JCI The Journal of Clinical Investigation

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J Clin Invest. 1977;60(2):295-301. https://doi.org/10.1172/JCI108777.

Research Article

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ABSTRACT The recent use of vasodilators to improve ventricular function in acute myocardial infarction led us to investigate the effects of nitroglycerin, nitroprusside, and phentolamine on coronary collateral flow. Dogs were studied 2–4 wk after an ameroid constrictor was placed around the left anterior descending (LAD) coronary artery. Retrograde flow and peripheral coronary pressure were measured from a cannula inserted in the LAD distal to the ameroid. Systemic arterial pressure was held constant by an aortic cuff. When administered intracoronary (i.c.), nitroglycerin, 0.3–100 μg/min, or nitroprusside, 3–100 μg/min, produced quantitatively similar, dose-dependent increases in retrograde flow. Neither drug, i.c., changed peripheral coronary pressure. Nitroglycerin, 3–300 μg/min, intravenous (i.v.), produced dose-dependent increases in retrograde flow; nitroprusside, i.v., increased retrograde flow only in high doses (100–300 μg/min). Nitroglycerin and nitroprusside, i.v., produced similar increases in peripheral coronary pressure. Phentolamine, 1–300 μg/min, i.v., decreased retrograde flow, and did not change peripheral coronary pressure. Nitroprusside was considerably more potent than nitroglycerin in decreasing systemic arterial pressure and in reducing total coronary resistance. Thus, (*a*) although i.c. nitroglycerin and nitroprusside produce similar effects on collateral function, i.v. nitroglycerin is more effective than i.v. nitroprusside in augmenting collateral flow; (*b*) phentolamine has deleterious effects on collateral function; and (*c*) the relative vasodilator potencies of nitroglycerin and nitroprusside vary in different vascular beds; thus, for a given reduction in systemic arterial pressure, nitroprusside is less effective in increasing retrograde flow.

INTRODUCTION

Reducing the impedance to left ventricular ejection by administration of such vasodilators as nitroglycerin (1, 2), nitroprusside (3, 4), or phentolamine (4, 5) has been shown to result in hemodynamic improvement in patients with acute myocardial infarction. However, an additional goal of vasodilator therapy in patients with acute myocardial infarction is the reduction in ischemic injury. Vasodilators might lessen ischemia through any of several mechanisms. Reduced ventricular filling would decrease wall tension and lower myocardial oxygen requirements. Decreased wall tension could also reduce intramural coronary artery compression and thereby contribute to an increase in collateral flow. Furthermore, vasodilators may directly increase collateral blood flow. Although it has been shown that nitroglycerin has the capacity to reduce ischemia (2, 6–10) and to increase collateral blood flow (11–13), similar actions have not been demonstrated for other vasodilators currently being employed clinically. Indeed, recent evidence[1] suggests that nitroprusside, in contrast to nitroglycerin, may actually increase the degree of myocardial ischemia present during acute myocardial infarction (14).

Because augmentation of collateral blood flow probably plays an important role in the alleviation of ischemic injury, the present investigation was under-

Received for publication 7 April 1976 and in revised form 11 April 1977.

[1] Pearlman, A. S., R. L. Engler, R. A. Goldstein, K. M. Kent, and S. E. Epstein. Relative effects of nitroglycerin and nitroprusside on acute myocardial ischemia in dogs with preexisting multivessel occlusive disease. Submitted for publication.

taken to compare the effects of nitroglycerin, nitroprusside, and phentolamine on coronary collateral function. In addition, because vasodilators may vary in their site of action, the relative vasodilator potencies of nitroglycerin and nitroprusside were determined for the systemic and coronary arterial beds.

