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L-Arginine Infusion Dilates Coronary Vasculature in Patients Undergoing Coronary Bypass Surgery

Arthur W. Wallace, M.D., Ph.D., Mark B. Ratcliffe, M.D.,† Daniel Galindez, M.D.,‡ James S. Kong, B.S.§*

Background: **Nitric oxide–dependent factors (serotonin, activated platelets, acetylcholine) cause vasodilation in normal coronary arteries but vasoconstrict atherosclerotic vessels. This experiment tested the hypothesis that intravenous systemic infusions of L-arginine, a precursor for nitric oxide production, dilate the coronary vascular bed of patients undergoing coronary artery bypass graft surgery.**

Methods: **Twenty patients scheduled for coronary artery bypass graft surgery surgery were studied in a prospective, blinded, randomized clinical trial. Saphenous vein graft blood flow was measured with a transit time flow probe, and coronary vascular resistance was calculated. After weaning from bypass, patients were given a venous infusion (placebo or 10% arginine hydrochloride [30 g]) over 15 min. Arterial blood samples for the determination of L-arginine and L-citrulline levels were drawn before, 10 min after starting infusion, and 10 min after end of infusion.**

Results: **The placebo group experienced an increase in mean arterial pressure and coronary vascular resistance and a decrease in graft blood flow. Patients in the L-arginine group maintained their baseline values. Mean arterial pressure (L-arginine, 88 ± 17 to 92 ± 13 mmHg *vs.* placebo, 80 ± 12 to 92 ± 9 mmHg, $P = 0.021$), coronary vascular resistance (L-arginine, 97,000 ± 60,000 to 99,600 ± 51,000 dynes · s · cm^{-5} *vs.* placebo, 81,000 ± 69,000 to 117,000 ± 64,000 dynes · s · cm^{-5}, $P = 0.05$), and graft blood flow (L-arginine, 55 ± 25 to 50 ± 19 ml/min *vs.* placebo, 60 ± 34 to 46 ± 18, $P = 0.05$) remained more stable in the L-arginine–treated patients.**

Conclusions: **Systemic L-arginine infusion reduced postbypass coronary vasoconstriction. There were no adverse events associated with the drug infusion. (Key words: CABG; clinical trial; nitric oxide; vascular resistance.)**

IN patients with atherosclerotic coronary arteries, the basal secretion of nitric oxide (NO) is reduced,[1] and NO-mediated endothelium-dependent relaxations fail to occur.[1–3] As a consequence, NO-dependent factors that cause vasodilation in normal coronary arteries may cause vasoconstriction in atherosclerotic vessels.[3] This paradoxic effect is endothelium-dependent and is thought to be caused by the inability of the endothelium to synthesize adequate amounts of NO, thus leaving unopposed vasoconstriction. Moreover, after ischemic reperfusion, coronary arteries lose the ability to dilate in response to NO-dependent factors (prostaglandin F2α and platelets).[4]

L-arginine (L-ARG), the precursor for NO,[5–7] increases the levels of NO and causes vasodilation.[8–11] Although L-ARG infusions have been shown to improve endothelial function in patients with coronary atherosclerosis,[12–18] it is unknown if L-ARG vasodilates coronary arteries in patients with postbypass reperfusion injury. After coronary artery bypass graft (CABG), patients have severely injured coronary endothelium and may not respond to L-ARG infusions.

This experiment tested the hypothesis that post–cardiopulmonary bypass infusions of L-ARG improve coronary blood flow and decrease coronary vascular resistance. This experiment measured the ability of L-ARG to increase NO-dependent vasodilation in patients who have just undergone cardioplegic arrest and myocardial revascularization.

Methods

Consent

With informed consent and institutional review board approval, 20 patients aged more than 40 yr undergoing

* Assistant Professor in Residence, Department of Anesthesiology, University of California.

† Assistant Professor in Residence, Department of Surgery, Division of Cardiothoracic Surgery, University of California.

‡ Manager of Clinical Trials, Anesthesiology Service, Veterans Administration Medical Center.

§ Research Fellow, Department of Anesthesiology, University of California.

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Address reprint requests to Dr. Wallace: Veterans Administration Medical Center Anesthesia (129), 4150 Clement Street, San Francisco, California 94121. Address electronic mail to: awallace@best.com

elective CABG surgery at the San Francisco Veterans Administration Medical Center were studied in this prospective, randomized, blinded clinical trial. Patients with aortic or mitral valvular disease requiring valve repair or replacement, left bundle branch block, previous coronary surgery, or esophageal disease were excluded from the study.

