Effects of Nitroglycerin and Nitroglycerin-Methoxamine During Acute Myocardial Ischemia in Dogs with Pre-existing Multivessel Coronary Occlusive Disease

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SUMMARY
Nitroglycerin (TNG) reduces ischemic injury during acute coronary occlusion in dogs with otherwise normal coronary arteries, but its effect in the presence of pre-existing multivessel coronary disease is unknown. We therefore examined the influence of TNG on acute ischemia in dogs with chronic multivessel coronary occlusions. The left anterior descending (LAD) coronary artery was acutely occluded by a balloon cuff in conscious dogs two weeks after placement of ameroid constrictors to produce gradual occlusion of the obtuse marginal and posterior descending coronary arteries. Adequacy of balloon and ameroid coronary occlusion and degree of collateralization were assessed by coronary angiography. Nitroglycerin decreased arterial pressure and increased heart rate. Myocardial ischemia, determined after LAD occlusion by summing ST-segment elevation (ΣST) from eight intramyocardial electrodes, lessened with TNG in those six dogs whose heart rate increased less than 50%, but increased in those four whose heart rate increased >50%.

When TNG-induced change in either heart rate or arterial pressure was prevented by adding methoxamine, ΣST was diminished even more (avg decrease 25%; P < 0.05). We conclude that, in the presence of pre-existing multivessel coronary occlusions, 1) TNG reduces ischemic injury during experimental acute coronary occlusion provided arterial pressure and heart rate responses are not excessive and 2) uniform improvement occurs when pressure and rate responses are abolished by an alpha-adrenergic agonist. Although results in animal studies must be extrapolated to the clinical situation with caution, these findings suggest that a similar pharmacologic approach might be applicable to the treatment of acute myocardial infarction in man, even in the presence of multivessel disease.

Additional Indexing Words:
Hypotension
Myocardial oxygen consumption
Coronary angiography
Ameroid constrictors
Methoxamine
Collateral circulation

SEVERAL INVESTIGATIONS in our laboratory have demonstrated that nitroglycerin is capable of diminishing the degree of ischemic injury occurring during experimental acute coronary occlusion. Reduction in ischemia produced by nitroglycerin was assessed by measuring differences in ST-segment elevation recorded from intramyocardial electrodes, as well as by determining changes in the magnitude of myocardial creatine phosphokinase depression and by gross anatomic examination of the left ventricle. Additional studies showed that nitroglycerin (its hypotensive and heart rate speeding effects prevented by simultaneous administration of methoxamine) reduces the incidence of ventricular fibrillation occurring during experimental acute coronary occlusion, suggesting that the drug's capacity to diminish ischemic injury is of functional importance.

In each of these studies the beneficial effects of nitroglycerin were demonstrated in a model of acute myocardial ischemia in which a coronary artery was acutely occluded in dogs with otherwise normal coronary arteries. Acute myocardial infarction in man, however, occurs most often in the presence of chronic multivessel coronary occlusive disease. The presence of well-developed coronary collateral vessels might significantly modify the ischemic response to nitroglycerin itself and to nitroglycerin-induced alterations in hemodynamics. For example, it is possible that, in the presence of multivessel disease,
nitroglycerin (and other vasodilators) might increase blood flow to myocardium supplied by normal coronary vessels at the expense of flow to myocardium supplied by diseased vessels ("coronary steal"). It was not certain, therefore, whether the decrease in ischemia and reduction in ventricular fibrillation found in our previous studies could be extrapolated to the situation in which multiple vessels were chronically occluded.

The present study was undertaken to determine the effects of nitroglycerin on electrocardiographic evidence of ischemia in an experimental model of acute myocardial infarction superimposed upon chronic coronary occlusive disease. Reversible acute occlusion of the left anterior descending (LAD) coronary artery was produced in closed-chest conscious dogs two weeks after gradual occlusion of circumflex branches had been initiated by placement of ameroid constrictors. In addition, we examined the relation between nitroglycerin-induced beneficial influence on ischemia and nitroglycerin-induced changes in blood pressure, heart rate, and left ventricular filling pressure in the animals with chronic coronary occlusion.

