Reduction of infarct size in patients with inferior infarction with intravenous glyceryl trinitrate

A randomised study

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SUMMARY Glyceryl trinitrate was previously said to be contraindicated in patients with acute myocardial infarction. Its intravenous administration during acute infarction, however, was associated with a beneficial effect as determined by ST segment mapping. Most recently in a selected group of patients with acute infarction and abnormal haemodynamics, intravenous glyceryl trinitrate was shown to reduce infarct size estimated by enzymes. The present study was performed to verify the safety of intravenous glyceryl trinitrate in patients with infarction under conventional clinical conditions without invasive monitoring and to determine its effect on infarct size in a prospective randomised trial involving 85 patients with infarction (43 treated and 42 control). Treated patients received glyceryl trinitrate within 10 hours of the onset of symptoms (mean 6:0 hours), and the dose was titrated to preset limits for changes in heart rate and blood pressure. In patients with inferior infarction, infarct size estimated by enzymes in the treated was only 12:2±1:8 versus 19:1±3:6 CK gram equivalents per metre squared in the placebo group. A similar but statistically insignificant trend was observed for subendocardial infarction but no difference was observed for anterior infarction. Ventricular arrhythmias determined from 24 hour tapes were more frequent in treated patients though this was not statistically significant. Lignocaine requirements in treated and control (1692±250 vs 1512±232 mg/24 h) were similar, as were the requirements for morphine (11:4±1:8 vs 12:2±2:2 mg/24 h). Results indicate that intravenous glyceryl trinitrate can be administered safely during evolving infarction without invasive monitoring and reduces infarct size in patients with inferior infarction.

Glyceryl trinitrate has been used for treatment of chest pain syndromes since 1879 and has since played a major role in the management of patients with angina pectoris. Because, however, sublingual glyceryl trinitrate sometimes induces hypotension and tachycardia in patients with evolving infarction it was thought to be contraindicated in this setting. In the 1970s intravenous glyceryl trinitrate was used instead, based in part on results of studies in experimental animals suggesting a beneficial effect on ischaemic myocardium. The use of an intravenous rather than a sublingual or oral preparation made it possible to titrate the dosage to avoid deleterious effects on systemic arterial blood pressure. Preliminary studies in 12 patients with acute myocardial infarction showed that glyceryl trinitrate infused for 30 minutes was associated with improved haemodynamics and more rapid regression of ST segment elevation. Subsequently, the same group observed similar results with administration of glyceryl trinitrate for up to three hours in 30 patients with acute infarction. In selected patients with acute myocardial infarction and abnormal haemodynamics, intravenous glyceryl trinitrate was recently found to improve haemodynamics and reduce infarct size estimated with enzymes. It now appears that afterload reduction in the setting of cardiac failure with or without infarction impairs cardiac perfusion. Reduction of afterload and preload with intravenous glyceryl trinitrate may also reduce infarct size in patients with
Reduction of infarct size in patients with inferior infarction with intravenous glyceryl trinitrate

Cardiac failure. The safety and efficacy of intravenous glyceryl trinitrate in patients with incomplete infarction, however, have not been assessed.

This study was performed with two major objectives. First, to verify the safety of administration of intravenous glyceryl trinitrate to patients with infarction under conventional, clinical conditions without resort to invasive monitoring; and second, to determine prospectively its effect on infarct size in a randomised trial, with prior categorisation of patients according to the site of infarction. The latter we felt might be important since the heart rate and haemodynamic responses to inferior infarction are different and concomitant involvement of the right ventricle is unique.