METHODS

Assessment of collateral function. The retrograde flow-peripheral coronary pressure technique (11, 13) was chosen to determine the effects of nitroglycerin, nitroprusside, and phentolamine on collateral function. The reason for this decision was that we considered it essential to perform dose-response curves for each drug, because the arbitrary selection of one or two doses would not provide adequate pharmacologic information to compare the potencies of the drugs under investigation. Although retrograde flow cannot be equated with collateral flow, it may be assumed that changes in retrograde flow will reflect relative changes in collateral flow. Peripheral coronary pressure represents a balance between blood delivery through collateral channels and outflow through arterioles to capillaries. Changes in peripheral coronary pressure will therefore reflect changes in collateral flow, changes in arteriolar resistance, or both. The retrograde flow technique has the advantage in this study of allowing multiple determinations in a single animal, whereas a technique such as microsphere distribution would allow only a few determinations in each animal. This, in turn, permits control measurements and the effects of several doses of one drug to be compared with the effects of a second drug (or second route of administration) in a single animal.

Determination of retrograde flow and peripheral coronary pressure. 25 dogs weighing 18–26 kg were studied. The experimental procedure has been described in detail in a separate communication (13). Briefly, an ameroid constrictor was placed around the left anterior descending (LAD)[2] coronary artery, resulting in gradual occlusion of the artery; 2–4 wk were allowed for development of collateral vessels. At the time of study, the dogs were anesthetized with sodium pentobarbital, 40 mg/kg, i.v. The experimental preparation is shown in Fig. 1. Retrograde flow and peripheral coronary pressure were measured from side arms of a cannula inserted in the LAD distal to the ameroid. Retrograde flow was collected for 5- to 30-s intervals into glass tubes that were later weighed to determine the amount of flow. Peripheral coronary pressure, measured from a side arm of the cannula connected to a physiological pressure transducer (Statham P23Gb, Statham Instruments, Div. of Gould Inc., Oxnard, Calif.), was monitored between collections of retrograde flow. Drugs were administered through a cannula in the left main coronary artery (i.c.) or through a cannula in a limb vein. The left main coronary artery was continuously perfused with blood from the dog's carotid artery. During the stabilization periods between drug studies, the distal LAD was also perfused with blood from the carotid artery. An electromagnetic flow probe (Carolina Medical Electronics, Inc., King, N. C.) was placed in the circuit between the carotid and the left coronary artery. Systemic arterial pressure, left atrial pressure, EKG, and coronary flow were continuously monitored. Because retrograde flow and peripheral coronary pressure are directly related to coronary perfusion pressure (15), systemic arterial pressure was held constant by manipulation of an inflatable cuff around the descending aorta. Clotting was prevented by administration of heparin (10,000 U/h). The animals were continuously respired with room air. Arterial oxygen saturation was maintained above 90% by addition, when necessary, of a low-flow of 100% O_2 at the intake valve of the respirator. Care was taken that oxygen saturation did not exceed 94%. Arterial pH was maintained between 7.35 and 7.45 by adjustments in the ventilation rate and administration of bicarbonate, as needed.

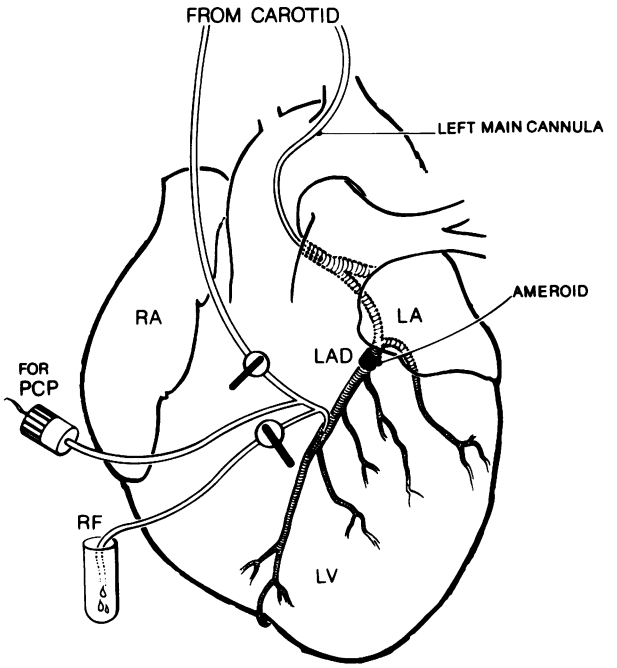

FIGURE 1 Experimental preparation. Anterior surface of the dog heart. Cannulas were inserted in the left main coronary artery and in the LAD coronary artery distal to the ameroid constrictor. Both vessels were supplied with blood from the carotid artery. When inflow to the distal LAD from the carotid was clamped, retrograde flow (RF) and peripheral coronary pressure (PCP) were measured from side arms of the LAD cannula.

