

Persistent reduction in left ventricular asynergy in patients with acute myocardial infarction by intravenous infusion of nitroglycerin

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ABSTRACT Intravenous nitroglycerin (NG) infusion in patients with acute myocardial infarction (AMI) has been shown to improve left ventricular function and myocardial perfusion and to decrease ischemic injury and creatine kinase (CK) indexes of infarct size. To determine whether early NG infusions in patients with AMI decreases the extent of left ventricular asynergy, we used two-dimensional echocardiography to measure asynergic segments (akinesis and/or dyskinesis) at four serial short-axis levels from base to apex (mitral, M; chordal, C; midpapillary, MP; low papillary, LP) in 22 patients with a first anterior AMI. Patients were randomized between infusions of NG ($n = 11$) or 5% dextrose in water (controls, $n = 11$) within 5.6 hr after the onset of pain. NG infusion rates were titrated to lower mean arterial pressure to an average level of 7% below control (but not below 80 mm Hg) and were maintained at this level for the duration of the infusions (39 hr). After NG, left ventricular function improved as left ventricular filling pressure decreased ($p < .005$), and Σ ST on precordial ST segment mapping decreased ($p < .001$). These parameters did not change in control subjects. Computed CK infarct size was smaller in the NG group than in the control group ($p < .05$). Before the infusions, the mean extent of left ventricular asynergy (% left ventricular circumference) were similar in both groups: M, 18% vs 21%; C, 22% vs 23%; MP, 26% vs 24%; LP, 32% vs 29%. In addition, the computed total left ventricular asynergy (% surface area) was also similar for these two groups before therapy (25% vs 25%). There was no change in left ventricular asynergy from pretreatment values by 1 hr and 10 days among control subjects: M, 18% vs 18% vs 17%; C, 22% vs 23% vs 22%; MP, 26% vs 26% vs 22%; LP, 32% vs 33% vs 33%; total 25% vs 25% vs 24% (multiple measures analysis of variance). In contrast, there was a significant decrease ($p < .001$) in left ventricular asynergy from pretreatment values by 1 hr and 10 days with NG: M, 21% vs 10% vs 8%; C, 23% vs 12% vs 10%; MP, 24% vs 13% vs 9%; LP, 29% vs 14% vs 10%; total, 25% vs 12% vs 9%. Thus the prompt decrease in left ventricular asynergy in the NG group persisted for at least 10 days or 7 to 9 days after NG infusions were stopped. These effects on hemodynamics, Σ ST, CK infarct size, and asynergy suggest that careful early and prolonged low-dose NG infusion might reduce the extent of infarction.

Circulation 68, No. 6, 1264-1273, 1983.

INTRAVENOUS infusion of nitroglycerin (NG) has been shown to improve left ventricular function^{1,2} and myocardial perfusion³ in some patients with acute myocardial infarction (AMI). The decrease in Σ ST on precordial ST segment mapping^{1,2} and perfusion de-

fects on thallium-201 imaging³ in these patients suggested a decrease in the extent of myocardial ischemia, which supported the findings in studies in dogs⁴⁻⁷ and humans.⁸⁻¹⁰ Recently, NG infusion was shown to reduce creatine kinase (CK) and CK-MB indexes of infarct size.¹¹ Since myocardial infarction results in left ventricular asynergy,¹²⁻¹⁴ the beneficial effects of NG infusion in early stages of infarction might be expected to result in a reduction in the extent of left ventricular asynergy.

This study was performed to determine the effect of early intravenous NG therapy on left ventricular asynergy in a group of patients with anterior AMI. The dose of NG was carefully titrated to decrease mean arterial pressure (MAP) by 10%. A similar dose of NG was

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Supported in part by grants from the Canadian Heart Foundation and Special Services of the University of Alberta Hospital.

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Received May 23, 1983; revision accepted Aug. 18, 1983.

Dr. Sussex is a Clinical Research Fellow, supported by the Alberta Heritage Foundation for Medical research.

Presented in part at the 55th Scientific Sessions of the American Heart Association, Dallas, November 1982.

found to reduce infarct size in conscious dogs¹⁵ and produced beneficial effects in patients.^{1-3, 11} Since two-dimensional echocardiography (2D-echo) provides tomographic images of the heart,¹⁶ we used a modification of existing 2D-echo methods for assessing left ventricular asynergy^{12-14, 17-21} in parasternal short-axis views. We also expressed total left ventricular asynergy as percent of left ventricular surface area for correlation with Σ ST and CK infarct size.

Methods

Patients. Twenty-two patients admitted to the coronary care unit with a first anterior, transmural AMI within 2.9 ± 0.4 hr (range 1 to 6) from the onset of persistent chest pain and with an adequate 2D-echo examination on admission were randomly selected to receive NG ($n = 11$) or to serve as controls ($n = 11$) (table 1). On admission, seven patients were in Killip class I,²² 10 in class II, and five in class III. All patients had evidence on the electrocardiogram (ECG) of persistent ST segment elevation greater than 0.2 mV in at least two standard precordial leads of a 12-lead ECG, with subsequent development of pathologic Q waves and cardiac enzyme evidence of AMI. Patients with heart block or cardiogenic shock (Killip class IV) on admission and those with past histories of infarction or heart failure were excluded. All patients received nasal oxygen and intravenous morphine for pain and were maintained on continuous lidocaine infusion (1 mg/min) throughout the short-term study. Written informed consent was obtained before each study.

Treatments. The solutions for NG infusions were prepared by the hospital pharmacy by dissolving 9.5% NG powder (Parke-Davis) in 65 ml of 100% ethyl alcohol and 55 ml of sterile water. The solution was passed through a 0.22 μ m millipore filter and transferred to glass vials, each containing 10 mg/ml. These vials were tested for sterility and pyrogen. All vials were refrigerated, protected from light, and used within 4 weeks. Before infusions, the solutions were further diluted in 5% dextrose in water to a final concentration of 120 μ g/ml in glass bottles. These solutions were infused through standard intravenous sets. Although polyethylene tubing with special infusion pumps have recently been recommended to avoid NG adsorption to plastic²³ or polyvinyl chloride, we did not observe any adverse effects in our patients. Infusions were begun at a rate of 5 μ g/min and increased by 5 to 20 μ g/min every 5 min in the first 30 min until the MAP was reduced by 10% of its control value but not less than 80 mm Hg. The infusion rate was maintained at this level for at least 24 hr. The infusion was slowed or temporarily stopped if the MAP fell more than 10%. The average infusion rate required to lower MAP by 10% was 29 ± 6 μ g/min (range 5 to 120) and was achieved within 30 min. After 24 hr the NG infusion was tapered gradually and discontinued, with an average duration of the infusion of 38.8 ± 4.0 hr (range 24 to 63).