Subjects and methods

Patient population

Patients were studied prospectively and randomised to the placebo or treated group. The study involved 114 patients who were admitted to the Barnes Hospital coronary care unit with suspected acute myocardial infarction. Criteria for entry were: (1) chest pain suspected to be of cardiac origin; (2) electrocardiographic abnormalities suggesting acute myocardial ischaemia or infarction; (3) onset of symptoms within 12 hours of randomisation; (4) systolic blood pressure of 100 mmHg or greater and a heart rate of less than 120 beats/minutes. Patients with cardiogenic shock were excluded because of hypotension. Patients with severe cardiac failure or pronounced hypertension were excluded frequently on the basis of either tachycardia, hypotension, or the need for specific antihypertensive treatment. The diagnosis of acute myocardial infarction was confirmed by serial rises of plasma MB CK with subsequent decline to baseline. The site of infarction (inferior, anterior, indeterminant) was determined from the pre-randomisation electrocardiogram. Patients were categorised before randomisation according to the site of infarction which was classified as anterior if new Q waves or ST-T changes developed in two or more of the six precordial leads. It was classified as inferior if similar changes occurred in at least two of the three inferior limb leads. The development of new Q waves within 24 hours led to a classification of transmural infarction. ST-T changes without development of Q waves led to a classification of non-transmural infarction. Infarction was classified as indeterminant if a conduction defect was present such as left bundle-branch block which might mask the development of Q waves. Informed consent was obtained from all patients.

Preparation and administration of glyceryl trinitrate

Glyceryl trinitrate was prepared by the Barnes Hospital pharmacy and immediately refrigerated. Tablets (0.4 mg) were crushed, dissolved in 5% dextrose and water, and diluted to provide a concentration of 200 µg/ml. The solution was passed through a millipore filter before testing for verification of sterility and lack of pyrogenicity. To avoid impaired potency, a fresh solution was prepared every two weeks. After enrolment of a patient in the study, a randomisation envelope was selected which indicated the group to which the patients should be assigned, that is glyceryl trinitrate or placebo. Treatment with intravenous glyceryl trinitrate was initiated as soon as possible after admission of the patient to the coronary care unit at a dose of 10 µg/min and increased by 10 µg/min increments after 10 minute intervals until the desired end-point was achieved (see below). The glyceryl trinitrate solution was kept in a glass container and infused through plastic tubing as short as possible to minimise adsorption. The desired end-point consisted of either a 10% reduction in systolic blood pressure, attainment of a systolic blood pressure of 95 mmHg, or attainment of a maximum dose of 200 µg/min, whichever occurred first. The infusion was reduced if systolic arterial pressure decreased to 90 mmHg or less or if the heart rate increased by more than 20 beats/minute or slowed to less than 50 beats/minute. During initial titration heart rate and blood pressure were monitored every five minutes and hourly thereafter. Hypotension was treated by stopping the infusion, raising the legs, and administering fluids intravenously, and if concomitant bradycardia occurred, atropine was administered. Infusion of glyceryl trinitrate was continued for 24 hours and then tapered over four hours. During the first 24 hours digitalis, sublingual and oral nitrates, and propranolol were precluded.

Patients in the placebo group received a slow intravenous infusion of 5% dextrose and water and vital signs were monitored as in the treated group to determine the changes in blood pressure and heart rate. Otherwise, they were managed identically to patients in the treatment group. Morphine was used for relief of pain and dose recorded for each patient in an attempt to characterise potential responses of chest pain to intravenous glyceryl trinitrate. During the initial 24 hours no other analgesics were used.

Enzymic estimation of infarct size

Blood samples were obtained beginning at the time of admission from a peripheral vein through an indwelling heparin lock and every four hours for the first 96 hours for determination of total plasma creatine kinase (CK) and MB CK activity. Samples were collected in EGTA (5 mmol) and centrifuged to remove the cellular components. Mercaptoethanol (10 mmol) was added to the separated plasma to preserve enzyme
activity during storage of samples at -20° C. Total plasma CK activity was assayed spectrophotometrically. In our laboratory 100 IU/L is the upper limit of normal for total plasma CK activity. Plasma MB CK activity was assayed quantitatively with the glass bead batch adsorption technique which has a sensitivity of 2 IU/L. The upper limit of normal for MB CK is 12 IU/L. Samples were assayed with and without creatine phosphate, the specific substrate for creatine kinase, to detect false positive reactions caused by adenylate kinase. Infarct size was estimated from serial changes in plasma CK activity.

