Effects of intravenous nitroglycerin on left ventricular function and ST segment changes in acute myocardial infarction

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It has been shown previously that 30-minute infusions of intravenous nitroglycerin in patients with acute myocardial infarction are able to lower left ventricular filling pressure and improve left ventricular function while lowering mean arterial pressure by only 7 mmHg (0.9 kPa). A decrease in ΣST in praecordial ST segment mapping studies during nitroglycerin infusion in patients with anterior infarction suggested a decrease in the extent of myocardial ischaemia. In the present study, 30 patients with acute myocardial infarction received 1- to 3-hour infusions of intravenous nitroglycerin at infusion rates sufficient to lower mean arterial pressure by an average of 22 mmHg (2.9 kPa). An improvement in ventricular function was noted in that subgroup of patients with the most severe left ventricular dysfunction. All patients with anterior myocardial infarction underwent serial ST segment mapping and, irrespective of the presence or absence of left ventricular failure, showed a decrease in ΣST during nitroglycerin infusion (P<0.005). These findings suggest that infusion of nitroglycerin improves left ventricular function and/or alters left ventricular compliance in patients with left ventricular failure complicating myocardial infarction and furthermore decreases ΣST in all patients, irrespective of the presence or absence of left ventricular failure, suggesting that the extent of myocardial ischaemia is decreased.

Vasodilator therapy with infusions of nitroprusside (Franciosa et al., 1972; Chatterjee et al., 1973), phentolamine (Kelly et al., 1973; Gould et al., 1974), or trimetaphan (Shell and Sobel, 1974) has been shown in patients with myocardial impairment to improve left ventricular function by reduction of afterload. A decrease in arterial pressure and thus in coronary perfusion might however result in an increase in the extent of myocardial ischaemia. It is uncertain whether the beneficial effect of afterload reduction in decreasing oxygen demand outweighs the potentially harmful effect of decreasing perfusion pressure and oxygen supply.

Sublingual nitroglycerin has been shown to improve ventricular function transiently in patients with myocardial infarction (Gold, Leinbach, and Sanders, 1972; Delgado et al., 1975). However, a precipitous fall in arterial pressure can occur when the drug is administered by the sublingual route, and a resulting reflex tachycardia could increase infarct size (Delgado et al., 1975). We have recently shown that intravenous nitroglycerin can be administered safely to patients with acute myocardial infarction (Flaherty et al., 1975). Left ventricular filling pressure was lowered from an average of 22 mmHg to 12 mmHg (2.9 to 1.6 kPa), with an average of 7 mmHg (0.9 kPa) reduction in mean arterial pressure and without an associated increase in pulse rate. Serial praecordial ST segment mapping studies in those patients with anterior infarction suggested a decrease in the extent of the...
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*Case 11 died on day 17 of pulmonary embolus.
†Case 29 died on day 3 in cardiogenic shock with complete heart block.
A, anterior; I, inferior; T, transmural; NTM, non-transmural. Clinical class (Killip, 1968).

myocardial ischaemia during nitroglycerin infusion.

This study reports: (1) the infusion of intravenous nitroglycerin for longer durations and at higher infusion rates compared with those of the initial study, resulting in a mean decrease in mean arterial pressure of 22 mmHg (2-9 kPa) below control levels, and (2) the effects of this afterload reduction on left ventricular function and on the extent of myocardial ischaemia in 30 patients with acute myocardial infarction.

**Patients studied**

**Control untreated patients**

Seventeen patients with acute anterior transmural myocardial infarction underwent serial praecordial mapping studies for two hours during which nitroglycerin was not infused. Spontaneous changes in ST segments in these patients were compared with those changes recorded in patients receiving infusions of intravenous nitroglycerin. Of the 17 patients, 9 had Swan Ganz and arterial catheters in place during the serial mapping studies and subsequently received nitroglycerin after the two-hour control period. The remaining 8 control patients either refused nitroglycerin treatment, or entered the hospital at a time when intravenous nitroglycerin was unavailable or when another nitroglycerin study was in progress. Untreated patients were studied within 24 hours (mean 7.8±0.9 hours) of the onset of chest pain. Their mean age was 57.3 years. Four of these patients were in class I and 13 were in class II (Killip, 1968). These patients were given nasal oxygen, intravenous morphine for pain, and had electrocardiographic and cardiac enzyme evidence of acute myocardial infarction.

