Reduction of CK and CK-MB Indexes of Infarct Size by Intravenous Nitroglycerin

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SUMMARY The effect of i.v. nitroglycerin administration on indexes of infarct size was examined in 31 patients with acute myocardial infarction. Serial creatine kinase (CK) and CK-MB isoenzyme determinations were used to calculate infarct size. Twenty-nine patients served as controls. Two subgroups of the study group were formed to evaluate differences between early and late intervention. In the first group (n = 22), continuous infusion of nitroglycerin over 48 hours was initiated within 8 hours (mean 4.5 hours) after the onset of symptoms. Peak CK activity for the nitroglycerin-treated patients (n = 9) in this subgroup was 544 U/1 vs 871 U/1 for the controls (n = 13) (p < 0.05). The rate of CK release was reduced from 79 to 33 U/1/hr (58%), as was total CK and CK-MB release (p < 0.02). Calculated infarct size was 69 gEq in the controls and 48 gEq in patients receiving nitroglycerin (CK-MB: 68 vs 43 gEq, p < 0.05). In the late intervention subgroup, nitroglycerin therapy was begun more than 8 hours (mean 12.8 hours) after the onset of symptoms. Here, too, use of the agent was associated with lower peak CK and CK-MB levels as well as a reduction in calculated infarct size (p < 0.05). Hemodynamic measurements, recorded every 4 hours, showed that nitroglycerin also reduced left ventricular filling pressure significantly and cardiac output increased. Blood pressure fell slightly, and systemic vascular resistance declined. The results indicate that i.v. nitroglycerin reduces CK and CK-MB release and thus calculated infarct size in both early and late intervention.

THE BENEFICIAL EFFECTS of i.v. nitroglycerin in acute myocardial infarction have been documented.1-4 Left ventricular filling pressure declines significantly, reducing preload. Cardiac output increases slightly and blood pressure decreases, reducing afterload. As a result, myocardial oxygen demand is diminished.5-8 Several authors have reported a reduction of myocardial ischemia5-7 in response to nitroglycerin, suggesting that the agent may minimize the ischemic border zone and reduce final infarct size.

Infarct size cannot be determined directly. However, measurement of the activity of creatine kinase (CK) and its CK-MB isoenzyme provides an indirect index of myocardial necrosis. In the present study, 60 patients were assigned randomly to a nitroglycerin or control group. In 21 cases, the study could be initiated within 8 hours after the onset of symptoms.

Methods

Sixty patients with clinical, electrocardiographic and enzymatic evidence of myocardial infarction were studied. Criteria included a history of prolonged chest pain, ST-segment elevation with the development of pathologic Q waves, and an increase in CK and CK-MB activity (CK > 50 U/l, CK-MB > 10 U/l). Hemodynamic variables and CK and CK-MB levels were recorded for at least 48 hours.

Hemodynamic Measurements

Upon admission, all patients had a Swan-Ganz thermodilution catheter inserted into the pulmonary artery via a brachial vein. Systolic, diastolic and mean pulmonary arterial and capillary wedge pressures, as well as right arterial pressure, were measured. Cardiac output was determined by both the thermodilution technique9 and the Fick principle (measurement of arteriovenous oxygen difference, hemoglobin and oxygen consumption). Blood pressure was taken with a cuff sphygmomanometer and stethoscope. Coronary perfusion pressure was calculated by subtracting diastolic pulmonary arterial pressure from mean arterial pressure. Values were obtained before nitroglycerin administration and thereafter at 4-hour intervals over 2 days.

Enzyme Activity Determinations

CK activity curves were recorded in all patients during the first 48 hours and longer in patients with persistently high values. In 50 patients, the CK isoenzyme CK-MB was also determined. For both enzyme calculations, blood was drawn hourly during the first 12 hours and subsequently at 3-hour intervals. A commercial test kit (Merck CK test10, 11) was used. Peak CK and CK-MB enzyme activity values (CK max and CK-MB max) were determined from individual activity curves. The beginning of enzyme activity increase is expressed as 0 hour. Thereafter, enzyme values were calculated every 6 hours to establish mean CK and CK-MB curves (fig. 3).