The control patients were given 5% dextrose in water intravenously without NG at a constant rate of 1 ml/min for the first 24 hr.

Measurements. During the first 48 hr all patients had the following measurements recorded at least twice over 1 hr before the treatments, repeated serially during the treatments (one to four hourly over the first 12 hr and four to 12 hourly over the next 36 hr) and at 1 hr after treatments were stopped: heart rate, blood pressure, pulmonary artery and capillary wedge pressures and cardiac output; precordial ST segment maps; CK activity; and 2D-echo studies. The 2D-echo studies were repeated on days 4 and 10. Additional data, during the infusions and the

subsequent interval to day 10, were collected on all complications and other drugs or therapies used during the study.

On admission, each patient had a Swan-Ganz thermodilution catheter inserted into the pulmonary artery and a plastic catheter into the radial artery. Pressures were recorded via transducers (HP 1290A) and bedside monitors (HP 78342A). Cardiac output was measured by the thermodilution technique.²⁴ Rate-pressure product (RPP), left ventricular stroke work index (LVSWI), left ventricular work (LVW), and peripheral resistance index (PRI) were derived as follows from hemodynamic measurements:

$$\text{RPP (mm Hg} \cdot \text{beats/min)} = \text{HR} \times \text{MAP}$$

where HR = heart rate;

$$\text{LVSWI (g} \cdot \text{m/m}^2) = [\text{SVI} \times (\text{MAP} - \text{PCWP}) \times 13.6]/1000$$

where SVI = stroke volume index and PCWP = pulmonary capillary wedge pressure;

$$\text{LVW (kg} \cdot \text{m/m}^2) = \text{LVSWI} \times \text{HR}$$

$$\text{PRI (mm Hg} \cdot \text{min/l/m}^2) = \text{MAP/CI}$$

where CI = cardiac index.

Initial 35-lead (five rows of seven leads) precordial maps²⁵ were used to determine the area of maximal ST segment elevation. Sixteen electrodes (four consecutive interspaces; four vertical rows) from this area were then selected and their positions marked on the chest for serial 16-lead maps,²⁶ with an ECG standardization of 1 mV = 20 mm. Blood samples for CK were drawn, via a heparin lock in an arm vein, before the infusions and two to four times hourly during the infusions for up to 48 hr or longer until baseline levels were reached. Total CK activity was measured with an automated system and the Worthington Statzyme CK reagent (New Jersey). This assay is based on Rosalki's method²⁷ but uses NAD instead of NADP. The modified method²⁸ of Shell et al.²⁹ was used to compute CK infarct size in gram-equivalents from CK activity curves (HP 9874A).

Initial complete 2D-echo studies¹⁶ were recorded on admission in all patients by means of a Dasonics V3400R phased array ultrasonograph. All 22 patients had clear acoustic windows and adequate images with visualization of all left ventricular walls in the four parasternal short-axis views (from base to apex at mitral, chordal, midpapillary and low papillary levels), the parasternal long-axis view, and apical four-chamber view. In all cases, the positions of patients and transducers were noted for use in serial studies restricted to the above views. Images were videotaped for review in real-time, slow-motion, and single-frame formats. Special emphasis was placed on obtaining good endocardial definition, avoiding oblique sections,¹² and recording over several cardiac cycles at end-expiration. To facilitate orientation of the views, internal anatomic landmarks were used: junctions of the ventricular septum and right ventricle and location of mitral valve leaflets, chordae, and papillary muscles.

Analysis of data. Precordial maps and echocardiograms were coded with random numbers so that neither patient identity nor the sequence of recordings were known by the observers who analyzed the data. Three serial 2D-echo studies from 12 subjects (five adult athletes and seven subjects without histories of ischemic heart disease and with normal ECGs and coronary angiograms), all of whom fulfilled the exclusion criteria for this study and had adequate 2D-echo images, were also coded and analyzed with those of the study patients.

The 2D-echo images were viewed on a 14-inch television screen (Varian), and left ventricular endocardial outlines of end-diastolic frames were traced on plastic overlays for the apical four-chamber and four serial short-axis views. Markings of the extent of left ventricular asynergy, defined as akinesis and/or

