Comparison Between the Effects of Nitroprusside and Nitroglycerin on Ischemic Injury during Acute Myocardial Infarction

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SUMMARY This clinical and experimental investigation was designed to delineate and compare the relative effects of sodium nitroprusside (NP) and nitroglycerin (TNG) on electrocardiographic ischemic injury following acute myocardial infarction in patients and following coronary artery occlusion in dogs. Accordingly, in ten patients with anterior acute myocardial infarction and ST-segment elevation stable for 60 min, the effects of NP (average 95 μg/min i.v.) and TNG (average 0.48 mg sublingually) were studied. The hemodynamic actions of NP and TNG were directionally similar. However, NP increased average ST-segment elevation (ST) by 2.0 ± 0.2 mm, while TNG reduced ST by 1.4 ± 0.4 mm. In order to clarify this disparity, coronary artery occlusions were carried out in 14 open-chest dogs. During control, NP and TNG time periods, epicardial electrograms were recorded and regional myocardial blood flow (RMBF) determined by the microsphere technique. Nitroprusside increased ST-segment elevation from 4.6 ± 0.6 to 5.7 ± 0.6 mV (P < 0.05) and reduced RMBF from 35 ± 3 to 27 ± 2 ml/min/100 g (P < 0.01) in the ischemic zones. In contrast, TNG reduced ST-segment elevation from 4.9 ± 0.7 to 3.0 ± 0.7 mV (P < 0.05), while increasing RMBF to 43 ± 4 ml/min/100 g (P < 0.05) and the end-diastolic/epicardial ratio from 0.57 ± 0.06 to 0.69 ± 0.07 (P < 0.01). Although TNG and NP exhibit similar hemodynamic effects, TNG reduced electrocardiographic ischemic injury, at least in part, by increasing perfusion of the ischemic areas and redistributing it favorably, while NP increased electrocardiographic ischemic injury, at least in part, by reducing perfusion. Therefore, TNG seems preferable to NP for reducing preload and afterload in patients during the early phase of acute myocardial infarction.

CARDIAC FAILURE, as manifested by shock and/or pulmonary edema, is the major life-threatening complication of acute myocardial infarction in hospitalized patients. This is most likely the consequence of an extensive infarction,1,2 hence reduction in the extent of myocardial necrosis may constitute a major therapeutic goal. Since the extent of myocardial necrosis depends on the energy balance in the ischemic zone,3 the reduction of preload and afterload, which may reduce myocardial oxygen requirements, has been proposed as a means of minimizing the area of necrosis. The drugs most widely used to decrease preload and afterload are nitroglycerin4-9 and sodium nitroprusside,10-13 which improve the cardiac performance in patients with acute myocardial infarction. Although it is known that nitroglycerin may lessen myocardial injury,4,5,6,8,9 no information is available comparing the action of these two drugs on the severity and the extent of myocardial damage. Accordingly, this study was designed to evaluate the effects of nitroglycerin (TNG) and nitroprusside (NP) both on the mechanical performance of the heart and on the electrocardiographic ischemic injury in patients with acute myocardial infarction. The study further sought explanations for their contrasting actions on myocardial damage through a comparison of their effects on coronary collateral flow in dogs.

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Supported in part by contract N0l-HV-53000 under the Cardiac Diseases Branch, Division of Heart and Vascular Diseases, National Heart and Lung Institute, NIH, and USPHS grant GM-18674.

A preliminary report was presented during the 1976 American College of Cardiology meeting and published in abstract form (Am J Cardiol 37: 127, 1976).

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Received February 2, 1976; revision accepted June 7, 1976.

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venously, and ventilated by a Harvard respirator. A poly-
ethylene cannula was placed in the carotid artery and
arterial pressure monitored with a Statham pressure trans-
ducer (model P23Db). Lead aVF of the ECG was con-
tinuously recorded to monitor the heart rate (HR); left
thoracotomy was performed in the fifth intercostal space
and the heart suspended in a pericardial cradle. The left
anterior descending coronary artery or its apical branch
was occluded after dissection from the adjacent tissue.

In seven dogs, 15 min after occlusion (control period), NP
was infused intravenously at a constant rate of 1.5 μg/
kg/min for 15 min. This dose reduced mean AP (AP) by
20.0 ± 2.7 mm Hg from the control value of 110 ± 8 mm
Hg. Once the infusion of NP was discontinued (at 30 min
after occlusion) AP promptly returned to the control values
and was 109 ± 10 mm Hg 35 min after occlusion. At 35
minutes after occlusion, TNG, 300 μg i.v., was adminis-
tered as a bolus, followed by a constant infusion of 5 μg/kg/min
for 10 min, which similarly reduced the mean AP by
18.5 ± 2.8 mm Hg.