The following additional measurements were determined using a computer program developed by Shell et al.12, 13

(1) Individual appearance curves of CK and CK-MB, including the quantity of enzymes normally lost through excretion, were standardized to 0 hour.

(2) The rate of CK and CK-MB release was calculated as 90% of total appearance divided by the time to 90% appearance (U/l/hr14).

(3) The disappearance rate (kd) was derived from the end point of the CK and CK-MB curve by the best fit regression line.15

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(4) CK and CK-MB infarct size (gEq) were calculated, taking individual disappearance rates (observed infarct size) into account.

Patients

Patients with myocardial infarction were included in the study if either diastolic pulmonary arterial or pulmonary capillary low pressures was over 15 mm Hg. This was done so as not to risk hypotension in patients with low ventricular filling pressures. Filling pressure ranged between 12-15 mm Hg in 10 patients, who were included in the total patient population (n = 60). Patients were given i.v. nitroglycerin by continuous infusion (n = 31) or received no specific therapy (control, n = 29). Treated and untreated patients were comparable as to age, localization of infarction and hemodynamics on admission (table 1).

In the early intervention group, therapy was initiated within 8 hours and in late intervention more than 8 hours after the onset of myocardial infarction. The early intervention group included 13 control and nine nitroglycerin-treated patients and the late intervention group included 15 control and 18 nitroglycerin-treated patients. The 10 patients with left ventricular filling pressures of 12-15 mm Hg were not included in the latter group although, coincidentally, all but one received medication late. Their exclusion permitted the late intervention group to include only patients with elevated filling pressure.

In the early intervention group, infarction occurred 1.5-7.3 hours (mean 4.5 hours) before the onset of therapy and, in the late intervention group, 8.3-23.3 hours (mean 12.8 hours) before the onset of therapy. Time of infarction was ascertained from the patients' recollection of the onset of severe chest pain. Patients were comparable as to age, infarct localization, initial hemodynamic values, and additional medication received (table 1).

Nitroglycerin (5 mg/ml in undiluted alcohol, Pohl-Boskamp, Inc. or 5 mg/ml in 66% alcohol, Merck) was administered in dosages of 0.75, 1.5 or 3 mg/hr, and rarely 6 mg/hr, according to initial diastolic pulmonary arterial and systemic blood pressure values. No strict dose schedule was used. If the fall in diastolic pulmonary arterial pressure was insufficient, the dose of nitroglycerin was slightly increased. The mean dose in the early intervention group was 2.9 mg/hr in the first 12 hours, 2.8 or 2.2 mg/hr thereafter, and 3.2 mg/hr toward the end of the treatment. In the late intervention group, mean dosages were 2.7 mg/hr, 3.2 or 3.9 and 3.6 mg/hr, respectively.

The t test for unpaired data was used for all statistical analysis. The one-tailed error probability was indicated. Tables and statistical data in the text permitted the late intervention group to include only patients with elevated filling pressure.

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**Table 1. Clinical Data**

<table>
<thead>
<tr>
<th></th>
<th>Total patient population</th>
<th>Early intervention</th>
<th>Late intervention</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Nitroglycerin</td>
<td>Control</td>
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<tr>
<td>n</td>
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<td>13</td>
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<td>Age (years)</td>
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<td>59 ± 11</td>
<td>59 ± 11</td>
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<td>(hours)</td>
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<td>Heart rate (beats/min)</td>
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<td>88 ± 19</td>
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<td>Diastolic pulmonary</td>
<td>20 ± 5</td>
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<td>arterial (mm Hg)</td>
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<tr>
<td>Cardiac output</td>
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<td>5.1 ± 1.2</td>
<td>4.9 ± 1.6</td>
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<td>thermodilution (l/min)</td>
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<tr>
<td>Cardiac output</td>
<td>4.4 ± 1.6</td>
<td>4.6 ± 1.1</td>
<td>4.5 ± 2.2</td>
</tr>
<tr>
<td>(Fick) (l/min)</td>
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<tr>
<td>Mean arterial blood</td>
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<td>pressure (mm Hg)</td>
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<td>Lidocaine</td>
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<td>Morphine</td>
<td>19</td>
<td>12*</td>
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*p < 0.05 (χ² test).
The figures show the mean ± SEM. A p value < 0.05 was considered significant.