CALCULATION OF EXTENT OF LV ASYNERGY IN SHORT AXIS VIEWS

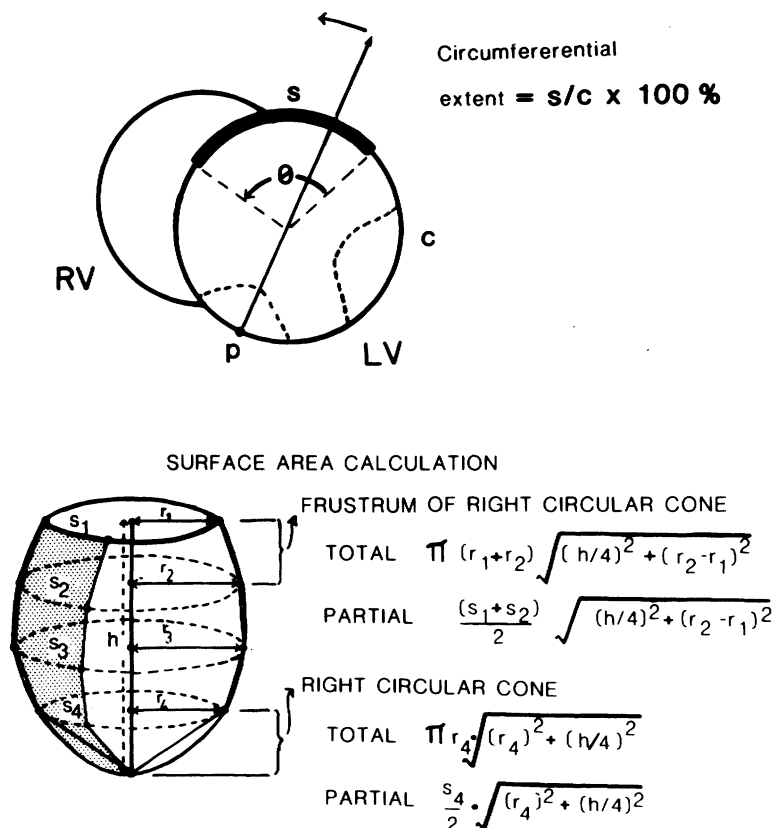


FIGURE 1. Method for calculation of extent of left ventricular asynergy. *Top*, Extent of asynergy (s), marked on end-diastolic outlines of parasternal short-axis images at four serial levels from base to apex on 2D-echo, was expressed as percent of circumference (c). A point (p) at the midpoint of mitral, chordal, or papillary muscle landmarks was identified. An axis was constructed from this point to the anterior wall to bisect the area of the left ventricular section. Radial coordinates were defined from this axis and the angular extent (θ) of asynergy measured. Radii (r) were measured from the midpoint of this line. *Bottom*, Calculation of total left ventricular asynergy, as percent surface area of the endocardial shell constructed from the four short-axis sections and height (h) derived from the left ventricular long-axis length in the apical four-chamber view. The left ventricle is assumed to consist of three frustums of a right circular cone and an apical cone.

dyskinesia, were made on each outline by careful visual assessment of wall motion on repeated to-and-fro playbacks in real time, as described previously by other investigators.^{13, 14, 30} We verified that the asynergic segments showed no inward endocardial motion and no systolic thickening by visual assessment, comparison of wall thicknesses in systole and diastole (Varian, light pen system), and comparison of aligned diastolic and systolic outlines. The endocardial outlines and asynergic segments were digitized electronically (HP 9874A), and asynergy in each short-axis section was expressed as percent of its circumference (figure 1). In addition, since both spontaneous and therapy-induced changes in left ventricular size and asynergy might occur, the radii of the sections and the angular extent of asynergy (θ) were measured after construction of an axis from the posterior wall to bisect the area of the left ventricular section^{14, 31} and definition of radial coordinates from this line (figure 1). Finally, the total extent of left ventricular asynergy, as percent surface area of the endocardial shell, was computed from the apical four-chamber and serial short-axis data (figure 1). Similarly, left ventricular end-diastolic volumes were computed from the end-diastolic outlines of two long-axis views (parasternal long and apical four-chamber) and the four short-axis views by means of the modified Simpson rule.³¹ The tracings and asynergy markings made by two observers for all patients were compared and the consensus after further review was used to compute final data. For all 22 patients, there was 100% concordance in detecting the location of asynergy between the observers but they differed by 3.4 ± 0.5 mm in marking asynergy in short-axis sections, with a regression coefficient between the two sets of values of .96 ($p < .001$; $n = 440$). For one observer, variability was 1.9 ± 0.3 mm over two

sets of observations in 24 studies, with an r value of .97 ($p < .001$; $n = 96$), and the outer boundaries of asynergy had to be shifted by 1.8 ± 0.3 mm.

Statistics. Data at different steps were coded for analysis at the end of the study. The following statistical methods were used: (1) unpaired and paired t tests to calculate the significance of differences within and between the two treatment groups, (2) linear regression analysis by the least-squares fit method, and the significance of r values and slopes by analysis of variance (ANOVA), (3) the 2 by 2 χ^2 test (with ANOVA) to assess the significance of differences in event frequency between the two groups, and (4) repeated measures ANOVA for comparing serial data in each group. Results are given as mean \pm SEM, with p values.

Results

There were no statistically significant differences ($p > .1$) between the NG group ($n = 11$) and the control group ($n = 11$) in age, sex, interval between onset of pain to admission, initiation of infusions, initial Killip class, initial hemodynamics, or Σ ST on precordial mapping (table 1).

Hemodynamics. The hemodynamic changes at three time intervals over the first 24 hr are summarized for the two groups in figure 2. With NG infusion the only significant change over the three intervals (multiple measures ANOVA) was in left ventricular filling pres-

TABLE 1
Patient data

Parameter	NG group (n = 11)		Controls (n = 11)	
Sex	7M, 4F		10M, 1F	
Age (yr)	59 ± 3	(46–67) ^A	54 ± 4	(39–75)
Body surface area (m ²)	1.89 ± 0.06		1.93 ± 0.04	
Onset of pain to admission (hr)	3.0 ± 0.3	(2–6)	2.7 ± 0.7	(1–6)
Admission to first 2D-echo (hr)	2.2 ± 0.2	(1–4)	2.5 ± 0.3	(1–4)
Onset of pain to infusions (hr)	5.9 ± 0.4	(4–8)	5.4 ± 0.3	(3–8)
History of hypertension (n)	2		1	
Initial arterial pressure (mm Hg)				
Systolic	130 ± 6	(90–160)	129 ± 6	(100–160)
Diastolic	82 ± 3	(60–100)	83 ± 4	(70–115)
Mean	98 ± 4	(87–117)	99 ± 5	(80–130)
Initial heart rate (bpm)	73 ± 4	(60–100)	75 ± 5	(42–110)
Initial RPP (mm Hg × bpm × 10 ³)	7.25 ± 0.59		7.34 ± 0.56	
Initial cardiac index (l/min/m ²)	2.8 ± 0.3	(1.3–4.0)	2.7 ± 0.2	(1.3–3.9)
Initial PCWP (mm Hg)	19 ± 1.1	(13–25)	23 ± 2.9	(13–30)
Initial clinical class (Killip)	I:4; II:5; III:2		I:3; II:6; III:2	
Initial ΣST (16-lead map) (mV)	37.7 ± 3.4		35.2 ± 3.9	
Mortality during study period	0 ^B		2 ^C	

PCWP = pulmonary capillary wedge pressure; RPP = rate-pressure product.

^AValues are expressed as mean ± SEM; ranges are in parentheses.

^BOne patient developed ventricular fibrillation and died on day 12.