Drugs. Solutions of each drug were prepared immediately before use. Nitroglycerin (tablets, Eli Lilly and Co., Indianapolis, Ind.), nitroprusside (crystalline sodium nitroferricyanide, Fisher Scientific Co., Pittsburgh, Pa.), and phentolamine (lyophilized phentolamine mesylate, CIBA-GEIGY Corp., Summit, N. J.) were each dissolved in saline. Amounts refer to micrograms of the salt. The experimental procedure for each intervention was as follows. (*a*) LAD inflow was clamped. (*b*) Systemic arterial pressure was adjusted to 100 mm Hg. (*c*) 2 min were allowed for stabilization. (*d*) Control measurements of retrograde flow and peripheral coronary pressure were taken. (*e*) The drug was infused, either i.c. or i.v. For each drug, the infusion rate was adjusted to administer progressively increasing amounts from 0.3–100 μg/min, i.c., or 1–300 μg/min, i.v. 90 s (i.c. administration) or 3 min (i.v. administration) of infusion were allowed before determinations of retrograde flow and peripheral coronary pressure for each drug concentration. (*f*) At the end of each dose-response curve, LAD inflow was restored. A total of 20–30 min elapsed between the time LAD inflow was halted and restored. In control studies, values of retrograde flow and

[2] *Abbreviation used in this paper*: LAD, left anterior descending.

peripheral coronary pressure were stable for this time interval if no drug was administered. At least 1 h was allowed to elapse between successive dose-response curves in the same dog. The effects of nitroglycerin on retrograde flow and peripheral coronary pressure have been reported in a separate communication (13).

Determinations of vascular resistance. The effects of nitroglycerin and nitroprusside on collateral resistance and total coronary resistance were determined from the values of retrograde flow and total coronary flow obtained in the above studies. Collateral resistance (*R* collateral) was calculated from the equation:

$$R \text{ collateral} = \frac{\overline{SAP}}{RF},$$

where $\overline{SAP}$ is mean systemic arterial pressure and *RF* is retrograde flow. Changes in "collateral" resistance signify net changes in the resistances of the collateral vessels themselves, of the large coronary arteries that supply the collateral vessels, or both. Our model does not distinguish between the two types of vessels. Thus "*R* collateral" represents the entire collateral circuit. Total left coronary resistance (*R* total coronary) was calculated as follows:

$$R \text{ total coronary} = \frac{\overline{SAP}}{CF},$$

where $\overline{SAP}$ is mean systemic arterial pressure and *CF* is left main coronary flow. For this study, mean coronary artery perfusion pressure was considered equivalent to $\overline{SAP}$ and $\overline{SAP}$ was used in calculations of *R* collateral and *R* total coronary. The left main coronary artery was perfused by a cannula of 20 ml volume, 80 cm in length and with a resistance to flow that caused a pressure drop of 3, 8, and 11 mm Hg at flows at 116, 150, and 184 ml/min, respectively. Control coronary flow averaged 95.6±7.5 ml/min ($n = 9$). Flow was increased to a maximum of 109.0±14.6 ml/min ($n = 5$) with 100 μg/min nitroglycerin, i.c., and to 141.2±12.6 ml/min ($n = 4$) with 100 μg/min nitroprusside, i.c. With arterial pressure held constant at 100 mm Hg, the maximum error introduced was approximately 6%.

Inasmuch as arterial pressure was maintained constant in the above studies, the effects of nitroglycerin and nitroprusside on total peripheral resistance were determined in a separate study. Four normal dogs were anesthetized with sodium pentobarbital, 40 mg/kg, i.v.; through a left thoracotomy an electromagnetic flow probe (Carolina Medical Electronics) was placed around the ascending aorta. Systemic arterial pressure, right atrial pressure, aortic flow, and EKG were continuously monitored. Drugs were administered by constant intravenous infusion. Total peripheral resistance (*R* peripheral) was calculated from the equation:

$$R \text{ peripheral} = \frac{\overline{SAP} - \overline{RAP}}{AoF},$$

where $\overline{SAP}$ is mean systemic arterial pressure, $\overline{RAP}$ is mean right atrial pressure, and *AoF* is aortic flow.