Methods

Preparatory Surgery

Approximately two weeks (13 ± 2 days) prior to study, ten mongrel dogs (16–35 kg) underwent left thoracotomy under sodium thiopental/halothane general anesthesia. An inflatable silicone balloon cuff was sutured around the LAD coronary artery three to four cm from its origin (fig. 1).

Ameroid constrictors5 of an appropriate diameter (0.7 to 1.5 mm) were placed around the obtuse marginal and posterior descending coronary arteries (or their largest branches) as near as possible to their origin from the left circumflex coronary artery. (In one animal, a diminutive, subepicardial posterior descending artery could not be dissected). The bare ends of eight teflon-coated electrode wires were implanted to a depth of 3–5 mm in the myocardium supplied by the LAD coronary artery and fixed in place by lead beads. In four of the animals, three similar electrodes were implanted into the inferior wall of the left ventricle, an area supplied by the vessels having ameroid constrictors. An implantable electromagnetic flow probe was placed over merliene mesh around the ascending aorta, one to two cm above the aortic valve. In some animals, a 1 mm heparin-filled polyethylene catheter was introduced into the left atrial appendage and fixed by purse string suture. All wires and catheters were brought through an intercostal space inferior to the incision and secured in a subcutaneous pouch.

A group of four dogs (angiographic controls) had a similar procedure but with placement only of the LAD balloon and myocardial electrodes.

Study Protocol

One hour prior to study, the animals were sedated with morphine sulfate 1 mg/kg i.m. and diazepam 1 mg/kg i.v. Intermittent smaller doses of the two drugs were then given immediately after periods of coronary occlusion whenever necessary to achieve analgesia and light sedation while maintaining corneal reflexes, jaw tone, and a state of arousability. To enhance the influence of nitroglycerin on venous pooling, animals were studied in 30° head-up tilt. In all dogs arterial O2 saturation and pH was maintained in the physiologic range (two animals required intubation and positive pressure ventilation intermittently). Instrument leads and catheters were exteriorized from the subcutaneous pouch. A catheter was placed percutaneously via the femoral artery into the aorta in all animals and a flow-directed catheter passed transvenously into the pulmonary artery in five animals. Electrograms from the myocardial wires were recorded on a multichannel direct writer recorder at a paper speed of 50 mm/sec and at a sensitivity of 10 mV/cm. ST segments were measured as the deflection from the isopotential point 100 msec after the onset of the initial QRS deflection, a time well before the beginning of the T wave. The sum of the values was expressed as ΣST. Arrhythmias or beats exhibiting aberrant conduction were not used for analysis. Previous studies from our laboratory have shown an excellent correlation between ST-segment change early after occlusion and the degree and extent of subsequent myocardial infarction.2 Hence myocardial ischemia as measured electrophysiologically in this preparation by ΣST was assumed to correlate with the degree and extent of myocardial infarction that would have occurred subsequently if coronary occlusion had been maintained. Measurements included aortic flow (cardiac output minus coronary flow) in six dogs, cardiac output by thermodilution6 in three dogs, aortic pressure in all dogs, directly measured left atrial pressure in two dogs, and pulmonary capillary wedge pressure in four dogs. All manometer zeroes were set at the midthorax level.

In the first group of ten dogs, the effects of nitroglycerin alone and combined with methoxamine were evaluated by producing repeated 15 min balloon occlusions in the same animal and measuring ΣST at 5 min intervals. Nitroglycerin was prepared as a 1 to 2 mg/cc solution by dissolving sub-

![Diagrammatic representation of lateral view of the heart showing the site of the inflatable balloon cuff on the left anterior descending coronary artery (LAD) and the ameroid constrictors on the obtuse marginal (OM) and posterior descending (PD) coronary arteries. Chronically implanted myocardial electrodes, left atrial (LA) catheter, pacing electrode and aortic (A) flow probe also are shown. PA = pulmonary artery.](http://circ.ahajournals.org/content/circulation/51/4/463/suppl_1/fig1)