^CTwo patients died of cardiogenic shock on days 2 and 3, respectively.

sure, reflected by the pulmonary capillary wedge pressure, which decreased by 37%, from a mean of 19 ± 1 mm Hg during the control period to a sustained mean level of 12 ± 1 mm Hg throughout the NG infusion ($p < .005$). Although the maximal reduction in MAP was seen at 30 min (mean 7%, range 6% to 12%), from a mean of 98 ± 3 mm Hg during the control period to a mean of 91 ± 3 mm Hg by 30 min ($p < .001$), the levels between 1 hr (95 ± 3 mm Hg) and 24 hr (96 ± 6 mm Hg) were not significantly lower than the control

value. There was no statistically significant change in heart rate, rate-pressure product, peripheral resistance index, cardiac index, left ventricular stroke work index, and left ventricular work over the three intervals. However, when 24 hr values were compared with control values (paired *t* test) there was a 16% decrease in peripheral resistance index, a 14% increase in cardiac index (2.8 ± 0.2 vs 3.2 ± 0.2 l/min/m²; $p < .005$), a 16% increase in left ventricular stroke work index ($p < .05$), and a 21% increase in left ventricular work ($p < .05$). These hemodynamic effects persisted for at least 1 hr after the NG infusion was stopped. Among control subjects, none of the hemodynamic changes over the three intervals were significant. However, in a comparison of 24 hr values with control values there was a 23% decrease in MAP ($p < .005$), a 22% decrease in rate-pressure product ($p < .005$), a 22% decrease in cardiac index ($p < .005$), a 42% decrease in left ventricular stroke work index ($p < .005$), and a 36% decrease in left ventricular work ($p < .05$). The 24 hr values of these parameters and pulmonary capillary wedge pressure in controls differed from corresponding values in the NG groups ($p < .05$) by multiple comparisons least significant difference test.

The relation between left ventricular stroke work indexes and left ventricular filling pressures before and after 24 hr of NG infusion for each of the 11 patients is plotted in figure 3. There is a shift leftward in all patients and a shift upward in all but two patients. The net shift was toward the normal region, with a slightly higher stroke work index at a lower left ventricular filling pressure.

Precordial mapping. Over the first 24 hr the mean ΣST did not change significantly among control subjects. Thus the mean ΣST over the control period was 12% greater than the 1 hr value (35.2 ± 3.9 vs 31.1 ± 3.5 mV; $p < .05$) but not significantly different from the 24 hr value (35.2 ± 3.9 vs 30.4 ± 4.4 mV; $p > .2$). In contrast, NG produced a 60% decrease in mean ΣST over the first hour (37.7 ± 3.4 vs 14.9 ± 2.1 mV; $p < .001$) and a further 17% decrease by 24 hr (14.9 ± 2.1 vs 12.4 ± 2.2 mV; $p < .05$). The mean percent decrease in ΣST over the first hour was significantly greater in the NG group compared with controls ($59.3 \pm 4.8\%$ vs $11.8 \pm 4.4\%$; $p < .001$).

CK infarct size. There was no statistically significant difference between the NG and control groups in peak CK levels (1807 ± 287 vs 2226 ± 283 IU/l). However, mean CK infarct size was smaller for the NG group compared with controls (30.1 ± 4.4 vs 51.4 ± 10.0 g-Eq; $p < .05$).

Asynergy. No left ventricular asynergy was detected

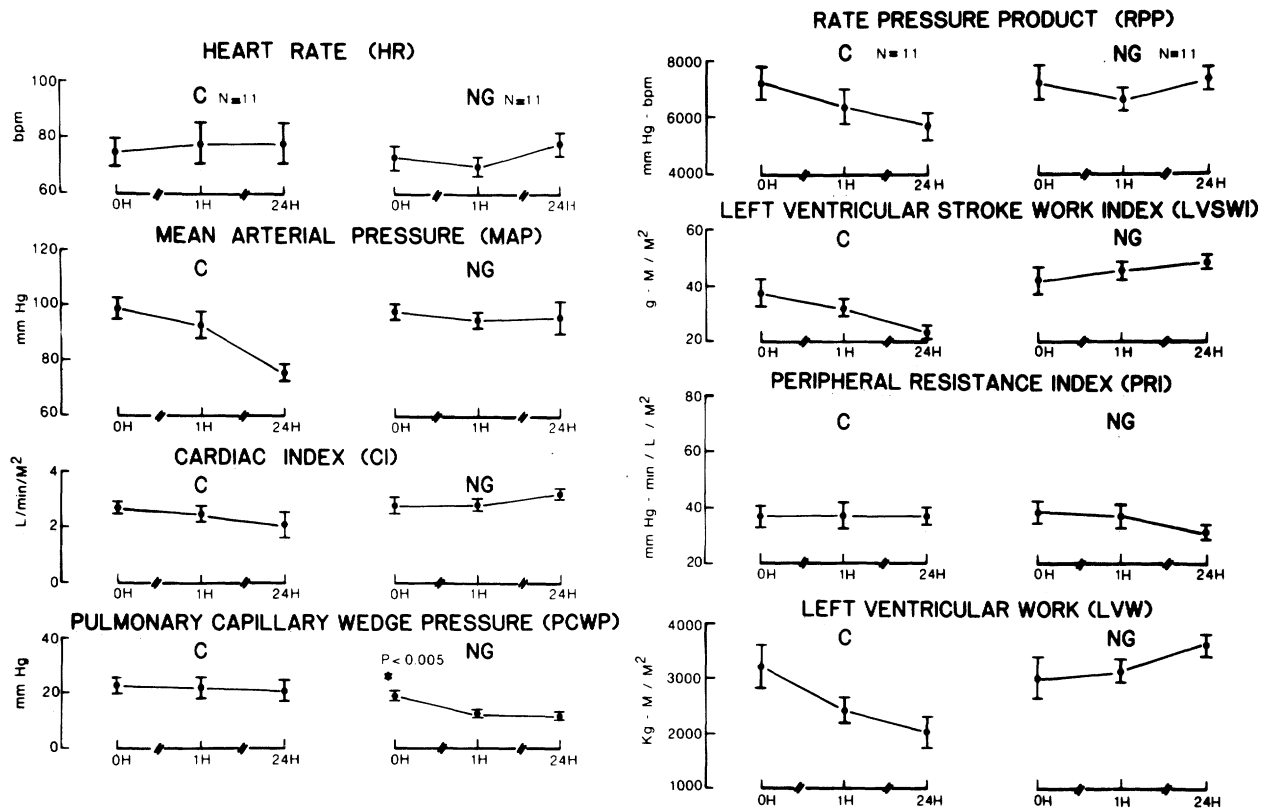


FIGURE 2. Effect of NG infusion on hemodynamics. Values (mean \pm SEM) at three time intervals (0, 1, and 24 hr) are shown for NG and control (C) groups. Measured parameters are shown on the left and derived parameters on the right. *p value by multiple measures ANOVA.

on 2D-echo among the 12 normal subjects (three serial studies, 144 parasternal short-axis sections, 36 apical four-chamber sections, 36 parasternal long-axis sections).