Anesthetic Care

History was taken and physical examination performed preoperatively, with specific attention to cardiac disease, myocardial infarction, current angina, congestive heart failure, arrhythmias, and cardiac catheterization data. Patients were premedicated with diazepam (0.15 mg/kg orally) and morphine (0.15 mg/kg intramuscularly) 60 min before arrival at the operating room. Before induction of anesthesia, five-lead electrocardiography equipment, a peripheral intravenous line, a 20-gauge radial arterial line, and a right internal jugular pulmonary artery catheter with thermodilution cardiac output were placed. Baseline measurements of cardiac output, pulmonary artery pressure, pulmonary artery wedge pressure, and arterial blood gas values were obtained. A standard anesthetic of fentanyl (25–125 μg/kg intravenously) and midazolam (0.1–0.5 mg/kg intravenously) was administered, with muscle relaxation achieved by vecuronium (0.1 mg/kg). Controlled ventilation with 100% oxygen was used to maintain a Pa_{O_2} greater than 80 mmHg and a Pa_{CO_2} between 35 and 45 mmHg, as determined by arterial blood gas sampling. Inadequate anesthesia was treated with boluses of fentanyl (1–5 μg/kg intravenously).

Experimental Period

The patients underwent standard bypass surgery and were subsequently weaned from bypass in routine fashion. Changes in the infusion rates of vasoconstrictors, vasodilators, or inotropic agents or the administration of anesthetics could result in systemic and coronary vascular changes. We therefore did not start the experimental period until the patient was stable after bypass. Stability was defined as (1) completion of the protamine infusion, (2) no change in anesthetic management for preceding 10 min, (3) systolic blood pressure greater than 100 mmHg, and (4) cardiac index greater than 2.0 $l \cdot min^{-1} \cdot m^{-2}$. Once the experimental period began, no changes in the infusion rate or administration of any drugs were allowed. Constant infusions (neosynephrine or dopamine) were allowed if necessary for weaning from bypass. No NO donors (nitroprusside or nitroglycerine) or vasodilators (inhaled agents) were used during the experimental period. The only change during the experimental period was the administration (initiation, infusion, and termination) of the study drug (placebo or L-ARG).

Once patients met criteria for stability after bypass, the experiment began. Baseline hemodynamic levels were recorded. A transit time flow probe (H4SB Transonics Systems, Ithaca, NY) was placed on one of the saphenous grafts. Grafts were chosen that perfused beds with severe (greater than 80% stenosis) proximal disease. The saphenous grafts served as convenient locations to measure blood flow and provide a method of measuring the resistance in the myocardial beds fed by the graft. A decrease in resistance of the vascular bed would result in a subsequent increase in saphenous graft blood flow.

Patients were given an infusion into the right internal jugular cordis (placebo [300 ml of saline solution] or 10% arginine hydrochloride [30 g/300 ml; R-Gene 10 Kabi Pharmacia, Piscataway, NJ]) provided by the pharmacy in a double-blind fashion. The dosage was chosen to achieve a predicted concentration of approximately 10^{-2} M, the maximal level demonstrated to improve endothelial function.[13] In patients randomized to receive the active drug, 30 g of L-ARG was infused over 15 min. The placebo group received an equal volume (300 ml) of normal saline solution, with all other procedures identical between the two test groups.

Systolic, diastolic, and mean arterial pressures; central venous pressure; heart rate; O_2 saturation (Propaq 106EL, Protocol Systems, Beaverton, OR); and saphenous bypass-graft blood flow (Transonics HT207, Transonics Systems, Ithaca, NY) were recorded by computer (Compaq Contura 400C, Houston, TX) using custom software (MCMS, IREF, San Francisco, CA) every 10 s from 10 min preinfusion to 15 min after termination of infusion and stored for later analysis.

Laboratory Studies

Three arterial blood samples were drawn, one before sample infusion, one 10 min after starting the infusion, and one 10 min after the end of the infusion for the measurement of serum levels of L-ARG and L-citrulline (L-CIT; amino acid assays were performed by Quest Diagnostics, Teterboro, NJ, with an ion-exchange chromatographer, the Beckman 6300 amino acid analyzer, Beckman, Fullerton, CA). Creatine phosphokinase (CPK) (Kodak Ektachem technique, Kodak, Rochester, NY) and creatinine phosphokinase myocardial band (CPK-MB) analysis (Abbott IMX immunoassay; Abbott, Abbott Park,

IL) were performed at the hospital laboratory on the first postoperative day as an indicator of myocardial infarction. A CPK-MB isoenzyme concentration of greater than 100 ng/ml in any postoperative sample was chosen as the threshold for biochemical evidence of myocardial infarction.[19] Serum osmolality was measured using a freezing-point osmometer at the hospital laboratory.

