection fraction. Over time, the myocardium changes in shape, and enlarges through a process of remodeling. This process is associated with myocyte hypertrophy and excessive fibrosis (34,35).

There are substantial data to indicate that neuroendocrine activation including activation of the sympathetic nervous system and arginine vasopressin contribute to excessive systemic vascular resistance and heightened impedance to left ventricular ejection, thereby contributing to worsening pump function in patients with congestive heart failure (31,36–38).

Endothelial function in congestive heart failure. Recently it has been recognized (5–7,14) that substances derived from endothelial cells take part in the regulation of vascular tone. Nitric oxide formed from L-arginine is the endogenous nitrovasodilator, which is released under basal conditions and in response to shear forces, local hormones, neurohumoral mediators and platelet-derived products (7,16). In addition, the endothelium is a source of contracting factors such as endothelin-1, cyclooxygenase products, and possibly angiotensin II (6,39,40). Alteration in endothelium-dependent vascular regulation occurs in clinical and experimental congestive heart failure. The stimulation of endothelial L-arginine pathway by acetylcholine is blunted, whereas the production of potent vasoconstrictor endothelin is augmented (1,39,41). These alterations in endothelial function could contribute to the changes of the peripheral circulation in congestive heart failure. In the forearm circulation of patients with congestive heart failure, the vasodilator effects of acetylcholine and metacholine, both of which act on muscarinic receptors, are blunted (1,14,16).

The impaired endothelium-dependent response to acetylcholine appears independent of the etiology of heart failure. In the human femoral artery, the acetylcholine-induced increase in blood flow is abolished in most patients with congestive heart failure, and the response to nitroglycerin is attenuated (4,14). In the femoral artery of dogs with pacing-induced congestive heart failure, the acetylcholine-induced increase in diameter is attenuated whereas the response to nitroglycerin is not reduced (15). Similarly, in the coronary circulation of patients with dilated cardiomyopathy, the increase in coronary blood flow in response to acetylcholine is reduced, whereas the effects of adenosine, an endothelium-independent vasodilator, are only slightly diminished (3).

The cardiac and hemodynamic responses to load alteration and to administration of vasodilators were extensively studied in patients with impaired left ventricular function and congestive heart failure. Reduction in afterload and an optimal preload are the hallmarks of vasodilator therapy in congestive heart failure. Immediate hemodynamic improvement, with increased stroke volume, cardiac output and decreased total peripheral resistance, were shown by various vasodilators given to patients with congestive heart failure (8–10).

In the early and late stages of cardiovascular disease, both basal and stimulated release of endothelial mediators can be affected. The local endogenous vasodilator system may be highly important in trying to maintain tissue perfusion and antagonize neurohumoral vasoconstrictor forces. In our study, increased availability of L-arginine, by intravenous infusion, resulted in augmented secretion of nitric oxide, marked peripheral vasodilation and improved cardiac output. Thus, the constitutive nitric oxide synthase can be stimulated by the higher

availability of its substrate. The inducible form of the enzyme can be activated by various pharmacologic probes such as acetylcholine and metacholine (42,43), agents that were not used in our study. Recently, L-arginine was shown to augment acetylcholine-induced vasodilation in patients with hypercholesterolemia (44) and to improve the magnitude of maximal vasodilation induced by acetylcholine and vasodilation during peak reactive hyperemia in patients with congestive heart failure but not in control subjects (16).

Limitations of the study. Certain limitations of our study, in both the methods and the pathophysiologic conclusions, should be addressed. The study was nonrandomized and uncontrolled, and the study group comprised only 12 patients. The methods of measurements were noninvasive, the hemodynamic changes were relatively small and the effect of L-arginine was not evaluated in a dose-response manner. We (21,22) have previously compared Doppler echocardiography with thermodilution techniques in multiple studies to assess the hemodynamic response to load alterations, vasodilators and inotropic agents. On the basis of this experience and that of other groups (23,45,46), we believe that in short-term hemodynamic studies, Doppler echocardiographic results are as accurate as thermodilution data and provide significant information regarding directional changes.

There are no published data regarding long-term administration of L-arginine in patients with congestive heart failure. In light of the impairment of endothelial-dependent vasodilation in these patients and the immediate beneficial effect of intravenous L-arginine, it would be interesting to evaluate in a controlled manner the immediate hemodynamic and long-term clinical response to oral therapy with L-arginine.

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