The circumferential and angular extents of left ventricular asynergy at five time intervals (control period, 1 hr, 24 hr, 48 hr, and 10 days) for the four short-axis levels, from base to apex, are summarized in table 2 and figure 4. All patients had asynergy in anteroapical, anterior, and apical left ventricular regions, involving segments 1, 5, 8, and 9 in the segmental classification of Heger *et al.*¹³ Before the treatments, the circumferential and angular extents of left ventricular asynergy, as well as the radii of the sections and the angular extent of left ventricular asynergy normalized to the corresponding radii, were similar for the two groups at all four levels (figure 4 and table 2). In both groups the extent of left ventricular asynergy (as % left ventricular circumference, angular extent in degrees, or the angular extent to radius ratio) was greater at the apex than at the base ($p < .05$). There were no significant changes in mean extent of left ventricular asynergy at the four levels over the 10 days among controls. In contrast, there was a highly significant ($p < .001$), prompt, and sustained reduction in left ventricular asynergy with NG infusion. The mean percent reductions in left ven-

tricular asynergy, as percent circumference, for the four levels after 24 hr of NG infusion were as follows: mitral, 67%; chordal, 61%; midpapillary, 54%; low papillary, 66%. At 10 days, or 7 to 9 days after the NG infusions, the percent reductions in left ventricular asynergy (% circumference) for the four corresponding levels were 62%, 57%, 63%, and 66%, respectively. There was no statistically significant change in the mean radii of the sections in either group, although there was a slight downward trend (NS) during NG infusions (figure 4). The computed left ventricular end-diastolic volumes for the five intervals (0, 1, 24, and 48 hr and 10 days) for the NG group were as follows: 136 ± 13 , 123 ± 11 , 121 ± 9 , 122 ± 9 , and 137 ± 10 cm³, respectively. Corresponding values for the control group were as follows: 129 ± 9 , 129 ± 9 , 140 ± 10 , 135 ± 9 , and 134 ± 11 cm³, respectively. The changes in angular extent of left ventricular asynergy, in degrees and after normalizing to radii (figure 4), paralleled those in circumferential extent for all four levels, with significant and persistent reductions among patients in the NG group and no change among control subjects. Two patients in the control group had more extensive asynergy toward the left ventricular apex and died at 25 and 55 hr, respectively, so that comparisons (multiple measures ANOVA) were done

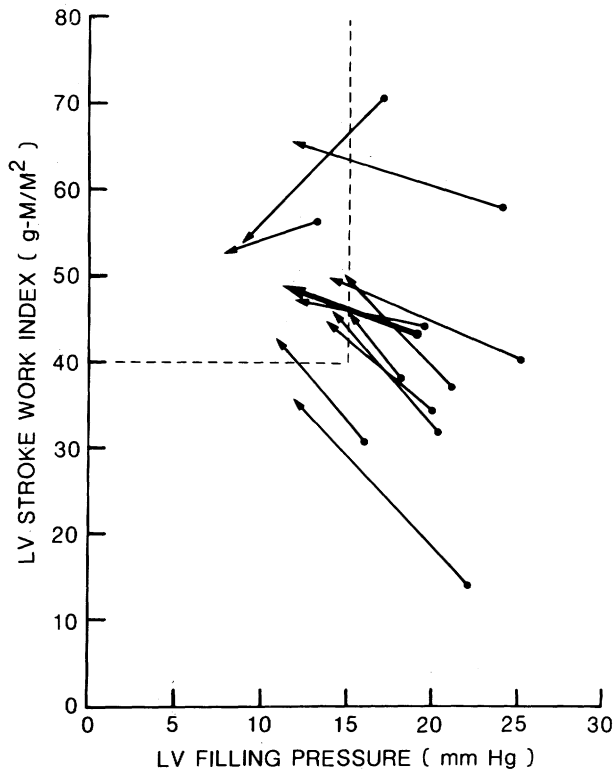


FIGURE 3. Effect of NG on left ventricular stroke work index and filling pressure. Points represent zero hour values and arrowheads represent 24 hr values. The heavy arrow indicates mean for the group. Dotted lines indicate the normal region with stroke work index ≥ 40 g-m/m² and filling pressure ≤ 15 mm Hg.

only for the nine patients who survived 10 days. By day 10 the extents of left ventricular asynergy at all four levels were less in the NG group than in the control group ($p < .025$), indicating a persistent effect of NG infusion.

The computed total extent of left ventricular asynergy, as percent surface area, for the two groups is summarized in table 3. Total left ventricular asynergy before the infusions was similar for control and NG groups (25% vs 25%; $p = \text{NS}$). There was no change among control subjects over the 10 days (25% vs 24%; $p = \text{NS}$). In contrast, with NG infusions, total left ventricular asynergy decreased by 50% at 1 hr (25% vs 12%; $p < .001$) and the decrease was sustained at 61% between 24 and 48 hr (25% vs 10%; $p < .001$). At 10 days the mean total left ventricular asynergy was 60% less than the pre-NG value (9% vs 25%; $p < .001$) and 62% less than the 10 day value in controls (9% vs 24%; $p < .001$).

The relation between the percent change in ΣST and the percent change in computed total left ventricular asynergy over the first hour is plotted for all patients in figure 5. There is a separation of NG and control groups, with the percent changes in ΣST and left ven-

tricular asynergy being greater with infusion of NG. Despite one patient in the control group who had a 41% spontaneous fall in ΣST by 1 hr, a significant direct correlation ($r = .65$; $p < .005$) was found. A similar relation was found between percent changes in ΣST and total left ventricular asynergy over the first 24 hr.