Holter Electrocardiography

Ambulatory Holter electrocardiographic monitoring using a three-channel AM Holter electrocardiogram recorder (with ST-segment detection; Series 8500, Marquette Electronics, Milwaukee, WI) began 12 h before anesthetic induction and was continued for 36 h postoperatively. Holter analysis technique was identical to that used in previous work.[20] Electrocardiographic ischemic episodes were defined as reversible ST-segment changes lasting at least 1 min and involving either a shift from baseline (adjusted for positional changes) of ≥ 0.1 mV of ST depression (with slope ≤ 0), or a shift from baseline of ≥ 0.2 mV of ST elevation at the J-point.

Twelve-lead Electrocardiography

Twelve-lead electrocardiograms were obtained preoperatively, immediately postoperatively, and on postoperative days 1 and 2. All electrocardiographic data were subsequently analyzed by two investigators unaware of clinical data. Minnesota codes I1 or I2 were used to identify new Q waves. Persistent changes in the ST-T waves were identified by Minnesota codes IV or V.[21]

Data Analysis and Statistics

Time-dependent hemodynamic data were divided into three time segments: preinfusion (5 min), during the infusion (15 min), and postinfusion (10 min). For each patient, hemodynamic parameters (cardiac output, mean arterial pressure, central venous pressure, graft blood flow, coronary vascular resistance, and systemic vascular resistance) were averaged over each of the time segments. Because the time course of the response was not know before study initiation, the decision was made to average the entire time segment. Coronary vascular and systemic vascular resistances were calculated using:

$$\text{coronary vascular resistance} = \frac{\text{diastolic blood pressure} - \text{central venous pressure}}{\text{graft blood flow}}$$

$$\text{systemic vascular resistance} = \frac{\text{mean arterial pressure} - \text{central venous pressure}}{\text{cardiac output}}$$

Table 1. Presurgery Demographic Data

	L-Arginine (n = 8)	Placebo (n = 12)	*P* Value
Age (yr)	66 ± 3	65 ± 3	0.359
Unstable angina	4/8	3/12	0.199
Prior myocardial infarction by history and ECG	4/8	11/12	0.054*
Hypertension	6/8	10/12	0.381
Hypercholestrolemia	4/8	7/12	0.330
Medications			
Nitrates	4/8	6/12	0.350
Calcium channel blockers	3/8	5/12	0.352
β-Adrenergic blockers	6/8	8/12	0.358
Aspirin	5/8	7/12	0.352
Diabetes	6/8	5/12	0.132
Number of stenosed vessels			
1	0/8	0/12	N/A
2	2/8	0/12	0.147
3 or more	6/8	12/12	0.147
Left main	2/8	6/12	0.381

N/A = not applicable.

Two-way repeated measures analysis of variance with one-factor repetition (SigmaStat 2.03S, SPSS, Chicago, IL) was used to test for the difference between the two study groups as hemodynamic values (mean arterial pressure, central venous pressure, systemic vascular resistance, cardiac output, graft flow, and coronary vascular resistance) varied with time. Dunnett method of multiple comparisons *versus* a control group was used if the *P* values were significant for the two-way repeated-measures analysis of variance. The Fisher exact test was used for categorical data. A *P* value less than 0.05 was taken as statistically significant. Values in text are listed as mean ± SD.

Results

Of the 20 patients that were randomized for the study, a computer malfunction resulted in the loss of the hemodynamic data of three patients (two in the placebo group and one patient in the L-ARG group). All 20 patients were included in summary results, but only the 17 subjects with hemodynamic data were included in hemodynamic analysis. Table 1 shows the baseline demographic data for the two groups. There was an increased number of preoperative myocardial infarctions in the placebo group. The two groups show no other significant differences.

There were no statistically significant differences in perioperative adverse events between the two groups (table 2). There were no deaths in the study. Five pa-

Table 2. Postsurgery Data

	L-Arginine (n = 8)	Placebo (n = 12)	*P* Value
Myocardial infarction (CPKMB > 100 μg/l)	0/8	1/12	0.60
Q-wave MI by ECG	1/8	4/12	0.26
Postinfusion ischemic episodes by ECG(Holter)	0/8	3/12	0.19
Ventricular failure	0/8	1/12	0.60
Life-threatening dysrhythmias by ECG	1/8	1/12	0.51
Cardiac death	0/8	0/12	N/A
Number of grafted vessels			
1	0/8	0/12	N/A
2	3/8	1/12	0.14
3	5/8	10/12	0.24
4	0/8	1/12	0.60
5	0/8	0/12	N/A

N/A = not applicable.

tients developed new Q waves on electrocardiography consistent with a diagnosis of myocardial infarction. Only one of these patients developed a CPK-MB concentration greater than 100 ng/ml. This patient also had postbypass ischemic episodes as assessed by Holter analysis.