**Nitroglycerin-treated patients**

Thirty patients with acute myocardial infarction received intravenous infusions of nitroglycerin also within 24 hours (mean 8.3±0.9 hours) of the onset of chest pain (Table 1). Patients less than 75 years of age admitted to the coronary care unit with a high probability of an acute myocardial infarction by
history and/or acute electrocardiographic abnormalities were candidates for the study. Patients meeting the above criteria were admitted to the study with informed consent, if intravenous nitroglycerin and the research team were available. The mean age of the nitroglycerin-treated patients was 56.3 years. There were 29 patients with transmural infarctions (15 anterior and 14 inferior) and one with a nontransmural inferior infarction. Ten of these patients were in Killip class I, 18 were in class II, and 2 were in class III. Excluded from this study were patients in cardiogenic shock and patients not in clinical shock, but with mean arterial pressures less than 75 mmHg (10.0 kPa). All patients were given nasal oxygen and intravenous morphine for pain. All patients had electrocardiographic and cardiac enzyme evidence of acute infarction and all were in sinus rhythm.

The 30 patients were retrospectively divided into 3 groups according to their initial left ventricular filling pressure and stroke work index. This division allowed evaluation of nitroglycerin therapy in patients with normal, mildly impaired, and moderately impaired left ventricular function.

Group I 10 patients with LVFP ≤12 mmHg (1.6 kPa).
Group II 10 patients with LVFP >12 mmHg (1.6 kPa) and SWI ≥40 g m per m².
Group III 10 patients with LVFP >12 mmHg (1.6 kPa) and SWI <40 g m per m².

Methods

Praecordial mapping studies in untreated patients

A 48-lead praecordial ST segment map consisting of 6 rows of 8 leads was obtained in all 17 control patients with anterior transmural myocardial infarctions using an electrocardiographic standardization of 1 mV = 20 mm (Reid et al., 1974). Serial 16-lead recordings were made at 30-minute intervals for 2 hours. The 16 leads selected were the 2 rows of 8 leads which initially showed the maximum ST segment changes. The chest was marked for exact repositioning of the leads and the sum of the ST segment elevations in the 16 leads was defined as SST. If a given praecordial map showed both ST elevations and depressions, only the ST segment elevations were summed (Maroko et al., 1972). Each of the serial praecordial ST segment maps obtained in the untreated patients was coded with a random number by a technician other than the one who would be analysing the ST segment changes. The technician reading the maps, therefore, had no knowledge of the sequence in which the maps had been obtained.

Protocol for nitroglycerin infusion in treated patients

The protocol for infusion of intravenous nitroglycerin was as follows. Left ventricular filling pressure as reflected by mean pulmonary artery wedge pressure or the pulmonary artery diastolic pressure was measured with a No. 7 Swan Ganz thermomigration catheter (Model No. 93-118-7F) introduced by cutdown through an antecubital vein. Arterial pressure was measured with a short plastic catheter inserted percutaneously or by cutdown into the radial artery. Arterial and venous pressures were measured with Statham P23Db and P37b transducers, respectively, and recorded on a Brush Mark II-40 four-channel direct writing recorder. Cardiac output was determined by thermomigration technique (Ganz and Swan, 1972). The injectate consisted of 10 to 15 ml 5 per cent dextrose at room temperature. Each cardiac output reported is the mean of at least two serial measurements with a maximum allowed variance between individual measurements of 10 per cent. The reproducibility of these cardiac output measurements was previously reported (Flaherty et al., 1975).

Aqueous solutions of nitroglycerin (500 µg/30 ml) were prepared as previously described, refrigerated, protected from light, and used within 4 weeks of preparation (Flaherty et al., 1975). Significant loss of biological activity has been noted with storage greater than 4 weeks.

