Coronary Artery Occlusion in the Conscious Dog

Effects of Alterations in Arterial Pressure Produced by Nitroglycerin, Hemorrhage, and Alpha-Adrenergic Agonists on the Degree of Myocardial Ischemia


SUMMARY

Nitroglycerin is generally believed to be contraindicated during acute myocardial infarction because the resultant decrease in coronary perfusion pressure and reflex tachycardia might extend the area of ischemia. To determine the effects of nitroglycerin and alterations in arterial pressure on the degree of myocardial ischemia, the left anterior descending coronary artery was occluded for repeated 15-min periods in closed-chest conscious dogs. The degree of myocardial ischemia was estimated by summing the S-T segment elevation (ΣST) recorded from 12 myocardial electrodes. Although heart rate increased and arterial pressure decreased, ΣST after 15 min of coronary occlusion was 14 ± 3 mv (P < 0.02) less during nitroglycerin therapy than during control occlusions. When the same alteration in arterial pressure was produced by venous hemorrhage, ΣST tended to be greater than during control occlusions (+14 ± 7 mv, NS); the difference between the nitroglycerin and hemorrhage interventions was highly significant (28 ± 9 mv, P < 0.02). ΣST was also less than control when phenylephrine was administered in doses sufficient to increase arterial pressure 25 mm Hg (-16 ± 3 mv, P < 0.005) and 50 mm Hg (-15 ± 2 mv, P < 0.001). When the decrease in arterial pressure and reflex tachycardia induced by nitroglycerin were reversed by simultaneous infusion of methoxamine, ΣST was greatly reduced from control (-50 ± 16 mv, P < 0.02) and was significantly less than that occurring during nitroglycerin alone (-25 ± 5 mv, P < 0.001). We conclude that nitroglycerin may be a useful agent during acute myocardial infarction, particularly when the fall in coronary perfusion pressure and increase in heart rate are prevented by the simultaneous administration of an alpha-adrenergic agonist.

Additional Indexing Words:
Hypotension Hypertension Phenylephrine Methoxamine

Although nitroglycerin is used routinely in the treatment of angina pectoris, this drug is traditionally believed to be contraindicated in the treatment of ischemic pain caused by acute myocardial infarction on the grounds that the nitroglycerin-induced decrease in arterial pressure and reflex increase in heart rate would extend the ischemic process. However, the interrelation of the various factors known to influence the balance between myocardial oxygen supply and oxygen demand is sufficiently complex to make an a priori assessment of the net effect of any particular drug or intervention on the degree of myocardial ischemia difficult. This is particularly true for an agent such as nitroglycerin with its potential capacity to alter afterload, preload, and myocardial blood flow.

The present study was designed (1) to define the effects of alterations in arterial pressure on the degree of myocardial ischemia, and (2) to study the effects of nitroglycerin on the ischemic process when administered alone and in combination with doses of an alpha-adrenergic agonist sufficient to abolish the nitroglycerin-induced decrease in systemic arterial pressure and reflex increase in heart rate.

Methods

Thirty-eight mongrel dogs weighing 15-24 kg were studied. Myocardial electrograms were recorded as...
unipolar leads (the right and left forelimb and left hindlimb leads each with a resistance of 5000 ohms serving as the indifferent electrode) using a multichannel direct-writing recorder, with a low-frequency response of 0.1 Hz, at a sensitivity of 5 mv/cm. Arterial pressure was monitored through a catheter (no. 5 Elecath) inserted percutaneously into a femoral artery and advanced until the tip was positioned in the central aorta. Venous pressure was measured through a large catheter inserted into a jugular vein with the tip positioned in the superior vena cava. Statham 23Db pressure transducers were used with zero reference at the midthorax level.

Following control recordings, the balloon was rapidly inflated to produce total occlusion of the coronary artery. Recordings were made after 5, 10, and 15 min of occlusion and the balloon was then rapidly deflated. Consecutive occlusions were separated by 45–60 min. All interventions were performed in random order.