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lingual tablets (Nitroglycerin, U.S.P., Lilly) in physiologic saline. The drug was administered intravenously as an initial bolus (0.5 mg) followed by a continuous infusion (0.3 to 1.7 mg/min) that was maintained throughout occlusion. Since individual dogs responded differently to the same amount of nitroglycerin (reflecting either different responsiveness or differences in potency of the different commercial batches of the drug), the rate of infusion was adjusted such that each animal had an increase in heart rate of 20–75 beats/min and/or a fall in blood pressure of 10–30 mm Hg. In the nitroglycerin-methoxamine experiments, the rate of infusion of nitroglycerin was adjusted in the same manner for each animal, then reflex heart rate and blood pressure changes were reversed by intravenous methoxamine prior to occlusion. This rate of infusion of nitroglycerin was sustained throughout the occlusion period and intravenous methoxamine (0.5–1.0 mg) given intermittently to prevent blood pressure and heart rate change. In the studies in which drugs were administered, the LAD was occluded after hemodynamic changes resulting from the drugs had stabilized. Inflation pressure in the occlusive cuff was maintained above 500 mm Hg during occlusion. Each intervention was separated by 45–60 min, by which time ST segments, heart rate, cardiac output and filling pressure had returned to baseline. The reproducibility of ST changes and stability of this preparation has been documented in earlier work.1 Additional doses of morphine and diazepam to maintain sedation were given only after release of occlusion, allowing sufficient time (45–60 min) for dissipation of any resultant hemodynamic changes. Control and treatment occlusions were performed in random order, and each dog served as its own control.

After completion of the experiment, leads and catheters were returned to the subcutaneous pouch which was then sutured closed.

Selective Coronary Angiography

Two to three days after experimental study, seven of the animals again received morphine/diazepam sedation for selective coronary angiographic evaluation. Using a modified Judkins left coronary catheter, serial films were taken at two per second in the lateral projection in all animals. Left anterior oblique projections were also utilized when necessary to visualize specific coronary segments. In each animal, arteriograms were performed in the basal state and 15 min after the LAD balloon had been inflated with the same volume of saline used in experimental studies. Studies were graded as to adequacy of balloon occlusion, adequacy of amoroid occlusion, presence of collateral vessels to arteries distal to amoroid constrictors, and during balloon occlusion, as to presence of collaterals connecting that portion of the LAD system distal to the occluded balloon cuff with both chronically occluded and unoccluded branches of the left coronary artery.

Four angiographic control animals (without amoroid constrictors) were studied in an identical fashion after at least 15 min of balloon occlusion. All control animals had ST-segment elevation characteristic of acute ischemia recorded from intramyocardial electrodes at the time of angiography.

Postmortem Studies

After radiologic studies, the dogs were sacrificed. The presence or absence of myocardial necrosis was evaluated by gross inspection of the myocardium and by microscopic analysis of hematoxylin and eosin stained sections obtained from areas supplied by the LAD, obtuse marginal and posterior descending coronaries.

Results

When the LAD coronary artery was occluded acutely without drug administration (control occlusions) mean arterial pressure, heart rate, and cardiac output were not changed significantly from preocclusion values. However, filling pressure (pulmonary capillary wedge or direct left atrial) increased from 4.6 ± 0.8 mm Hg before occlusion to 6.2 ± 0.7 mm Hg (P < 0.05) after 10 min and 15 min of ischemia.

When the LAD was occluded acutely in the same dogs but nitroglycerin infused alone, mean systemic blood pressure averaged 13% lower, heart rate 37% higher, and left atrial or PCW pressure 40% lower than comparable values in the same dogs during control ischemia (Table 1). Cardiac output was not significantly changed by nitroglycerin. When all ten dogs were considered as a group, nitroglycerin alone produced no significant change in ischemic injury, as measured by $\Sigma$ST (Table 1 and Fig. 2). When subgrouped by heart rate response, however, ST elevation was 64% greater after nitroglycerin in the four animals with nitroglycerin-induced postocclusion heart rate increase (relative to untreated postocclusion heart rate) of more than 50%. In contrast ST elevation

![Figure 2](http://circ.ahajournals.org/)

**Figure 2** Effect of nitroglycerin (TNG) and nitroglycerin with methoxamine (TNG/METH) during acute ischemia. Each line represents the mean values of the sum of ST-segment elevations ($\Sigma$ST) recorded from each of the intramyocardial electrodes during repeated 15 min occlusions.