**Results**

**Total Patient Population (n = 60)**

Mean infarct size was significantly lower in the nitroglycerin group, 44 ± 22 gEq vs 57 ± 32 gEq in the control group (p < 0.05). The corresponding CK-MB values were 36 ± 28 gEq in the nitroglycerin group vs 59 ± 38 gEq in controls (p < 0.002) (fig. 1). Peak CK (496 vs 737 U/l) and CK-MB values (60 vs 87 U/l) and the rate of CK (33 vs 59 U/l/hr) and CK-MB release (4.4 vs 8.7 U/l/hr) were significantly lower in the nitroglycerin group (table 2).

**Early Intervention**

**CK and CK-MB Enzyme Activity Values**

Peak CK and CK-MB time-activity curves reached considerably lower individual and mean values in the nitroglycerin group compared with controls (fig. 2, table 2).

**CK and CK-MB Activity Curves**

Nitroglycerin was given a mean of 1.1 hours after the increase of CK values. Enzyme activities increased sharply in control patients, while in the nitroglycerin group the rate of increase was markedly slower and a lower plateau was reached. Thereafter, the slopes of both curves were parallel. A significant difference in enzyme activities between the groups was seen at 6 and 12 hours (fig. 3).

**CK and CK-MB Appearance Curves**

CK and CK-MB appearance curves of individual patients were flatter and reached a lower plateau in the treated group (fig. 4).
Plateau. Subsequently, had lower generally groups. CK-MB after the onset of symptoms.

**Rate of CK and CK-MB Release**

The rate of CK and CK-MB release \[ t \] (fig. 5, table 2) was significantly lower in the treated group.

**Disappearance Rate**

The CK disappearance rate did not differ between the groups. The CK-MB rate did (table 2).

**Infarct Size Calculated from CK and CK-MB**

Infarct size calculated from CK values was reduced in the treated patients (\( p < 0.10 \)) and declined further when CK-MB values (\( p < 0.05 \); table 2) were used.

**Late Intervention**

CK and CK-MB Enzyme Activity Values

Peak CK and CK-MB values of individual patients were generally lower in the nitroglycerin group, and mean values for this group were reduced significantly (fig. 6, table 2).

**CK and CK-MB Activity Curves**

Nitroglycerin therapy was initiated a mean of 6.3 hours after the onset of a CK increase. Before therapy,
CK and CK-MB increased comparably in both groups (figs. 7 and 8). Both peak value and plateau were lower in the treated group, however, and reached statistical significance between 18–36 hours.

**Figure 6.** Peak CK and CK-MB levels determined from individual enzyme activity curves in nitroglycerin-treated patients and in controls. Even in late intervention, lower peaks were reached in the treated group.

**Figure 7.** Mean CK activity curves in nitroglycerin-treated patients and in control subjects in late intervention group (> 8 hours). The onset of increased enzyme activity is expressed as 0 hour. In some patients who reached the hospital late, the onset was determined from patients' recollection of the appearance of symptoms (extrapolation to 0 hour). Myocardial infarction generally preceded CK increase by 6–9 hours. Nitroglycerin infusion was started 12.8 hours (mean) after infarction and 6.3 hours after CK increase. Between 0–12 hours, there was a sharp rise in both groups, but nitroglycerin-treated patients subsequently showed lower peaks than controls. Between 18–36 hours, nitroglycerin-treated patients had significantly lower values than controls.