The following study protocols were followed: (1) In seven dogs the effect of nitroglycerin on the degree of myocardial ischemia was studied without control of heart rate or arterial pressure. The dogs were positioned in the 30° head-up position; an intravenous bolus of 400 μg of nitroglycerin was followed by a continuous infusion of 200–400 μg/min. The LAD was occluded after the circulatory changes induced by nitroglycerin had stabilized. (2) Nitroglycerin was administered to seven dogs, as in group 1, but the heart rates during the control occlusion and the intervention were identical. This was achieved by atrial pacing during control occlusions at a rate which occurred or was anticipated following administration of nitroglycerin. Subsequently, these same dogs were restudied to determine the effect of venous hemorrhage sufficient to produce the same alteration in arterial pressure as that produced by the nitroglycerin. Heart rate during the control and postphlebotomy occlusions was held constant as above. (3) In nine dogs the effect of phenylephrine-induced increases in mean arterial pressure on the degree of myocardial ischemia was studied. Phenylephrine was administered intravenously at a rate sufficient to produce 25-mm Hg (nine experiments), 50-mm Hg (seven experiments), and 75-mm Hg (six experiments) increases in mean arterial pressure. The LAD was occluded after the circulatory changes induced by phenylephrine had stabilized. Heart rate was held constant by atrial pacing. In addition, in three dogs the effects of increasing mean arterial pressure by 25 mm Hg was assessed both at constant heart rate and when rate was allowed to fall reflexly. (4) The effect of the combination of nitroglycerin and an alpha-adrenergic agonist (methoxamine in nine dogs and phenylephrine in one) was studied. Methoxamine or phenylephrine was administered intravenously at a rate sufficient to abolish the fall in arterial pressure and increase in heart rate produced by the nitroglycerin (200–400 μg/min).

After stabilization of heart rate and arterial pressure, the LAD was occluded. (5) In six dogs coronary occlusion was maintained for 1 or 2 hours at which time nitroglycerin and methoxamine were administered for 15 min intervals and the effect on S-T segment elevation observed.

The conclusions reached in the present study are based on the assumption that the degree of ischemic injury produced during coronary occlusion is reflected by changes in the magnitude of S-T segment elevation. The evidence for this has been discussed previously and, although possible, it would appear unlikely that the alterations induced in the present study are solely related to direct effects of the interventions on the transmembrane action potential.

Statistical methods: Student's t test was used to compute the significance of paired data.

Results

Effects of Lowering Systemic Arterial Pressure

Nitroglycerin. Following injection of the bolus of nitroglycerin, there was an early decrease in aortic pressure and associated increase in heart rate. During infusion of the drug at steady-state conditions, mean arterial pressure was an average of 14 ± 1 mm Hg lower than control, and heart rate 20 ± 2 beats/min higher than control. The total S-T segment elevation in the 12 leads after 15 min of coronary occlusion during infusion of nitroglycerin averaged 72 mv; this value was 12 ± 2 mv (P < 0.005) less than that obtained during control occlusions at normal heart rate and blood pressure (fig. 1). When nitroglycerin was administered to produce an equivalent fall in arterial pressure but baseline heart rates were increased by atrial pacing

![Figure 1](image-url)  
**Figure 1**  
*Effect of nitroglycerin (TNG) on total S-T segment elevation during 15-min coronary artery occlusions.* (Left) Duration of occlusion in minutes is plotted on the abscissa, with total S-T segment elevation (2ST) in millivolts on the ordinate. The data points represent the means of the results in seven dogs. (Right) The results are replotted to better depict the spread of the data. Duration of occlusion is plotted on the abscissa while the difference in total S-T segment elevation (millivolts) between occlusions during nitroglycerin and control occlusions (interrupted line) is plotted on the ordinate. The vertical bars represent 2 SEM. Despite an increase in heart rate (HR) and decrease in mean arterial pressure (BP), occlusions during nitroglycerin resulted in significantly less 2ST than occurred during control occlusions.
so that identical rates were obtained during control and nitroglycerin studies, \( \Sigma ST \) averaged 14 ± 3 mv (\( P < 0.02 \)) less than during control occlusions.

**Hemorrhage.** There was no significant difference between the changes in heart rate or in systolic, diastolic, or mean aortic pressures produced by nitroglycerin and hemorrhage in the seven dogs studied. Similarly, in three dogs the left ventricular ejection time (LVET), diastolic time per minute, and central venous pressure were not significantly different between the two interventions. However, following hemorrhage \( \Sigma ST \) averaged 150 mv 15 min after coronary occlusion, a value \( 14 \pm 7 \) mv (ns) greater than control (fig. 2). The relative effects of nitroglycerin and hemorrhage are compared in figure 3. While hemorrhage tended to increase the S-T segment response to ischemia, nitroglycerin reduced it; the mean difference between the two interventions was highly significant (28 ± 9 mv, \( P < 0.02 \)).