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### Table 1

**Hemodynamic and ST-segment Observations Before and During Acute Ischemia**

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X ± SEM: 78 ± 6; 103 ± 3; 14 ± 1; 86 ± 6; 105 ± 4; 46 ± 8; 120 ± 9; 88 ± 4; 46 ± 8; 76 ± 4; 109 ± 3; 4 ± 1; 31 ± 8.

P < 0.01 < 0.001 NS NS NS < 0.025 <0.01

Hemodynamic and ST-segment data in each dog prior to coronary occlusion (no ischemia), and after 15 minutes of coronary occlusion with no drug administration (control ischemia), during occlusion with nitroglycerin administration (TNG treated ischemia) and during occlusion with nitroglycerin and methoxamine administration (TNG/METH treated ischemia). The interventions were randomized and the heart rate (HR), mean systemic arterial pressure (SAP), filling pressure (FP—see text), and sum of ST segment elevation of 8 intramyocardial electrodes (ΣST) were not significantly different during the nonischemic periods prior to any of the three occlusion periods: HR = 78 ± 6; 78 ± 4; 79 ± 6; SAP = 103 ± 3; 104 ± 3; 101 ± 2; FP = 4.6 ± 0.8; 3.8 ± 0.8; 4.2 ± 0.6; and ΣST = 13.6 ± 1.1; 13 ± 1.2; 12.5 ± 1.3. X ± SEM = mean ± standard error of the mean; P = P values relative to the corresponding observation during control ischemic observations by the student's t-test; NS = not significant.
was 31% lower than control in the six dogs with nitroglycerin-induced heart rate increase less than 50% (fig. 3). Thus, in nitroglycerin-treated dogs a strong correlation existed between heart rate and ΣST (fig. 4). A relation between filling pressure and ischemic injury was also suggested when changes in filling pressure were plotted against the degree of ischemia: filling pressure tended to fall more (>50%) in animals improved during nitroglycerin infusion when compared to those worsened during nitroglycerin. (table 1). This relation, however, did not achieve statistical significance.

The importance of the detrimental effect of hypotension accompanied by excessive reflex tachycardia was further supported by the finding that when methoxamine was administered with nitroglycerin to maintain heart rate and blood pressure constant, ischemic injury consistently decreased. Thus, ΣST after 10 min of coronary occlusion in the control experiments was 48 ± 9 mV but only 31 ± 7 mV (P < 0.02) when nitroglycerin and methoxamine were administered together; after 15 min of occlusion, ΣST in the control experiment was 44 ± 8 mV but 31 ± 8 mV when the drugs were given (P < 0.01, table 1 and fig. 2). Although methoxamine reversed nitroglycerin-induced changes in blood pressure and heart rate, filling pressure was significantly lower than comparable values during control occlusion (35% avg decrease, P < 0.01) and was similar to values observed during nitroglycerin infusion alone (table 1).

ST segments recorded from electrodes placed into the inferior wall of the left ventricle did not change during acute LAD coronary artery occlusion in four dogs. These ST segments remained unaltered by acute occlusion in the studies in which nitroglycerin alone and nitroglycerin plus methoxamine were administered.