L-arginine had minimal effects on the peripheral vasculature in patients after cardiopulmonary bypass (fig. 1, table 3). Mean arterial pressure increased in the control patients compared with the patients receiving L-ARG (L-ARG, 88 ± 17 to 92 ± 13 mmHg, *vs.* placebo, 80 ± 12 to 92 ± 9 mmHg; $P = 0.021$). This difference was between preinfusion and postinfusion periods ($P < 0.050$). There was no significant change in cardiac output ($P = 0.945$), systemic vascular resistance ($P = 0.284$), or central venous pressure ($P = 0.655$) with drug infusion.

The coronary vasculature of placebo-treated patients constricted during the experimental period (81,000 ± 69,000 to 117,000 ± 64,000 dynes · s · cm^{-5}, $P = 0.05$; table 3); in the L-ARG group the resistance remained constant (97,000 ± 60,000 to 99,600 ± 51,000 dynes · s · cm^{-5}; $P = 0.05$). Saphenous graft blood flow decreased in the control patients (60 ± 34 to 46 ± 18 ml/min); it remained more stable in the L-ARG–treated patients (55 ± 25 to 50 ± 19 ml/min; $P = 0.05$). The initial response to the L-ARG infusion is an increase in graft flow and a decrease in coronary vascular resistance. The top panel of figure 2 shows a representative example of the increase in saphenous graft flow with L-ARG infusion in one patient and compares it with the recording of graft flow in a placebo-treated patient. The bottom panel of figure 2 shows the calculated coronary vascular resistance in the same two patients. The typical response is an increase in graft blood flow immediately following L-ARG infusion initiation, with a peak approximately 2.5 min later. The increase in graft blood flow tapers off following the initial maximum, but the graft blood flow remains markedly higher than the control group. Coronary vascular resistance decreases immediately following L-ARG infusion initiation and reaches a minimum approximately 2.5 min after infusion initiation. It then returns to baseline after termination of the infusion. In summary, saphenous graft blood flow normally decreases after cardiopulmonary bypass. L-ARG infusions prevent the decrease. Coronary vascular resistance increases after cardiopulmonary bypass—L-ARG infusions prevent that increase (fig. 3).

Before the infusion, serum concentrations of L-ARG and L-CIT in patients receiving placebo and L-ARG are not significantly different (table 4). Ten minutes after the start of the infusion, serum concentrations of L-ARG in patients receiving L-ARG are two orders of magnitude higher than those of placebo patients (L-ARG, 6,900 ± 600 μmol, *vs.* placebo, 81 ± 8 μmol; $P < 0.05$). Ten minutes after termination of the infusion, the serum concentration of L-CIT in L-ARG patients is statistically significantly higher than in the placebo patients (L-CIT, 38 ± 3.9 μmol, *vs.* placebo, 25 ± 1.3 μmol; $P < 0.05$).

The L-ARG infusion increased serum osmolality (272 ± 36.7 to 299 ± 7.2 mOsm/kg) compared with the placebo group (291 ± 9 to 291 ± 140 mOsm/kg; $P = 0.05$).

Discussion

This study demonstrated that systemic L-ARG infusions dilated coronary vasculature in patients after cardiopulmonary bypass without significant systemic vascular effects. Infusions of L-ARG significantly increased the serum L-ARG concentration and had a small effect on serum L-CIT concentrations. There was no statistically significant difference in postsurgical adverse events.

This study was a small, prospective, randomized clinical trial designed to test the hypothesis that L-ARG infusions would improve coronary blood flow. It was not designed with significant power to identify changes in prevalence of myocardial ischemia, myocardial infarction, or death. These data were collected as safety monitors, with no expectation of statistically significant outcomes.