There was a close direct correlation ($r = .98$; $p < .001$) between CK infarct size and total left ventricular asynergy at 24 hr in controls (figure 6). The points for the NG group are shifted leftward and showed marked scatter with high values in four patients, so that the regression for the NG group was not significant ($y = 0.75x + 22.84$; $\text{SEE} = 15.21$, $r = .21$, $p = \text{NS}$).

Complications. During the 10 day study period, no significant complications developed during NG infusion or after NG was discontinued. However, one NG-treated patient died of ventricular fibrillation on day 12. Four hours before death in this patient, acute infarct expansion¹⁸ was suspected on the basis of chest pain without ECG changes, left ventricular failure, and regional increase in left ventricular diameter and circumferential extent of left ventricular asynergy (at midpapillary and low papillary levels) on 2D-echo. Six patients among controls developed complications: two patients developed cardiogenic shock and died on days 2 and 3, respectively, despite appropriate therapy; a third patient developed an acute ventricular septal defect on day 2 and underwent successful surgical repair on day 23; two other patients developed acute infarction expansion¹⁸ on day 6, while a sixth patient had left ventricular failure without evidence of expansion. Between the second and tenth days, two patients in the NG group received furosemide and digoxin, while seven patients in the control group received furosemide and two received digoxin. None of the patients showed evidence of infarct extension.³²

Discussion

The results of this study indicate that the beneficial effects of early intravenous NG therapy on left ventricular hemodynamics and ischemic injury were associated with improved left ventricular contractile function, a decrease in left ventricular asynergy on 2D-echo, and decreased CK infarct size. In 11 patients, NG therapy was begun at a mean interval of 6 hr after the onset of pain and was given for at least 24 hr, with a mean duration of 39 hr. The dose of NG was carefully regulated to achieve a 10% decrease in MAP in the first 30 min. As noted by Flaherty et al.,^{1,2} even with only a mean 7% fall in MAP, there was a 37% reduction in left ventricular filling pressure, suggesting that the predominant effect of NG at the low dose used in this

TABLE 2
Left ventricular asynergy on two-dimensional echocardiography^A

Timing	NG group (n = 11)				Control group (n = 11) ^B			
	M	C	MP	LP	M	C	MP	LP
Circumferential extent of LV asynergy (%)								
0 hr	21 ± 2 ^C (10–28)	23 ± 2 ^C (13–35)	24 ± 1 ^C (14–30)	29 ± 2 ^C (22–40)	18 ± 3 (0–38)	22 ± 2 (13–35)	26 ± 2 (16–41)	32 ± 4 (14–47)
1 hr	10 ± 1 (4–20)	12 ± 2 (0–20)	13 ± 2 (4–23)	14 ± 3 (0–32)	18 ± 3 (0–34)	23 ± 2 (8–37)	26 ± 2 (18–36)	33 ± 4 (15–40)
24 hr	7 ± 2 (0–17)	9 ± 1 (5–17)	11 ± 2 (0–23)	10 ± 2 (0–20)	19 ± 3 (0–32)	23 ± 3 (8–39)	25 ± 2 (17–36)	32 ± 3 (17–38)
48 hr	7 ± 2 (0–17)	10 ± 1 (4–19)	11 ± 2 (0–21)	10 ± 2 (0–19)	18 ± 3 (0–34)	22 ± 2 (10–36)	25 ± 2 (16–38)	33 ± 3 (17–42)
10 days	8 ± 2 (0–21)	10 ± 2 (0–21)	9 ± 2 (0–19)	10 ± 2 (0–20)	17 ± 3 (0–31)	22 ± 3 (12–39)	22 ± 2 (15–38)	33 ± 3 (19–45)
Angular extent θ of LV asynergy (degrees)								
0 hr	72 ± 8 ^C (10–117)	75 ± 7 ^C (18–105)	78 ± 5 ^C (39–98)	90 ± 6 ^C (57–126)	64 ± 12 (0–137)	75 ± 7 (56–119)	79 ± 7 (46–128)	104 ± 12 (37–151)
1 hr	36 ± 5 (18–72)	36 ± 6 (0–72)	37 ± 3 (23–64)	42 ± 10 (0–87)	64 ± 12 (0–125)	76 ± 7 (31–134)	78 ± 7 (57–110)	101 ± 12 (45–148)
24 hr	23 ± 5 (0–53)	32 ± 5 (16–64)	34 ± 5 (0–64)	31 ± 5 (0–56)	69 ± 11 (0–129)	76 ± 8 (34–134)	76 ± 6 (54–114)	104 ± 8 (52–146)
48 hr	22 ± 5 (0–56)	32 ± 5 (10–72)	33 ± 5 (0–69)	31 ± 5 (0–54)	64 ± 11 (0–121)	74 ± 8 (41–137)	76 ± 5 (47–129)	100 ± 9 (54–142)
10 days	27 ± 7 (0–67)	33 ± 6 (0–79)	30 ± 7 (0–84)	30 ± 5 (0–56)	60 ± 11 (0–120)	73 ± 9 (43–138)	68 ± 9 (44–134)	107 ± 10 (64–148)

C = chordal level; LP = low papillary level; M = mitral level; MP = midpapillary level; LV = left ventricular.

^AValues expressed as mean ± SEM; ranges are in parentheses.

^BTwo patients from the control group died at 28 and 55 hr, respectively.

^Cp < .001, significance of difference between pretreatment and posttreatment values by multiple measures ANOVA.