The other seven dogs served as control and received no
drugs, though all the measurements were made in the same
manner and at the same times as in the treated dogs.

In all 14 dogs epicardial electrograms, myocardial blood
flow, and the hemodynamic parameters were evaluated 15,
30, and 45 min after coronary artery occlusion.

Evaluation of Electrocardiographic Myocardial Injury

Epicardial unipolar electrograms were recorded from 13
to 16 sites on the anterior surface of the left ventricle as
previously described,5 in sites that were clearly recognizable
and selected both from within the area supplied by the
occluded branch as well as from portions of the left ventricle
remote from this area. The epicardial electrograms were
recorded prior to and 15, 30, 35, and 45 min after the occlu-
sion, and the average ST-segment elevation (ST) for each
map was obtained by dividing the sum of ST-segment
elevations in all sites by the number of sites. Both in patients
and in dogs ST-segment elevation was measured from the
T-P interval to the J point. Tracings with prolonged QRS
duration (i.e., 0.12 sec in patients and 0.06 sec in dogs) were
excluded.14

<table>
<thead>
<tr>
<th>TABLE 1. Observations in Patients</th>
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<td>Pt/Sex/Age</td>
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<td>Pt/Sex/Age</td>
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<tr>
<td>1/M/55</td>
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<td>2/M/70</td>
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<td>7/M/38</td>
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<td>8/M/40</td>
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<tr>
<td>9/M/47</td>
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<tr>
<td>10/M/55</td>
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<tr>
<td>Mean</td>
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Measurements of Regional Myocardial Blood Flow (RMBF)

Cardiac output and RMBF were measured 15, 30, and 45
min after coronary artery occlusion using carbonized micro-
spheres, size 7–10 μ (3M Company), labeled with gamma-
emitting radionuclides 141Ce, 45Sc, and 85Sr, according to
techniques previously described.15, 16 The microspheres,
suspended in a solution of sucrose, 50%, with two drops of
Twee 80 in order to avoid aggregation, were subjected to
ultrasound for 45 min before use. Fifteen, 30, and 45 min
after the occlusion, 4 ml containing 1.5 × 106 of one type of
labeled microsphere were injected over 15 sec through a
catheter placed in the left atrium; during the next 15 sec the
catheter was flushed with 5 ml saline. Simultaneously, a
reference sample was collected through a catheter placed in
the femoral artery using a 50 ml heparinized plastic syringe
placed in a Harvard withdrawal pump operating at a con-
stant rate of 15.3 ml/min. No changes in heart rate or
arterial pressure were observed after the injection.

At the end of the experiment, 45 min after the occlusion,
the heart was rapidly excised and seven or eight transmural
biopsies (weighing 2.59 ± 0.06 g) were obtained. They con-
tained all the ischemic tissue as well as normal portions from
the anterior and posterior ventricular walls. The biopsies
were then divided into endocardial and epicardial layers.
The radioactivity of the reference blood sample and of the
tissue specimens was counted in a Nuclear Chicago well
counter (model 4233). Calculations of RMBF and cardiac
output (CO) were made as described by Utley et al.17

Endocardial, epicardial, and transmural RMBF of the
normal and of the ischemic sites were compared separately,
considering each site where the flow was less than 50
ml/min/100 g to be ischemic. The comparison of the flows
was made between the values obtained after the control
period of 15 min and those collected after 30 and 45 min,
using the Student’s paired t-test.

Results

Effects of Sodium Nitroprusside and Nitroglycerin in Patients

The administration of NP in the ten patients studied
reduced the AP by 26 ± 3 mm Hg (from 105 ± 8 to 82 ± 5
FIGURE 1. Effects of nitroprusside (NP) on mean systemic arterial pressure (AP), pulmonary capillary wedge pressure (PCW), heart rate (HR), and ST-segment elevation (ST) in patients. All numbers are mean ± 1 standard error. *P < 0.05; **P < 0.01 (N = 10). Note the decrease in AP and PCW and the concomitant increase in ST-segment elevation compared to control values.