ANALYSIS OF VENTRICULAR ARRHYTHMIAS

Cardiac rhythm was recorded continuously for the first 24 hours on continuous 24 hour tape in both the placebo and glyceryl trinitrate treated groups. Tapes were analysed for ventricular arrhythmias with the use of the automated Argus/2H computer system developed at Washington University with editing by a cardiologist unaware of clinical data. Analysis included the number of ventricular extrasystoles and the number of episodes of complex ventricular arrhythmias (couplets and ventricular tachycardia) during the interval. The indications for lignocaine in the treatment of ventricular arrhythmias were the same in both treated and control groups, namely 10 ventricular extrasystoles or more occurring per minute for two consecutive minutes, or appearance of couplets, ventricular tachycardia, or an isolated ventricular extrasystole occurring on the T wave. None of the patients received prophylactic lignocaine. Lignocaine requirements were recorded for both control and treated patients.

STATISTICAL ANALYSIS

Statistical analysis was performed with an unpaired t test and confidence limits were determined. Changes in heart rate and blood pressure within each group were evaluated with a paired t test. Data are expressed as means ± standard error.

Results

PATIENT CHARACTERISTICS

Of the 114 patients enrolled in the study, myocardial infarction was confirmed based on MB CK values in 85 (75%). The remaining 29 patients, 15 in the placebo and 14 in the treated group, did not develop infarction and were excluded from the analysis of results. These patients, however, were followed throughout their hospital stay. Thus, of the 15 patients in the placebo group and of the 14 patients in the glyceryl trinitrate treated group, two patients subsequently experienced acute myocardial infarction later during the same period in hospital. None of these 29 patients died. The clinical characteristics of the treated and placebo populations with acute myocardial infarction are shown in Table 1. There were no significant differences in age, gender, locus of infarction, clinical class, prevalence of previous infarction, or interval from onset of symptoms to randomisation. The small number of patients in class III presumably was the result of the exclusion of patients with tachycardia, hypotension, or those needing specific antihypertensive therapy. As shown in Table 2, among placebo and glyceryl trinitrate treated patients stratified according to site of infarction, there were no statistical differences between the age, gender, interval from onset of symptoms to randomisation, clinical class, or prevalence of previous infarction. The mean interval from onset of symptoms to randomisation was 6.0 ± 0.4 hours in the treated group and 6.4 ± 0.5 hours in the placebo group.

HAEMODYNAMIC RESPONSES

The mean rate of administration of intravenous glyceryl trinitrate necessary to obtain a desired end-point was 57 ± 21 μg/min. It was achieved at an average of 1.74 ± 0.6 hours after onset of infusion. A 10% reduction in systolic blood pressure was the desired end-point reached in 80% of the treated patients, and an increase in heart rate of 20 beats/minute or more was the limiting factor in the remaining 20%. The maximum and minimum rates of administration were 150 and 10 μg/min. There were no significant differences in the total dose administered to patients with inferior, anterior, or subendocardial infarction. The mean systolic blood pressure on entry was 113 mmHg.
Reduction of infarct size in patients with inferior infarction with intravenous glyceryl trinitrate

Table 2 Clinical characteristics of control and treated patients stratified according to size of infarction

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inferior</td>
<td>Anterior</td>
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<tr>
<td>Age (y) (mean±SE)</td>
<td>61±2</td>
<td>65±2</td>
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<tr>
<td>Female</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Interval to randomisation (h) (mean±SE)</td>
<td>6±1±0-7</td>
<td>6-4±0-6</td>
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<tr>
<td>Clinical class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Previous infarction</td>
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Table 3A Haemodynamic responses (control patients)

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Blood pressure (mmHg)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Before randomisation</td>
<td>2 hours after randomisation</td>
</tr>
<tr>
<td>Inferior infarction</td>
<td>78±4-2</td>
<td>74±4-5</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>80±4-7</td>
<td>79±2-9</td>
</tr>
<tr>
<td>Subendocardial</td>
<td>84±6-0</td>
<td>81±6-2</td>
</tr>
</tbody>
</table>