The infusion of nitroglycerin was begun at 10 µg/min using a Harvard constant infusion pump. The rate of administration was increased stepwise at 3- to 5-minute intervals until the mean arterial pressure fell approximately 20 mmHg (2.7 kPa) below the control level. The study was designed so that the infusion was slowed or temporarily discontinued if arterial pressure fell to less than 50 mmHg (6.7 kPa) diastolic or if the heart rate rose by more than 20 beats/minute or fell to less than 50 beats/minute. A decrease in infusion rate was necessary only during the initial dose finding period in 12 of the 30 patients. The infusion rate was then maintained at the final level for a period of 1 to 3 hours. The average final infusion rate of nitroglycerin was 57.3 µg/min (range 10-199 µg/min). In 5 patients mean arterial pressure could not be lowered by more than 11 mmHg (1.5 kPa) despite increasing the infusion rate of nitroglycerin to 199 µg/min. However, mean arterial pressure did increase by 16 to 34 mmHg (2.1 to 4.5 kPa) after termination of the nitroglycerin infusion, suggesting that baseline arterial pressure was increasing during the infusion period in these 5 patients.

Haemodynamic values including arterial pressure,
hour before 48-lead map, 16-lead recordings were made one stroke work index when the total group of 30 transmural myocardial infarctions, but not on those subsequent each performed were at the starting cardiac output, heart rate, and left ventricular filling pressure were measured on two occasions at least 10 minutes apart during the control period before starting the nitroglycerin infusion. These measurements were then repeated at 15-minute intervals throughout the infusion period. From these measurements derived values were obtained as follows:

*Stroke work index (SWI):*

\[
\text{SWI} (\text{g m per m}^2) = \frac{\text{SVI} \times (\text{MSP} - \text{LVFP}) \times 1.36}{100}
\]

SVI = stroke volume index
MSP = mean systolic arterial pressure
LVFP = left ventricular filling pressure

*Pressure-time per minute index (PTM):*

\[
\text{PTM} (\text{mmHg per min}) = \text{MSP} \times \text{ET} \times \text{HR}
\]

HR = heart rate, ET = systolic ejection time, measured from the radial artery pressure record.

*Peripheral resistance index (PRI):*

\[
\text{PRI} (\text{mmHg min/l per m}^2) = \frac{\text{MAP} \times \text{CI}}{100}
\]

MAP = mean arterial pressure, CI = cardiac index.

Serial praecordial ST segment mapping studies were performed on those 15 patients with anterior transmural myocardial infarctions, but not on those 15 patients with inferior infarction. After an initial 48-lead map, 16-lead recordings were made one hour before starting nitroglycerin infusion and then at 15 to 30-minute intervals simultaneously with each subsequent haemodynamic measurement. \(\Sigma ST\) was computed as previously described for the control patients.

In the same ‘blind’ reading procedure described for ST segment maps in the untreated group was employed for the praecordial ST maps obtained in the treated group. The technician reading the maps could not, therefore, differentiate maps obtained during the 2-hour control period from those obtained during nitroglycerin infusion. In 12 of the 15 patients the initial control ST segment map was obtained with all haemodynamic monitoring equipment and catheters in place. In the remaining 3 patients the lines were in the process of being placed at the time that the first control map was recorded.

**Results**

**Praecordial mapping studies in untreated patients**

The results of the two hours of control praecordial mapping studies in 17 patients with anterior transmural myocardial infarctions not receiving nitroglycerin therapy are presented in Table 2. There were no significant changes in \(\Sigma ST\) noted during the 2-hour period of observation.

**Haemodynamic and praecordial mapping studies in nitroglycerin treated patients**

The haemodynamic effects of intravenous nitroglycerin in the total group of 30 patients are summarized in Fig. 1. The haemodynamic measurements and derived values for each of the 30 patients, divided into the three haemodynamic subgroups, are presented in Table 3. All data in Table 3 and in the text are expressed as the mean ± one standard error of the mean.