RESULTS

Effects of intravenous nitroglycerin, nitroprusside, and phentolamine on retrograde flow and peripheral coronary pressure. Changes in retrograde flow and peripheral coronary pressure with i.v. nitroglycerin, nitroprusside, and phentolamine are shown in Fig. 2.

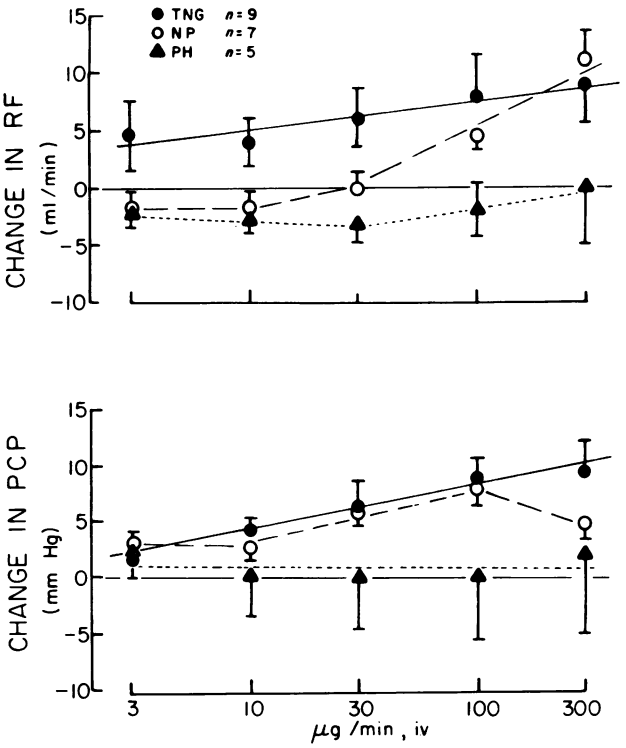

FIGURE 2 Effects of i.v. nitroglycerin (TNG), nitroprusside (NP), and phentolamine (PH) on retrograde flow (RF) and peripheral coronary pressure (PCP). Points represent average (vertical bars = SE) changes in RF and in mean PCP from control values. Average control (±SE) values of RF and PCP were 39.7 (±9.0) ml/min and 59.6 (±5.6) mm Hg for TNG, 25.9 (±5.8) ml/min and 65.0 (±7.0) mm Hg for NP, 16.8 (±1.4) ml/min and 50.0 (±7.9) mm Hg for PH.

Intravenous nitroglycerin, 3–300 μg/min, produced dose-dependent increases in retrograde flow. The values of retrograde flow were significantly greater than control ($P < 0.05$) beginning with 10 μg/min nitroglycerin. Intravenous nitroprusside, 1–30 μg/min, failed to change retrograde flow significantly; however, increments in retrograde flow were produced by higher doses ($P < 0.05$ at 100 and 300 μg/min). The change in retrograde flow was significantly greater ($P < 0.05$) with nitroglycerin than with nitroprusside at the lower doses (10–30 μg/min). Phentolamine, 1–300 μg/min, i.v., tended to progressively decrease retrograde flow, but the decrease lessened with higher doses (100–300 μg/min).

Nitroglycerin, 3–300 μg/min, i.v., and nitroprusside, 3–300 μg/min, i.v., produced quantitatively similar dose-dependent increases in peripheral coronary pressure. Both drugs produced significant ($P < 0.05$) increments in peripheral coronary pressure at 10 μg/min. The nitroprusside-induced increment in peripheral coronary pressure was less with 300 μg/min, but the difference was not statistically significant. Phentol-

amine, 1–300 μg/min, i.v., produced no consistent effect on peripheral coronary pressure.

Changes in left atrial pressure are shown in Table I. Control left atrial pressures averaged 4.6±0.3 mm Hg. Both i.v. nitroglycerin and i.v. nitroprusside produced small (<2 mm Hg) but significant reductions in left atrial pressure. Alterations in left atrial pressure produced by the two drugs did not differ significantly. Intravenous phentolamine did not change left atrial pressure.