Radiologic Findings

Selective coronary arteriograms in seven experimental dogs with chronic ameroid occlusion were compared to angiograms in four control dogs without ameroids. Ameroid occlusion was assessed as complete in five of seven dogs. An ameroid produced 90% occlusion of the obtuse marginal coronary artery in one animal, and the patency of the obtuse marginal in the seventh dog could not be established angiographically. Postmortem examination, however, revealed this vessel to be completely occluded. All chronically constricted arteries were supplied by collateral vessels, either from unoccluded portions of the circumflex or from the LAD. After acute balloon

![Graph](https://example.com/graph.png)

**Figure 3**

Comparison of effect of nitroglycerin (TNG) alone on ischemia between dogs with heart rate (HR) response to nitroglycerin less than or greater than 50% of the corresponding control occlusion. Each line represents the mean values of ΣST during 15 min occlusions.

![Graph](https://example.com/graph2.png)

**Figure 4**

Correlation between heart rate response to nitroglycerin infusions (without methoxamine) and degree of ischemia. Σ ST as percent of the corresponding control occlusion is plotted against observed heart rate (HR) as percent of the corresponding control occlusion. Each animal is represented by two points (an observation at 10 min and 15 min). Six animals consistently improved and four consistently worsened. The corresponding correlation coefficients (r) when values at 10 min and 15 min were calculated separately were: r = 0.834 and r = 0.915, respectively.
occlusion of the LAD, filling of the LAD system distal to the occlusion could be demonstrated in all dogs with ameroids when contrast material was injected into the left main coronary artery. Collateral vessels contributing to distal LAD filling were identified as originating from the LAD proximal to the balloon and from the circumflex coronary artery both proximal and distal to the ameroid constrictors. This contrasted to the findings of control animals which had no ameroid constrictors; only two of four of these animals demonstrated minimal filling of the LAD system distal to the acutely occluded segment. Representative angiograms showing these findings in a control dog and in a dog with ameroid constrictions are depicted in figure 5. Thus, the ameroid constrictors used in this preparation resulted in development of collateral vessels communicating with portions of coronary arteries distal to the chronic occlusions. These collateral vessels, originating from both the LAD and unoccluded circumflex coronary arteries, were capable of supplying the distal LAD coronary artery after this artery was occluded acutely.

Postmortem Findings

No dog with chronic ameroid-induced coronary constriction demonstrated grossly visible evidence of

Figure 5

Selective left coronary angiograms (lateral view) in a control dog (upper panels) and a dog with chronically implanted ameroid constrictors (lower panels). The two angiograms on the left represent studies before balloon occlusion while the radiographs on the right represent studies performed 15 min postocclusion. Note the collateral development to vessels distal to the ameroid constrictors and the increased filling of the distal left anterior descending vessels (from intracoronary and intercoronary channels) when the LAD balloon was acutely occluded. In contrast, the control animal had minimal filling of the distal LAD.
myocardial infarction in the areas supplied by the chronically occluded circumflex or acutely occluded LAD coronary arteries. Small areas of fibrosis surrounded the intramyocardial electrodes. One animal had a 0.5 by 1 cm scar at the site of ameroid occlusion of an obtuse marginal branch, presumably due to acute occlusion of a small vessel at the time of dissection and surgical placement of the ameroid. In five dogs, light microscopic studies of sections taken from the myocardium supplied by the obtuse marginal, the posterior descending and the LAD coronary arteries demonstrated no evidence of myocardial necrosis.

In the five experimental animals that did not undergo angiography, inspection of the vessels at the site of ameroid placement showed the vessels to be completely occluded. To estimate the extent of collateralization, an opaque liquid was injected under physiologic pressure into the left main coronary artery; adequacy of the collateral system in these animals appeared similar to that determined in the seven other dogs by angiography.

**Discussion**

Previous studies from our laboratory have demonstrated beneficial effects of nitroglycerin during experimental acute coronary artery occlusion.1, 3 The present study was designed to determine if nitroglycerin would decrease ischemic injury in the presence of chronic multivessel occlusive disease, as usually exists in acute myocardial infarction in man. This was accomplished by placing ameroid constrictors around the posterior descending and obtuse marginal coronary arteries two weeks prior to acute occlusion of the LAD coronary artery. The hydrophilic ameroid material slowly swells resulting in gradual occlusion of the coronary artery.4 Radiographic and postmortem evaluation demonstrated that the coronary arteries were occluded at the site of ameroid placement and that coronary collateralization was increased in dogs with ameroid occlusion compared to control dogs without ameroids. After acute balloon occlusion of the LAD coronary artery, injection of contrast material into the left coronary ostium showed that collateral flow reversed to fill the LAD distal to the occlusion in all dogs with ameroids. Thus, although this animal model is not entirely equivalent to acute myocardial infarction in man it is uniquely similar in that chronic coronary occlusion with collateral development serves as a background for an acute ischemic insult.