FIGURE 2. Effects of nitroprusside (NP) and nitroglycerin (NTG) on systemic mean arterial pressure (AP), pulmonary capillary wedge pressure (PCW), heart rate (HR), and average ST-segment elevation (ST) in patients. The dotted columns represent the control period before the administration of each drug, the striped columns the NP period, and the cross-hatched columns the NTG period. All numbers are mean ± 1 standard error. *P < 0.05; **P < 0.01 (N = 5). Note the directionally similar hemodynamic effects of both drugs when compared to control.
mm Hg) and PCW by 7 ± 1 mm Hg (from 19 ± 1 to 12 ± 1 mm Hg), and increased HR by 10 ± 3 beats/min (from 83 ± 5 to 93 ± 5 beats/min). In spite of these favorable hemodynamic effects on AP and PCW following the administration of the drug, the average ST-segment elevation rose by 2.0 ± 0.2 mm (from 4.6 ± 1.1 to 6.6 ± 1.2 mm) (table 1, fig. 1).

In the five patients who received both drugs, the administration of NP and TNG resulted in hemodynamic effects of similar direction (fig. 2). Nitroprusside reduced AP by 24 ± 5 mm Hg (from 105 ± 10 to 81 ± 8 mm Hg, \( P < 0.01 \)) and pulmonary capillary wedge pressure by 5 ± 1 mm Hg (from 19 ± 2 to 14 ± 3 mm Hg, \( P < 0.02 \)). Following the administration of TNG, AP fell similarly, by 14 ± 4 mm Hg (from 112 ± 9 to 98 ± 10 mm Hg, \( P < 0.05 \)) and the PCW by 9 ± 3 mm Hg (from 21 ± 4 to 12 ± 4 mm Hg, \( P < 0.01 \)). Nitroprusside increased heart rate by 12 ± 5 beats/min (from 88 ± 7 to 100 ± 9 [\( P < 0.05 \)]) while with TNG it did not change significantly (from 82 ± 10 to 83 ± 10 [NS]).

In contrast to their directional effects on arterial and wedge pressures, these drugs had different effects on ST-segment elevations. Average ST-segment elevation rose by 2.4 ± 0.3 mm (\( P < 0.01 \)) following NP administration. This elevation was transient and ST-segments returned to their pre-NP levels except in patient 8, in whom the elevation continued until treatment with TNG (figs. 2 and 3, table 1). Nitroglycerin reduced ST by 1.4 ± 0.4 mm (\( P < 0.02 \)) (figs. 2 and 3, table 1), demonstrating that unlike their hemodynamic effects the drugs had opposite effects on electrocardiographic ischemic injury, TNG was beneficial and NP deleterious.

Experimental Studies

In the seven treated dogs, the hemodynamic effects of the infusion of NP and TNG were similar (fig. 4, table 2). While heart rate was not changed by the drugs, AP fell in a comparable manner. Cardiac output was also reduced to a similar extent by both interventions. ST increased after administration of NP from the control value of 4.6 ± 0.6 mV, recorded 15 min after occlusion, to 5.7 ± 0.6 mV (\( P < 0.05 \)), recorded 30 min after occlusion. Infusion of TNG, from 35 to 45 min after occlusion, decreased ST-segment elevations to 3.0 ± 0.7 mV, a value significantly smaller than in the NP (\( P < 0.01 \)) or control periods (\( P < 0.05 \)) (fig. 5, table 2).

In the seven control dogs, AP, HR, CO, and ST, measured at 30 and 45 min after occlusion, did not change significantly from the values obtained at 15 min (table 2). Transmural blood flow in the nonischemic sites, measured 15 min after coronary occlusion, was 89.3 ± 4.2 ml/min/100 g and fell to 70.3 ± 3.7 ml/min/100 g (\( P < 0.01 \)) following 15 min of NP administration (fig. 6, left panel). In the ischemic sites transmural flow 15 min after the occlusion was 35.4 ± 2.7 ml/min/100 g; following 15 min of NP infusion flow had decreased to 27.4 ± 2.9 ml/min/100 g (\( P < 0.01 \)) (fig. 6, right panel). After the administration of TNG during the next treatment period, flow to the nonischemic sites was similar to that during the control period.
Table 2. Effects of Nitroprusside and Nitroglycerin on Hemodynamics and ST-Segment Elevation in Dogs