**Effects of Raising Systemic Arterial Pressure**

**Phenylephrine.** When mean arterial pressure was increased by phenylephrine, heart rate slowed markedly. Even when this reflex bradycardia was prevented by atrial pacing, \( \Sigma ST \) elevation after 15 min of coronary occlusion was significantly less when mean arterial pressure was increased by either 25 or 50 mm Hg above that which was present during control occlusions (fig. 4). Thus, \( \Sigma ST \) elevation was \( 16 \pm 3 \) mv (\( P < 0.005 \)) less after a pressure increase of 25 mm Hg, and \( 15 \pm 2 \) mv (\( P < 0.001 \)) less after a 50-mm Hg increase. Although a 75-mm Hg increase in pressure also tended to reduce \( \Sigma ST \), the mean difference was not statistically different from control (11 ± 5 mv, ns). In three dogs (fig. 5) mean arterial pressure was increased 25 mm Hg without atrial pacing, resulting

**Figure 3**

Comparison of the effects of hemorrhage (Hem.) and nitroglycerin (TNG) on \( \Sigma ST \) during 15-min occlusions. Duration of occlusion is on the abscissa while on the ordinate the difference in S-T segment elevation between control occlusions (interrupted line) and occlusions following the interventions is plotted. The data points represent the mean value for seven dogs. Occlusions during nitroglycerin resulted in significantly less \( \Sigma S-T \) segment elevation than occlusions during hemorrhage.

**Figure 2**

Effect of hemorrhage (Hem.) on \( \Sigma ST \) during 15-min occlusions. Venous hemorrhage sufficient to produce the same alteration in mean arterial pressure (BP) as that produced by nitroglycerin increased \( \Sigma ST \) although the difference did not achieve statistical significance. (Left) Absolute values of \( \Sigma ST \) are plotted. (Right) The differences in \( \Sigma ST \) from control (interrupted line) are depicted.

**Figure 4**

Effect of phenylephrine-induced increases in mean arterial pressure (BP) on \( \Sigma ST \) during 15-min occlusions (heart rate constant). Both 25- and 50-mm Hg increases in BP resulted in significantly less \( \Sigma ST \) than occurred during control occlusions. (Left) Absolute values of \( \Sigma ST \) are plotted. (Right) Differences in \( \Sigma ST \) from control (interrupted line) are plotted.
Effect of phenylephrine-induced increase in mean arterial pressure on ΣST. The data points represent the mean of the results in three dogs. Although ΣST was less when BP was increased and heart rate held constant, the decrease in ΣST was much greater when the heart rate was permitted to slow reflexly. (Left) Absolute ΣST values are plotted. (Right) Differences in ΣST from control (interrupted line).

in a reflex decrease in mean heart of 51 beats/min. ΣST was then 29 ± 5 ms less than control (P < 0.05).

Effect of Nitroglycerin with Arterial Pressure Held Constant

Nitroglycerin plus Methoxamine. Table 1 contains the values for heart rate, systolic, diastolic, and mean arterial pressures, LVET, diastolic time per minute, and central venous pressures measured after 15 min of coronary occlusion under control conditions, during nitroglycerin infusion, and during nitroglycerin plus methoxamine. Although nitroglycerin alone caused significant changes in all variables except venous pressure and diastolic time per minute, there were no significant differences from control when methoxamine was administered with nitroglycerin. As in the previous groups of
dogs, nitroglycerin resulted in less ΣST after 15 min of ischemia than control (24 ± 10 ms, P < 0.05) despite an increase in heart rate of 20 ± 5 beats/min (P < 0.005) and a decrease in mean arterial pressure of 15 ± 2 mm Hg (P < 0.001).

When nitroglycerin and methoxamine were administered simultaneously, ΣST was greatly reduced (50 ± 16 ms, P < 0.02) from control occlusions. In several dogs, S-T segment elevation was almost absent during occlusions with the combination therapy, although each dog responded in the expected manner during control conditions. The decrease in ΣST produced by nitroglycerin plus methoxamine was considerably greater than that produced by nitroglycerin alone (25 ± 5 ms, P < 0.001) (fig. 6).