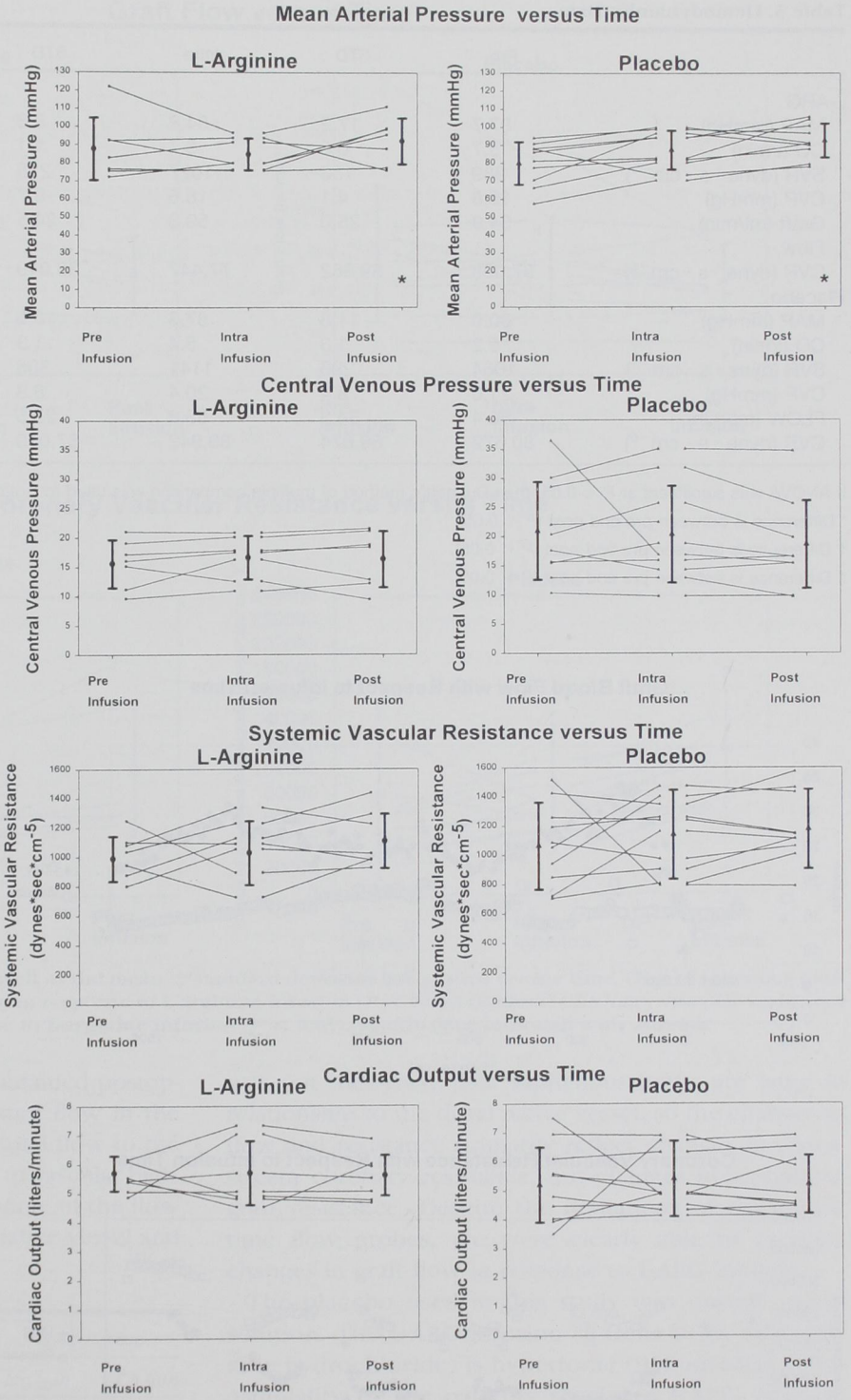

Fig. 1. Results for each individual patient as well as the mean ± standard deviation are plotted *versus* time. (*Top*) The mean arterial pressure response to L-arginine or placebo infusion. Mean arterial pressure decreased compared with placebo, in response to the L-arginine infusion ($P < 0.050$). (*Upper middle*) The central venous pressure response. (*Lower middle*) The systemic vascular resistance. (*Bottom*) The cardiac output response. Significance indicated with asterisk.

This study used transit time flow probes, which provide an accurate measure of absolute flow in the saphenous graft. There are, however, several problems with this technique. First, flow can only be measured after placement of the saphenous graft; no prebypass data can be acquired. Second, the flow probes must be removed

Table 3. Hemodynamics Data

	Pre	STD	Intra	STD	Post	STD	*P* Value
L-ARG							
MAP (mmHg)	87.7	17.2	84.8	8.8	92.2	12.7	0.021*
CO (l/min)	5.7	0.6	5.7	1.1	5.6	0.7	
SVR (dyne · s · cm^{-5})	989	153	1027	218	1106	186	
CVP (mmHg)	15.6	4.1	16.6	3.7	16.3	4.8	
Graft (ml/min) Flow	54.9	25.0	59.3	24.5	49.3	19.1	0.036†
CVR (dyne · s · cm^{-5})	97,008	59,962	77,447	38,019	99,606	50,590	0.003‡
Placebo							
MAP (mmHg)	80.0	11.8	87.3	10.8	92.5	9.5	0.021*
CO (l/min)	5.2	1.3	5.4	1.3	5.2	1.0	
SVR (dyne · s · cm^{-5})	1064	298	1141	305	1176	272	
CVP (mmHg)	21.0	8.4	20.4	8.3	18.6	7.5	
FLOW (ml/min)	60.4	34.3	53.3	25.5	45.9	18.4	0.036†
CVR (dyne · s · cm^{-5})	80,672	68,674	89,942	57,010	117,338	64,416	0.003‡

If ANOVA was significant at $P < 0.05$, then Dunnett's method of multiple comparison was used to isolate which groups differed.

* Difference is between pre and post ($P < 0.05$).