**Figure 8.** Mean CK-MB activity curves in nitroglycerin-treated patients and control subjects in late intervention group (> 8 hours). Nitroglycerin infusion was started 4.3 hours (mean) after the CK-MB increase. See legend for figure 7.

**CK and CK-MB Appearance Curves**

CK and CK-MB appearance curves of individual patients reached a lower plateau in the treated group. The upstroke of the two curves was similar in both groups.

**Rate of CK and CK-MB Release**

The rate of CK and CK-MB release was generally lower in the nitroglycerin group. The differences were not significant (table 2).

**CK and CK-MB Infarct Size**

Infarct size was reduced in the treated group, especially when calculated from CK-MB values. It was apparent that even late administration of nitroglycerin reduced CK and CK-MB release, and thus, infarct size (table 2).

Both groups of patients received comparable additional medication. However, controls needed more frequent doses of furosemide, atropine, dopamine, lidocaine and morphine (table 1). No major effects on hemodynamic measurements and enzyme values were observed, as these drugs were given periodically and in small doses.

**Hemodynamic Changes**

No definite differences in hemodynamics were observed between the early and late intervention groups. Data for the combined groups are shown in figures 9 and 10. Complete measurements were possible in 28 control and 27 nitroglycerin-treated patients. Diastolic pulmonary arterial pressure decreased more in the nitroglycerin group than in controls (19 ± 4 to 11 ± 3 mm Hg vs 20 ± 5 to 17 ± 6 mm Hg). Cardiac output increased considerably in the nitroglycerin group (5.1 ± 1.2 to 5.5 ± 1.4 l/min), while no changes were observed in controls. Initial
values for cardiac output were comparable in both groups. Heart rate increased slightly more in nitroglycerin-treated patients (88 ± 19 to 93 ± 16 beats/min, vs 87 ± 16 to 89 ± 16 beats/min). However, the difference was not statistically significant (fig. 9).

Mean blood pressure decreased in both groups (control, 109 ± 15 to 97 ± 15 mm Hg; nitroglycerin, 108 ± 19 to 93 ± 13 mm Hg). The fall in blood pressure was more pronounced in nitroglycerin-treated patients (p < 0.01 at 24 hours).

Systemic vascular resistance decreased more markedly in the nitroglycerin group than in controls, although initial values for this group before therapy were slightly lower than for the controls. Coronary perfusion pressure was slightly higher in nitroglycerin-treated patients at the end of the study (48 hours, NS).

**Discussion**

The hemodynamic effects of nitroglycerin in acute myocardial infarction have been documented in many studies. Its beneficial effect in left ventricular failure is undisputed. Left ventricular filling pressure decreases, and cardiac output usually increases. The salutary hemodynamic effects of nitroglycerin are particularly evident in pulmonary edema, the most serious consequence of left ventricular failure. Administration of nitroglycerin for 2 days confirmed these observations. These hemodynamic changes are also accompanied by a reduction in myocardial ischemia, reflected in the return of the ST segment toward the baseline in epicardial and chest ECG leads.

Braunwald and Maroko’s concept of limiting necrosis by reducing ischemia has been confirmed in animal experiments showing a close correlation between the severity of ischemia and morphologically and enzymatically determined infarct size. It remains to be clarified whether a similar reduction in ischemia is associated with a reduction in necrosis under clinical conditions.

In the administration of nitroglycerin, dosage is an important factor. In animals, small doses reduced...
ischemia while fivefold dosages increase it considerably.2 In humans, a dose of 6 mg/hr (but not 3 mg/hr) significantly increased ischemia in patients who were not in heart failure, whereas no increase was seen in patients with left ventricular failure.3 21 23 Thus, higher doses of nitroglycerin are to be given with caution, especially in patients without left ventricular failure. Therefore the dose must be adjusted carefully to produce a positive response on ischemia; a rigid schedule designed to achieve, for example, a 20% reduction of arterial pressure appears to be inappropriate. We attempted to reduce left ventricular filling pressure by 10–30% and to avoid more than a 10% reduction of arterial pressure.