Our results showed that dogs with chronic multivessel coronary obstruction, like dogs with previously normal coronary arteries,1, 7 may have marked attenuation of electrophysiologic evidence of ischemia when nitroglycerin is given during acute coronary occlusion. When the LAD coronary artery was occluded acutely in this canine model, nitroglycerin was capable of diminishing ischemic injury in all dogs in which nitroglycerin-induced fall in arterial pressure and reflex increase in heart rate were prevented by simultaneous administration of the vasoconstrictor methoxamine (fig. 2). However, when nitroglycerin was administered alone and heart rate and arterial pressure were allowed to vary spontaneously, ischemia decreased in dogs with multivessel occlusion only when excessive tachycardia did not occur. Thus, nitroglycerin improved myocardial ischemia whenever heart rate increased less than 50% of control occlusion, but worsened ischemia when heart rate rose by more than 50% (figs. 3, 4).

The decrease in ischemia produced by nitroglycerin presumably reflects a favorable net influence of the drug on the balance between myocardial oxygen requirements (MVO2) and myocardial oxygen delivery in the region of acute ischemia. A fall in MVO2 produced by the drug would favorably alter this balance and thereby diminish ischemia. In this regard, nitroglycerin diminished left ventricular filling pressure, an effect that was not reversed by a dose of methoxamine sufficient to prevent nitroglycerin-induced hypotension (table 1). Thus, if the decrease in filling pressure reflected a decrease in left ventricular volume, myocardial wall tension (and thereby MVO2) would diminish for any given level of ventricular systolic pressure.7 Nitroglycerin also acts to reduce MVO2 by diminishing ventricular systolic pressure. In contrast to filling pressure, however, reduction in arterial pressure did not correlate with changes in ischemia. This may be explained in part by the fact that in this study arterial pressure fell in response to nitroglycerin by an average of only 13%. Moreover, nitroglycerin-induced vasodilation has complex influences. For example, reduction in blood pressure not only tends to decrease MVO2 by diminishing wall stress, but it also tends to decrease myocardial oxygen delivery by diminishing coronary perfusion pressure. In addition, systemic vasodilatation caused by nitroglycerin also may be accompanied by a fall in resistance to coronary collateral flow,8, 9 thereby attenuating the effects a fall in perfusion pressure would have on flow to ischemic areas. Thus, the net effect of nitroglycerin-induced arterial pressure reduction on the balance of MVO2 and myocardial oxygen delivery may be variable and unpredictable.

Apart from any influence on MVO2, it also is possible that nitroglycerin actually diminishes ischemia by reducing resistance to coronary collateral flow and consequently increasing blood flow to ischemic myocardium. It may do this by dilating large precollateral vessels,10 by directly dilating coronary collateral vessels, or by lowering ventricular diastolic...
pressures and volumes and thereby reducing lateral compression of collateral vessels.\textsuperscript{11}

This study also points out potential deleterious effects of nitroglycerin during acute ischemia. Along with its oxygen sparing actions, nitroglycerin may act to augment MV\textsubscript{O}2 and hence increase ischemia by reflex-mediated tachycardia (fig. 4). The importance of this effect is emphasized by a direct relation of ischemic ST-segment elevation and heart rate during nitroglycerin infusion. Indeed, a sufficiently great increase in heart rate (greater than 50\%) may nullify all potential benefit of nitroglycerin so that a net detrimental influence on ischemia is observed (fig. 3). Thus, heart rate increase appears to exert the same unfavorable influence on ischemia during nitroglycerin infusion that it does during ischemia without nitroglycerin.\textsuperscript{11} This point is corroborated by the conversion of a heterogeneous ST-segment response to nitroglycerin when heart rate is allowed to vary spontaneously, to a uniformly beneficial response to the drug when reflex tachycardia is eliminated by methoxamine.