† Difference is between pre and post ($P < 0.05$).

‡ Difference is between pre and post ($P < 0.05$).

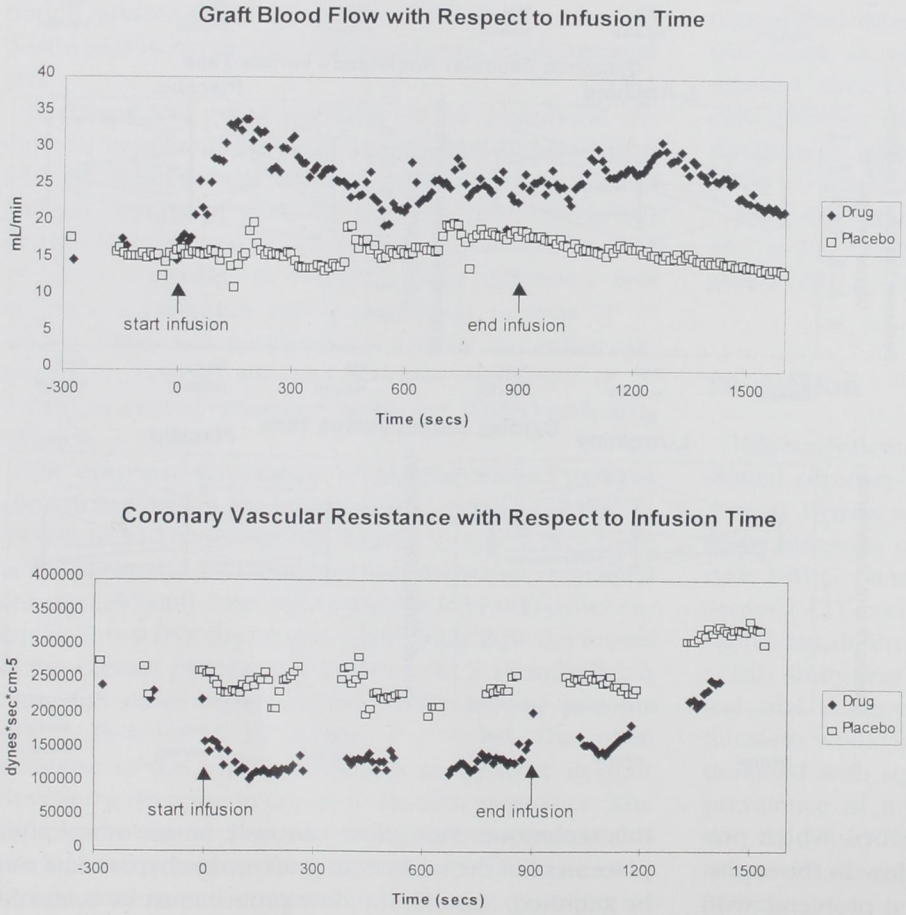

Fig. 2. Plots of saphenous graft flow and coronary vascular resistance *versus* time from two patients. Data are plotted from before the start of the infusion, during the infusion, and after completion of the infusion. Dark diamonds = L-ARG patient; hollow squares = placebo patient. (*Top*) The saphenous graft blood flow. (Bottom) The coronary vascular resistance.