Mean arterial pressure was lowered from a mean of 108.3±3.9 mmHg (14.4±0.5 kPa) during the control period to a mean of 86.7±3.1 mmHg (11.5±0.4 kPa) at the time of maximal afterload lowering effect of nitroglycerin (P < 0.001) (Fig. 1). The left ventricular filling pressure decreased from a mean of 16.7±1.4 mmHg (2.2±0.2 kPa) during the control period to 8.1±0.8 mmHg (1.1±0.1 kPa) at the time of maximal arterial pressure lowering (P < 0.001). Heart rate in the total group of 30 patients did not change significantly during nitroglycerin infusion. In only 7 of the 30 patients did the heart rate increase during nitroglycerin. In those 7 patients heart rate increases of only 2 to 10 beats/minute were noted. Cardiac index decreased 8.8 per cent (P < 0.05). There was no significant change in stroke work index when the total group of 30 patients was taken as a whole. Pressure-time per minute index fell 24.7 per cent (P < 0.001), and peripheral resistance index fell 11.3 per cent (P < 0.001).
The haemodynamic effects of intravenous nitroglycerin reported in Table 3 and Fig. 1 were measured at the time of maximal mean arterial pressure lowering. Similar results are obtained when the haemodynamic effects in the total group of 30 patients are examined at the end of the 1- to 3-hour infusion. Mean arterial pressure was then 93.7±3.4 mmHg (12.5±0.4 kPa), left ventricular filling pressure 10.6±0.9 mmHg (1.4±0.1 kPa), heart rate 81.8±3.0 beats/min, cardiac index 2.09±0.09 litre/min per m², and stroke work index was 35.3±1.9 g m per m².

When the effects of nitroglycerin infusion were examined in each haemodynamic subgroup, based on the patients' initial left ventricular function, the following differences were apparent (Table 3):
(1) Mean heart rate decreased 8 beats/min in group III (P < 0.05) and did not change significantly in groups I and II.

(2) Left ventricular filling pressure (LVFP) decreased 5-7 mmHg (0-8 kPa) in group I (P < 0.001), primarily reflecting the lower initial LVFP of 9-6 mmHg (1-3 kPa). The average decrease in LVFP was 9-9 mmHg (1-3 kPa) (P < 0.001) in group II and 10-2 mmHg (1-5 kPa) (P < 0.001) in group III; initial LVFPs were 18-5 and 22-1 mmHg (2-4 and 2-9 kPa), respectively.

(3) Mean arterial pressure was lowered 24-1 mmHg (3-3 kPa) in group I (P < 0.001), 23-8 mmHg (3-2 kPa) in group II (P < 0.001), and 17-1 mmHg (2-3 kPa) in group III (P < 0.001). There were no significant differences in blood pressure responses to nitroglycerin between the three groups by unpaired Student's t test.

(4) Cardiac index did not change significantly in either group II or III but decreased 0-33 l/min per m² in group I (P < 0.005).

FIG. 1 Effect of nitroglycerin infusion on haemodynamic variables (30 patients) and ΣST (15 patients). HR=heart rate, CI=cardiac index, SWI=stroke work index, MAP=mean arterial pressure, LVFP=left ventricular filling pressure, ΣST=sum of ST segment changes in 16 leads (means ± standard error of mean). Control—average of two sets of measurements made before starting infusion, TNG=measurements made at maximum afterload lowering effect of nitroglycerin infusion. P values of 0-05 or less are indicated, as calculated by paired Student's t test.
(5) Stroke volume index did not change significantly in any of the three groups.

(6) Stroke work index, which was lowest initially (26.5 g m per m²) in group III, remained unchanged (26.1 g m per m²) during nitroglycerin infusion while both groups I and II showed significant decreases (P < 0.005 and P < 0.02, respectively). Comparison of subgroup changes in stroke work index by unpaired Student’s t test revealed that the response of group III patients was significantly different from that of groups I and II (P < 0.02 and P < 0.05, respectively).

(7) Pressure-time per minute index decreased significantly in all three groups (P < 0.01, P < 0.001, and P < 0.001 for group I, II, and III, respectively).

(8) While peripheral resistance index (PRI) decreased significantly in the total group of treated patients (P < 0.001), the PRI decrease was significant only in group III (P < 0.01).