Figure 7 shows the ΣS-T segment response to administration of nitroglycerin plus methoxamine after 1 and 2 hours of coronary occlusion. Similar reductions in ΣST occurred at each time interval with the average reduction being 30 ± 6 ms (P < 0.005).

Nitroglycerin plus Phenylephrine. In one dog the effects of nitroglycerin plus phenylephrine on S-T elevation were compared to that produced by nitroglycerin alone. The results were similar to that seen with nitroglycerin plus methoxamine. After 15 min of coronary occlusion during control conditions ΣST was 135 ms, during nitroglycerin infusion 124 ms, while during nitroglycerin plus phenylephrine ΣST was only 106 ms.

Discussion

The results of the present investigation indicate that alterations in systemic arterial pressure importantly influence the degree of myocardial ischemic injury occurring during acute coronary artery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nitroglycerin</th>
<th>Control</th>
<th>Nitroglycerin plus methoxamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>125 ± 7</td>
<td>&lt;0.005</td>
<td>105 ± 7</td>
</tr>
<tr>
<td>Syst BP (mm Hg)</td>
<td>110 ± 3</td>
<td>&lt;0.001</td>
<td>128 ± 3</td>
</tr>
<tr>
<td>Diast BP (mm Hg)</td>
<td>84 ± 4</td>
<td>&lt;0.005</td>
<td>93 ± 3</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>94 ± 3</td>
<td>&lt;0.001</td>
<td>109 ± 3</td>
</tr>
<tr>
<td>VP (cm Hg)</td>
<td>3.6 ± 1</td>
<td>NS</td>
<td>3.6 ± 1</td>
</tr>
<tr>
<td>LVET (ms/ec)</td>
<td>160 ± 8</td>
<td>&lt;0.02</td>
<td>182 ± 7</td>
</tr>
<tr>
<td>Diast/min (sec)</td>
<td>41 ± 1</td>
<td>NS</td>
<td>41 ± 1</td>
</tr>
</tbody>
</table>

Abbreviations: BP = arterial pressure; VP = venous pressure; LVET = left ventricular ejection time; Diast/min = total diastolic time per minute; P₀ = probability value for paired comparison of nitroglycerin and control variables; P₁ = probability value for paired comparison of control and nitroglycerin plus methoxamine variables; P₂ = probability value for paired comparison of nitroglycerin and nitroglycerin plus methoxamine variables.
occlusion in the closed-chest conscious dog. The relation between arterial pressure and ischemic injury is not a simple one, however, and appears to depend not only on the directional change in blood pressure, but also on the specific type of intervention employed.

When arterial pressure was decreased by hemorrhage, the degree of myocardial ischemic injury occurring during acute coronary occlusion increased. The major factors contributing to this deleterious change undoubtedly were (1) the fall in coronary perfusion pressure, which probably led to a decrease in coronary collateral flow, and (2) a relative increase in myocardial oxygen consumption caused by the reflex increase in heart rate and, presumably, myocardial contractility. These changes favoring an increase in ischemic injury were apparently of sufficient magnitude to more than offset the potential beneficial effects on myocardial oxygen consumption accruing from the hemorrhage-induced decrease in afterload and ventricular volume.

Since hemorrhage-induced hypotension tended to augment the degree of myocardial ischemia, it was not surprising to find that an increase in systemic arterial pressure produced by phenylephrine had the opposite effect. Thus, increasing mean arterial pressure by 25 and 50 mm Hg resulted in a decrease in S-T segment elevation occurring during coronary occlusion, even when the beneficial contribution of the reflex slowing of heart rate was abolished by atrial pacing. The reduction in ischemic injury caused by phenylephrine probably can be attributed in large part to the increase in coronary perfusion pressure and to the baroreceptor-induced reflex withdrawal of sympathetic stimuli to the heart. These actions presumably more than counterbalanced the unfavorable effects accruing from the elevated systemic pressure, which would tend to increase myocardial oxygen consumption. It should also be pointed out that although the vasoconstrictor actions of phenylephrine could reduce coronary flow by increasing coronary vascular resistance, evidence exists suggesting that there is a paucity of alpha-adrenergic receptors in the coronary vascular bed. Thus, it is likely that phenylephrine exerts more potent vasoconstrictor actions on the systemic than on the coronary vasculature. Moreover, it is possible that any coronary vasoconstriction caused by phenylephrine would be exerted at a site distal to the takeoff of coronary collateral vessels.
because of the intense metabolic vasodilator stimulus present in ischemic areas, any constrictor activity that occurred might be more pronounced in the resistance vessels supplying normal myocardium, thereby producing a redistribution of coronary flow favoring the ischemic muscle.