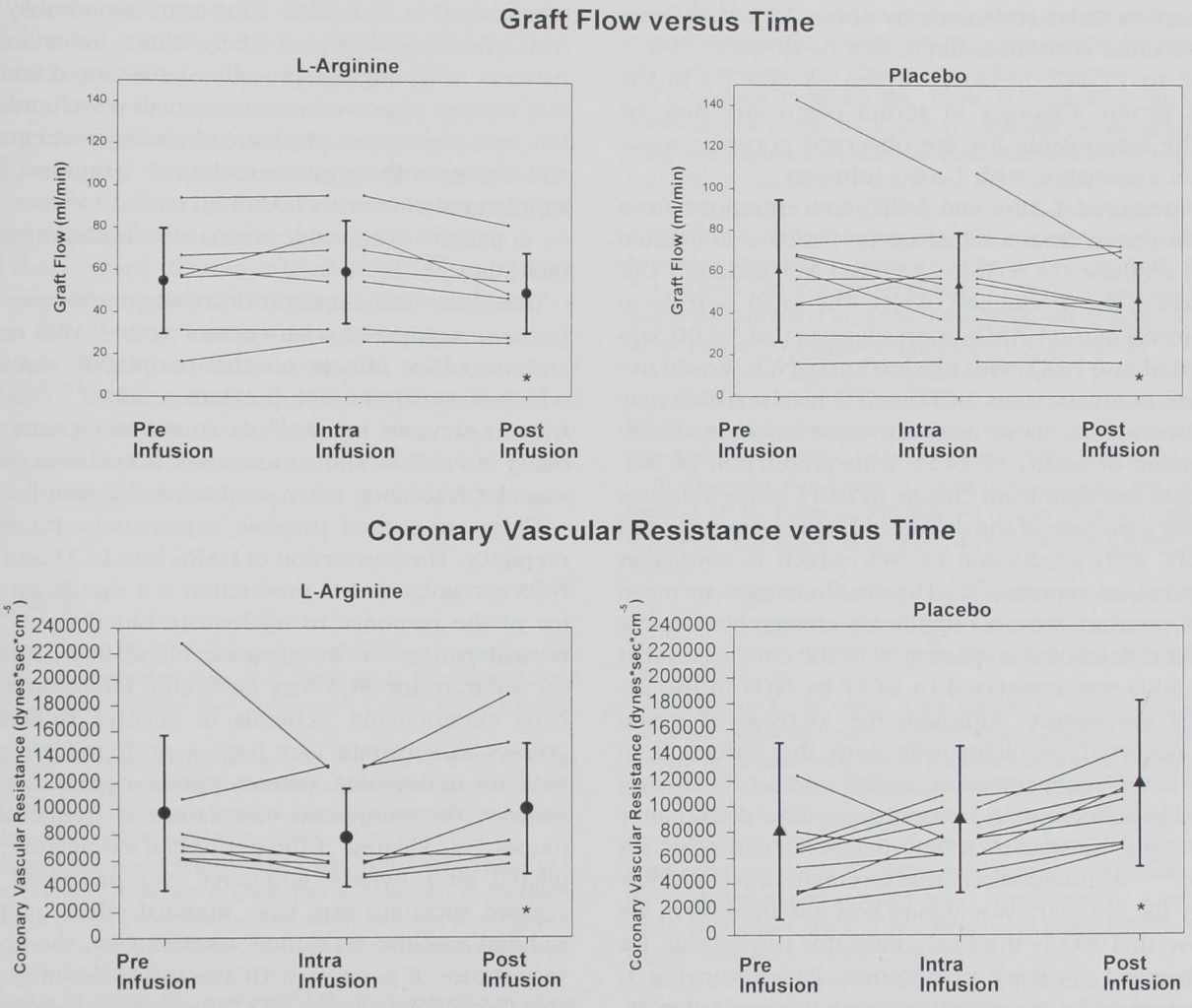

Fig. 3. Results for each individual patient as well as the mean ± standard deviation are plotted *versus* time. (*Top*) Saphenous graft blood flow increased compared with placebo, in response to L-arginine infusion ($P < 0.05$). (*Bottom*) Coronary vascular resistance decreased compared with placebo n response to L-arginine infusion ($P < 0.05$). Significance indicated with asterisk.

prior to chest closure; no data can be obtained postoperatively. Finally, the probes only measure flow in the saphenous grafts; they do not measure total flow to the vascular bed. We chose grafts that went to vascular beds with high-grade proximal stenosis, but some of the flow to these beds came from the proximal native vessel and was not measured. The saphenous grafts are large in relationship to the distal native vessel, so the changes in flow and resistance primarily reflect changes in downstream coronary resistance, not changes in saphenous graft resistance. Despite the limitations of the transit time flow probes, we were clearly able to measure changes in graft flow in response to L-ARG infusion.

Table 4. Amino Acid Levels

	L-Arginine Group		Placebo Group	
	L-Arg (μM)	L-Cit (μM)	L-Arg (μM)	L-Cit (μM)
Preinfusion	93 ± 31	30 ± 14	93 ± 26	30 ± 6
Intrainfusion	6,895 ± 1,526*	32 ± 12	80 ± 25	28 ± 7
Postinfusion	3,724 ± 1,099*	37 ± 10*	74 ± 17	26 ± 5

* $P < 0.05$, ANOVA and Dunnett's test.

The placebo used in this study was normal saline solution. The L-ARG infusion (R-Gene® 10, 10% arginine hydrochloride) is hypertonic (950 mOsm/l). The osmolality of the patients receiving L-ARG infusion increased by 10% (272 ± 36.7 to 299 ± 7.2 mOsm/kg); that of the placebo group remained constant (291 ± 9 to 291 ± 140 mOsm/kg; $P = 0.05$). This increase in osmolality would be predicted to decrease

coronary vascular resistance by about 15%.[22,23] Coronary vascular resistance decreased by 20% (97,008 ± 59,962 to 77,447 ± 38,019 dynes · s · cm^{-5}) in the L-ARG group. Changes in serum osmolality may be partially responsible for the observed coronary vasodilation associated with L-ARG infusion.