For all these drugs, systemic arterial vasodilator effects were counteracted by inflation of the aortic cuff, so that systemic arterial pressure did not change with increasing drug concentration. Thus, under conditions of constant coronary perfusion pressure, i.v. nitroglycerin and nitroprusside, but not phentolamine, produced increases in the indices of collateral function. Furthermore, i.v. nitroglycerin enhanced collateral function at lower doses than did nitroprusside. To determine whether this difference reflected merely a different potency or a differing site of action for the two drugs, the effects of nitroglycerin and nitroprusside were further tested.

Effects of intracoronary nitroglycerin and nitroprusside on retrograde flow and peripheral coronary pressure. Nitroglycerin, 0.3–100 μg/min, i.c., and nitroprusside, 0.3–100 μg/min, i.c., produced dose-dependent increases in retrograde flow (Fig. 3). The nitroglycerin-induced increases in retrograde flow were significant ($P < 0.05$) beginning at 0.3 μg/min; the nitroprusside-induced increases, at 3 μg/min. The nitroprusside-induced increments in retrograde flow were less than nitroglycerin-induced increments for any given dose, but the difference between the two was not significant. Neither drug, i.c., changed peripheral coronary pressure (Fig. 3). Also, neither drug, i.c., significantly altered left atrial pressure.

Comparison of nitroglycerin- and nitroprusside-induced changes in resistance in different vascular beds. Although intracoronary nitroglycerin, 0.3–100 μg/min, and intracoronary nitroprusside, 0.3–100 μg/min, produced quantitatively similar decreases in coronary collateral resistance (Fig. 4A), nitroprusside was significantly more potent in reducing total left coronary resistance (Fig. 4B). These changes in collateral and coronary resistance were determined under conditions of constant arterial pressure. In a separate study, arterial pressure was allowed to fall with increasing concentrations of i.v. nitroglycerin and nitroprusside, and total peripheral resistance was calculated (Fig. 4C). The two drugs appear to have a similar threshold dose (between 30 and 100 μg/min); however, the slope of the nitroprusside curve for the reduction in total peripheral resistance was considerably steeper. Thus, whereas nitroprusside was more potent than nitroglycerin in reducing total peripheral resistance and total coronary resistance, the two drugs administered i.c. produced equivalent effects on collateral resistance.

TABLE I

Left Atrial Pressure: Effect of Intravenous Nitroglycerin, Nitroprusside, and Phentolamine

Drug	Change in left atrial pressure (mm Hg)			
	10	30	100	300
	μg/min			
Nitroglycerin ($n = 8$)	−0.3* ±0.2	−0.7* ±0.3	−0.5 ±0.3	−0.6* ±0.3
Nitroprusside ($n = 7$)	−0.9 ±0.3	−1.1* ±0.3	−1.4* ±0.4	−1.2 ±0.2
Phentolamine ($n = 5$)	0.7 ±0.4	0.2 ±0.4	0 ±0.6	

Values are changes in left atrial pressure (Δ mm Hg) from control values, means±SE.
* Different from control, $P < 0.05$.

The selective effect of nitroglycerin on collateral resistance was more marked when i.v. nitroglycerin and nitroprusside were compared. As shown in Fig. 5A, i.v. nitroglycerin was more effective than i.v. nitroprusside in reducing collateral resistance ($P < 0.05$ at 10 and 30 μg/min). This order of potency (nitro-