Determining infarct size from CK and CK-MB enzyme activity is still a matter of controversy.33 CK release from the myocardium may be flow-dependent and can be calculated either individually or in a standardized fashion.15 17 18 84 Nevertheless, most authors report close correlations between enzymatically and morphologically determined infarct sizes.16 80 33 Norris et al.33 recently reported a close correlation between angiographically verified akinetic areas and enzymatically determined infarct sizes.

By careful randomization of patients into treatment and control groups, both populations proved to be comparable as to age, time from onset of infarction, localization and enzyme levels at admission. Initial hemodynamic measurements, such as heart rate, left ventricular filling pressure, cardiac output and blood pressure, were similar, ruling out an accidental selection bias (table 1).

The need for medication with various cardioprotective drugs was greatly reduced in the treated patients. Anginal pain, left ventricular failure, and ventricular ectopic beats were less frequent with concomitantly lower requirements of morphine, furosemide and lidocaine, respectively (table 1). This appears to be related to the beneficial effect of nitroglycerin on myocardial ischemia and reduction of infarct size.

The combined results of the early and late intervention groups indicate that significant reductions in peak CK and CK-MB values result from nitroglycerin treatment. CK and CK-MB infarct size are reduced as well. Infarct size in terms of CK-MB gEq differs more from control than CK gEq. This is true for the combined as well as individual early and late intervention subgroups. In gEq, the CK-MB isoenzyme appears to demonstrate better the difference between the treatment and control groups. The discrepancy between CK and CK-MB suggests that the latter is a more specific indicator of myocardial necrosis. This inconsistency, however, cannot be explained with certainty, although it should be noted that peak CK and CK-MB values correspond more closely to one another.

One should attempt to avoid any delay in initiating therapy. The value of early intervention has been documented in a recent experimental study. In animal studies, Rasmussen et al.33 found a 50% reduction in necrosis when propranolol was given before the onset of myocardial infarction. When treatment was initiated 3 hours after infarction, the reduction was only 30%, and after 6 hours no reduction was observed. Similar findings were reported in clinical studies by Peter et al.,37 who found necrosis reduced when propranolol was given within the first 4 hours after infarction.

The reduction in infarct size as indicated by CK and CK-MB analysis was similar in the early and late intervention group. Even in late intervention, peak enzyme values were lower with nitroglycerin. When therapy was begun, CK and CK-MB values decreased considerably in the treated group, while elevated values in control patients remained unchanged. This response may be because in humans, but not in the experimental animal, myocardial infarction is an ongoing process. Bleifeld et al.80 produced evidence supporting this hypothesis. In some patients, slow onset of infarction and a prolonged course was evident from the CK activity curves. Clinical symptoms with infarction and extension of the primary infarct are possible in humans.87 Thus, there is some evidence of differences between experimentally induced and human myocardial infarction. The period during which infarct size may be influenced thus appears to be longer in humans than in experimental animals. Periodic hemodynamic monitoring revealed characteristic findings. Nitroglycerin primarily reduced left ventricular filling pressure, and thus, preload. Decreased diastolic wall tension increases endocardial perfusion. Blood pressure decreased, but not extensively. The reduction of systemic vascular resistance, left ventricular filling pressure, and infarct size may account for the increased cardiac output in treated patients. Furthermore, the drug seems to stabilize coronary perfusion pressure to some extent. The decrease of preload and afterload indicates decreased oxygen demand and may explain the beneficial effects on myocardial ischemia.

In summary, nitroglycerin significantly reduced serum CK and CK-MB enzyme activity. It is beneficial if given within 8 hours after onset of symptoms. However, even in the late intervention group, nitroglycerin reduced CK and CK-MB compared with control patients. The infarct size calculated from the serum enzymes was 30% lower in the treated patients. Preliminary results suggest that treatment with nitroglycerin reduces early mortality from myocardial infarction without increasing the risk of late mortality.

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