Table 3B Haemodynamic responses (treated patients)

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before randomisation</td>
<td>2 hours after randomisation</td>
</tr>
<tr>
<td>Inferior infarction</td>
<td>82±3-5</td>
<td>80±3-4</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>78±3-7</td>
<td>82±5-0</td>
</tr>
<tr>
<td>Subendocardial</td>
<td>80±5-6</td>
<td>82±5-7</td>
</tr>
</tbody>
</table>

in treated and 134 mmHg in controls. Heart rate and blood pressure responses are shown in Table 3A and 3B, with changes in blood pressure for the whole group shown in Fig. 1. Since a 10% reduction in blood pressure was used as the end-point to determine the dose of glyceryl trinitrate in 80% of the patients, the mean blood pressure in the treated group after administration of glyceryl trinitrate was significantly less than initial blood pressure (p<0-05) (paired t test). In comparison with values in the placebo group this difference was not significant (unpaired t test). Initial diastolic blood pressure was similar in both groups and changed little over the first two hours. It then declined gradually and comparably in the two groups. Differences in absolute values or in trends in treated and placebo groups were not significant. Despite a slight increase in heart rate with administration of glyceryl trinitrate and a slight reduction in heart rate in controls, absolute values of heart rate and trends in the two groups were not significantly different.

Six patients developed significant hypotension dur-
Infarct Size

Infarct size index averaged 14.9±2.1 CK g equivalents per metre squared (CK g eq/m²) in control patients and 11.2±2.1 CK g eq/m² in glyceryl trinitrate treated patients (p=0.06) (Fig. 2). Analysis of patients stratified according to site of infarction showed a significant difference in infarct size among patients with inferior infarction. In controls in this group infarct size index was 19.1±3.6 in contrast to 12.2±1.8 in treated patients (Table 4). Thus, infarct size index in patients with inferior infarction was 36% less in treated compared with control patients (p<0.05). Infarct size in patients with subendocardial infarction showed a similar trend (6.4±2.6 CK g eq/m² in controls and 4.3±1.9 in treated patients) (Table 4) but the difference was not statistically significant. Infarct size index was nearly identical in treated and control patients with anterior infarction (Table 4).

Morphine Requirements

Morphine requirements during the first 24 hours were similar in treated and control patients as shown in Fig. 3, with a mean dose of 11.4±1.8 mg in treated and 12.2±2.2 mg in controls.

Table 4 Infarct size index in control and treated patients

<table>
<thead>
<tr>
<th>Infarct size index</th>
<th>Difference (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Treated</td>
<td></td>
</tr>
<tr>
<td>Overall population</td>
<td>14.9±2.1</td>
<td>11.2±1.4</td>
</tr>
<tr>
<td>Locus of infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>19.1±3.6</td>
<td>12.2±1.9</td>
</tr>
<tr>
<td>Subendocardial</td>
<td>6.4±2.6</td>
<td>4.3±1.9</td>
</tr>
<tr>
<td>Anterior</td>
<td>13.9±2.6</td>
<td>13.7±2.8</td>
</tr>
</tbody>
</table>
VENTRICULAR ARRHYTHMIAS

Patients in the treated group received an average of 1692±250 mg lignocaine during the initial 24 hours, similar to requirements in controls of 1512±232 mg (Fig. 4). Though ventricular extrasystoles were more frequent in the treated group than in the controls, the difference was not significant. Among treated and control patients with inferior infarction, the frequency of ventricular extrasystoles was 225±86 and 130±42 (p=NS). Corresponding values for patients with anterior infarction were 204±86 and 123±76 (p=NS), and for subendocardial infarction they were 153±75 ventricular extrasystoles/24 hours and 124±13 (p=NS) in control patients. Similar trends, again not significant, were noted for couplets and ventricular tachycardia. Treated patients had 5.07±1 episodes of couplets or ventricular tachycardia over the 24 hour period compared with 2.43±0.8 episodes per 24 hours in the control patients (p=NS).