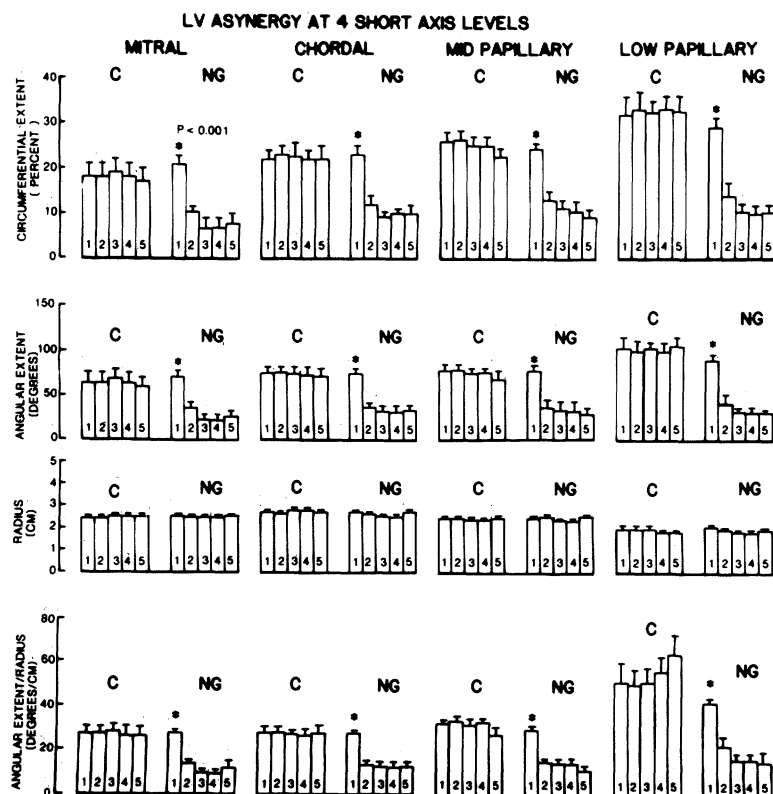


FIGURE 4. Effect of NG on circumferential and angular extents of left ventricular asynergy and radii at the four 2D-echo levels from base to apex. Mean ± SEM values at five time intervals (1 = 0 hr, 2 = 1 hr, 3 = 24 hr, 4 = 48 hr, 5 = 10 days) are shown for NG and control (C) groups. *p < .001 by multiple measures ANOVA. NG produced a marked and persistent decrease in circumferential and angular extents of left ventricular asynergy (two upper panels), no significant change in radii (third panel), and a significant and persistent decrease in angular extent of left ventricular asynergy normalized to corresponding radii of the sections (fourth panel).

TABLE 3

Computed total left ventricular asynergy (% surface area)^A

Timing	NG group (n = 11)	Control group (n = 11) ^B
0 hr	25 ± 1 (17–31) ^C	25 ± 2 (17–39) ^C
1 hr	12 ± 2 (4–21)	25 ± 2 (17–37)
24 hr	10 ± 1 (3–19)	25 ± 2 (18–38)
48 hr	10 ± 1 (2–21)	24 ± 2 (16–38)
10 days	9 ± 2 (0–19)	24 ± 2 (16–36)

^AValues expressed as mean ± SEM; ranges are in parentheses.^BANOVA on nine patients surviving 10 days.^Cp < .001, significance of difference between pretreatment and post-treatment values by multiple measures ANOVA.

study (mean 29 $\mu\text{g}/\text{min}$) is an increase in venous capacitance with venous pooling. With the decrease in left ventricular filling pressure to normal limits, stroke work index was initially maintained and subsequently increased by 16% toward the normal range, suggesting improved left ventricular contractile function as noted by Flaherty et al.^{1,2} Left ventricular work was also initially maintained and subsequently increased by 21%. Precordial ΣST decreased by 67% over the first 24 hr of NG infusion. Flaherty et al.² found a 26% decrease in ΣST with 1 to 3 hr NG infusions in similar doses given within 8.3 hr of the onset of pain to 15 patients. CK infarct size was 41% smaller in our NG patients compared with control subjects. Bussman et al.¹¹ found that a similar dose of NG, given for 48 hr to nine patients within 4.5 hr of the onset of pain, reduced CK infarct size by 30%, whereas CK-MB infarct size was 38% smaller compared with that in controls. We did not quantify CK-MB activity in all our patients.

In this study, left ventricular asynergy was decreased by NG at all four short-axis levels, from base to apex, compared with controls. By 24 hr of NG infusion the computed total left ventricular asynergy was 60% less than the 24 hr value in controls. More important, at 10 days or 7 to 9 days after NG therapy was terminated, the computed total left ventricular asynergy for the NG group was 64% less than the pretreatment value in that group and 67% less than the 10 day value in controls. Thus the decrease in left ventricular asynergy with NG persisted after NG therapy was stopped. Although there were fewer complications in our NG group compared with controls, the differences were not statistically significant, probably because of the small number of patients studied.

We restricted our measurement of asynergy to akinesis and/or dyskinesis because detection of hypokinesis on 2D-echo is not only difficult, but reliable criteria for its detection are lacking.²⁰ In experiments with dogs, Lieberman et al.²¹ found that systolic thickening

provided better separation of histologically normal and infarcted areas than did endocardial motion alone. They also found that the transmural extent of infarction was 1% to 20% in areas with decreased systolic thickening and 21% to 100% in areas with systolic thinning. In addition, systolic thickening was reduced at infarct margins, averaging 38% of that in normal zones. Since our asynergic segments showed no inward endocardial motion and no systolic thickening, we might have excluded areas with less than 20% infarction. The extent of left ventricular asynergy did not change significantly among controls by 24 hr, 48 hr, or 10 days. The computed total left ventricular asynergy by 24 hr in the 11 control patients correlated with CK infarct size. A similar correlation ($r = .87$) was found between computed total left ventricular asynergy from 2D-echo and CK-MB by Visser et al.,¹⁴ although they included hypokinesis in their calculation of asynergic area. In both our study and that of Visser et al.,¹⁴ a positive intercept (on extrapolation) was found on the left ventricular asynergy axis, suggesting that left ventricular asynergy overestimates infarct size. This overestimation might be caused by abnormal contraction found in normal myocardium adjacent to infarct zones.^{20, 21} Nevertheless, left ventricular asynergy was decreased by NG in our 11 patients. Previous echocardiographic studies in dogs have demonstrated the beneficial effects of NG on wall thickening³³ and asynergy.¹⁹ In our NG group there was a leftward displacement of the relation between total left ventricular asynergy and CK infarct size. High values for the CK infarct sizes in four patients resulted in a poor correlation with total left ventricular asynergy and suggested the possibility that NG infusion might have altered CK kinetics, with

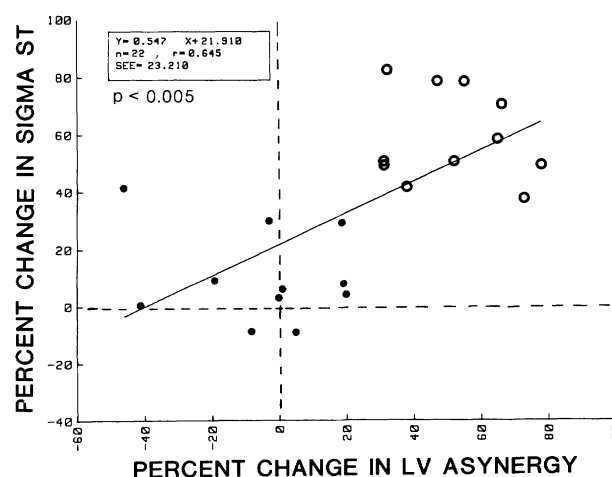


FIGURE 5. Percent changes in ΣST and computed total left ventricular asynergy over the first hour were greatest in patients receiving NG (open circles) than in control subjects (closed circles).