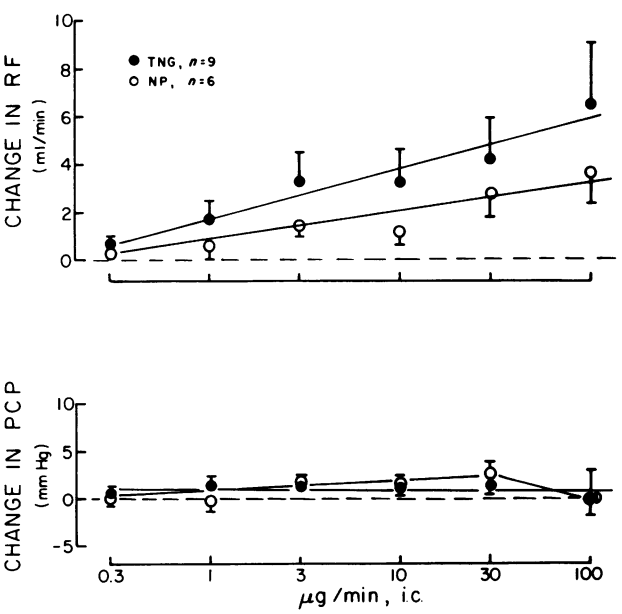

FIGURE 3 Effects of intracoronary nitroglycerin (TNG) and nitroprusside (NP) on retrograde flow (RF) and peripheral coronary pressure (PCP). Points represent average (vertical bars = SE) changes in RF and mean PCP from control values. Average control (±SE) values of RF and PCP were 33.9 (±5.1) ml/min and 63.0 (±5.0) mm Hg for TNG, and 16.3 (±3.3) ml/min and 56.4 (±4.0) mm Hg for NP.

glycerin > nitroprusside) was reversed for the reduction of arterial pressure (nitroprusside > nitroglycerin; $P < 0.05$ at 100–500 μg/min; Fig. 5B).

DISCUSSION

The salutary effects of nitroglycerin on ischemic myocardium have been well documented. Nitroglycerin reduces ST segment elevation after acute coronary occlusion in normal dogs (6) and in dogs with preexisting multivessel coronary occlusive disease (8). When administered with methoxamine during acute coronary occlusion (the latter drug given to abolish nitroglycerin's effects on arterial pressure and heart rate), it attenuates the loss of myocardial creatine phosphokinase (7) and reduces the incidence of ventricular fibrillation (16). Nitroglycerin also lowers ST segment elevation in acute myocardial infarction in man (2, 9, 10). Although the mechanism of nitroglycerin's protective action is not fully understood, it is likely that the beneficial effects are partially due to both a reduction in myocardial oxygen requirements and an enhancement of coronary collateral blood flow. Evidence for the latter mechanism is found in studies

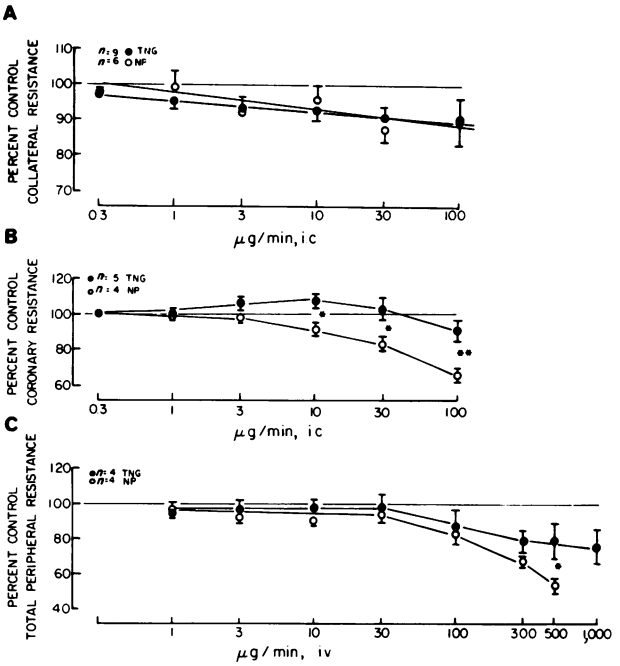

FIGURE 4 Effects of nitroglycerin (TNG) and nitroprusside (NP) on vascular resistance. Abscissae: in A and B, μg/min of drug by intracoronary (i.c.) administration; in C, μg/min of drug by i.v. administration. Ordinates are percents of the control values of collateral (A), total coronary (B), and total peripheral resistances (C). Points represent means; vertical bars = SE. In A and B, mean systemic arterial pressure was held constant at 96±2 mm Hg. In C, arterial pressure was allowed to fall with increasing drug concentrations. *TNG > NP; $P < 0.05$ **TNG > NP; $P < 0.01$.