Discussion

Among the 114 randomised patients, 85 were subsequently documented to have acute myocardial infarction, 43 of whom were treated with intravenous glyceryl trinitrate and 42 with placebo. Six treated patients developed transient hypotension, which was reversed rapidly with no overt clinical sequelae. Infarct size among patients with inferior infarction was significantly reduced by glyceryl trinitrate and was 36% less than infarct size in controls. Similar, but non-significant differences were observed in patients with subendocardial infarction.

Enzymatic estimates of infarct size in conventionally managed patients correlate closely with the severity of ventricular dysfunction,16-17 ventricular arrhythmias,18 early19-23 and long-term mortality,21-24 tomographic estimates,25 and morphological estimates of infarct size determined at necropsy in patients who succumb.23 In experimental animals, enzymatic estimates correlate closely with morphological estimates despite increased coronary flow induced by agents such as verapamil26 or nifedipine.27 Nevertheless, data in experimental animals28,29 suggest that the rate of release of CK into the circulation may be somewhat flow limited with sustained coronary occlusion. We have previously shown in dogs with experimental infarction that intravenous glyceryl trinitrate does not influence the CK disappearance rate or release ratio and that estimates of infarct size based on CK release correlated closely (r=0.85) with morphological estimates of infarct size.30 In this experimental preparation, however, infarction was produced by sustained coronary ligation. In patients with inferior infarction in whom we showed a beneficial effect in the present study, coronary flow may have been increased because of increased collateral flow or possibly relief of coronary arterial spasm. If, in fact, this were the case, greater washout of CK may have occurred as a result of increased flow. Thus, infarct size in treated patients would be overestimated, thereby masking, in part, beneficial effects. Accordingly, we may have underestimated the magnitude of salvage.

Glyceryl trinitrate is a potent agent for reversing cardiac ischaemia and relieving associated chest pain. The lack of apparent relief of chest pain (judging from morphine requirements) seen in patients with infarction who were given intravenous glyceryl trinitrate compared with those given placebo may be the result of the nature of pain associated with irreversible as opposed to reversible injury observed in patients with angina.

In contrast to results of a previous study31 suggesting that sublingual glyceryl trinitrate may reduce ventricular arrhythmias, the number of ventricular extrasystoles and complex arrhythmias was more frequent in treated patients in our study, though the differences were not statistically significant. Nevertheless, one should be aware of the potential for increased arrhythmias with administration of glyceryl trinitrate and take the necessary precautions. The increased ventricular extrasystolic activity might affect the magnitude and/or duration of altered haemodynamics and possible arrhythmogenicity caused by regional or subendocardial increase in coronary flow analogous to reperfusion-induced arrhythmias. The impact of glyceryl trinitrate on ventricular extrasystoles was independent of the effect on infarct size.

SIDE EFFECTS OF GLYCERYL TRINITRATE

The incidence of tachycardia as a factor limiting the dose of glyceryl trinitrate was low in our series (20%) in keeping with the results of others.79 In the previous clinical studies in which intravenous glyceryl trinitrate was administered to patients with acute myocardial infarction, tachycardia was uncommon. Thus, intravenous glyceryl trinitrate can be administered safely if blood pressure and heart rate are monitored frequently, and if dose is titrated according to preset limits for each.

COMPARISON OF RESULTS OF OTHER STUDIES

In the study by Bussman et al.9 intravenous glyceryl trinitrate was administered to 31 patients with acute infarction with raised left ventricular filling pressure, 18 of whom had anterior infarction. The end-point assessed was infarct size estimated from plasma CK. In keeping with our results, a beneficial effect on infarct size was observed. The population included patients with anterior and inferior infarction, but
results were not analysed separately for inferior infarction; thus it is not possible to determine if the beneficial effect of glyceryl trinitrate was restricted to patients with inferior infarction as in our study. Borer et al. showed that glyceryl trinitrate given alone is beneficial only in patients with cardiac failure. In a study by Flaherty et al., however, intravenous glyceryl trinitrate administered for 30 minutes to 12 patients with or without failure led to a greater decline in ST segment elevation than that seen in controls. Similar changes in ST segments were observed by the same group in a later study involving 15 patients with anterior infarction. Improvement in this variable, however, may not necessarily reflect an ultimate reduction in myocardial necrosis.