We measured L-ARG and L-CIT concentrations from samples drawn from a radial artery. L-ARG is converted by NO synthase (NOS) into L-CIT and NO, making L-CIT a marker of the production of NO. The small increase in L-CIT levels in the L-ARG group suggests that L-ARG was converted into L-CIT with production of NO. We did not measure coronary sinus L-CIT or NO levels, which may have provided a more accurate representation of the conversion of L-ARG to L-CIT with production of NO. The small but significant change in L-CIT levels indicates that only a fraction of the delivered L-ARG was converted to L-CIT with production of NO, which is consistent with previous reports.[24,25] The small changes in mean arterial pressure with no significant change in systemic vascular resistance is consistent with the conclusion that little L-ARG was converted to L-CIT by NOS in the peripheral vasculature. Although the increase in serum L-CIT occurred simultaneously with the reduction in serum L-ARG concentration, L-ARG and L-CIT did not change in stoichiometric proportions. This discrepancy may simply be due to other metabolic pathways for L-ARG.[26,27] Although direct measurement of NO production by the coronary vasculature was not attempted, we propose that NO is the likely mediator responsible for the observed coronary vasodilation. Patients in the L-ARG group had a significant increase in serum concentration of L-CIT, the physiologic byproduct in the production of NO from L-ARG by NOS.

There is some controversy concerning the systemic vascular effects of L-ARG infusions. Although most studies find that L-ARG infusions have minimal effects on blood pressure or cardiac output,[28–30] most demonstrate an improved endothelial function in patients with atherosclerosis.[12–14] L-ARG has been shown to considerably improve postischemic recovery of cardiac mechanical function after cardioplegic arrest and ischemia if given in the reperfusate (animal model of cardiac transplantation).[31–35] It also has been shown to improve coronary endothelial response to acetylcholine after cardiac transplant.[36] Intracoronary L-ARG infusions have been shown to improve endothelium-dependent coronary vascular function in patients with coronary artery disease.[15–18] Two studies[37,38] have demonstrated an improvement in clinical symptoms of coronary artery disease with oral administration of L-ARG. Long-term (6 months) oral L-ARG administration (3 g orally, three times a day) in patients with angiographically significant coronary artery disease improved coronary small-vessel endothelial function, decreased plasma endothelin concentrations, and significantly improved clinical symptoms.[38] Oral supplementation with L-ARG increased exercise capacity in patients with stable angina after healed myocardial infarction.[37]

This study found a slight decrease in systemic arterial pressure compared with control with L-ARG infusion, and no other effects on the peripheral vasculature, which is consistent with previous reports.[13,14,28] In contrast to previous reports[14] we found an increase in coronary blood flow and concomitant decrease in coronary vascular resistance when compared to control.

There are several possible explanations for this discrepancy. The conversion of L-ARG into L-CIT and NO by NOS is regulated. NO production is a significant regulator of the response to inadequate blood flow.[39–44] In normal patients with adequate blood flow, increasing the subtrate for NOS may have little effect. In vascular beds experiencing ischemia or relative ischemia, increases in substrate may have a profound effect.[45] In patients undergoing extracorporeal bypass for CABG surgery, the peripheral vasculature is frequently profoundly vasodilated. If the peripheral vasculature is fully dilated after bypass, additional NO produced by increased substrate may have minimal effect on the peripheral vascular resistance. Alternatively, the coronary vasculature of patients with atherosclerosis may be unable to produce enough NO.[1] Increases in substrate may then have a profound effect and result in vasodilation. It is not that the systemic vasculature is unresponsive and the coronary circulation is responsive to L-ARG infusions but rather where that vascular bed lies on the dose–response curve to L-ARG-NO. The change in coronary vascular resistance associated with L-ARG infusion was greatest in grafts that had low initial blood flow, suggesting that these beds may have been vasoconstricted and be on a steep portion of the L-ARG–NO dose–response curve.

The placebo group showed an increase in coronary vascular resistance with time. In the L-ARG group, however, this effect was offset by infusions of L-ARG. L-ARG infusion prevented an increase in coronary vascular resistance. The corollary is that if the resistance had been stable, L-ARG infusion would resulted in a net dilation of the vessel. Similar assessment can be made about the graft blood flow. It should be noted that graft blood flow

in the placebo group steadily decreased with time. Graft flow increased initially with L-ARG infusion and then remained higher than in the control group.

This study was too small to demonstrate any effects on clinical outcomes (myocardial infarction, death, or myocardial ischemia). Larger trials designed with sufficient power to determine clinical outcomes are required before any conclusions.

This study clearly demonstrates that infusions of L-ARG in patients undergoing CABG surgery have minimal effects on the systemic vasculature and improve coronary blood flow. Further trials are required to determine if infusions of L-ARG are able to reduce the incidence of postbypass myocardial ischemia and infarction by improving endothelial function. L-ARG infusion has potential as an anti-ischemic therapy for post-CABG surgery patients.

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