The finding of a deleterious action of excessive tachycardia is not incompatible with the consistent improvement during nitroglycerin observed in previous studies of acute ischemia in dogs with otherwise normal coronary arteries, since heart rates of greater than 50\% of those occurring during control occlusions were not observed.\textsuperscript{1} However, it is possible that tachycardia may be uniquely unfavorable in chronically occluded animals. Since collateral flow is thought to occur mostly in diastole,\textsuperscript{12} tachycardia-induced abbreviation of diastole may be especially deleterious in a preparation that is heavily dependent on flow through collaterals.

In our animals and in certain patients with multivessel coronary disease, some of the feeder arteries delivering blood flow to collateral vessels are narrowed, thereby limiting the maximal potential supply of blood available either to collaterals or to the nonischemic myocardium directly served by the feeder artery. Under these circumstances agents that nonspecifically reduce vascular resistance may theoretically result in a maldistribution of coronary flow ("coronary steal"). This possibility was not realized in the present study. Collaterals to the distal, acutely occluded LAD were supplied, at least in part, by obtuse marginal and posterior descending coronary arteries that were themselves chronically occluded with ameroïd constrictors. By causing excessive dilation of precapillary vessels in the natural bed of the obtuse marginal or posterior descending arteries, nitroglycerin might have stolen blood from the regions supplied by the LAD, thereby intensifying ischemia. Our data showed, however, that nitroglycerin reduced ischemia in the distribution of the LAD except when the drug caused excessive tachycardia. Alternatively, if nitroglycerin excessively dilated the collateral vessels, it might have alleviated ischemia in the regions supplied by the LAD while producing new ischemia in the regions supplied by the occluded obtuse marginal and posterior descending arteries. Electrodes implanted in these regions failed to record any evidence of ischemia induced by nitroglycerin. It should be emphasized that the absence of a coronary steal was probably due in part to the abundant collateral channels present in our model of experimental coronary occlusion. In patients with less prolific collateral development, however, it is still possible that nitroglycerin may enhance regional ischemia by promoting maldistribution of coronary flow.

Another potentially important finding of the present investigation is that nitroglycerin reduced ischemia in the absence of left ventricular failure. It is well established that nitroglycerin improves hemodynamic performance in patients with myocardial infarction who have cardiac failure manifest by elevated filling pressures.\textsuperscript{14} Preliminary results in man indicate that nitroglycerin also may decrease ischemia under these circumstances (personal communication). Our results suggest that nitroglycerin may reduce the magnitude of ischemic injury even when acute ischemia is not accompanied by cardiac failure.

In conclusion, the results of the present investigation demonstrate that nitroglycerin consistently decreases ischemic injury during experimental acute coronary occlusion even in the presence of chronic multivessel coronary disease, provided excessive reflex tachycardia and hypotension are prevented by administration by an alpha-adrenergic agonist. Since ischemia is probably the primary mechanism responsible for production of arrhythmias and cardiac failure occurring during acute myocardial infarction, nitroglycerin-induced reduction in ischemia might prevent or reduce the severity of these complications. Although the applicability of these experimental findings to acute myocardial infarction in man is unknown, the experimental evidence is sufficiently encouraging to warrant careful clinical evaluation of this therapeutic concept.

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References
4. Blumgart HL, Schlesinger MJ, Davis D: Studies on the relation of clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathological findings with particular reference to the significance of the collateral circulation. Am Heart J 19: 1, 1940
Effects of nitroglycerin and nitroglycerin-methoxamine during acute myocardial ischemia in dogs with pre-existing multivessel coronary occlusive disease.
R W Myers, J L Scherer, R A Goldstein, R E Goldstein, K M Kent and S E Epstein