In Fig. 2 is shown graphically the haemodynamic response to nitroglycerin infusion of an average patient in each of these three haemodynamic groups. The patients in groups I and II responded with a decrease in left ventricular filling pressure and a decrease in stroke work index, while the patients in group III responded with a fall in filling pressure at the same level of stroke work. Comparison of changes in stroke volume index allows separation of changes in pressure and heart rate from changes in contractility. While changes in stroke volume index did not reach statistical significance, group I and II patients did show small decreases in stroke volume, in contrast to patients in group III who showed a small increase.

The results of the serial praecordial mapping studies in the patients receiving nitroglycerin infusion are presented in Table 4 and Fig. 1. All of the 15 nitroglycerin treated patients undergoing serial praecordial mapping studies showed a decrease in ∆ST during infusion of nitroglycerin. The mean ∆ST for the group decreased from 66.2 ± 11.7 mm to 52.1 ± 9.6 mm at the time of maximum afterload lowering effect (P < 0.005), and to 49.0 ± 9.8 mm at the end of the infusion period (P < 0.005). This value of ∆ST at the end of the infusion was not significantly different from ∆ST at the time of maximum afterload lowering effect and remained significantly lower than control (P < 0.005). There was no significant change in ∆ST in the one-hour period before starting the infusion.

**Discussion**

In our previously reported study of intravenous nitroglycerin therapy in patients with acute myocardial infarction, we showed that raised left ventricular filling pressure could be safely lowered into the normal range, with an average decrease in mean arterial pressure of only 7 mmHg (0.9 kPa) (Fla...
herty et al., 1975). Thus, at the infusion rates used in the previous study (average 37 μg/min), it seemed that the venodilator action of nitroglycerin was greater than the arterial or arteriolar dilator action. With the higher infusion rates of nitroglycerin used in the present study (average 57 μg/min) a 22 mmHg (2.9 kPa) lowering of mean arterial pressure was associated with a decrease in left ventricular filling pressure comparable with that noted in the previous study. With these higher infusion rates further arterial dilator action was apparent. The extent of myocardial ischaemia, as assessed by precordial ST mapping studies, decreased in all 15 patients with anterior myocardial infarctions in the present study despite the greater degree of arterial pressure lowering.

Because of the larger number of patients in the present study, it was possible to examine the effect of nitroglycerin therapy on left ventricular function in 3 subgroups of patients, divided according to their initial haemodynamic state. Patients with normal or only mildly impaired left ventricular function showed no improvement in ventricular performance with vasodilator therapy; a decrease in stroke work index being associated with a decrease in left ventricular filling pressure. In contrast, patients with the most severely impaired left ventricular function as indicated by both raised left ventricular filling pressures and reduced stroke work indices (<40 g m per m²), showed an improvement in ventricular function; in this group of patients a decrease in left ventricular filling pressure was accompanied by a maintenance of left ventricular stroke work. Since a decrease in left ventricular filling pressure is associated with a decrease in venous return, maintenance of stroke work can be interpreted as showing an improvement in left ventricular contractility.

Thus, patients with the most depressed left ventricular function (group III) received the greatest haemodynamic benefit from nitroglycerin therapy. Patients with normal or only mildly depressed left ventricular function (groups I and II), presumably not in need of an improvement in ventricular performance, nevertheless showed a reduction in ΣST. In all the groups of patients the decreased oxygen demand indicated by the fall in pressure-time per minute index may move the myocardial oxygen supply-demand imbalance somewhat nearer equilibrium, and might in this way explain the observed reduction in extent of myocardial ischaemia. Confirmation of a reduction in the extent of ischaemia by ST segment mapping studies is important since in animal studies hypotension induced by haemorrhage has been shown to result in an increase in the extent of myocardial ischaemia when assessed by ST segment mapping (Smith et al., 1973).