While these findings demonstrate that alterations in arterial pressure can influence the degree of myocardial ischemia, as indicated above, the methods used to alter arterial pressure can in themselves profoundly influence the results. Thus, although nitroglycerin produced a reduction in arterial pressure similar to hemorrhage, this agent led to a decrease in S-T segment elevation occurring during coronary occlusion.

The mechanisms responsible for this unexpected effect are not clear. Although nitroglycerin is a potent dilator of normal coronary arteries,5, 6 it is commonly believed that the beneficial effect of this agent in patients with diseased coronary vessels is caused by its actions on the peripheral circulation, which lead to a reduction in myocardial oxygen demands.1, 4, 14 However, since the changes produced by nitroglycerin and hemorrhage on arterial pressure, heart rate, left ventricular ejection time, total diastolic time per minute, and central venous pressure were similar, the results of the present investigation suggest that the salutary effect of nitroglycerin on ischemic injury may at least be partly attributable to a direct action on the coronary vessels. Such an action is also suggested by the finding that when an alpha-receptor agonist (methoxamine or phenylephrine) is administered simultaneously with nitroglycerin in doses sufficient to abolish the nitrate-induced reduction in systolic pressure and increase in heart rate, further improvement occurs.

Despite this suggestive circumstantial evidence, our study was not specifically designed to determine how nitroglycerin reduces myocardial ischemia. We do not know with certainty whether nitroglycerin caused the same or a greater reduction in left ventricular volume than did hemorrhage; if a greater reduction occurred, this would have led to a greater diminution of myocardial wall stress and myocardial oxygen demands. Moreover, if the mean left ventricular diastolic pressure were reduced more by nitroglycerin than by hemorrhage, then any level of coronary perfusion pressure would be associated with a greater pressure gradient between the large epicardial and smaller myocardial and endocardial coronary vessels, an effect favoring increased coronary flow. Finally, hypotension caused by nitroglycerin, like that produced by hemorrhage, is known to provoke release of catecholamines from the adrenal medulla.15 It is possible, however, that a decrease in arterial pressure induced by vasodilatation is a less potent stimulus to the release of catecholamines than is the same degree of hypotension produced by hemorrhage, an intervention leading to vasoconstriction.

Although the model of acute myocardial infarction we employed is not entirely analogous to acute myocardial infarction in man, the data of the present study may be clinically relevant. For example, since patients developing cardiogenic shock have been found at necropsy to have large areas of infarcted muscle,16 there has been renewed interest in developing technics to limit the amount of tissue necrosis following acute coronary occlusion.17, 18 Our results suggest that nitroglycerin combined with an alpha-adrenergic agonist, the latter administered either to reverse any nitroglycerin-induced fall in coronary perfusion pressure or even to increase arterial pressure moderately, might diminish the amount of tissue death and thereby decrease the incidence of cardiogenic shock and perhaps the incidence of postinfarction cardiac failure. Moreover, since patients are rarely seen within minutes of the onset of acute coronary occlusion, it is of interest that in the present study when nitroglycerin and methoxamine were administered even after 1 and 2 hours of coronary occlusion there was still a prompt and impressive reduction in S-T segment elevation.

While the effects of these pharmacologic interventions on the degree of myocardial ischemia remain to be tested in man, several recent studies have shown that such vasodilators as nitroprusside19 and nitroglycerin20 can lead to improved hemodynamics when administered to patients with acute myocardial infarction. Although enhanced performance of the heart as a pump does not necessarily imply that ischemic injury is diminished (since salutary effects can result from improved function of the nonischemic myocardium), these results, in conjunction with those of the present investigation, suggest a wider role for vasoactive drugs in the therapy of patients with acute myocardial infarction.

References


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