<table>
<thead>
<tr>
<th></th>
<th>First control (15 min)</th>
<th>Nitroprusside (30 min)</th>
<th>Second control (35 min)</th>
<th>Nitroglycerin (45 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>APr</td>
<td>CO</td>
<td>ST</td>
</tr>
<tr>
<td>Treated dogs (N = 7)</td>
<td>139.0</td>
<td>±9.0</td>
<td>2597</td>
<td>±510</td>
</tr>
<tr>
<td>Nontreated dogs (N = 7)</td>
<td>147.3</td>
<td>±10.8</td>
<td>2779</td>
<td>±541</td>
</tr>
</tbody>
</table>

All numbers are mean ± 1 standard error.
*Different from control, P < 0.05.
**Different from control, P < 0.01.
††Different from NF, P < 0.05.
†Different from NTG, P < 0.01.
*Time after coronary artery occlusion.
**Comparison made with the first control (15 min).
Abbreviations: HR = heart rate (beats/min); CO = cardiac output (ml/min); APr = mean arterial pressure (mm Hg); ST = mean ST-segment elevation (mV).

Table 3. Effects of Nitroprusside and Nitroglycerin on Regional Myocardial Blood Flow in Dogs

<table>
<thead>
<tr>
<th></th>
<th>Normal sites</th>
<th>Ischemic sites</th>
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<tbody>
<tr>
<td></td>
<td>Endocardial flow</td>
<td>Epicardial flow</td>
</tr>
<tr>
<td>Control (15 min)†‡</td>
<td>89.8 ± 4.3</td>
<td>84.7 ± 4.3</td>
</tr>
<tr>
<td>NF (30 min)</td>
<td>70.6 ± 4.4**</td>
<td>67.1 ± 3.4**</td>
</tr>
<tr>
<td>TNG (45 min)</td>
<td>88.5 ± 6.3†‡</td>
<td>82.0 ± 5.0†‡</td>
</tr>
</tbody>
</table>

All numbers are mean ± 1 standard error.
†Different from control, P < 0.05.
‡Different from control, P < 0.01.
§Different from control, P < 0.05.
††Different from control, P < 0.01.
†‡Different from control, P < 0.01.
*Time after coronary artery occlusion.
than ± sites it to continued flow and (table 3). Therefore, in the nonischemic sites NP reduced flow and TNG had no effect; in the ischemic sites NP continued to reduce RMBF while TNG increased it. In the seven control dogs, there were only small changes in the RMBF at 30 and 45 min: thus, the transmural flow in the nonischemic zone changed from 94.4 ± 3.7 to 92.4 ± 4.3 ml/min/100 g between 15 and 45 min, and in the ischemic area, from 24.5 ± 2.6 to 21.9 ± 2.6 ml/min/100 g.

The endo/epicardial flow ratio in the nonischemic sites did not change significantly (table 3). The endo/epicardial flow ratio in the ischemic zone was 0.57 ± 0.06 after the initial 15 control min. It did not change significantly after NP infusion and was 0.52 ± 0.07 (NS) at 30 min. However, after TNG it increased significantly to 0.69 ± 0.07 (P < 0.01 when compared either to the control or NP periods) (fig. 7, table 3), showing that TNG had a beneficial effect on flow redistribution. In the nontreated group the endo/epicardial ratio did not change significantly either in the nonischemic or in the ischemic zones.

Discussion

In recent years nitroprusside and nitroglycerin have been used to reduce preload and afterload during the treatment of cardiac failure following myocardial infarction. Their beneficial hemodynamic effects are clearly defined. Moreover, by decreasing the cardiac work and the oxygen consumption, it is possible that these drugs can decrease the extent of necrotic tissue; in an experimental model, Kjekshus has shown that reduction in preload decreases ischemic myocardial damage. However, since these drugs may have important additional pharmacologic effects, the present investigation was designed primarily to compare their actions in patients with acute myocardial infarction, paying special attention to their effects on ischemic injury. For this purpose we evaluated ST-segment elevations since it has been demonstrated that epichardial ST-segment elevations following acute coronary artery occlusion correlate with the amount of necrosis as reflected in histologic appearance and creatine phosphokinase depletion of myocardial biopsies obtained 24 hours after occlusion.

The system that was used in this study (i.e., single lead) is probably less sensitive than the multiple lead electrocardiogram in assessing the amplitude of electrocardiographic changes, and this latter technique should be preferred when evaluating drug-induced alterations. However, the single lead allowed us to observe directional changes and had the advantage of allowing continuous monitoring, which is important with fast-acting and potentially harmful drugs.