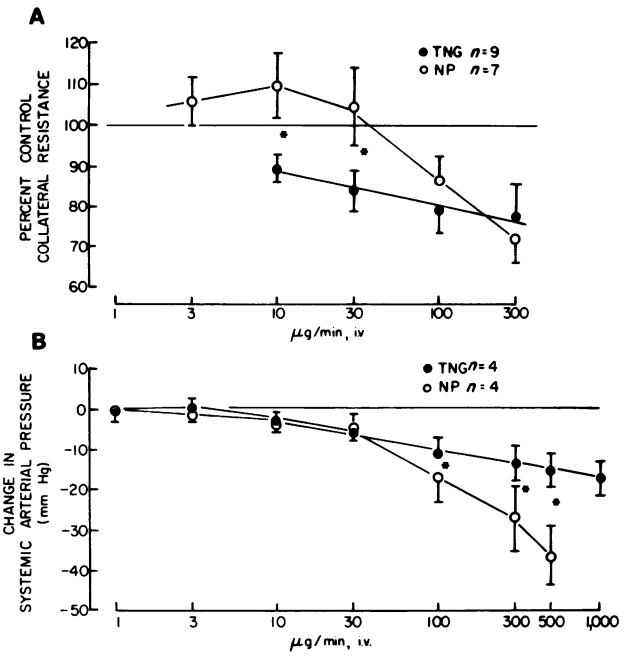

FIGURE 5 Comparison of coronary collateral and systemic vascular effects of i.v. nitroglycerin (TNG) and nitroprusside (NP). In A, points represent average percent of the control collateral resistance; in B, points are average changes in mean systemic arterial pressure from the control values; vertical bars = SE. In A, mean systemic arterial pressure was held constant at 97±2 mm Hg. *in A, NP > TNG; $P < 0.05$ *in B, TNG > NP; $P < 0.05$.

demonstrating that nitroglycerin augments coronary collateral function in dogs (11, 13, and footnote 3) and man (12, 17).

Diminution of ischemic injury with nitroprusside or phentolamine, however, has not been demonstrated. Our results suggest that phentolamine might be less effective than either nitroglycerin or nitroprusside in reducing ischemic damage because it failed to augment collateral flow. Also, in recent studies comparing the effects of nitroglycerin and nitroprusside on ischemic injury during acute coronary occlusion in the dog, ST segment elevation was reduced by nitroglycerin but increased by nitroprusside (14 and footnote 4), and regional coronary flow was increased by nitroglycerin but reduced by nitroprusside (14). The results of the present study suggest that these contrasting effects on ischemic injury might well be due to the fact that nitroglycerin has a different potency spectrum of vasodilator activity in various vascular beds than does

[3] Smith, H. J., R. A. Goldstein, K. M. Kent, R. Aamodt, and S. E. Epstein. Reduction of myocardial ischemia by nitroglycerin and methoxamine: mechanisms of action. Submitted for publication.

[4] Pearlman, A. S., et al. Submitted for publication.

nitroprusside. These differences are complex, but probably are best understood by considering separately the direct and the indirect effects of these drugs on the coronary circulation.

The direct effects of nitroglycerin and nitroprusside on the coronary circulation were determined by intracoronary infusion of the drugs. When administered in this manner, nitroglycerin and nitroprusside produced quantitatively similar dose-dependent decreases in coronary collateral resistance; however, nitroprusside was considerably more potent than nitroglycerin in decreasing total coronary arterial resistance. Likewise, nitroprusside was more potent than nitroglycerin in lowering systemic vascular resistance. Thus, the relative direct vasodilator potencies of nitroglycerin and nitroprusside are not the same for the three vascular beds studied: nitroprusside = nitroglycerin in the coronary collateral circulation, but nitroprusside > nitroglycerin in the coronary and peripheral arterial circulations.