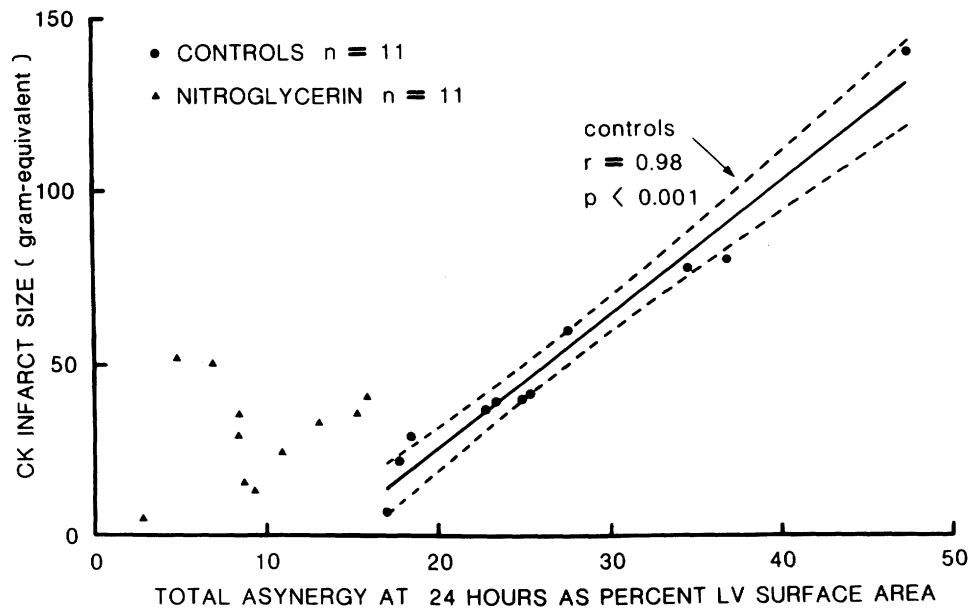


FIGURE 6. Effect of NG on the relation between CK infarct size and computed total left ventricular asynergy. A close direct relation is seen in control subjects. Dotted lines indicate 95% confidence limits. With NG the relation is shifted leftward with wider scatter in CK infarct sizes.

more rapid CK washout. The change in precordial Σ ST, a measure of directional change in ischemic injury,²⁵ by 24 hr also correlated with the change in computed total left ventricular asynergy in the NG-treated patients.

Several mechanisms might explain the improvement in left ventricular function and left ventricular asynergy by intravenous NG during acute infarction in man. NG might have improved the balance between myocardial oxygen supply and demand. Since NG-induced dilation of peripheral veins³⁴ leads to decreased venous return and left ventricular filling pressure, decreased venous return might be expected to decrease end-diastolic volume and wall tension by virtue of the La Place relation, thereby decreasing myocardial oxygen consumption.³⁵ Moreover, the decrease in MAP caused by dilation of peripheral arteries might further decrease wall tension and improve left ventricular function.³⁶ In this study, the prolonged low-dose infusion of NG produced a marked fall in left ventricular filling pressure with a small fall in MAP and peripheral resistance index. Although the radii of the short-axis left ventricular sections and computed diastolic volumes were less with NG, the differences were not statistically significant. However, even the slightly smaller end-diastolic volume might have contributed to the leftward shift to another Starling curve with improved left ventricular function. Since left ventricular asynergy decreased significantly and paralleled decreases in ischemic injury and CK infarct size, one might infer improved left ventricular compliance and

contractile function. Low doses of intravenous NG have been shown to increase collateral blood flow to ischemic regions between 2 and 6 hr after coronary occlusion and decrease infarct size in conscious dogs.¹⁵ The increase in collateral flow might be caused by a decrease in subendocardial compression in diastole secondary to decreased left ventricular filling pressure, as well as by a direct dilation of collateral vessels by NG. Capurro *et al.*⁷ showed that when NG and methoxamine were given between 10 and 70 min after coronary occlusion to closed-chest, sedated dogs, the increase in collateral flow lasted for at least 5 hr, suggesting that once collaterals are opened by NG, they might stay open. However, a similar effect with intravenous NG infusion has not been demonstrated in man. Since low-dose NG is known to markedly decrease tone in large conduit vessels,³⁷ such an effect might also have increased flow in downstream vessels, including possible collaterals arising more distally. In patients with acute infarction, Flaherty *et al.*³ found a decrease in thallium perfusion defects with low-dose intravenous NG therapy. Thus it is possible that increased flow to ischemic regions might also have contributed to the decrease in Σ ST, CK infarct size, and left ventricular asynergy in our patients.

In conclusion, early intravenous NG therapy in 11 patients with transmural anterior AMI given in a low dose to reduce MAP by 7%, decreased the extent of left ventricular asynergy on 2D-echo by 60%. This effect of NG was associated with improved left ventricular hemodynamics, decreased precordial Σ ST, and

decreased CK infarct size. The decrease in left ventricular asynergy after early intravenous NG therapy persisted for at least 10 days. The findings with prolonged low-dose NG infusion in this preliminary study need to be verified in larger detailed clinical studies.

We thank Joanne Dutchak for typing the manuscript, Christine Wortman, B.Sc., for coding the data, Cheryl Trudell for technical assistance, and Robert Cahn, M.Sc., for computing and statistical analysis.

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