Despite similar hemodynamic effects, contrasting results were observed with the two drugs: TNG reduced electrocardiographic myocardial injury while NP increased it. It should be pointed out that in this study TNG was always administered after NP because of the long action of the latter. However, since NP increases the electrocardiographic injury, despite its favorable effects on the hemodynamic parameters, this sequence of administration of the two drugs did not introduce bias in favor of TNG. Moreover, our find-
ings with TNG are similar to those reported previously.  

The possibility cannot be excluded that the difference in fall of arterial pressure observed in patients with the two drugs (−26 vs −14 mm Hg for NP and TNG, respectively) may play a role in their different action on electrocardiographic ischemic injury and that the deleterious effects of NP were due to an excessive decrease in arterial pressure. However, patients in whom the mean arterial pressure was reduced by only 10 mm Hg (i.e., patients 5 and 9, table 1) also showed an increase in electrocardiographic injury. Moreover, hypertensive patients in whom NP reduced the pressure to normal limits (patients 1, 6 and 7, table 1) showed an increase in ST-segment elevation, suggesting therefore that the deleterious effects of NP on ischemic injury operate at both normal and hypertensive levels of arterial pressure.

The increase in heart rate that occurred after NP administration could be a factor in augmenting ST-segment elevation. However, since this increase in heart rate was rather moderate (average 10 beats/min) and since patients 2, 4, 7, and 10 (table 1) had changes of heart rate of only +2, −6, +5 and +5 beats/min, respectively, and yet increased their ST-segment elevations, it seems that the increase in heart rate was not an important factor.

The experimental part of the study is in accord with this interpretation since there was no disparity between NP and TNG with regard to heart rate and arterial pressure, while ST-segments changed in opposite directions. The opposite effects of the two drugs in patients stimulated us to evaluate the comparative effects of these two drugs on electrocardiographic ischemic injury in an animal model, in which the experimental conditions could be better standardized and myocardial blood flow could be studied simultaneously in an effort to explain the mechanism for the alterations in the extent of electrocardiographic myocardial damage.

The observations in open-chest dogs with coronary occlusion confirmed the electrocardiographic findings in patients and demonstrated that the magnitude of ischemic injury was increased by nitroprusside and reduced by nitroglycerin (figs. 2, 3, and 5). The measurements of regional myocardial blood flow explained, at least in part, the paradoxical action of the two drugs. Nitroprusside decreased myocardial flow to the ischemic tissue while TNG both augmented and redistributed it more favorably, increasing the endo/epicardial flow ratio.

The alterations in ST-segment elevations seem to be the result of changes in regional flow in the ischemic area since their simultaneous measurements showed that reductions in flow, as a consequence of NP administration, were accompanied by increases in ST-segment elevation, while an augmentation of flow, brought about by TNG, was accompanied by a reduction in ST-segment elevation (fig. 8).

The differences between the action of the two drugs on regional myocardial blood flow cannot be explained by their hemodynamic effects since both drugs had similar actions. Therefore, the different effects on the coronary bed of the drugs must account for the disparate effects on RMBF and electrocardiographic ischemic injury. It has been suggested that TNG acts in the coronary circulation primarily by dilating large conductance vessels while its action on the small resistance vessels is of a small magnitude and transitory. This effect on the conductance vessels may account for the increase and the redistribution of flow in the ischemic areas, in spite of the fall in perfusion pressure. In contrast, NP may decrease the collateral flow to the area of ischemia due to a reduction in perfusion pressure or due to its dilating action on the resistance vessels, resulting in a "coronary steal." The blood from the underperfused zone, already under maximal metabolic dilating stimulus, may be shunted to the adjacent nonischemic myocardium, where the vascular resistance can still be reduced by the drug, analogous to the original description of the coronary steal mechanism as applied to restriction of flow by stenosis.

This study indicates that both NP and TNG can produce important hemodynamic improvements in patients with acute myocardial infarction through a reduction of preload.
and afterload; however, the contrasting effects of these drugs on the severity of myocardial electrocardiographic ischemic injury, in both patients and dogs, and their effect on collateral blood flow in the latter, suggest that TNG may be preferable to NP when reductions of preload and afterload are desirable during the early phase of acute myocardial infarction.

Acknowledgments

The authors gratefully acknowledge the technical assistance of Ms. Alice Carmel and Mr. Daniel White, and the secretarial assistance of Ms. Merrilee Spence.

References


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Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction.
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Circulation. 1976;54:766-773
doi: 10.1161/01.CIR.54.5.766

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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