These differences have important implications. First, if the drugs are administered in doses that produce similar decreases in arterial pressure, a relatively higher dose of nitroglycerin would be required to produce any given decrease in systemic arterial pressure; this would result in a greater reduction in collateral resistance than that achieved by the lower dose of nitroprusside. Second, the large reduction in total coronary resistance produced by nitroprusside probably was due largely to dilatation of coronary arterioles, because Winbury et al. (18) have shown that the contribution to total coronary arterial resistance of the large coronary arteries is small compared to the resistance offered by coronary arterioles (large coronary arteries contribute only about 5% of the total coronary resistance). Nitroprusside, by preferentially dilating coronary arterioles, under certain conditions, could predispose to changes that would lead to a coronary steal situation. For example, nitroprusside enhanced collateral function in our model, as indicated by an increase in retrograde flow. However, under conditions of myocardial ischemia and proximal narrowing of the coronary artery supplying the collateral vessels, nitroprusside-induced dilatation of the arterioles supplying nonischemic myocardium could reduce pressure within the narrowed artery. This would necessarily reduce the pressure at the origin of the collateral vessels, and thereby reduce collateral flow; i.e., there would be a redistribution of blood from ischemic to nonischemic regions. Third, nitroglycerin did not cause any substantial effect on total coronary resistance, a finding compatible with the studies of Fam and McGregor (19) and of Winbury et al. (18) which demonstrated that nitroglycerin preferentially dilates large coronary vessels and has relatively little effect on coronary arterioles. These considerations may explain why, in the presence of acute myocardial ischemia produced in dogs with previous multiple coronary occlusions, ischemic injury was increased by nitroprusside but reduced by nitroglycerin.[5]

In contrast to the direct actions in the coronary circulation resulting from intracoronary administration of nitroglycerin and nitroprusside, the effects of i.v. administration are more complicated because the net effect is dependent upon a complex interplay between the direct and indirect actions of these drugs. Although retrograde flow increased after either intracoronary or i.v. administration of nitroglycerin and nitroprusside, peripheral coronary pressure increased only when the drugs were administered i.v. Alterations in arterial pressure as a cause of changes in collateral function were eliminated by maintaining systemic arterial pressure at constant levels. Therefore, the increase in peripheral coronary pressure produced by nitroglycerin and nitroprusside when administered i.v. may be attributable, at least partly, to dilatation of the venous system. Although the observed changes in left arterial pressure with nitroglycerin and nitroprusside were small, they were significant (Table I). The resulting decrease in left ventricular filling pressure and volume might lead to a diminution in diastolic wall tension and thereby decrease the compressive forces exerted on collateral channels, thus indirectly reducing resistance to collateral flow. In addition, the decrease in systolic wall tension would reduce MVO_2, which in turn would lead to autoregulatory induced constriction of coronary arterioles. This change would also cause peripheral coronary pressure to increase.

When administered i.v., nitroglycerin exerted its beneficial effects on collateral function at considerably lower doses than did nitroprusside. This contrasts to the results of intracoronary administration, which demonstrated the drugs to be equally potent. The differing potencies of the two drugs when administered i.v. could be explained if nitroglycerin were a more potent venodilator than nitroprusside. Intravenous phentolamine, on the other hand, failed entirely to increase either retrograde flow or peripheral coronary pressure. These results indicate that the category of "vasodilator drugs" encompasses a heterogeneous group of compounds that display markedly different capacities to dilate various vascular beds. In support of this view are additional studies in man which suggest that nitroglycerin preferentially dilates veins, phentolamine acts mainly on the arterioles, and nitroprusside exerts a balanced effect on arterial and venous systems (20–22).

Thus, our results demonstrate that three commonly used vasodilators, when administered i.v., differ

[5] Pearlman, A. S., et al. Submitted for publication.

substantially in their effects on coronary collateral function. Nitroglycerin is more effective than nitroprusside in reducing collateral resistance; phentolamine does not reduce collateral resistance and may even have a deleterious effect. Moreover, inasmuch as nitroprusside is more potent than nitroglycerin in decreasing peripheral resistance and systemic arterial pressure, the relative selectivity of nitroglycerin for improving collateral function should be further enhanced if the two drugs are administered in doses that produce similar reductions in arterial pressure.

ACKNOWLEDGMENTS

The authors are grateful for the technical assistance of Mrs. Kathleen G. Muth and Mr. William H. Parker.

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