The exact mechanism or mechanisms by which intravenous nitroglycerin reduces myocardial ischaemia despite a reduction in systemic arterial and therefore coronary perfusion pressure remains uncertain. The decrease in left ventricular filling pressure noted in the present study is probably a result of peripheral venous dilatation (Mason and Braunwald, 1965). The resulting decrease in venous return would result in a decrease in left ventricular end diastolic volume and intramyocardial wall tension and thus a decrease in myocardial oxygen consumption (Williams, Glick, and Braunwald, 1965). The decrease in mean arterial pressure, caused by peripheral arterial dilatation, would be expected to decrease myocardial wall tension further and also to result in an improvement in left ventricular function (Tsakiris et al., 1968). The improvement in ΣST, might, therefore, be explained best by the reduction of both end diastolic volume and systolic pressure, with the resultant additive reduction in left ventricular wall tension, a primary determinant of oxygen consumption.

Nitroglycerin might also result in a redistribution of coronary blood flow to more ischaemic subendocardial regions as was suggested by the animal studies of Becker, Fortuin, and Pitt (1971). Smith et al. (1973) have furthermore shown in dogs with experimental myocardial infarction that when phenylephrine or methoxamine is added to nitroglycerin in a dose sufficient to restore arterial pressure to control levels, the beneficial effects of nitroglycerin on ΣST persisted or were in fact enhanced, suggesting a direct effect of nitroglycerin on the coronary circulation, possibly by enhancing collateral flow.

The mechanism by which intravenous nitroglycerin improves left ventricular function is also uncertain. The response of patients with severe left ventricular failure suggests an improvement in left ventricular contractility with a leftward shift to another Starling curve, while the response of those patients with normal or only mildly depressed left ventricular function suggests a leftward shift down the same Starling curve. These latter two groups of patients are probably showing a decrease in left ventricular preload resulting from peripheral venous pooling, though in the absence of a measure of left ventricular volume one could not with certainty exclude changes in left ventricular compliance. The haemodynamic response of patients to nitroglycerin therapy could also be interpreted as showing an increase in left ventricular compliance; a reduction in stiffness could at least in part explain the reductions of left ventricular filling pressures noted.
The haemodynamic effects of nitroglycerin on patients with left ventricular failure complicating acute myocardial infarction appear to differ when the drug is administered by the sublingual rather than the intravenous route (Williams, Amsterdam, and Mason, 1975). In a group of patients with left ventricular failure, comparable to the patients in group III in the present study, peripheral resistance did not decrease after sublingual administration of nitroglycerin. The authors concluded that the decrease in arterial pressure noted with nitroglycerin was secondary to the decrease in cardiac output noted and not the result of a fall in peripheral resistance. While in the present study no statistically significant change in peripheral resistance was noted when nitroglycerin was administered by the intravenous route to patients with normal left ventricular function, peripheral resistance did decrease significantly in group III patients with moderately severe left ventricular failure. Furthermore, in this same group of patients intravenous nitroglycerin produced a significant decrease in heart rate while sublingual nitroglycerin did not. The route of administration of nitroglycerin appears, therefore, to be an important determinant of at least the peripheral vascular effects when this drug is administered to patients with left ventricular failure in the setting of acute myocardial infarction.

From the present study, it is not possible to comment on whether or not there is a long-term beneficial effect of nitroglycerin therapy administered during the acute phase of a myocardial infarction. Longer infusions of nitroglycerin, and therefore more prolonged reduction in the extent of myocardial ischaemia, might potentially preserve ischaemic myocardium. Assessment of the effect of nitroglycerin therapy on infarct size will await development of new techniques for the noninvasive assessment of the extent of ischaemic damage.

In summary, intravenous nitroglycerin was administered safely with continuous haemodynamic monitoring to patients with acute myocardial infarction. Infusion of nitroglycerin improved left ventricular function and/or altered left ventricular compliance in those patients with more severe left ventricular failure. Infusion of nitroglycerin also resulted in a reduction in left ventricular failure and/or altered left ventricular compliance in those patients with more severe left ventricular failure. Infusion of nitroglycerin also resulted in a reduction in left ventricular failure and preload on the extent of myocardial ischaemia is beneficial.

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Effects of intravenous nitroglycerin on left ventricular function and ST segment changes in acute myocardial infarction.

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