MECHANISM OF ACTION
The mechanism responsible for the observed beneficial effect of glyceryl trinitrate on infarct size in patients with inferior infarction cannot be ascertained from our study. Potential mechanisms include increases in coronary flow and decreases in myocardial oxygen requirements. Glyceryl trinitrate is a potent dilator of large conductance vessels but autoregulation in downstream arterioles which respond to the local tissue metabolic needs keeps coronary flow constant in normal animals.

Similar results have been observed in the conscious animal with sustained coronary occlusion (occlusion induced acutely). Thus, total transmural flow does not increase in normal or ischaemic zones. Redistribution of flow, however, with a relative or absolute increase in subendocardial flow in ischaemic areas is typical. Nevertheless, the magnitude of the increase expressed in absolute terms is modest and may not be adequate to protect ischaemic myocardium. Subendocardial flow in ischaemic areas averages approximately 0.1 to 0.15 ml/min per g, that is 10 to 15% of normal and, despite reported increases of up to 50%, the absolute flow is only 15 to 22% of normal.

Jugdutt et al. showed that glyceryl trinitrate led to a reduction in infarct size. In contrast, we found that though administration of glyceryl trinitrate for 12 hours to conscious dogs was associated with an increase in subendocardial flow of 35%, infarct size, determined morphologically, was similar in treated and control dogs. In this model, however, infarction was induced by sustained coronary occlusion and a beneficial effect of glyceryl trinitrate through relief of coronary spasm, which is a potential mechanism in man, was not applicable in this animal model. It is possible, though speculative, that glyceryl trinitrate may be more prone to relieve spasm in the right coronary artery than in the left. In a previous study, Oliva et al. showed that intracoronary administration of glyceryl trinitrate restored coronary patency in 66% of patients with inferior infarction compared with only 25% of patients with anterior infarction. Other investigators have also suggested that spasm is more frequent in the right than in the left coronary vasculature. It remains controversial, however, whether spasm is indeed more frequent in the right coronary artery. In contrast to the minimal effect of glyceryl trinitrate on overall transmural regional perfusion after acute coronary ligation in animals, glyceryl trinitrate elicits substantial increases in flow when collaterals have been induced previously. In patients, multiple coronary stenoses and collateral vessel development precede myocardial infarction frequently. Thus, glyceryl trinitrate may have the potential for augmenting collateral flow.

Decreased myocardial oxygen demand seems less likely to account for the beneficial effects observed, since reduction in blood pressure of even greater magnitude in experimental animals does not consistently decrease infarct size. Since inferior infarction, however, is often associated with some infarction of the right ventricle, the beneficial effects on overall (right plus left) enzymatically estimated infarct size may be mediated in part through favourable effects of glyceryl trinitrate on right ventricular loading conditions and oxygen requirements. Since this investigation did not attempt to evaluate the mechanism of action of glyceryl trinitrate, it is difficult to assess why patients with anterior infarction did not show similar beneficial effects. It should be emphasised, however, that the apparent lack of effect may be a function of small sample size. Alternatively, it is possible that the exclusion of patients with hypertension, tachycardia, hypotension, and cardiogenic shock differentially removed patients with more extensive damage and a greater potential for salvage from the subset of patients with anterior infarction. This is in part suggested by the smaller infarct size observed in patients with anterior infarction.

In conclusion, the results of the present study indicate that glyceryl trinitrate can be administered safely to patients with acute myocardial infarction without the use of invasive monitoring, provided that blood pressure and heart rate are monitored frequently and maintained within narrowly defined, preset limits. Our results indicate that glyceryl trinitrate reduces infarct size in patients with inferior infarction.

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Reduction of infarct size in patients with inferior infarction with intravenous glyceryl trinitrate


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